Bayer CropScience

Document Title

Amendment of Summary of the toxicological studies

Thiacloprid FS 400 (400 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

2016-10-06

Author(s)

[redacted]

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-497911-01-1
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2016-10-20	Update of document to include information to demonstrate negligible exposure	M-497911-02-1

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

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

This document summarises the information related to the toxicological studies and exposure (operators, workers and bystanders) for the plant protection product Thiacloprid FS 400 (Specification 102000022825) which contains the active substance thiacloprid. Thiacloprid FS 400 has not 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 or operator/worker/bystander exposure.

This formulation has been registered in many member states of the European Union since 2010.

CP 7.1 Acute toxicity

Summary of acute toxicity

The acute toxicity studies were performed with the formulated product thiacloprid FS 400 G (specification no. 102000021815, batch 2009-000968) and thiacloprid FS 400A G (specification no. 102000022825, batch 2009-007772).

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

Thiacloprid FS 400 contains the active substance thiacloprid (400 g/L) according to the specifications 102000021815 and 102000022825.

Full details of the formulation specifications and the related Bridging Statement can be found in the confidential part of this submission.

The table below summarises the results of the acute toxicity, skin and eye irritation and skin sensitisation studies conducted with the formulated product Thiacloprid FS 400.

Study	Result	Reference
Acute oral rat	LD_{50}: > 300 - < 2000 mg/kg bw	[redacted], U. (2009) CP 7.1.1/01 Report AT05264 [M-347604-01-1]
Acute dermal rat	LD_{50}: > 2000 mg/kg bw	[redacted], U. (2009) CP 7.1.2/01 Report AT05639 [M-358950-01-1]
Acute skin irritation rabbit	Not irritating	[redacted], C. (2010) CP 7.1.4/01 Report AT05735 [M-361477-01-1]
Acute eye irritation rabbit	Not irritating	[redacted], C. (2010) CP 7.1.5/01 Report AT05736 [M-361479-01-1]
Skin sensitisation mouse (Local Lymph Node Assay)	Not sensitising	[redacted]. H. W. (2009) CP 7.1.6/01 Report AT05697 [M-360203-01-1]

Thiacloprid FS 400 is moderately toxic after acute oral administration and non-toxic after acute dermal application to rats. An acute inhalation toxicity study is not triggered for this product. Thiacloprid FS 400 is not irritating to the skin and eyes of rabbits and shows no skin sensitising potential in the Local lymph node assay in mice.

~~The active substance thiacloprid is classified with Carc. Cat. 2, H351 (suspected of causing cancer). As the formulation thiacloprid FS 400 contains 400 g/L of the active ingredient the classification as Carcinogenicity Cat. 2, H351 also has to be applied to the formulation.~~

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 FS 400 contains 400 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 to the study results and the classification of the active ingredient the following classification/labelling is triggered for thiacloprid FS 400:

- Regulation (EC) No 1272/2008 (CLP): Acute Tox. 4; H302 (harmful if swallowed)
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];[redacted]; 2009; M-347604-01-1
Title:	Thiacloprid FS 400 G - Acute toxicity in the rat after oral administration
Report No.:	AT05264
Document No.:	M-347604-01-1
Guidelines:	**OECD 423; Directive 40/2008/EEC; Part B, Method B.1. tris; Regulation (EC) No. 1907/2006 (REACH); US-EPA 712-C-98-190, OPPTS 870.1100; The test item is a product known to be stable and homogenous in both undiluted and in ready-to-use formulation with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed. The deviation does not limit the assessment of results.**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: Thiacloprid FS 400 G

Specification no.:	102000021815
Description:	red liquid, suspension
Lot/Batch no:	2009-000968
Content:	414.4 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2011-02-25

2. Vehicle: tap water

3. Test animals:

Species:	rat
Strain:	Wistar rat, Hsdf pb:Wu
Age:	approx. 8 – 12 weeks
Weight at dosing:	170 g – 203 g
Source:	[redacted], Netherlands
Acclimatisation period:	at least 5 days
Diet:	standard diet [redacted] 3883 PM S15 Maus/Ratte Haltung, [redacted] Switzerland, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	group caged conventionally in polycarbonate cages, bedding: low dust wood granulate (Lignocel BK 8-15, Firma Rettenmaier, Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	300 – 2000 mg/kg bw
Application route:	oral (gavage)
Application volume:	10 mL/kg bw

Fasting time:	before administration: approx. 16h – 24h after administration: approx. 2h – 4h
Group size:	3 females/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 result*			Occurrence of signs	Time of death	Mortality (%)
Female rats						
(1st) 300	0	3	3	1h – 5h	--	0
(2nd) 300	0	3	3	6h – 2d	--	0
2000	3	3	3	45' – 2h	50' – 2h	100
LD_{50}: > 300 mg/kg bw < 2000 mg/kg bw						

* 1st number = number of dead animals, 2nd number = number of animals with toxic signs, 3rd number = number of animals used
': minutes h: hours d: days

B. Clinical observations

In animals dosed with 300 mg/kg bw: temporary tremor, decreased motility and narrowed palpebral fissure.

In animals dosed with 2000 mg/kg bw: abdominal position, tremor, temporary clonical cramps, labored breathing and narrowed palpebral fissure.

C. Body weight

There were no toxicologically significant effects on body weight or body weight gain in rats treated with 300 mg/kg body weight.

D. Necropsy

The necropsies performed at the end of the study revealed no particular findings in animals treated with 300 mg/kg bw. The same applies to the animals treated with 2000 mg/kg bw, which died during the observation period.

III. Conclusion

Thiacloprid FS 400 is moderately toxic after acute oral administration to rats.

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

~~- EU directive 1999/45/EC: Xn (harmful)~~
~~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]d; [redacted]; 2009; M-358950-01-1
Title:	Thiacloprid FS 400A G - Acute toxicity in the rat after dermal application
Report No.:	AT05639
Document No.:	M-358950-01-1
Guidelines:	**OECD 402; Directive 440/2008/EEC, Part B, Method B.3.; Regulation (EC) No 1907/2006 (REACH), US-EPA 712-C-98-192, OPPTS 870.1200; none**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: Thiacloprid FS 400A G

Specification no.:	102000022825 - 01
Description:	red liquid, suspension
Lot/Batch no:	2009-007772
Content:	407.2 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2011-09-22

2. Vehicle: none

3. Test animals:

Species:	rat
Strain:	Wistar rat, Hsd/c pb:Wu
Age:	approx. 9 – 13 weeks
Weight at dosing:	males: 257 g – 292 g; females: 233 g – 244 g
Source:	[redacted], Netherlands
Acclimatisation period:	at least 5 days
Diet:	standard diet [redacted] 3883 PM S15 Maus/Ratte Haltung, [redacted] Switzerland, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	individually in polycarbonate cages; bedding: low dust wood granulate (Lignocel BK 8-15, Firma Rettenmaier, Germany).

B. Study design and methods

1. Animal assignment and treatment:

Dose:	Dose (mg/kg bw)	Surface area (cm²)	Range (mg/cm²)
males	2000	30	17.1 - 19.5
females	2000	30	15.5 - 16.3

Application route:	dermal, semi-occlusive dressing
Exposure:	24 hours
Group size:	5 rats/sex/group

Post-treatment observation period: 14 days

Observations: mortality, clinical signs, skin effects, body weight, 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						
2000	0	0	5	--	--	0
Female rats						
2000	0	1	5	6d - 7d	--	0
LD_{50}: > 2000 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: days

B. Clinical observations

In one female partial formation of scale and indurations of the treatment area was observed.

Locally, a partial red discoloration of the treatment area was noted in all treated animals. The most plausible interpretation is a discoloration by the red colour of the test item, which is not considered to be a toxicologically relevant effect.

C. Body weight

There were no toxicologically significant effects on body weight or body weight development.

D. Necropsy

The necropsies performed at the end of the study revealed no particular findings.

III. Conclusion

Thiacloprid FS 400 is non-toxic after acute dermal application to rats.

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

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

CP 7.1.3 Inhalation toxicity

An acute inhalation toxicity study has not been performed with thiacloprid FS 400. The physical nature of this seed treatment product is a flowable suspension.

According to Commision Regulation (EU) No 284/2013 an acute inhalation toxicity study is not triggered in the case of thiacloprid FS 400, since this flowable concentrate for seed treatment is

- not a gas or liquifies gas;
- is not a smoke generating plant protection product or fumigant;
- is not used with fogging/misting equipment;
- is not a vapour releasing plant protection product;
- is not supplied in an aerosol dispenser;
- is not in a form of a powder or granules containing a significant proportion of particles of diameter < 50 µm (> 1% on a weight basis);
- is not to be applied from aircraft in cases where inhalation exposure is relevant;
- does not contain an active substance with a vapour pressure > $1 \cdot 10^{-2}$ Pa (the vapour pressure of the active ingredient is $3x10^{-12}$ hPa at 20°C) and is not to be used in enclosed spaces such as warehouses or glasshouses;
- is not to be applied by spraying.

Furthermore, relevant inhalative exposure is not expected during treatment and handling of the seed since:

- droplets of the neat product are too big to be inhaled;
- the treated seed *per se* is not inhalable according to its diameter;
- a high adherence of the product to maize seeds was verified (103%, [redacted], 2010, M-371129-01-1).

III. Conclusion

An acute inhalation toxicity study is not considered necessary for the purpose of classification and labelling of thiacloprid FS 400 and should therefore be avoided respecting animal welfare.

The following classification/labelling is triggered:

~~- EU directive 1999/45/EC: none~~

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

CP 7.1.4 Skin irritation

Report:	[redacted]p; [redacted]; 2010; M-361477-01-1
Title:	Thiacloprid FS 400A G - Acute skin irritation/corrosion on rabbits
Report No.:	AT05735
Document No.:	M-361477-01-1
Guidelines:	**OECD 404; Directive 440/2008/EEC; US-EPA 712-C-98-196, OPPTS 870.2500; none**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: Thiacloprid FS 400A G

Specification no.:	102000022823-01
Description:	red liquid, suspension
Lot/Batch no:	2009-007772
Content:	407.2 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2011-09-22

2. Vehicle: none

3. Test animals:

Species:	rabbit
Strain:	New Zealand White rabbit, Crl:KBL(NZW)BR
Age:	young adult
Weight at dosing:	2.8 kg – 3.2 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "[redacted]" 4mm ([redacted] Germany), approximately 100 g/animal/day; roughage: hay, irradiated (Harlan Nederland, Horst, Netherland) or hay pellets ([redacted] Germany)
Water:	tap water, *ad libitum*
Housing:	individually in cage units Metall/Noryl by EBECO

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0.5 mL/patch
Application route:	dermal, semi-occlusive dressing
Exposure:	4 hours
Group size:	3 females
Observations:	clinical signs, skin effects, body weight (at the beginning of the study)

II. Results and discussion

A. Findings

The test compound could not be removed completely from the skin leading to a red discoloration of the treated skin area in all three animals. This red discoloration was visible up to 72 h after patch removal in rabbits 1 and 3 and up to 14 days after patch removal in rabbit 2. The finding is considered as toxicologically non-relevant, since it is caused by the red color of the formulation.

No signs of skin irritation and no systemic intolerance reactions were observed.

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	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na
2	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na
3	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na

na: not applicable

Response: -- = negative for mean scores <1.5 (GHS)
(Directive 1999/45/EC as amended)
(Regulation (EC) No 1272/2008)

(+) = mild irritant for mean scores ≥1.5 - <2.3 (GHS category 3)

\+ = irritant for mean scores ≥2.3 (Directive 1999/45/EC as amended)
≥2.3 (Regulation (EC) No 1272/2008 and GHS category 2)

III. Conclusion

Thiacloprid FS 400 is not irritating to the skin of rabbits.

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

~~- EU directive 1999/45/EC: none~~

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

CP 7.1.5 Eye irritation

Report:	[redacted]4; [redacted]; 2010; M-361479-01-1
Title:	Thiacloprid FS 400A G - Acute eye irritation on rabbits
Report No.:	AT05736
Document No.:	M-361479-01-1
Guidelines:	**OECD 405; Directive 440/2008/EEC; US-EPA 712-C-98-195, OPPTS 870.2400; none**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: Thiacloprid FS 400A G

Specification no.:	102000022825-01
Description:	red liquid, suspension
Lot/Batch no:	2009-007772
Content:	407.2 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2011-09-22

2. Vehicle: none

3. Test animals:

Species:	rabbit
Strain:	New Zealand White rabbit, Crl:KBL(NZW)BR
Age:	young adult
Weight at dosing:	2.9 kg – 3.0 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "[redacted] K-Z" 4mm ([redacted] Germany), approximately 100g animal/day; roughage: hay, irradiated (Harlan Nederland, Horst, Netherland) or hay pellets ([redacted] Germany)
Water:	tap water, *ad libitum*
Housing:	individually in cage units Metall/Noryl by EBECO

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0.1 mL
Application route:	instillation into the conjunctival sac of one eye
Rinsing:	approx. 24 hours after instillation
Group size:	3 females
Observations:	clinical signs, eye effects, body weight (at the beginning of the study)

II. Results and discussion

A. Findings

One hour after instillation the test compound adhered to the cornea and conjunctiva of all three animals. Except for a transient redness of the conjunctivae (grade 1) in one rabbit 1 h after instillation of the test compound there were no signs of irritation to the eyes and 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	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na
2	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na
3	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	1*
	Chemosis conjunctivae	0	0	0	0.0	--	na

Response for mean scores:		Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema	
--	= negative	<1	<1	<2	<2	(Regulation (EC) No. 1272/2008 and GHS)
		<2	<1	<2.5	<2	(Directive 1999/45/EC as amended)
(+)	= 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 as amended)
++	= irreversible effects/ serious damage	≥3	≥1.5			(Regulation (EC) No. 1272/2008 and GHS category 1)
		≥3	≥2			(Directive 1999/45/EC as amended)

na : not applicable * in respect of the result 1 h post application

III. Conclusion

Thiacloprid FS 400 is not irritating to the eyes of rabbits.

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

~~- EU directive 1999/45/EC: none~~

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

CP 7.1.6 Skin sensitization

Report:	[redacted]; 2009; M-360203-01-1
Title:	Thiacloprid FS 400 G (Project: Thiacloprid (YRC 2894)) - Local lymph node assay in mice (LLNA/IMDS)
Report No.:	AT05697
Document No.:	M-360203-01-1
Guidelines:	**OECD 406, OECD 429; Guideline 2004/73/EC, Method B.6., B.42.; US-EPA 712-C-03-197, 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 Pluronic/NaCl solution for administration were not performed. This deviation does not limit the assessment of the results.**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material:	Thiacloprid FS 400A G
Specification no.:	102000022825-01
Description:	red liquid, suspension
Lot/Batch no:	2009-007772
Content:	34.4% (w/w)
Stability of test compound:	guaranteed for study duration; expiry date: 2011-09-22
2. Vehicle:	Pluronic PE 9200 / 0.9% NaCl solution, 1% v/v
3. Test animals:	
Species:	mouse
Strain:	NMRI mouse, Hsd Win:NMRI
Age:	8 weeks
Weight at dosing:	27 g – 33 g
Source:	[redacted], Netherland
Acclimatisation period:	at least 6 days
Diet:	PROVIMI KLIBA SA 3883 maintenance diet for rats and mice ([redacted], Switzerland), *ad libitum*
Water:	tap water, *ad libitum*
Housing:	adaptation period: group housing of up to 8 mice per cage in conventional Makrolon® type III cages; study period: individually in type II cages; bedding: low-dust wood shavings Lignocel BK 8-15 (Rettenmaier & Soehne, GmbH & Co, Rosenberg, Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0 (vehicle control) - 2% - 10% - 50%
Application route:	epicutaneously onto the dorsal part of both ears
Application volume:	25 µL/ear
Exposure:	application on three consecutive days
Group size:	6 females/group
Observations:	body weight (at start and termination of the study), ear swelling, ear weight, local lymph node weight, cell count determination

II. Results and discussion

A. Findings

The body weights of the animals were not affected by the treatment.

In comparison to vehicle treatment there was no increase in the stimulation indices for cell counts or for weights of the draining lymph nodes after application of the test item thiacloprid FS 400A G.

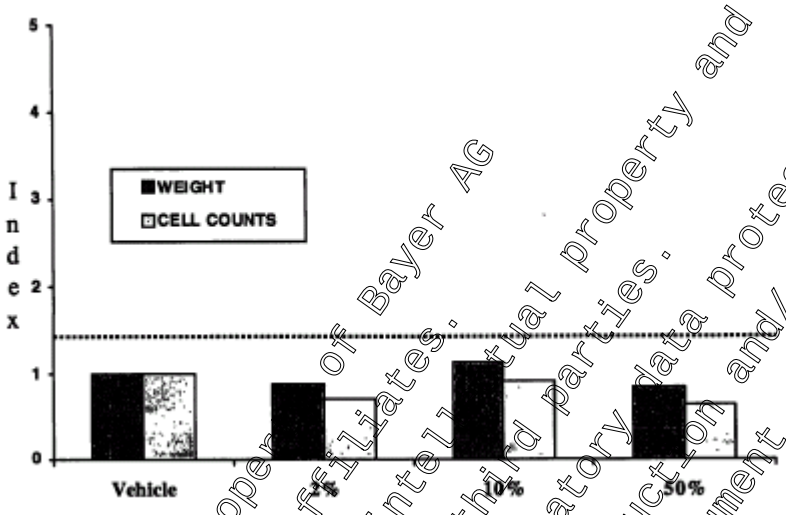
The "positive level", which is 1.4 for the cell count index (which is calculated by dividing the mean cell count of the animals of a treatment group by the respective value of the animals of the control group), was never reached or exceeded in any dose group.

The "positive level" of ear swelling, which is 2x10^{-2} mm increase, i.e. about 10% of the control values, was also not reached or exceeded in any dose group.

A slight, statistically significant decrease in the stimulation index for cell counts was determined for the group treated with the maximum concentration of 50%. This decrease is in the normal range of variance for these parameters, and is such of no biological relevance. Although the reason for this decrease is not known, the authors presume that it could be a consequence of osmosis in the tissues and/or cytotoxicity induced by the relatively high local concentration of the test item.

The Local Lymph Node Assay test methodology was checked for reliability in a test on female NMRI mice using Alpha Hexyl Cinnamic Aldehyde at concentrations of 2%, 10% and 50%. The sensitivity as well as the reliability of the experimental technique was thus confirmed by this study ([redacted], H. W., 2009, report AT05433 [M-462318-01-1]).

Figure 7.1.6-1 Stimulation indices of the weight and cell counts of the local lymph nodes in the Local lymph node assay with thiacloprid FS 400



III. Conclusion

The results show that thiacloprid FS 400 has no sensitising potential in mice after dermal application up to the tested maximum concentration of 50%. Additionally, no indication for a non-specific (irritant) activation was detected. Therefore, the tested maximum concentration of 50% turned out to be the NOEL for the parameters investigated in this study with respect to skin sensitisation.

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

~~- EU directive 1999/45/EC: none~~

- 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 FS 400.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies were performed.

CP 7.2.1 Operator exposure

~~Exposure is estimated using the SEEDTROPEX model. A summary of the cGAP used for the risk assessment is presented in Table 7.2.1-1.~~

Table 7.2.1-1 Critical GAP determined by the application parameters

Crop	Formulation		Application				Application rate			Remarks
	Type	Conc. of as	Method kind	Growth stage & season	Number min max	Interval between applications (min)	g as/hL min max	Water L/ha min max	g as/ha min max	
Maize	FS	400	Seed treatment	BBCH 00	1	-	1 mg as/seed or 50 g a.s./unit	-	110	Sowing rate: 2.2 unit/ha (1 unit = 50 000 seeds) 0.125 L product/unit)

Thiacloprid FS 400 is applied to maize seeds with a maximum rate of 125 mL/unit of seeds (1 U = 50 000 seeds) equivalent to 1 mg a.s./seed or 50 g a.s./unit. The treated seed is sown in the field with a sowing rate of max. 2.2 units/ha equivalent to 110 g 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:

The extent of dermal absorption of thiacloprid formulated as an FS 400 formulation has been investigated in an *in vitro* comparative study using human and rat skin and an *in vivo* rat study. The neat product and a 4-fold dilution were examined for representative use conditions.

The "Triple pack" approach is used to estimate the human *in vivo* dermal absorption values:

- 0.1% for the neat formulation (400 g a.s./L)
- 0.2% for the low dose (100 g a.s./L).

These values are proposed for use in risk assessments (for details see CP 7.3).

Summary

A summary of the exposure estimates resulting from the cGAP is presented in the following table.

Table 7.2.1-2: Summary of exposure estimates and proportion of the AOEL (based on SeedTROPEX)

Crop	Method of Application	PPE	Model	Activity	Systemic exposure[∞] (mg/kg bw/day)	% of AOEL (0.02 mg/kg bw/day)
Maize	Seed treatment	Standard PPE*	SeedTROPEX	All activities	0.0590	295
		Standard PPE + RPE during	SeedTROPEX	All activities	0.0084	42

		cleaning				
	Seed sowing	Standard**	SeedTROPEX	Loading/ sowing	0.0028	14

∞ Dermal absorption: 0.1% during mixing/loading, bagging and loading/sowing, 0.2% during calibration and cleaning
* Working clothing (at least one layer)during all tasks, protective gloves during mixing/loading, calibration and cleaning

** Standard clothing consisting of at least one layer of work clothing, protective gloves when handling treated seed

Assessment

The Seed-TROPEX model predicts an acceptable exposure to thiacloprid during seed treatment and seed sowing.

During seed treatment, coverall and gloves must be worn during all operations except bagging (coverall but no gloves) and a particle filtering half mask (FFP2) during cleaning. The results are highly conservative because the basic assumption of the SeedTROPEX model is that all seed treatment activities (mixing/loading, calibration, bagging, cleaning) are performed by one and the same person. The real exposure is considered to be lower because maize seed treatment operations are typically performed by 4-5 operators. For the hypothetical operator performing the multiple activities of calibration, mixing/loading, bagging and cleaning, exposure was estimated to be 0.0084 mg/kg bw/day which is 42% of the AOEL (60 operator).

Exposure during maize sowing is predicted to be 0.0028 mg/kg bw/day which is 14% of the AOEL. Exposure is calculated for operators wearing adequate work clothing (e.g. a work jacket or a long-sleeved shirt and long-legged work trousers). Gloves are considered to be used in case of direct hand contact with treated seed.

It is noted here that the SeedTROPEX model was developed to provide estimates of exposure for the seed treatment and sowing of cereals (the model is exclusively compiled from experimental studies conducted with cereal seed). Cereal seed treatment, however, is different from maize seed treatment (use of stickers, film coating agents, mixture with additional plant protection products, degree of automation, etc.) for which an application is made for Sonido® FS 400. The model is therefore considered to likely overestimate the realistic exposure in maize seed treatment and sowing. Seed-TROPEX estimates provided here are therefore considered as conservative first Tier surrogates to evaluate exposure during seed treatment and loading/sowing of maize seed.

Experimental data obtained from operator exposure studies are available to further evaluate the exposure of operators to thiacloprid during seed treatment and seed sowing.Two exposure studies were performed to monitor the exposure during seed treatment and during seed sowing.

The seed treatment study was conducted in 2014 in modern maize seed treatment plants. The study was undertaken with Sonido® FS 400 (400 g a.s./L thiacloprid) in three different seed treatment plants in France. All sites displayed a high level of automation and engineering control.

The seed sowing study was carried out with Sonido® FS 400 treated maize seed on 10 farms in France using modern seed sowing equipment with deflector technology.

A summary of the risk assessment based on these studies is presented below.

Table 7.2.1-3: Summary of exposure estimates and proportion of the AOEL (based on exposure studies)

Crop	Method of Application	PPE	Source (experimental study)	Systemic exposure* (mg/kg bw/day)	% of AOEL (0.02 mg/kg bw/day)
Maize	Seed treatment	With 1)	Sonido® FS 400	0.00033	1.7
	Seed loading/sowing	With 2)	Sonido® FS 400	0.00008	0.4

1) Mixing/loading: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Cleaning: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds
2) Loading: cotton coverall, protective gloves, mask, goggles
Sowing: cotton coverall, occasionally protective gloves during maintenance outside cabin

The 75th percentile estimates are calculated from the data base of each study. Systemic exposure during seed treatment derived from the Sonido® FS 400 study is 0.00033 mg/kg bw/day. This estimate equates to 1.7% of the AOEL. Systemic exposure during seed loading/sowing derived from the Sonido® FS 400 study is 0.00008 mg/kg bw/day. This estimate equates to 0.4% of the AOEL.

It is concluded that modern seed treatment and sowing equipment provide low levels of exposure. Seed treatment facilities today are highly automated. They provide engineering control for closed systems and air exhaust systems as technically and economically feasible today to reduce dust development to a minimum. Modern maize sowing equipment today is using deflector technology in pneumatic systems certified for at least 90% dust drift reduction when compared to benchmark machinery.

It is concluded that the use of Thiacloprid FS 400 with modern seed treatment and sowing equipment will result in negligible risks for operators during maize seed treatment and maize sowing.

CP 7.2.1.1 Estimation of operator exposure

Operator exposure estimates are calculated using the SeedTROPEX Model.

The critical European GAP providing the highest exposure is achieved when calculations are performed with the maximum dose rate of 50 g a.s./U seed (0.125 L product/U) and with the max. sowing rate of 2.2 U/ha. These scenarios are selected for risk assessment.

SeedTROPEX provides exposure calculations for seed treatment and seed sowing. The seed treatment activities are differentiated for four work tasks:

- calibration,
- mixing/loading,
- bagging, and
- cleaning.

All tasks are considered individually, however, it is assumed that one single operator performs all tasks during a daily working shift.

There is no option in the SeedTROPEX model to differentiate varying levels of protection (exposure with or without personal protective equipment). For seed treatment, it already includes the use of coveralls and gloves for all tasks - except for bagging during which only a coverall is considered. The

estimated actual dermal exposure values, therefore, reflect this level of clothing/PPE. The database for loading and sowing consists of a combination of exposure values for operators with and without gloves. The model data are therefore conservative for operators wearing gloves according to the label. A further conservatism is included in the model when using the total potential dermal exposure values for operators wearing no PPE. This rather reflects the exposure of operators wearing virtually no clothing and is unrealistic.

Generic exposure figures are expressed in mL/operation (taking into account the concentrations of active substances in different seed dressing liquids). For bagging, a constant generic figure – expressed as mg/h – is proposed in the model.

Since the delivery, some of the generic exposure values have been revised and the values currently being used are presented in the following table.

Table 7.2.1.1-1: SeedTROPEX task related generic exposures of seed treatment plant operators

TASK		Total Potential Dermal Exposure (ml/op)*	Estimated Actual Dermal Exposure (ml/op)*	Inhalation Exposure (ml/op)*
Calibration		0.033	0.014	0.001
Mixing / Loading	Fast-Couple	0.0052	0.005	0.0001
	Pre-mix	0.0047	0.001	0.0001
Bagging (mg/hr)	all data	1.84	0.698	0.0054
	worst			0.054
Cleaning		0.872	0.083	0.016

* exposure during bagging in mg/hour

It is assumed that the daily work of operators will involve 1 calibration and 1 cleaning operation, 8 hours of bagging and the required number of mixing/loading operations. Estimations consider the application in seed treatment plants with a low level of automation. A conservative daily seed treatment rate of 1700 U/day (about 30 tonnes of treated seed) is considered in the calculation. This amounts to about 212.5 L product handled per day. As the product is supplied in large containers (usually 1000 L) one mixing/loading operation will be necessary per day. The product will be mixed with water and other products, therefore, a dilution factor of at least 2 is considered in the calculation.

The following assumptions are taken into account when using SeedTROPEX.

Crop: Maize

Seed treatment:

Concentration of a.s.:	400 g a.s./L
Work rate:	1700 U/day (30 tonnes grain/day)
Application rate:	125 mL/U
Dilution factor:	2
Amount handled:	212.5 L/day (85 kg a.s./day)

~~No. of calibration operations: 1~~

~~No. of mixing/loading operations: 1~~

~~Hours of bagging: 8~~

~~No. of cleaning operations: 1~~

~~Body weight: 60 kg~~

~~Clothing scenario~~

~~seed treatment: Coverall and gloves during all operations except bagging (coverall but no gloves), with and without particle filtering half mask (FFP2) during cleaning~~

~~sowing: Coverall, gloves when handling treated seed~~

~~The sowing rate is 2.2 U/ha (1U = 50000 seeds) i.e. 0.110 kg a.s./ha handled (50 g a.s./U). Assuming a sowing rate of 20 ha/day operators would handle about 2.2 kg a.s./day. The sowing rate, however, is not taken into account in the SeedTROPEX model.~~

~~The detailed spreadsheet calculations are presented in the following tables.~~

~~Table 7.2.1.1-5: Calculation of exposure to thiacloprid during maize seed treatment~~

TASK	Total Potential Dermal Exposure (mg/op)*	Estimated Actual Dermal Exposure (mg/op)	Inhalation Exposure (mg/op)	*Frequency of operation/ day*	Total Potential Dermal Exposure (mg/day)	Estimated Actual Dermal Exposure (mg/day)	Inhalation Exposure (mg/day)
Calibration	6.51	2.85	0.200	*1*	6.5115	2.8456	0.2000
Mixing / Loading	2.0769	2.077	0.051	*1*	2.0769	2.0769	0.0512
Bagging (mg/hr) worst case scenario	1.84	0.698	0.0054 0.054	*8*	14.7200	5.5840	0.0432
Cleaning	174	16.67	3.2	*1*	174.3514	16.6728	3.2000

~~* standard clothing of the operators is one layer of work clothing (long-sleeved work jacket and trousers) during all tasks and in addition protective gloves (except for bagging) when handling formulated product and treated seeds and cleaning machinery~~

~~Predicted systemic exposures as a proportion of the AOEL is presented in the following:~~

~~**Table 7.2.1.1-6: Exposure as a proportion of the AOEL**~~

Standard PPE	Systemic exposure [mg/kg bw/day]	% of AOEL	Standard PPE + RPE during cleaning	Systemic exposure [mg/kg bw/day]	% of AOEL
Calibration	0.0034	17	Calibration	0.0034	17
Mixing / Loading	0.0009	4	Mixing / Loading	0.0009	4
Bagging	0.0008	4	Bagging	0.0008	4
Cleaning (no RPE)	0.0539	269	Cleaning (with RPE)	0.0032	16
Multiple activity task (total)	**0.0590**	**295**	**Multiple activity task (total)**	**0.0084**	**42**

~~Table 7.2.1.1-7: Calculation of exposure to thiacloprid during maize seed sowing~~

Route of exposure	Specific exposure[1)] [mg/hr]		Exposure duration [hours/day]		Estimated exposure [mg/person/day]		Absorption [%]		Systemic exposure [mg/person/day]
I =	0.02	x	8	=	0.1600	x	100	=	0.1600
D =	0.73	x	8	=	5.8647	x	0.1	=	0.0059
						Total [mg/person/day]:			0.1659
						Total [mg/kg bw/day][#]:			0.0028

I = estimated inhalation exposure; D = estimated dermal exposure

[1)] Working clothing (e.g. a coverall), protective gloves when handling treated seed or contaminated surfaces

[#] 60 kg body weight

~~CP 7.2.1.2 Measurement of operator exposure~~

~~Experimental data obtained from operator exposure studies are available to evaluate the exposure of operators to thiacloprid during seed treatment and seed sowing. Two exposure studies were conducted to measure exposure to thiacloprid during both use scenarios.~~

~~The seed treatment study was performed with SONIDO® FS 400 (thiacloprid, 400 g a.s./L, 3 sites). The study was performed in plants with state of the art seed treatment technology. This involved a high degree of automation and engineering control and reflects the high technical standards currently used in maize seed treatment in Europe. Another study was conducted to monitor the exposure to thiacloprid during seed sowing. Sowing of maize treated with SONIDO® FS 400 was performed with state of the art pneumatic sowing machinery i.e. using precision planters working with the vacuum singulation principle including deflector technology.~~

~~The studies are summarized in the following. They are all in compliance with the current OECD Principles of Good Laboratory Practice (GLP).~~

~~**Report:** [redacted]; 2014; M-492984-01-1~~
~~Title: Determination of operator exposure to thiacloprid during seed treatment of maize with Sonido® FS 400~~
~~Report No.: MR-14/102~~
~~Document No.: M-492984-01-1~~
~~**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; not specified**~~
~~**GLP/GEP: yes**~~

~~Material and methods~~

~~The dermal and inhalation exposure of 13 operators was monitored in 2014 in an operator exposure study conducted in three professional maize seed treatment plants in France when using Sonido® FS 400 (thiacloprid, 400 g a.s./L).~~

~~The product is a water-based seed dressing liquid formulated as a flowable concentrate (FS formulation). It contains the insecticidal active substance thiacloprid (400 g/L declared). The product was supplied in 1000 liter containers. The seed treatment of maize grain was conducted with the maximum application rate of 125 mL/unit (1 unit = 50000 grain). The study was performed from January through to February 2014 during the typical maize seed treatment season. Operators were monitored for a whole work shift (about 8 hours). They performed their normal daily routine work consisting of a combination of activities (mixing/loading, seed supply, seed sampling, operation of bagging and stacking line, forklift transfer to storage, cleaning of treatment chamber and of bagging/stacking line area, etc.) depending on the plant's work task organisation. The selected plants represent a state-of-the-art technical standard in maize seed treatment with a high degree of automation and engineering control for low dust development. This includes seed purification before treatment (use of dust-free seed), use of dust extraction systems (during seed treatment/bagging), use of binders in the seed treatment slurry, closed transport, treatment and bagging lines and a high degree of automation reducing manual activities to a minimum. Batch treaters were used at all sites. 2460-2690 units (33 to 47 tonnes of seed) were treated corresponding to a consumption of 308 – 336 L product (132-135 kg a.s. thiacloprid) per day.~~

~~Exposure measurements were performed via passive dosimetry techniques. Body exposure was evaluated on cotton underwear worn beneath the operator's usual work clothing (at least one layer of freshly washed outer clothing, e.g. jacket and trousers). Exposure of the head was measured via face neck wipes. Exposure of the hands was determined via hand washes with detergent. Varying work clothing and additional Personal Protective Equipment (PPE) such as filter mask, protective gloves and/or protective coverall was worn during the day depending on the activity but not used as dosimeters (a detailed overview is presented in Table 1). Inhalation exposure was determined by use of a personal air sampling pump connected to an IOM sampler with glass fibre filter located in the breathing zone of the operator. Samples were collected on completion of the daily work tasks. Additional inhalation samples were collected during cleaning operations.~~

~~Field recoveries were set up with standard in solvent to evaluate the stability of active substance on the various sampling media.~~

~~The samples were extracted with a mixture of acetonitrile/water and analysed for residues of thiacloprid using LC-MS/MS detection. The analytical method was validated by recovery experiments prior to the analysis of the test samples. The limit of quantitation (LOQ) was established at 0.01 µg//sample for the cotton garments, 0.001 µg//sample for the face/neck wipes and the inhalation filters and 1 µg//sample for the hand wash solution.~~

~~Results~~

~~The analytical method was validated with lab recoveries of 96% - 100%. Field recoveries of 86% - 102% demonstrated the stability of the active substance in the dosimeters from time of sampling until analysis.~~

~~Actual dermal exposure was calculated as the sum of residues on inner dosimeters, hand wash and face/neck wipes. Inhalation exposure was calculated from residues in the air filter adjusted for an average breathing rate of 20.8 L/min. Head exposure was calculated from residues in face/neck wipes. Potential inhalation values represent workers wearing no mask. The exposure values for individual workers are tabulated below.~~

Tab. 7.2.1.2-1: Individual exposures (µg/person)

-	Exposure (µg/person)												
	Plant 1				Plant 2				Plant 3				
	OA	OB	OC	OD	OE	OF	OG	OH	OI	OJ	OK	OL	OM	MIN	MAX
Actual dermal															
• body	14.1	33.6	48.9	20.3	76.6	617	793	1010	89.9	27.0	4.88	3.60	1.88	1.88	1010
• head	1.46	2.22	1.55	6.77	2.23	31.1	54.9	117	1.60	1.56	1.93	0.190	0.376	0.19	117
• hands															
- mixing/loading	51.6				32.5								10.2	10.2	32.5
- other activities		26.8	14.8	247	77.2	1.46	73.2	89.3	63.5	80.9	5.87			5.87	247
Potential inhalation*															
- cleaning				0.509				907		2.90				0.509	907
- other activities	7.95	4.38	4.86	12.8	29.6	137	150	60.2	4.60	5.03	1.93	1.09	0.550	0.550	150

Inhalation exposure is calculated from residues on air filter adjusted to a respiration rate of 20.8 L/min. Head exposure is calculated from residues in face/neck wipes. Potential dermal exposure is the sum of residues on all dermal dosimeters. Actual dermal exposure is the sum of residues on inner dosimeters + hand wash + face/neck wipes.

The following critical values can be summarized from these data.

Tab. 7.2.1.2-2: Individual exposures

Operator ID	Individual tasks	Exposure (mg/person)	
		Actual dermal	Potential inhalation
OA	Mixing/loading, treatment/bagging line	0.0672	0.00795
OB	Seed supply, bagging line	0.0626	0.00438
OC	Palletizing, forklift driving	0.0653	0.00486
OD	Cleaning, bagging line	0.2745	0.01332
OE	Mixing/loading	0.1114	0.02963
OF	Seed supply, treatment/bagging line	0.7253	0.13686
OG	Palletizing	0.9942	0.14986
OH	Seed supply, cleaning, bagging line	1.2002	0.96710
OI	Palletizing, forklift driving	0.1808	0.00460
OJ	Cleaning, treatment/bagging line	0.0921	0.00794
OK	Palletizing, forklift driving	0.0877	0.00193
OL	Seed supply, bagging line	0.0097	0.00109
OM	Mixing/loading	0.0124	0.00055
	75th perc.	**0.2745**	**0.02963**

III. Conclusion:

Dermal and inhalation exposure is generally low. Actual dermal exposure of all operators was 9.66-1200 µg/person. The typical operator's work included a combination of tasks depending on the work organisation. Many operators assisted in activities apart from their main task or replaced their colleagues e.g. during breaks. But none of the operators was performing a combination of all activities. Therefore, specific task exposure scenarios were not developed. Exposure results demonstrate that actual exposure is more or less likewise distributed between the operators. Potential inhalation exposure ranged from 0.550-150 µg/person calculated for an average breathing rate of 20.8 L/min. One operator had an exceptionally high potential inhalation dose of 967 µg. The likely reason for this dose is considered to be the excessive use of compressed air used by this operator during the cleaning of the treatment chamber (94% of the total respirable dose was received during this activity). Actual inhalation exposure of this operator, on the other hand, is to be evaluated by the use of a filter mask. A recommendation is concluded that the use of pressurized air should be replaced by other cleaning device e.g. vacuum systems.

Workers were adequately equipped with working clothing and PPE. Relevant clothing/PPE scenarios may be considered in risk assessment.

Risk assessment

The experimental conditions are analogous with those prevalent during typical seed treatment of maize with state-of-the-art technology in Europe. The measured values of the experimental study are taken for the risk assessment.

Since workers performed several activities specific exposure subsets are not observed. Therefore, a deterministic exposure estimate is taken from the whole data base. Taking as surrogates the more conservative 75th percentile values the following results are obtained for thiacloprid in SONIDO® FS 400.

Tab. 7.2.1.2-3: Calculation of systemic exposures

Operator ID	Individual tasks	Body weight (kg)	Exposure (mg/kg bw/day)		
			Actual dermal	Potential inhalation	Systemic * (incl. RPE)
OA	Mixing/loading, treatment/bagging line	80	0.0008	0.00010	0.00010
OB	Seed supply, bagging line	90	0.0007	0.00005	0.00005
OC	Palletizing, forklift driving	75	0.0009	0.00006	0.00007
OD	Cleaning, bagging line	80	0.0034	0.00017	0.00017
OE	Mixing/loading	65	0.0017	0.00046	0.00033
OF	Seed supply, treatment/bagging line	70	0.0104	0.00196	0.00198
OG	Palletizing	82	0.0121	0.00183	0.00185
OH	Seed supply, cleaning, bagging line	88	0.0136	0.01099	0.00123
OI	Palletizing, forklift driving	87	0.0021	0.00005	0.00006
OJ	Cleaning, treatment/bagging line	98	0.0009	0.00008	0.00005
OK	Palletizing, forklift driving	75	0.0012	0.00003	0.00003
OL	Seed supply, bagging line	75	0.0001	0.00001	0.00001
OM	Mixing/loading	84	0.0001	0.00001	0.00001
		75th perc.	**0.0034**	**0.00046**	**0.00033**

* Systemic exposure is calculated from actual dermal using 0.1% dermal absorption of residues obtained during mixing/loading (exposure to concentrate product) and using 0.2% dermal absorption of residues obtained during all other tasks (diluted product). Inhalation exposure is assumed to be totally absorbed (100% absorption via inhalation). During cleaning, all operators will wear a mask. The inhalation exposure values during cleaning are therefore adjusted for a mitigation factor of 0.05 for FFP3 mask.

The 75th percentile of the individual systemic exposures to thiacloprid amounts to 0.00033 mg/kg bw/day. This exposure estimate assumes that seed treatment is performed with a high level of automation and that operators are appropriately protected (PPE). The estimated exposure is equivalent to 1.7% of the thiacloprid AOEL (0.02 mg/kg bw/day).

Report:	[redacted]ö; [redacted]; [redacted]; 2014; M-492986-01-1
Title:	Determination of operator exposure to thiacloprid during loading and sowing of Sonido® FS 400 treated maize seed in France
Report No.:	MR-14/112
Document No.:	M-492986-01-1
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; not specified**
GLP/GEP:	**yes**

Material and methods

The study was conducted in the French regions of Pau (Aquitaine) and Rennes (Normandy) during the typical season of maize sowing in April/May 2014. 11 operators on 10 farms were monitored during loading and sowing of maize seed treated with SONIDO® FS 400 (thiacloprid, 400 g a.s./L).

The daily sowing rate per operator ranged from 6.6 ha - 19.8 ha. A series of different maize varieties were sown with sowing rates of 1.5 - 2.3 U/ha (1 unit = 50000 grain). A variety of state-of-the art pneumatic precision sowing equipment with deflector technique was used. The operators performed their daily work according to their usual working practice (6 - 10 hrs). They handled 9 - 33 U per day of treated seeds. This corresponds to 0.359 – 1484 kg of thiacloprid per day.

Exposure measurements were performed via passive dosimetry techniques. Outer dosimeters consisted of cotton/polyester work clothing (long-sleeved jacket and trousers). Cotton underwear (long-sleeved T-shirt and long trousers) were used as inner dosimeters. Exposure of the head was measured via face/neck wipes. Hand exposure was determined from residues in/on protective gloves and in hand wash water. Inhalation exposure of operators was determined by use of a personal air sampling pump connected to an IOM sampler with glass fibre filter located in the breathing zone of the operator. Separate inhalation samples were collected during loading and during sowing. Samples were collected on completion of the daily work tasks. Potential dermal exposure was calculated as the sum of residues detected on the outer clothes, the underwear, the protective gloves, hand washes, and face-neck wipes. Actual dermal exposure was calculated as the sum of the residues detected on the underwear, in the hand washes, and in the face/neck wipes.

Field recoveries were set up with standard in solvent to evaluate the stability of active substance on the various sampling media.

The samples were extracted with a mixture of acetonitrile/water and analysed for residues of thiacloprid using LC-MS/MS detection. The analytical method was validated by recovery experiments prior to the analysis of the test samples. The limit of quantitation (LOQ) was established at 0.01 µg//sample for the cotton garments (outer and inner dosimeter), 0.001 µg//sample for the face/neck wipes and the inhalation filters and 1 µg//sample for the hand wash solution and the protective gloves.

~~Results~~

~~The experimental conditions were representative with modern technology in maize seed sowing. Workers were adequately equipped with working clothing and PPE. The minimum clothing consisted of a cotton/polyester coverall and sturdy footwear. Protective gloves, a respiration mask and goggles were worn during loading. During sowing, protective gloves were occasionally worn for repair/maintenance work.~~

~~Recovery results showed that residues were stable during transport and storage. Recovery values were between 91% - 99% with relative standard deviations (RSD) of 2.2% - 8.1%.~~

~~Potential dermal exposure ranged from 416 - 5570 µg/person and actual dermal exposure ranged from 40.4 - 640 µg/person. Potential inhalation exposure was 3.37 - 51.2 µg/person calculated for an average breathing rate of 20.8 L/min. Potential inhalation values represent workers wearing no mask.~~

~~The exposure values for individual workers are tabulated below:~~

Tab. 7.2.1.2-7: Operator exposure to thiacloprid

	Residues (µg/person)											
	OA	OB	OC	OD	OE	OF	OJ	OK	OL	OM	ON	MIN	MAX
Potential dermal													
body	1518	1970	858	1042	2445	1789	273	423	2538	628	1301	273	2538
head	8.35	4.69	8.90	5.95	27.1	41.9	5.37	2.14	11.4	10.2	35.6	4.69	41.9
hands	1414	493	1773	356	3104	535	137	693	1643	281	1618	137	3104
Total potential dermal	**2940**	**2468**	**2639**	**1404**	**5577**	**2366**	**416**	**1123**	**4192**	**919**	**2894**	**416**	**5577**
Actual dermal													
body	75.6	109	50.5	105	126	76.3	19.7	51.6	75.7	41.91	122	19.7	126
head	8.35	4.69	8.90	5.95	27.1	41.9	5.37	2.14	11.4	10.2	35.6	4.69	41.9
hands	54.4	40.7	39.7	58.9	486	78.4	15.2	21.8	57.5	25.0	10.9	10.9	486
Total actual dermal	**138**	**155**	**99**	**170**	**640**	**197**	**40**	**81**	**145**	**77**	**169**	**40.4**	**640**
Potential inhalation*													
loading	21.7	23.8	46.6	18.6	95.6	4.75	1.79	17.3	31.1	13.1	44.9	1.79	46.6
sowing	4.43	3.39	3.59	5.28	19.6	6.79	1.58	1.67	3.32	2.05	6.30	1.58	19.6
Total potential inhalation	**26.1**	**27.2**	**50.2**	**23.9**	**35.2**	**11.5**	**3.37**	**19.0**	**34.4**	**15.2**	**51.2**	**3.37**	**51.2**

* Inhalation exposure is calculated from residues on air filter adjusted to a respiration rate of 20.8 L/min. Head exposure is calculated from residues in face/neck wipes. Potential dermal exposure is the sum of residues on all dermal dosimeters. Actual dermal exposure is the sum of residues on inner dosimeters + hand wash + face/neck wipes.

The following critical values can be summarized from these data (from Table 1, whilst converting to mg/person).

Tab. 7.2.1.2-8: Individual exposures to thiacloprid

Operator ID	Exposure (mg/person)			
	Potential dermal	Actual dermal	Potential inhalation	
			Loading	Sowing
OA	2.940	0.138	0.0217	0.0044
OB	2.468	0.155	0.0238	0.0034
OC	2.635	0.099	0.0486	0.0036
OD	1.404	0.170	0.0186	0.0053
OE	5.577	0.640	0.0156	0.0196
OH	2.366	0.197	0.0475	0.0068
OJ	0.416	0.040	0.0018	0.0016
OK	1.123	0.081	0.0173	0.0017
OL	4.192	0.145	0.0311	0.0033
OM	0.919	0.077	0.0131	0.0021
ON	2.894	0.169	0.0449	0.0063
75th perc.	**2.917**	**0.1695**	**0.0380**	**0.0058**

III. Conclusion:

The results provide a representative picture of the exposure of farmers to thiacloprid when using pneumatic sowing equipment with deflector technology for the sowing of SONIDO® FS 400 treated maize seed. The exposure level and the variation between operators are low.

Workers were adequately equipped with working clothing and PPE. Comparison of potential and actual dermal exposure demonstrates that clothing and gloves provide efficient protection.

The potential for inhalation exposure during loading is higher than during sowing. The loading was conducted with respiratory protection (filter mask) by all operators. Actual inhalation exposure is therefore reduced accordingly and may be considered in risk assessment.

Risk assessment

The experimental conditions are analogous with those prevalent during seed sowing of maize with state-of-the-art technology in Europe. The measured values of the experimental study are taken for the risk assessment.

Taking as surrogates the more conservative 75th percentile values the following results are obtained.

Table 7.2.1.2-9: Calculation of systemic exposure

Operator ID	Body weight (kg)	Exposure (mg/kg bw/day)			
		Actual dermal	Potential inhalation		Systemic * (incl. RPE)
			Loading	Sowing	
OA	76	0.0018	0.0003	0.0001	0.00007
OB	72	0.0021	0.0003	0.0000	0.00007
OC	80	0.0012	0.0006	0.0000	0.00008
OD	87	0.0020	0.0002	0.0001	0.00007
OE	83.5	0.0077	0.0002	0.0002	0.00025
OH	85	0.0023	0.0001	0.0001	0.00009
OJ	78	0.0005	0.0000	0.0000	0.00002
OK	77	0.0010	0.0002	0.0000	0.00003
OL	72	0.0020	0.0004	0.0000	0.00007
OM	64	0.0042	0.0002	0.0000	0.00004
ON	76	0.0022	0.0006	0.0001	0.00011
	75th perc.	**0.0022**	**0.00038**	**0.00007**	**0.00008**

* Systemic exposure is calculated from actual dermal exposure using 0.9% dermal absorption (exposure to dust), from potential inhalation exposure during loading considering that operators wear a mask (mitigation factor of 5% for FFP3 mask) and from potential inhalation exposure during sowing (no PPE) .

Based on the more conservative 75th percentile the systemic exposure to thiacloprid is 0.00008 mg/kg bw/day. This exposure estimate assumes that seed sowing is performed with modern sowing equipment and that operators are appropriately protected (gloves, mask, goggles during loading; gloves during sowing when handling contaminated surfaces). This exposure estimate is equivalent to 0.4% of the thiacloprid AOEL (0.02 mg/kg bw/day).

CP 7.2.2 Bystander and resident exposure

The incidental presence of bystanders in industrial seed treatment facilities can be excluded by management measures. If not, exposure of bystanders would be of short duration and normally lower than that of seed treatment operators who are occupationally exposed all day long. Therefore, it is reasonable to assume that there will be no undue risk for bystanders.

CP 7.2.2.1 Estimation of bystander and resident exposure

Not necessary.

CP 7.2.2.2 Measurement of bystander and resident exposure

Not necessary.

~~CP 7.2.3 Worker exposure~~

~~Re-entry of maize fields will not result in any exposure because dislodgeable foliar residue will not be available after sowing of treated maize seed. Therefore, it is reasonable to assume that there will be no undue risk for workers.~~

~~CP 7.2.3.1 Estimation of worker exposure~~

~~Not necessary.~~

~~CP 7.2.3.2 Measurement of worker exposure~~

~~Not necessary.~~

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[1].

According to this guidance two aspects are considered:

- Available risk mitigation measures 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, 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 FS 400 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 FS 400 is the seed treatment of maize grain. A summary of the use conditions is presented in the following table.

Table 7.2-1 Critical GAP determined by the application parameters

Crop	Formulation	Application	Application rate	Remarks

[1] 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

	Type	Conc. of as	Method kind	Growth stage & season	Number min max	Interval between applications (min)	g as/hL min max	Water L/ha min max	g as/ha min max	
Maize	FS	400	Seed treat-ment	BBCH 00	1	-	1 mg as/seed or 50 g as/unit	-	110	Sowing rate: 2.2 unit/ha (1 unit = 50 000 seeds) 0.125 L product/unit)

In order to minimize exposure as much as possible the following engineering control measures and safety recommendations are proposed:

Operators/workers:

Seed treatment: State-of-the-art technical standard in industrial maize seed treatment characterized by a high degree of automation and engineering control (enclosed processing lines) ensuring low dust development. Provision of engineering control for closed systems and air exhaust systems as technically and economically feasible to reduce dust development to a minimum.

Sowing: Use of precision planters working with the vacuum singulation principle including deflectors on vacuum pneumatic seed drills designed to reduce dust drift.

Bystanders/residents: Deflectors on vacuum pneumatic seed drills designed to reduce dust drift.

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[2].

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 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.

[2] The Guidance of EFSA on assessment of exposure (EFSA, 2014) is providing a harmonized risk assessment and calculation tool covering the various exposure groups, however, methods to evaluate exposure during seed treatment and sowing is not included. These application methods and exposure scenarios are therefore considered on a case by case basis and supported by a robust scientific case and data, including exposure studies.
It is noted here that the SeedTROPEX model was used in the AIR dossier to provide estimates of exposure to thiacloprid during seed treatment and seed sowing. However, the model is exclusively compiled from experimental studies conducted in cereal seed treatment which is considerably different from maize seed treatment (use of stickers, film coating agents, degree of automation, etc.). The model is therefore not appropriate to evaluate the proposed scenario of use with the aim to minimize exposure of humans.

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 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 derivation of the hazard specific AOELs for each effect is described in detail in Appendix I.

The 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 I)			
Dystocia, rat	22	20	0.2
Developmental Toxicity (for details see Appendix I)			
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

AAOEL

The EFSA guidance[3] 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 (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.

Following the noting at the Standing Committee meeting in May, the Commission has published a guidance[4] 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[5] that refers to formal derivation of an AAOEL by using e.g. 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 established based on the acute neuroxicity study.

Dermal absorption:

The extent of dermal absorption of thiacloprid formulated as an FS 400 formulation has been investigated in an *in vitro* comparative study using human and rat skin and an *in vivo* rat study. The neat product and a 4-fold dilution were examined for representative use conditions.

The "Triple pack" approach is used to estimate the human *in vivo* dermal absorption values:

- 0.1% for the neat formulation (400 g a.s./L)
- 0.2% for the low dose (100 g a.s./L).

These values are proposed for use in risk assessments (for details see CP 7.3).

CP 7.2.1 Operator exposure

The EFSA guidance on non-dietary exposure (EFSA model) is proposed to be used for harmonized risk assessment. However, this guidance does not provide recommendations for seed treatment formulations. A model to estimate the exposure of operators during seed treatment and seed sowing is the SeedTROPEX Model. Estimates using this model were provided in the original AIR dossier of Thiacloprid and are not presented in this dossier again. Since the SeedTROPEX Model is compiled from experimental studies on cereal seed treatment/sowing it is only conditionally qualified for exposure assessment of maize seed treatment/sowing. Therefore, experimental field studies were conducted to monitor the exposure during seed treatment and sowing using the FS 400 formulation. Operator exposure studies were conducted in modern maize seed treatment plants and on farm using up-to-date sowing equipment. These studies are higher tier field studies and considered to be more realistic than the model. The exposure studies were performed including available risk mitigation measures for the proposed use of the product, with the aim to minimize the exposure.

[3] 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

[4] 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.

[5] 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,

One operator exposure study was performed with Sonido FS 400 (400 g/L thiacloprid) to monitor the exposure during maize seed treatment. All tasks typically performed during a working day were monitored including cleaning. Another generic operator exposure study was conducted during maize seed treatment using the product Regent FS 500 (500 g/L fipronil). The study is consulted in addition in order to confirm the results obtained with Sonido FS 400. A 3rd exposure study was performed with Sonido FS 400 to monitor the exposure during sowing of maize seed treated with Sonido FS 400.

The experimental data obtained from these studies are used to demonstrate the negligible exposure of operators during seed treatment and seed sowing.

Summary

Alternative approaches are applied to verify that the exposure is negligible.

In a 1st tier, the level of exposure 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

Scenario	PPE	Source (Product, experimental study)	Systemic exposure$^{\infty}$ (mg/kg bw/day)		% of AOEL# (0.02 mg/kg bw/day) / MoE°	% of AAOEL# (0.03 mg/kg bw/day) / MoE °	Add. Margin of Exposure ≥10?
			Longer-term	Acute			
Maize, seed treatment	With 1)	Sonido® FS 400 (M-492984-01-1)	0.00043 (param. 75th perc.)	0.00198 (sample max.)	2.2% 4651	6.6% 1515	Yes
Maize, seed treatment	With 2)	Regent® FS 500 (M-261077-01-1)	0.00015 (param. 75th perc.)	0.00042 (sample maximum)	0.8% 13333	1.4 7143	Yes
Maize, sowing	With 3)	Sonido® FS 400 (M-492986-01-1)	0.00011 (param. 75th perc.)	0.00023 (param. 95th perc.)	0.5% 18182	0.8% 13216	Yes

$^{\infty}$ 0.1%-0.2% dermal absorption
#NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity), SF = 100
° Margin of Exposure (MoE)= NOAEL/system. Exposure; NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)
1) Mixing/loading: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Cleaning: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds,
2) Mixing/loading, calibration: cotton coverall + protective gloves + Tyvek type coverall
Cleaning: cotton coverall + protective gloves + Tyvek type coverall + mask
Bagging, palletizing: cotton coverall
3) Loading: cotton coverall, protective gloves, mask, goggles
Sowing: cotton coverall, occasionally protective gloves during maintenance outside cabin

The risk calculations for negligible exposure include mitigation measures for the relevant routes of exposure. The empirical 75th/95th percentile and the parametric 75th/95th percentile exposure estimates were calculated from the data of each study.

Systemic longer-term exposure of operators during seed treatment derived from the Sonido® FS 400 study is 0.00043 mg/kg bw/day (parametric 75th perc.). This estimate equates to 2.2% of the AOEL. The low longer-term exposure is confirmed by the generic data derived from the Regent® FS 500 study. Systemic longer-term exposure of 0.00015 mg/kg bw/day (empirical and parametric) is calculated resulting in 0.8% of the AOEL.

Systemic acute exposure of operators during seed treatment derived from the Sonido® FS 400 study is 0.00198 mg/kg bw/day (sample maximum). This estimate equates to 6.6% of the AAOEL. The acute exposure derived from the Regent® FS 500 study is 0.00042 mg/kg bw/day (sample maximum). This estimate equates to 1.4% of the AAOEL.

Systemic longer-term exposure during seed loading/sowing derived from the Sonido® FS 400 study is 0.00011 mg/kg bw/day (parametric 75th perc.). This estimate equates to 0.6% of the AOEL.

Systemic acute exposure during seed loading/sowing derived from the Sonido® FS 400 study is 0.00023 mg/kg bw/day (parametric 95th perc.). This estimate equates to 0.8% of the AAOEL.

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	PPE	Source (exp. study)	Systemic exposure[a] longer-term (acute) [mg/kg bw/day]	Hazard specific overall NOAEL (hazard/specific endpoint) [mg/kg bw/day]	Margin of Exposure[b] longer-term (acute)
Seed treatment	With [1)]	Sonido® FS 400 (M-492984-01-1)	0.00043 (0.00198)	Fertility: 20 (dystocia, rat)	46512 (10101)
				Developmental toxicity:	
				10 (increase in post implantation loss)	23256 (5051)
				17.5 (increase in stillbirths)	40698 (8838)
				22 (increase in cannibalized & missing pups)	51163 (11111)
				20 (reduced pup weights)	46512 (10101)
Seed treatment	With [2)]	Regent® FS 500 (M-261077-01-1)	0.00015 (0.00042)	Fertility: 20 (dystocia, rat)	133333 (47619)
				Developmental toxicity:	
				10 (increase in post implantation loss)	66667 (23810)
				17.5 (increase in stillbirths)	116667 (41667)
				22 (increase in cannibalized & missing	14667

				pups)	(52381)
				20 (reduced pup weights)	133333 (47619)
Seed sowing	With 3)	Sonido® FS 400 (M-492986-01-1)	0.00011 (0.00023)	Fertility: 20 (dystocia, rat)	181818 (86975)
				Developmental toxicity: 10 (increase in post implantation loss)	90909 (43478)
				17.5 (increase in stillbirths)	159090 (76087)
				22 (increase in cannibalized & missing pups)	200000 (95652)
				20 (reduced pup weights)	181818 (86957)

* for more details refer to Table 7.2-2

∞ 0.1%-0.2% dermal absorption, the higher of the empirical 75th /95th perc. and the parametric 75th /95th percentile is presented

° Margin of Exposure = hazard specific NOAEL/system. exposure

1) Mixing/loading: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Cleaning: Impermeable coverall, protective gloves, particle filtering half mask, goggles
Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds

2) Mixing/loading, calibration: cotton coverall + protective gloves + Tyvek type coverall
Cleaning: cotton coverall + protective gloves + Tyvek type coverall + mask
Bagging, palletizing: cotton coverall

3) Loading: cotton coverall, protective gloves, mask, goggles
Sowing: cotton coverall, occasionally protective gloves during maintenance outside cabin

The evidence of negligible exposure using the critical effect NOAEL for the risk assessment is shown using the higher of the empiric or the parametric 75th percentile for the longer-term exposure and using the sample maximum or parametric 95th percentile for the acute exposure. The risk assessment demonstrates that the toxicological reference values are an order of magnitude of 4-5 higher than the experimentally determined systemic exposures.

Conclusion

According to Regulation No 1107/2009 on the placing of plant protection products on the market and Commission Regulation No 284/2013 implementing Regulation No 1107/2009 estimations of operator exposure have to be made for the respective type of application and equipment used and have to consider all operations including the mixing/loading, the application of the plant protection product and also the cleaning and the routine maintenance of application equipment. All operations have been monitored in two operator exposure studies and estimations of operator exposure are performed based on these studies.

The seed treatment studies were conducted in modern maize seed treatment plants. One study was undertaken with Sonido® FS 400 (400 g a.s./L thiacloprid) and another one with Regent® FS 500 (500 g a.s./L fipronil). A total of 40 persons were monitored in six different seed treatment plants in France. The monitoring included all activities that are typically performed during seed treatment (seed supply, mixing/loading, controlling the treatment/bagging/palletizing line, forklift driving, cleaning).

All sites displayed a state-of-the-art technical standard in industrial maize seed treatment characterized by a high degree of automation and engineering control (enclosed processing lines) for low dust development. They provide engineering control for closed systems and air exhaust systems as technically and economically feasible today to reduce dust development to a minimum.

The seed sowing study was carried out with maize seed treated with Sonido® FS 400. Operators were monitored on 10 French farms using modern seed sowing equipment with deflector technology. This technology is the state-of-the-art technical standard in commercial maize seed sowing for low dust development. The deflector technology in pneumatic systems is certified for at least 90% dust drift reduction when compared to benchmark machinery.

The new Sonido® FS 400 formulation contains an inbuilt film-coating agent with a binder to supplement a 2nd allowance of binder which is typically added by the seed treatment facility. This recipe maximizes the adhesion of product to the corn and avoids dust abrasion during treatment, bagging, storage, transport and drilling.

The level of exposure is achieved with standard working clothing and readily obtainable PPE. The level of PPE that was worn is reasonable but not excessively high.

The clothing of seed treatment operators included at least one layer of outer clothing (e.g. work jacket and trousers or coverall). As seed treatment is typically performed during the colder winter season some of the operators additionally wore a long sleeved shirt, a T-shirt, a vest, or a pullover. As indicated on the label chemical resistant gloves, impervious coverall, mask and goggles were worn during mixing/loading and cleaning. Disposable gloves were also worn from time to time when getting into contact with contaminated surfaces or treated seed. This was mandated by the seed treatment facility safety guidance.

The clothing of the seed sowing operators consisted of one layer of outer clothing (work jacket and trousers). As indicated on the label chemical resistant gloves and a mask were worn during loading the hopper. During drilling, protective gloves were only worn outside the cab to avoid contact with contaminated surfaces.

It is demonstrated that modern seed treatment and sowing equipment provide very low levels of exposure. The available risk mitigation measures provide an additional margin of exposure (MoE) of about 100 and higher and therefore a higher level of safety beyond the threshold already considered as safe.

It is concluded that the use of Thiacloprid FS 400 with modern seed treatment and sowing equipment will result in insignificant exposure during maize seed treatment and maize sowing.

The following risk mitigation measures are proposed for the scenario of use with the aim to minimize exposure of humans to the active substance as much as technically possible (for details refer to chapter Method of Application, KCP 3.5):

- Seed treatment
  - State-of-the-art technical standard in maize seed treatment including a high degree of automation and engineering control for low dust development; this includes
    - seed purification before treatment (use of dust-free seed),
    - closed transfer systems (liquids) - equipment designed and manufactured to be used to move the formulated product from the original container into the seed treatment chamber, and to accurately measure the volume of chemical being transferred with compatible packaging
    - use of stationary LEV (local exhaust ventilation) systems in indoor situations i.e. dust extraction systems during seed treatment process and during bagging,
    - use of binders/stickers in the seed treatment slurry,
    - closed treatment line, treatment chamber and bagging line

  - automated palletizing
  - automated application systems reducing manual activities to a minimum.
- Formulation adding a separate film-coating product containing a binder to maximize the adhesion and avoid dust abrasion

- Seed sowing

State-of-the-art technical standard in maize seed sowing; this includes

  - sowing machinery i.e. precision planters working with the vacuum singulation principle including deflectors on vacuum pneumatic seed drills designed to reduce dust drift

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 FS 400 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 and AAOEL). Margins of Exposure of 3-5 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 operators to thiacloprid can be mitigated to negligibly low levels under realistic conditions of use.

CP 7.2.1.1 Estimation of operator exposure

The SeedTROPEX model was used to estimate the exposure of operators during seed treatment and seed sowing in the original AIR dossier of Thiacloprid and results are not presented here again.

Exposure estimates in this dossier are based on experimental data from field studies (seed treatment and seed sowing) using the FS 400 formulation. Operator exposure studies were conducted in modern maize seed treatment plants and on farm using up-to-date sowing equipment.

CP 7.2.1.2 Measurement of operator exposure

Experimental data are available from operator exposure studies. These studies are used to evaluate the exposure of operators to thiacloprid during seed treatment and seed sowing.

Two exposure studies were performed to monitor the exposure during seed treatment. One seed treatment study was performed with SONIDO® FS 400 (thiacloprid, 400 g a.s./L, 3 sites) and another one with REGENT® FS 500 (fipronil, 500 g a.s./L, 3 sites). Both studies were performed in plants representing state-of-the-art seed treatment technology. This involved a high degree of automation and engineering control. Both studies reflect the high technical standards currently used in maize seed treatment in Europe. A justification for the use of both studies in risk assessment is given below in the comparison of the use conditions of both products.

Table 7.2.1.2-1: Comparison of proposed use of 'SONIDO® FS 400' (thiacloprid, 400 g/L) and use of 'REGENT® FS 500' (fipronil, 500 g/L):

Product	Active	Dose rate		Crop	Application method
		g a.s./U	g a.s./ 100 kg seed*		

Sonido® FS 400	Thiacloprid	50	285	Maize	Seed treatment - high degree of automation
Regent® FS 500	Fipronil	43.75	250	Maize	Seed treatment - high degree of automation

* based on avg. TKG of 0.351 kg/1000 seeds

Both products are formulated as flowable concentrates for seed treatment (FS formulation) with similar composition. On the basis of a.s. applied, work rate, water volume and method of application, the generic study is an appropriate surrogate for the a.s. component of 'Sonido® FS 400'.

A third study was conducted to monitor the exposure to thiacloprid during seed sowing. Sowing of maize treated with SONIDO FS 400 was performed with state-of-the-art pneumatic sowing machinery i.e. using precision planters working with the vacuum singulation principle including deflector technology.

Exposure during seed treatment

Report: KCP 7.2.1.2/02 [redacted] H.; [redacted] C.; 2014; M-492984-01-1
Title: Determination of operator exposure to thiacloprid during seed treatment of maize with Sonido FS400
Report No.: MR-14/102
Document No.: M-492984-01-1
Guideline(s): OECD guidance document for the conduct of studies of occupational exposure to pesticides during agricultural application, Series on Testing and Assessment No. 9, 1997
Guideline deviation(s): not specified
GLP/GEP: yes

Material and methods

The dermal and inhalation exposure of 13 operators was monitored in 2014 in an operator exposure study conducted in three professional maize seed treatment plants in France when using Sonido® FS 400. The product is formulated as a flowable concentrate (FS) and contains the insecticidal active substance thiacloprid (400 g a.s./L). The test item was delivered to the test sites in original containers containing 1000 liters of product. This packaging is typical for this kind of product.

The product is a water-based seed dressing liquid formulated as a flowable concentrate (FS formulation). It contains the insecticidal active substance thiacloprid (400 g/L declared). The product was supplied in 1000 liter containers. The seed treatment of maize grain was conducted with the maximum application rate of 125 mL/unit (1 unit = 50000 grain). The study was performed from January through to February 2014 during the typical maize seed treatment season. Operators were monitored for a whole work shift (about 8 hours). They performed their normal daily routine work consisting of a combination of activities (mixing/loading, seed supply, seed sampling, operation of bagging and stacking line, forklift transfer to storage, cleaning of treatment chamber and of bagging/stacking line area, etc.) depending on the plant's work task organization. The selected plants represent a state-of-the-art technical standard in maize seed treatment with a high degree of

automation and engineering control for low dust development. This includes seed purification before treatment (use of dust-free seed), use of dust extraction systems (during seed treatment/bagging), use of binders in the seed treatment slurry, closed transport, treatment and bagging lines and a high degree of automation reducing manual activities to a minimum. Batch treaters were used at all sites. 2460-2690 units (33 to 47 tonnes of seed) were treated corresponding to a consumption of 308 – 336 L product (132-135 kg a.s. thiacloprid) per day.

Exposure measurements were performed via passive dosimetry techniques. Body exposure was evaluated on cotton underwear worn beneath the operator's usual work clothing (at least one layer of freshly washed outer clothing, e.g. jacket and trousers). Exposure of the head was measured via face neck wipes. Exposure of the hands was determined via hand washes with detergent. Varying work clothing and additional Personal Protective Equipment (PPE) such as protective gloves and/or protective coverall and/or filter mask was worn during the day depending on the activity but not used as dosimeters. Inhalation exposure was determined by use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter located in the breathing zone of the operator. Samples were collected on completion of the daily work tasks. Additional inhalation samples were collected during cleaning operations.

Field recoveries were set up with standard in solvent to evaluate the stability of active substance on the various sampling media.

The samples were extracted with a mixture of acetonitrile/water and analyzed for residues of thiacloprid using LC-MS/MS detection. The analytical method was validated by recovery experiments prior to the analysis of the test samples. The limit of quantitation (LOQ) was established at 0.01 µg//sample for the cotton garments, 0.001 µg//sample for the face/neck wipes and the inhalation filters and 1 µg//sample for the hand wash solution.

Results

The analytical method was validated with lab recoveries of 96% - 100%. Field recoveries of 86% - 102% demonstrated the stability of the active substance in the dosimeters from time of sampling until analysis.

Actual dermal exposure was calculated as the sum of residues on inner dosimeters, hand wash and face/neck wipes. Inhalation exposure was calculated from residues in the air filter adjusted for an average breathing rate of 20.8 L/min. Head exposure was calculated from residues in face/neck wipes. Potential inhalation values represent workers wearing no mask. The exposure values for individual workers are tabulated below.

Tab. 7.2.1.2-2: Individual exposures (µg/person)

	Exposure (µg/person)															
	Plant 1				Plant 2					Plant 3						
	OA	OB	OC	OD	OE	OF	OG	OH	OI	OJ	OK	OL	OM	MIN	MAX
Actual dermal																
• body	14.1	33.6	48.9	20.3	76.6	617	793	1010	89.9	27.0	4.88	3.60	1.88	1.88	1010
• head	1.46	2.22	1.55	6.77	2.23	31.1	54.9	117	1.61	1.56	1.93	0.190	0.376	0.19	117
• hands																
- during mixing/loading	51.6				32.5								10.2	10.2	32.5	
- during other activities (including cleaning)		26.8	14.8	247		77.2	146	73.2	49.3	63.5	80.9	5.87		5.87	247	
Potential inhalation*																
- during cleaning				0.509				907		2.90				0.509	907	
- during other activities	7.95	4.38	4.86	12.8	29.6	137	150	60.2	4.60	5.03	1.93	1.09	0.550	0.550	150	

* Inhalation exposure is calculated from residues on air filter adjusted to a respiration rate of 20.8 L/min. Head exposure is calculated from residues in face/neck wipes. Actual dermal exposure is the sum of residues on inner dosimeters + hand wash + face/neck wipes.

The following values are summarized from these data.

Tab. 7.2.1.2-3: Individual exposures

Operator ID	Individual tasks	Exposure (mg/person)*	
		Actual dermal	Potential inhalation
OA	Mixing/loading, treatment/bagging line	0.0672	0.00795
OB	Seed supply, bagging line	0.0626	0.00438
OC	Palletizing, forklift driving	0.0653	0.00486
OD	Cleaning, bagging line	0.2745	0.01332
OE	Mixing/loading	0.1114	0.02963
OF	Seed supply, treatment/bagging line	0.7253	0.13686
OG	Palletizing	0.9942	0.14986
OH	Seed supply, cleaning, bagging line	1.2002	0.96710
OI	Palletizing, forklift driving	0.1808	0.00460
OJ	Cleaning, treatment/bagging line	0.0921	0.00794
OK	Palletizing, forklift driving	0.0877	0.00193
OL	Seed supply, bagging line	0.0097	0.00109
OM	Mixing/loading	0.0124	0.00055

*The following PPE was worn in addition to standard work clothing:
- Mixing/loading: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Cleaning: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds

Conclusion

Dermal and inhalation exposure is generally low. Actual dermal exposure of all operators was 9.66-1200 µg/person. The typical operator's work included a combination of tasks depending on the work organisation. Operators typically assisted in different activities apart from their main task or replaced their colleagues e.g. during breaks. But none of the operators was involved in a combination of all activities. Therefore, specific task exposure scenarios were not developed. Exposure results demonstrate that actual exposure is likewise distributed between the operators. Potential inhalation exposure ranged from 0.550-150 µg/person calculated for an average breathing rate of 20.8 L/min. One operator had an exceptionally high potential inhalation dose of 967 µg. The likely reason for this dose is considered to be the excessive use of compressed air used by this operator during the cleaning of the treatment chamber (94% of the total respirable dose was received during this activity). Actual inhalation exposure of this operator, on the other hand, is to be evaluated by the use of a filter mask. A recommendation is concluded that the use of pressurized air should be replaced by other cleaning device e.g. vacuum systems.

Workers were adequately equipped with working clothing and PPE. Relevant clothing/PPE scenarios may be considered in risk assessment.

Risk assessment

The experimental conditions represent state-of-the-art technology in Europe and are formulation specific for SONIDO® FS 400. The measured values of the experimental study are taken for the risk assessment.

Since workers performed several activities specific exposure subsets are not observed. Therefore, a deterministic exposure estimate is taken from the whole data base. Taking as surrogates the more conservative 75th percentile values the following results are obtained for thiacloprid in SONIDO® FS 400.

Tab. 7.2.1.2-4: Calculation of systemic exposures

Operator ID	Individual tasks	Body weight (kg)	Exposure (mg/kg bw[#]/day)		
			Actual dermal	Potential inhalation	Systemic * (incl. RPE)
OA	Mixing/loading, treatment/bagging line	80	0.0008	0.00010	0.00010
OB	Seed supply, bagging line	90	0.0007	0.00005	0.00005
OC	Palletizing, forklift driving	75	0.0009	0.00006	0.00007
OD	Cleaning, bagging line	80	0.0034	0.00013	0.00017
OE	Mixing/loading	65	0.0017	0.00046	0.00033
OF	Seed supply, treatment/bagging line	70	0.0104	0.00196	0.00198
OG	Palletizing	82	0.0121	0.00183	0.00185
OH	Seed supply, cleaning, bagging line	88	0.0136	0.00099	0.00123
OI	Palletizing, forklift driving	87	0.0021	0.00005	0.00006
OJ	Cleaning, treatment/bagging line	98	0.0009	0.00008	0.00005
OK	Palletizing, forklift driving	75	0.0012	0.00003	0.00003
OL	Seed supply, bagging line	75	0.0001	0.00001	0.00001
OM	Mixing loading	84	0.0001	0.00001	0.00001
				75th percentile	**0.00033**
				75th parametric estimate	**0.00043**
				95th percentile	**0.00190**
				95th parametric estimate	**0.00326**
				Maximum	**0.00198**

[#] Individual body weight

* Systemic exposure is calculated from actual dermal exposure using 0.1% dermal absorption of residues obtained during mixing/loading (exposure to concentrate product) and using 0.2% dermal absorption of residues obtained during all other tasks. Inhalation exposure of operators is calculated for a breathing rate of 1.25 m³/h (20.8 L/min) and assumed to be totally absorbed (100% absorption via inhalation). Inhalation exposures during cleaning (operators OD, OH, OJ) are adjusted for wearing a mask (mitigation factor 0.05 for FFP3 mask).

Summary

For risk assessments in relation to longer term exposures, the EFSA Guidance notes that exposures are derived as the higher of:

(a) the 75th percentile of the distribution of measurements in the sample (the level of exposure an individual in the population can experience repeatedly each day over a season); or

(b) a statistical estimate of the 75th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

The relevant estimate for longer-term exposure is therefore the parametric 75th percentile of 0.00043 mg/kg bw/day which equates to 2.2% of the AOEL.

For risk assessments in relation to acute exposures (i.e. those that could occur in a single day), exposure estimates should, as a default, be derived as the higher of:

(a) the 95th percentile of the distribution of measurements in the sample (the level of exposure an individual in the population can experience over a single day); or

(b) a statistical estimate of the 95th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution (EFSA PPR Panel, 2010).

'The agreed selection rule considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen.'

The relevant estimate for acute exposure is therefore the sample maximum of 0.00198 mg/kg bw/day which equates to 6.6% of the AAOEL.

Tab. 7.2.1.2-5: Exposure of seed treatment operators

Exposure	With PPE*		
	Systemic exposure (mg/kg bw/d)	% of AOEL (0.02 mg/kg bw/day)	% of AAOEL (0.03 mg/kg bw/day)
Longer-term (parametric 75th percentile)	0.00043	2.2%	-
Acute (sample maximum)	0.00198	-	6.6%
Log normal?	Yes		

* The following PPE was worn:
- Mixing/loading: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Cleaning: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds

Report:	KCP 7.2.1.2/03 [redacted],; [redacted]; 2005; M-261077-01-1
Title:	Regent (R) 500 FS - Worker exposure during treatment of maize seeds
Report No.:	M-261077-01-1
Document No.:	M-261077-01-1
Guideline(s):	Not specified
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and methods

Exposure was monitored in three seed treatment plants in France using REGENT® FS 500, a water-based FS formulation containing the active substance fipronil (500 g/L).

The product was applied with an application rate of 87.5 mL/unit of seeds equivalent to 43.75 g a.s./U (1 U = 17.5 kg). A slurry was prepared with additional preparations and/or water to give a dilution rate of 1.2x - 3.5x. 24 male workers (six, nine and nine at each site) were monitored during a complete working shift. Most of the workers were involved in several tasks.

The seed treatment process was performed with a high degree of automation. At all sites, the transfer of product during mixing/loading was performed by introducing a suction probe into the storage tank. The product was then automatically pumped into a mixing tank (computer driven). Calibration was automatically performed by the treatment system at site 1 (manually at site 2 and 3). The bagging at all sites was automated. This included automated feeding of empty bags into the system, fixing of the bags on the filler station, labelling of bags, closing of bags by sewing and placing of bags on pallets (manually operated at site 3). Operator’s tasks were starting the machinery, ensuring that bags and labels were available for the feeding section of the system, checking the control system, maintenance and taking care of incidents. In all plants, air extractors were located close to the seed filling station. The bagging systems were enclosed and ventilated in plant 1, half-enclosed with air-extraction in plant 3 and open but with air extraction in plant 2. Cleaning was performed manually with compressed air and/or water under pressure.

Dermal exposure was determined via whole body dosimetry including working clothing and PPE that workers typically wear under the prevailing conditions. Hand and head exposure was determined with hand wash procedures and face/neck wipes. Inhalation exposure was measured with personal air samplers. The dosimeter samples were extracted and analysed for residues of fipronil by LC-MS/MS detection.

Field recovery was assessed at all sites to evaluate the stability of fipronil samples on the various media. Non-fortified dermal and inhalation blank samples were set up, packed and stored in an identical manner.

The analytical method was validated with fipronil by recovery experiments prior to the analysis of the test samples. The limit of quantitation (LOQ) was 0.01 µg/specimen for glass fibre filters, 0.5 µg/specimen for hand washings, 0.1 µg/specimen for face/neck wipes, 1 µg/specimen for underwear, cotton coverall and Tyvek protective suit and 20 µg/sample for protective gloves (1 pair).

Results

Potential inhalation exposure is calculated from residues in the air filter adjusted for a respiration rate of 1.25 m^3/h (20.8 L/min). Head exposure is calculated from residues in face/neck wipes. Potential dermal exposure is the sum of residues on all dermal dosimeters, actual dermal exposure is the sum of residues of inner dosimeters, hand wash and face/neck wipes.

Workers were adequately equipped with working clothing and PPE. Protective gloves were worn during mixing/loading, calibration and cleaning. Some (5 of 12) workers occasionally wore gloves during bagging when touching treated seed.

Inhalation values represent workers wearing no mask. During cleaning, masks were mostly worn and sometimes additional face shields were worn.

The exposure values for individual workers are tabulated below.

Tab. 7.2.1.2-5: Individual task exposures (µg/person)*

	Exposure (µg/person)																	
	Calibration			Mixing/loading			Bagging			Bagging - pallets			Cleaning					
Operator ID	potential dermal[1]	actual dermal[2]	Inhalation [4]	potential dermal	actual dermal[3]	inhalation	potential dermal	actual dermal[3]	inhalation	potential dermal	actual dermal[2]	inhalation	potential dermal	actual dermal[3]	inhalation			
1				7683	47.3	1.61												
2							683	194	7.02									
3													39266	172	1.97			
4							3379	623	11.5				14243	344	115			
5							1441	456	4.60				43285	981	513			
6													67821	295	45.6			
7				3985	103	4.51												
8							4016.5	869	19.6									
9	18205	17.5	0.202				7228.5	386	20.2									
10													98082	291	38.1			
12													207789	52.0	81.0			
14													11834	66.1	19.2			
15	3230	11.4	4.71				2138	304	11.5									
16							933	126	6.48									
18							2018	444	21.7									
19				3121	7.72	0.824												
20	1914	158	0.620				7031	182	5.18									
21							861	58.6	3.49									
22											32.9	0.925	22713	95.0	9.97			
23											29.9	1.28	5541	76.6	9.68			
24							1548	111	8.11									
25							7789	106	3.52									
26											20.2	3.92	9261	385	24.0			
27											30.4	2.90	5856	123	14.7			

* summarized from Table 13, 14, 15, 16 and 17 of the study report
[1] sum of outer and inner dosimeter, face/neck wipes, hand washes
[2] sum of face/neck wipes, hand washes
[3] sum of inner dosimeter, face/neck wipes, hand washes
[4] residues on air filter adjusted to a respiration rate of 20.8 L/min

The exposure values are summarized in the following table.

Tab. 7.2.1.2-6: Individual operator exposures (mg/person)

Operator ID	Individual tasks*	Exposure (mg/person)		
		Potential dermal[1]	Actual dermal[2]	Potential inhalation
1	Mixing / loading [1, 2, 3]	7.68	0.047	0.0016
2	Bagging [1]	0.683	0.194	0.0070
3	Treatment [1, 2a, 4]/ cleaning [1, 2, 3, 5]	39.3	0.172	0.0020
4	Bagging [1]/ cleaning [1, 2, 3, 4]	17.6	0.967	0.1265
5	Bagging [1, 4a]/ cleaning [1, 2, 3, 4]	44.7	1.437	0.5176
6	Treatment [1, 2a] / cleaning [1, 2, 3, 4, 5]	67.8	0.295	0.0456
7	Mixing / loading [1, 2, 3, 4]	3.98	0.103	0.0045
8	Bagging [1]	4.02	0.869	0.0196
9	Bagging [1, 2a] / calibration [1, 2, 3]	25.4	0.403	0.0285
10	Cleaning [1, 2, 3, 4]	98.1	0.291	0.0381
12	Cleaning [1, 2, 3]	208	0.052	0.0810
14	Cleaning [1, 2, 3]	11.8	0.066	0.0192
15	Bagging [1]/ calibration [1, 2, 3]	5.37	0.315	0.0162
16	Bagging [1]	0.933	0.126	0.0065
18	Bagging [1]	2.02	0.444	0.0217
19	Mixing / loading [1, 2, 3]	3.12	0.008	0.0008
20	Bagging [1, 2a] / calibration [1, 2, 3]	8.94	0.340	0.0058
21	Bagging [1, 2a]	0.861	0.059	0.0035
22	Bagging - pallets [1]/ cleaning [1, 2, 3, 4]	22.7	0.128	0.0109
23	Bagging - pallets [1]/ cleaning [1, 2, 3]	5.54	0.106	0.0110
24	Bagging [1, 2a]	1.55	0.111	0.0081
25	Bagging [1, 2a]	7.78	0.106	0.0035
26	Bagging-pallets [1, 3]/cleaning [1, 2, 3, 4]	9.26	0.461	0.0279
27	Bagging-pallets [1]/ cleaning [1, 2, 3, 4]	5.86	0.160	0.0176

* Clothing/PPE worn:

[1] cotton coverall,
protective gloves, [2a] occasionally
[3] Tyvek
[4] mask, [4a] occasionally
[5] face shield

Conclusion

The study results represent exposure from treatment of maize seed in professional plants. Seed treatment processes were performed with a high degree of automation. Workers were adequately equipped with working clothing and PPE. Three workers were involved only in mixing/loading. Other workers were mainly involved in a combination of tasks such as calibration, bagging, stacking (pallets) and cleaning. Dermal and inhalation exposure were highest during the cleaning procedures. However, impervious coverall (Tyvek) was always worn and masks were mainly worn during this activity. Relevant clothing scenarios may be considered in risk assessment.

Risk assessment

The experimental conditions of the above presented study are representative for seed treatment of maize with state-of-the-art technology in Europe.

The measured values of the experimental fipronil study are taken for the risk assessment (no normalisation for a.s. handled).

Since workers performed several activities specific exposure subsets are not observed. Therefore, a deterministic exposure estimate is taken from the whole data base. In order to predict the operator exposure to thiacloprid the fipronil data are taken as measured.

Tab. 7.2.1.2-7: Calculation of systemic exposures

Operator ID	Individual tasks	Body weight (kg)	Exposure (mg/kg bw/day)			
			Potential dermal	Actual dermal	Potential inhalation	Systemic *
1	Mixing / loading	69	0.11134	0.00069	0.00002	0.00002
2	Bagging	77	0.00887	0.00252	0.00009	0.00010
3	Treatment / cleaning	61	0.64370	0.00281	0.00003	0.00001
4	Bagging / cleaning	64	0.27534	0.01511	0.00198	0.00030
5	Bagging / cleaning	79	0.56616	0.01819	0.00035	0.00042
6	Treatment / cleaning	68	0.99736	0.00433	0.00067	0.00004
7	Mixing / loading	76	0.05243	0.00135	0.00006	0.00006
8	Bagging	70	0.05738	0.01241	0.00028	0.00030
9	Bagging / calibration	71	0.35821	0.00568	0.00040	0.00041
10	Cleaning	70	1.40118	0.00416	0.00054	0.00004
12	Cleaning	74	2.80796	0.00970	0.00109	0.00006
14	Cleaning	71	0.16667	0.00093	0.00027	0.00002
15	Bagging / calibration	75	0.07158	0.00420	0.00022	0.00022
16	Bagging	65	0.01436	0.00195	0.00010	0.00010
18	Bagging	95	0.02124	0.00468	0.00023	0.00024
19	Mixing / loading	78	0.04001	0.00010	0.00001	0.00001
20	Bagging / calibration	63	0.14198	0.00539	0.00009	0.00010
21	Bagging	72	0.01195	0.00081	0.00005	0.00005
22	Bagging - pallets / cleaning	72	0.31546	0.00178	0.00015	0.00002
23	Bagging - pallets / cleaning	80	0.06926	0.00133	0.00014	0.00002
24	Bagging	64	0.02418	0.00173	0.00013	0.00013
25	Bagging	86	0.09047	0.00124	0.00004	0.00004
26	Bagging - pallets / cleaning	70	0.13230	0.00658	0.00040	0.00009
27	Bagging - pallets / cleaning	68	0.08612	0.00235	0.00026	0.00006
					75th percentile	0.000153
					75th parametric estimate	0.000150
					95th percentile	0.000394

95th parametric estimate	**0.000490**
Maximum	**0.000420**

Individual body weight

* Systemic exposure is calculated from actual dermal using 0.1% dermal absorption of residues obtained during mixing/loading (exposure to concentrate product) and using 0.2% dermal absorption of residues obtained during all other tasks (diluted product). Inhalation exposure is calculated with a breathing rate for operators of 1.25 m^3/h (20.8 L/min) and assumed to be totally absorbed (100% absorption via inhalation). Inhalation exposures during cleaning (operators 3, 4, 5, 6, 10, 12, 14, 22, 23, 26 and 27) are adjusted for wearing a mask (mitigation factor 0.05 for FFP3 mask).

Summary

For risk assessments in relation to longer term exposures, exposures are derived as the higher of:

(a) the 75th percentile of the distribution of measurements in the sample or

(b) a statistical estimate of the 75th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

The relevant estimate for longer-term exposure is therefore the 75th percentile of 0.00015 mg/kg bw/day which equates to 0.8% of the AOEL.

For risk assessments in relation to acute exposures (i.e. those that could occur in a single day), exposure estimates should, as a default, be derived as the higher of:

(a) the 95th percentile of the distribution of measurements in the sample or

(b) a statistical estimate of the 95th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

'The agreed selection rule considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum is chosen.'

The relevant estimate for acute exposure is therefore the sample maximum of 0.00042 mg/kg bw/day which equates to 1.4% of the AAOEL.

Tab. 7.2.1.2-5: Exposure of seed treatment operators

Exposure	With PPE*		
	Systemic exposure (mg/kg bw/d)	% of AOEL (0.02 mg/kg bw/day)	% of AAOEL (0.03 mg/kg bw/day)
Longer-term (75th percentile)	0.00015	0.8%	-
Acute (sample maximum)	0.00042	-	1.4%
Log normal?	Yes		

* *The following PPE was worn:
- Mixing/loading: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Cleaning: Impermeable coverall, chemical resistant gloves, particle filtering half mask, goggles
- Other activities: Disposable gloves when getting into contact with contaminated surfaces or treated seeds

Exposure during seed sowing

Report:	KCP 7.2.1.2/02 [redacted]; [redacted]; 2014; M-492986-01-1
Title:	Determination of operator exposure to thiacloprid during loading and sowing of Sonido FS 400 treated maize seed
Report No.:	MR-14/112
Document No.:	M-492986-01-1
Guideline(s):	OECD guidance document for the conduct of studies of occupational exposure to pesticides during agricultural application, Series on Testing and Assessment No. 9, 1997
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and methods

The study was conducted in the French regions of Pau (Aquitaine) and Rennes (Normandy) during the typical season of maize sowing in April/May 2014. 11 operators on 10 farms were monitored during loading and sowing of maize seed treated with Sonido® FS 400 (thiacloprid, 400 g a.s./L).

The daily sowing rate per operator ranged from 6.6 ha - 19.8 ha. A series of different maize varieties were sown with sowing rates of 1.5 – 2.3 U/ha (1 unit = 50000 grain). A variety of state-of-the-art pneumatic precision sowing equipment with deflector technique was used. The operators performed their daily work according to their usual working practice (6 - 10 hrs). This included all tasks such as opening the bag containing the treated seed, loading the treated seed into the hopper, sowing the treated seed in the field, repair of malfunctions, transport from and to fields, etc. A cleaning event (removing seed remains off the hopper) was also monitored, however, not separately reported. The exposure from this task is included in the sowing data.

Operators handled 9 – 33 U per day of treated seeds. This corresponds to 0.359 – 1.484 kg of thiacloprid per day.

Exposure measurements were performed via passive dosimetry techniques. Outer dosimeters consisted of cotton/polyester work clothing (long-sleeved jacket and trousers). Cotton underwear (long-sleeved T-shirt and long trousers) were used as inner dosimeters. Exposure of the head was measured via face/neck wipes. Hand exposure was determined from residues in/on protective gloves and in hand wash water. Inhalation exposure of operators was determined by use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter located in the breathing zone of the operator. Separate inhalation samples were collected during loading and during sowing. Samples were collected on completion of the daily work tasks. Potential dermal exposure was calculated as the sum of residues detected on the outer clothes, the underwear, the protective gloves, hand washes, and face-neck wipes. Actual dermal exposure was calculated as the sum of the residues detected on the underwear, in the hand washes, and in the face/neck wipes.

Field recoveries were set up with standard in solvent to evaluate the stability of active substance on the various sampling media.

The samples were extracted with a mixture of acetonitrile/water and analysed for residues of thiacloprid using LC-MS/MS detection. The analytical method was validated by recovery experiments prior to the analysis of the test samples. The limit of quantitation (LOQ) was established at 0.01

µg//sample for the cotton garments (outer and inner dosimeter), 0.001 µg//sample for the face/neck wipes and the inhalation filters and 1 µg//sample for the hand wash solution and the protective gloves.

Results

The experimental conditions were representative with modern technology in maize seed sowing. Workers were adequately equipped with working clothing and PPE. The minimum clothing consisted of a cotton/polyester coverall and sturdy footwear. Protective gloves, a respiration mask and goggles were worn during loading. During sowing, protective gloves were occasionally worn for repair/maintenance work.

Recovery results showed that residues were stable during transport and storage. Recovery values were between 91% - 99% with relative standard deviations (RSD) of 2.2% - 8.1%.

Potential dermal exposure ranged from 416 – 5577 µg/person and actual dermal exposure ranged from 40.4 – 640 µg/person. Potential inhalation exposure was 3.37 – 51.2 µg/person calculated for an average breathing rate of 20.8 L/min. Potential inhalation values represent workers wearing no mask.

The exposure values for individual workers are tabulated below.

Tab. 7.2.1.2-8: Operator exposure to thiacloprid during loading/sowing

	Residues (µg/person)												
	OA	OB	OC	OD	OE	OF	OJ	OK	OL	OM	ON	MIN	MAX
Potential dermal													
- body	1518	1970	858	1042	2445	1789	273	423	2538	628	1741	273	2538
- head	8.35	4.69	8.90	5.95	22.1	41.9	5.57	7.14	11.4	10.2	35.6	4.69	41.9
- hands	1414	493	1773	356	3104	535	137	693	1643	281	1118	137	3104
Total potential dermal	**2940**	**2468**	**2639**	**1404**	**5577**	**2366**	**416**	**1123**	**4192**	**919**	**2894**	**416**	**5577**
Actual dermal													
- body	75.6	109	50.5	105	126	76.3	19.7	51.6	75.7	41.91	122	19.7	126
- head	8.35	4.69	8.90	5.95	27	41.9	5.57	7.14	11.4	10.2	35.6	4.69	41.9
- hands	54.4	40.7	39.7	58.9	486	78.4	15.2	21.8	57.5	25.0	10.9	10.9	486
Total actual dermal	**138**	**155**	**99**	**170**	**640**	**197**	**40**	**81**	**145**	**77**	**169**	**40.4**	**640**
Potential inhalation*													
- loading	21.7	23.8	46.6	18.6	35.6	4.75	1.79	17.3	31.1	13.1	44.9	1.79	46.6
- sowing	4.43	3.39	3.59	5.28	19.6	6.79	1.58	1.67	3.32	2.05	6.30	1.58	19.6
Total potential inhalation	**26.1**	**27.2**	**50.2**	**23.9**	**55.2**	**11.5**	**3.37**	**19.0**	**34.4**	**15.2**	**51.2**	**3.37**	**51.2**

* Inhalation exposure is calculated from residues on air filter adjusted to a respiration rate of 1.25 m³/h (20.8 L/min). Head exposure is calculated from residues in face/neck wipes. Potential dermal exposure is the sum of residues on all dermal dosimeters. Actual dermal exposure is the sum of residues on inner dosimeters + hand wash + face/neck wipes.

The following critical values are summarized from these data (from Table 1, whilst converting to mg/person).

Tab. 7.2.1.2-9: Individual exposures to thiacloprid

Operator ID	Exposure (mg/person)			
	Potential dermal	Actual dermal	Potential inhalation	
			Loading	Sowing
OA	2.940	0.138	0.0217	0.0044
OB	2.468	0.155	0.0238	0.0034
OC	2.635	0.099	0.0466	0.0036
OD	1.404	0.170	0.0186	0.0053
OE	5.577	0.640	0.0156	0.0196
OH	2.366	0.197	0.0475	0.0068
OJ	0.416	0.040	0.0018	0.0016
OK	1.123	0.081	0.0173	0.0017
OL	4.192	0.145	0.0374	0.0033
OM	0.919	0.077	0.0131	0.0021
ON	2.894	0.169	0.0449	0.0063

Conclusion

The results provide a representative picture of the exposure of farmers to thiacloprid when using pneumatic sowing equipment with deflector technology during sowing of SONIDO® FS 400 treated maize seed. The exposure level and the variation between operators are relatively low.

Workers were adequately equipped with working clothing and PPE. Comparison of potential and actual dermal exposure demonstrates that clothing and gloves provide efficient protection.

The potential for inhalation exposure during loading is higher than during sowing. The loading was conducted with respiratory protection (filter mask) by all operators. Actual inhalation exposure is therefore reduced accordingly and will be considered in risk assessment.

Risk assessment

The experimental conditions represent prevalent exposure situations during seed sowing of maize with state-of-the-art technology in Europe. The measured values of the experimental study are taken for the risk assessment.

Table 7.2.1.2-10: Calculation of systemic exposure

Operator ID	Body weight (kg)	Exposure (mg/kg bw#/day)			
		Actual dermal	Potential inhalation		Systemic * (incl. RPE)
			Loading	Sowing	
OA	76	0.0018	0.0003	0.0001	0.00007

OB	72	0.0021	0.0003	0.0000	0.00007
OC	80	0.0012	0.0006	0.0000	0.00008
OD	87	0.0020	0.0002	0.0001	0.00007
OE	83.5	0.0077	0.0002	0.0002	0.00025
OH	85	0.0023	0.0001	0.0001	0.00009
OJ	78	0.0005	0.0000	0.0000	0.00002
OK	77	0.0010	0.0002	0.0000	0.00003
OL	72	0.0020	0.0004	0.0000	0.00007
OM	64	0.0012	0.0002	0.0000	0.00004
ON	76	0.0022	0.0006	0.0001	0.00011
				75th percentile	**0.000080**
				75th parametric estimate	**0.000109**
				95th percentile	**0.000183**
				95th parametric estimate	**0.000227**
				Sample maximum	**0.000252**

Individual body weight

* Systemic exposure is calculated from actual dermal exposure using 0.1% dermal absorption (exposure to dust; inhalation exposure during loading is calculated considering that operators wear a mask (mitigation factor of 0.05 for FFP3 mask); inhalation exposure during sowing is calculated from potential inhalation exposure (no mask); for all operators a breathing rate of 1.25 m^3/h (20.8 L/min) is calculated.

Summary

For risk assessments in relation to longer term exposures, exposures are derived as the higher of:

(a) the 75th percentile of the distribution of measurements in the sample or

(b) a statistical estimate of the 75th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

The relevant estimate for longer-term exposure is therefore the parametric 75th percentile of 0.000111 mg/kg bw/day which equates to 0.5% of the AOEL.

For risk assessments in relation to acute exposures (i.e. those that could occur in a single day), exposure estimates should, as a default, be derived as the higher of:

(a) the 95th percentile of the distribution of measurements in the sample or

(b) a statistical estimate of the 95th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

'The agreed selection rule considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen.'

The relevant estimate for acute exposure is therefore the parametric 95th percentile of 0.00023 mg/kg bw/day which equates to 0.8% of the AAOEL.

Tab. 7.2.1.2-5: Exposure of seed sowing operators

Exposure	With PPE*		
	Systemic exposure (mg/kg bw/d)	% of AOEL (0.02 mg/kg bw/day)	% of AAOEL (0.03 mg/kg bw/day)
Longer-term (75th percentile)	0.00011	0.5%	-
Acute (sample maximum)	0.00023	-	0.8%
Log normal?	Yes		

*The following PPE was worn:
Cotton/polyester coverall and sturdy footwear was always worn; protective gloves, a respiration mask and goggles were worn in addition during loading; during sowing, protective gloves were occasionally worn for repair/maintenance work.

CP 7.2.2 Bystander and resident exposure

No validated models are available to conduct exposure calculations for bystanders and residents during seed sowing operations.

The draft Guidance for Authorization of Plant Protection Products for Seed Treatment[6] presents default values for dust deposition which may be used to estimate the bystander/resident exposure.

For the FS 400 formulation, specific dust deposition data are available from two experimental dust drift studies conducted during sowing of maize seed treated with the representative FS 400 formulation. Results of these studies are therefore used to determine the bystander and resident exposure.

Assessments are provided for exposure via dust drift and surface deposits. Exposure via vapour is not considered since the treated seed is covered with soil and thiacloprid is non-volatile (vapour pressure is 3×10^{-10} Pa at 20°C). Exposure via entry into treated crops is excluded since no dislodgeable residues are expected on foliage.

Summary

The level of exposure resulting from the critical GAP is compared with the toxicological reference values for longer-term (AOEL) and acute exposure (AAOEL). A margin of exposure (MoE) to the critical endpoint is calculated to demonstrate that an additional MoE of at least 10 to the already established endpoint exists.

A summary of the risk assessments provided for residents and bystanders is presented below.

Table 7.2.1-1: Assessment of resident exposure

[6] Draft, Authorisation of Plant Protection Products for Seed Treatment, SANCO/10553/2012, January 2014.

Exposure scenario	Target group	Scenario	Systemic exposure∞ [mg/kg bw/day]	% of AOEL [0.02 mg/kg bw/day]	MoE[1]	Add. MoE ≥ 10?
Maize seed drilling with deflector technology	Child	Dust drift	11.86×10^{-7}	0.006	> 1 mio	Yes
		Vapour	-	-	-	-
		Surface deposits	6.97×10^{-7}	0.004	> 1 mio	Yes
		Entry into treated crops	-	-	-	-
		All pathways	16.52×10^{-7}	0.008	> 1 mio	Yes
	Adult	Dust drift	6.02×10^{-7}	0.003	> 1 mio	Yes
		Vapour	-	-	-	-
		Surface deposits	0.13×10^{-7}	0.001	> 1 mio	Yes
		Entry into treated crops	-	-	-	-
		All pathways	5.92×10^{-7}	0.003	> 1 mio	Yes

∞ based on experimental dust drift study, ([redacted] and [redacted], 2010, M-384428-01-1), dermal absorption of 0.2%, 100% absorption *via* inhalation route

[1] Margin of Exposure (MoE): NOAEL exposure: longer-term NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)

Exposure of residents to dust drift is negligibly low for all routes of exposure. Child exposure as a result from all pathways is 0.008% of the AOEL and adult exposure from all pathways is 0.004% of the AOEL.

Table 7.2.1-2: Assessment of bystander exposure

Exposure scenario	Target group	Scenario	Systemic exposure∞ [mg/kg bw/day]	% of AAOEL [0.03 mg/kg bw/day]	MoE[1]	Add. MoE ≥ 10?
Maize seed drilling with deflector technology	Child	Dust drift	17.76×10^{-7}	0.006	> 1 mio	Yes
		Vapour	-	-	-	-
		Surface deposits	14.06×10^{-7}	0.004	> 1 mio	Yes
		Entry into treated crops	-	-	-	-
	Adult	Dust drift	8.59×10^{-7}	0.003	> 1 mio	Yes
		Vapour	-	-	-	-
		Surface deposits	0.26×10^{-7}	0.0001	> 1 mio	Yes

		Entry into treated crops	-	-	-	-

∞ based on experimental dust drift study ([redacted] and [redacted], 2010; M-384428-01-1), dermal absorption of 0.2%, 100% absorption *via* inhalation route

[1] Margin of Exposure (MoE): NOAEL/exposure; acute NOAEL = 0.03 mg/kg bw/day based on neurotoxicity study

Exposure of bystanders to dust drift is negligibly low for all routes of exposure. All child and adult exposure routes result in less than maximum 0.006% of the AAOEL.

In a 2nd tier, the Margin of Exposure to the study which is critical for the relevant classification under Regulation (EC) No 1272/2008 may be calculated. However, it has already been demonstrated above that MoEs to the established endpoints are greater than 1 mio. Therefore, calculations of MoE to the study which is critical for the relevant classification are considered to be dispensable.

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 FS 400 under realistic and practical conditions of use involving professional risk mitigation measures.

The results from dust drift studies demonstrate that resident and bystander exposure is far beyond the threshold already considered as safe (additional safety factor >>10 to the AOEL and AAOEL).

The applicant therefore considers that exposure of adult and child residents and bystanders to thiacloprid is negligibly low under realistic conditions of use.

CP 7.2.2.1 Estimation of bystander and resident exposure

Bystander/resident exposure during seed treatment:

> It has to be taken into account that maize seed treatment is performed indoors in professional plants. Incidental presence of persons unrelated to work is unlikely during seed treatment and is prohibited by the plant's safety regulations. The exposure of any persons whose tasks are related to work (seed treatment and seed sowing operators) have been measured in the exposure studies (see chapter KCP 7.2.1). Dust drift is not expected to be relevant for bystanders and residents living in the vicinity of the seed treatment facility because maize seed treatment is an indoor application.

Bystander/resident exposure during seed sowing:

A potential for bystander and resident exposure may not be excluded during seed sowing operations due to drift of abraded dust from treated seed. However, a validated model/guidance to calculate bystander/resident exposure during sowing is currently not established. The draft guidance on the authorization of seed treatment products recommends the default environmental concentrations in 2- and 3-dimensional structures. However, dust drift studies have been performed with the representative FS 400 formulation and 2D and 3D dust deposition values were measured for the product under evaluation. The estimation of bystander/resident exposure is therefore performed with the experimental data (see chapter 7.2.2.2).

CP 7.2.2.2 Measurement of bystander and resident exposure

Measurement of 2-D and 3-D dust deposition

Two dust drift studies were conducted in order to determine the 2- and 3-dimensional surface deposits of dust during sowing of maize seed treated with Thiacloprid FS 400. The studies are used to determine the bystander/resident exposure during maize sowing.

Report:	KCP 7.2.2.2/01; [redacted], P.; [redacted], S.; 2010; M-393034-01-1
Title:	Measurement of drift deposition of seed treatment particles in the off-crop abraded from Thiacloprid FS 400 treated maize seeds, emitted during sowing with a vacuum-pneumatic machine
Report No.:	NNP-DUST-04
Document No.:	M-393034-01-1
Guideline(s):	Special designed study protocol, considering recommendations of the BBA Drift Guideline Part VII, 2-1.1, 1992
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods:

Test item: Commercial maize seeds (Variety Ronaldinio, purchased from KWS Mais GmbH, Grimsehlstr. 31, D-37574 Einbeck, Germany) were treated with the seed treatment formulation Thiacloprid FS 400 (TOX-No. TOX09093-00), nominally 50 g thiacloprid/Unit, together with Thiram (TMTD) SC 700 at a rate of 43 mL/Unit, the film-coating product Imprанil DLN W 50 at 15 mL/Unit and Talcum Gloss powder at 30 g/Unit (1 Unit = 50,000 seeds). The seed treatment operation was performed in the commercial seed treatment plant of [redacted] GmbH (D-[redacted], Germany). A total of 12 Units were treated with a commercial Satec Twin 50 batch treater. The analyzed content of thiacloprid on the treated seeds was 51.44 g as/Unit (TOX-No. TOX09167-00).

The aim of the study was to quantify the drift of seed treatment dust and its deposit in the off-crop area (g as/ha) using passive collectors downwind from the drilled area during and after sowing of Thiacloprid FS 400 treated maize seeds with a vacuum-pneumatic sowing machine.

The sowing machine used was a vacuum-pneumatic Kverneland, Accord Optima HD with a deflection system at ground level into outer manuring blades. Working width of the machine was 4.5 m. The dressed maize seeds were stored in bags, each containing one single Unit (= 50,000 seeds). The Heubach dust abrasion test indicated under the standardised laboratory test conditions a dust abrasion value of 0.04 g dust/100,000 seeds eight days after seed treatment and 0.07 g dust/100,000 seeds on the day after drilling.

Before drilling, the hoppers of the sowing machine were filled on the yard in front of the machine-hall of Bayer CropScience's Application Technology Unit, Building 5912, D-40789 Monheim, approximately 2.5 km away from the trial site (access to the trial site was via paved roads and field paths). For the drift experiment, each hopper of the sowing machine was filled with one complete seed bag. Particular care was taken to transfer the entire content of each seed bag into the hopper, including any dust from transport-related seed treatment abrasion.

The size of the drilling plot was 1.08 ha (200 m x 54 m). The actual drilling rate was 102.44 g as thiacloprid/ha. An average wind speed of 2.2 m/s and a mean deviation from the wind direction perpendicular to the edge of the sowing area of 2.6° were the conditions during sowing and the following waiting period of 30 minutes.

The sampling systems were installed prior to the drilling procedure at distinct locations along the downwind long edge of the drilling area (base line). The distance to the first row of maize seeds (zeroline) was 3 m. Petri dishes of two different sampling types were placed in metal placeholders on the soil surface and filled with either a glycerol/water mixture (1/1, v/v) or quartz sand moistened with glycerol/water mixture (1/1, v/v). Gauze netting was installed to a construction fence (2 m high and 5 m wide) and wetted with a glycerol/water mixture (1/1, v/v) to enhance dust adhesion.

Sowing started at the zero-line. After drilling of 12 rows in alternating directions, there was a subsequent waiting period of 30 minutes to allow the settlement of all dust particles which had been dispersed during drilling. The uniquely labelled Petri dishes that contained the quartz sand were closed with their lids directly after the waiting period and were transported to the laboratory. There, the content was transferred into uniquely labelled polyethylene container. All other passive collectors were transferred in uniquely labelled polyethylene container on the field starting after expiration of the waiting period of 30 minutes.

From all collected dust samples thiacloprid was extracted and analysed. Further details concerning the analysis are documented in the GLP study report. All the samples (exception soil) were extracted in the original containers. Procedural fortification at adequate levels was processed concurrently with sample analysis for recoveries.

Findings:
The residue findings in the Petri dishes pre-filled with glycerol/water were between <LOD (< 0.0014 g a.s./ha) and 0.052 g a.s./ha. The mean value was below the LOQ (< 0.014 g a.s./ha) and the 90th-%tile value was 0.022 g a.s./ha.

The thiacloprid residues in the Petri dishes prepared with moistened quartz sand were between <LOQ (< 0.014 g a.s./ha) and 0.110 g a.s./ha. The mean values of this samples was 0.019 g a.s./ha and the 90th-%tile was 0.034 g a.s./ha. Relating the 90th-percentile of the ground deposition to the application rate in the field results in a drift rate of 0.033%.

The residue findings in the gauze netting ranged from 0.082 g a.s./ha to 0.162 g a.s./ha, with a mean value of 0.121 g a.s./ha and a 90th-%tile value of 0.155 g a.s./ha. Relating the 90th-%tile value to the actual application rate results in an aerial drift rate of 0.151%.

The higher of the dust deposition values (measured in Petri dishes pre-filled with moistened quartz sand) are presented in the table below.

Table 7.2.2.2-1: Summary of dust deposition during sowing of maize treated with Sonido FS 400 (collectors: Petri dishes pre-filled with moistened quartz sand)

Study	Measured **(corrected for dose rate)** [g a.s./ha]	
	[redacted], P. and [redacted] S. (2010)	
	2-D deposits (Petri dishes)	3-D deposits (gauze nettings)
Mean	0.0194 **(0.0209)**	0.1207 **(0.1296)**
75th perc.	0.0220 **(0.0236)**	0.1390 **(0.1493)**

Parametric 75th perc.	0.0240 **(0.0257)**	0.1397 **(0.1500)**
95th perc.	0.0376 **(0.0403)**	0.1585 **(0.1702)**
Parametric 95th perc.	0.0505 **(0.0543)**	0.1821 **(0.1955)**
Maximum	0.1100 **(0.1181)**	0.1620 **(0.1740)**

Discussion and conclusion:
The results indicate that dust drift (ground deposition and aerial drift) from maize seeds treated with Sonido FS 400 was low. The maximum value of the 90th-%tile for ground deposition was 0.033% and the 90th-%tile for aerial drift was 0.151%.

Report: KCP 7.2.2.2/02 [redacted].; 2012; M-426528-01-1
Title: Thiacloprid FS 400 - Investigating the dust deposition during sowing of thiacloprid FS 400 treated maize seeds with modified (deflected) vacuumpneumatic sowing machinery
Report No.: S10-03080
Document No.: M-426528-01-1
Guideline(s): Working document 1607/VI/97 rev. 1 with the part integration of the BBA Drift Guideline Part VII, 2-1.1 (1992)
Guideline deviation(s): none
GLP/GEP: yes

Material and methods
Test item: Thiacloprid FS 400

Analyzed content of active ingredient: 50.29 g a.i./50000 seeds

Active ingredients: thiacloprid

Batch: 2010-006680

The field study was conducted in Germany during autumn 2010. The purpose of the study was to establish the drift pattern of dust emitted from a vacuum-pneumatic drilling machine (Gaspardo MTE) with deflector technique during sowing of Thiacloprid FS 400 treated maize seed.

The plot size was 200 m x 54 m and was drilled with maize with downwind collection of emitted dust. Thirty Petri dishes filled with glycerol/water (1/1, v/v) and 30 Petri dishes with sand wetted with glycerol/water (1/1, v/v) were placed at 3 m distance from the zero line (first driller row + ½ row) spacing together with three gauze netting of 5 m length and 2 m height. Petri dishes were placed horizontally on the ground. The gauze netting was attached to mobile building fences. The minimum distance between fence and the closest row of Petri dishes was 13 m. Both the gauze and the rows of Petri dishes were oriented parallel to the driving directions of sowing.

Soil samples from the upper 10 cm were taken for soil characterization and for residue analysis. Soil samples from the upper 5 cm were taken for the determination of the water content.

Petri dishes and gauze netting samples respective samples were analysed for the residues of thiacloprid. Soil samples were not analysed for residues.

The study was conducted following the working document 1607/VI/97 rev. 1 with the part integration of the BBA Drift Guideline Part VII, 2-1.1 (1992).

Findings

Maize, pre-treated with Thiacloprid FS 400 (provided by Bayer CropScience), was sown in the vicinity of [redacted] (Baden-Württemberg) on 11 October 2010. The plot size was 200 m x 54 m.

The dust from the mechanical abrasion of the dressed seed item which emitted during seeding with a modified (deflected) vacuum-pneumatic drilling machine was collected using Petri dishes and gauze netting. The drilling rate was 93340 seeds/ha. A total area of 1.08 ha was drilled. This drilling rate of treated seeds was equivalent to an actual application rate of 93.88 g a.i./ha.

The average wind speed during drilling was 3.87 ± 0.60 m/s (1.69 m/s to 6.69 m/s) and the average deviation to the intended wind direction was -26.47° ± 8.53°.

Residues were found in all Petri dishes filled with a glycerol/water mixture with an overall average of 0.016 ± 0.023 g a.i./ha. The average amount of thiacloprid over the three areas was 0.017 % of the actual field application rate. The 90th percentile (0.021 g a.i./ha) was equivalent to 0.022 % of the actual field application rate.

In Petri dishes filled with a glycerol/water/sand mixture, only 10 of the 30 Petri dishes contained residues above the LOD (0.004 g a.i./ha). Seven out of 10 residue values were below the LOQ (0.014 g a.i./ha). The average amount of thiacloprid over all three areas was 0.025 g a.i./ha which is equivalent to 0.026 % of the actual field rate. This value was heavily influenced by one extreme value which was by a factor of more than 10 above the next lower value. Excluding this extreme value from the evaluation would lower the mean value from 0.025 g a.i./ha to 0.006 g a.i./ha.

The 90th percentile (0.016 g a.i./ha) was equivalent to 0.017 % of the actual field application rate.

For Gauze the highest amount of thiacloprid was 0.022 g a.i./ha. The mean amount over the three areas was 0.014 ± 0.003 g a.i./ha. The 90th percentile (0.016 g a.i./ha) was equivalent to 0.017 % of the actual field application rate.

Conclusion

The drilling of Thiacloprid FS 400 treated maize on a 1.08 ha field resulted in dust containing residues of thiacloprid. The average amount of residues was 0.017 % of the actual field rate for the glycerol/water and 0.026 % of the actual field rate for the glycerol/water/sand mixture. The 90th percentile for the residues in gauze netting was equivalent to 0.017 % of the actual field application rate.

<u>Risk assessment for residents and bystanders</u>

Resident and bystander exposure during sowing maize grain treated with Sonido FS 400 is estimated based on the results of the experimentally determined 2- and 3-dimensional dust drift when using pneumatic drilling equipment with deflector technique. The higher values of the first study are taken for the risk assessment. The dose rate in the first study was 102.44 g a.s./ha. Therefore, the drift values are adjusted for a maximum of 110 g a.s./ha according to the critical GAP.

For the calculation of individual route exposures, the higher of the empirical or the parametric estimates is taken. Where the parametric estimate exceeds the maximum value the latter is taken for risk assessment. The total resident exposure considering all pathways is based on the mean value. A summary is presented in the following table.

Table 7.2.2.2-1: Selection of dust drift deposition values

	Measured dust deposition (corrected for dose rate)	
	2D deposits (surface deposits)	3D deposits (dust drift)
	[g a.s./ha]	[g a.s./ha]
Mean	0.0209	0.1296
75th percentile	0.0236	0.1493
Parametric 75th perc.	0.0257	0.1500
95th percentile	0.0403	0.1702
Parametric 95th perc.	0.0543	0.1956
Maximum	0.1181	0.1740

* source: [redacted] and [redacted] (2010)

The following pathways are considered for risk assessment:

- dust drift (at the time of sowing)
- vapour (after the PPP has been applied) – not relevant as treated seed is buried into soil and a.s. is non-volatile
- surface deposits
- entry into treated crops – not relevant as no DFR expected after sowing

As suggested in the EFSA guidance the individual route exposure scenarios for residents are calculated with the parametric 75th percentile values (both for dust drift and surface deposits) and the total exposure over all pathways is calculated using the mean values.

The individual route exposure scenarios for the bystanders are calculated with the maximum 3D value for dust drift and the parametric 95th perc. 2D value for surface deposits.

Resident exposure

1. Dust drift (at the time of sowing)

Dermal exposure

Dermal exposure of adult and child residents is calculated using the experimental three dimensional (3D) dust deposition values (parametric 75th percentile 0.1500 g a.s./ha equivalent to 0.0150 mg a.s./m^2 for individual route exposure and mean 0.1296 g a.s./ha equivalent to 0.0130 mg a.s./m^2 for all pathways) on child/adult body surface of 4800 cm^2 (child) and 16370 cm^2 (adult) and adjustment for light clothing (EFSA Guidance, reduction of 18%).

Inhalation exposure

Guidance to calculate inhalation exposure from dust drift deposition is not available. Therefore, an expert judgment is made in the following.

Inhalation exposure is calculated based on air concentration and breathing rate.

Air concentration:

The concentration of the a.s. in the air during the experimental study is determined assuming that the total amount measured in the gauze netting (3D deposition) was deposited during a single pass. The deposition was measured with 12 sowing passes for duration of 30 minutes of drilling of about 1ha (each single pass 2.5 min.). The calculation of inhalation exposure from dust drift is aligned with the BREAM approach in which it was observed that the majority of spray drift occurred following the first pass of the sprayer and therefore the exposure values used for the resident assessment was based on the 75th percentile value from a single pass (and therefore the volume of air inhaled during a single pass). The concentration is furthermore determined by the air volume that has passed during the exposure time of 2.5 min (single pass). The average wind speed in the study was 2.2 m/sec. Therefore, the total deposited amount (0.0150 mg a.s./m^2, 75th perc. and 0.0130 mg a.s./m^2, mean) was deposited from an air volume of 330 m^3 (150 x 2.2) passing one square meter deposition area. The concentration of thiacloprid in the air was therefore

- 0.0000454 mg a.s./m^3 (75th perc. 0.0150 mg a.s./330 m^3) and
- 0.0000393 mg a.s./m^3 (mean, 0.0130 mg a.s./330 m^3).

Breathing rate:

Based on the daily resident inhalation rates of 1.07 m^3/day/kg for a child and 0.23 m^3/day/kg for an adult the respiration volumes during the exposure period of 2.5 min are

- Child: 0.0019 m^3/kg (1.07 m^3/day/kg : 24h : 60 min. x 2.5 min)
- Adult: 0.0004 m^3/kg (0.23 m3/day/kg : 24h : 60 min. x 2.5 min).

Dermal and inhalation exposure of residents is calculated as follows.

Child	Adult
Parametric 75th perc.:	Parametric 75th perc.:
SE = (3D x SA_{CH} x (100%-AF)) x DA) /BW_{Ch} + C x BR_{Ch}	SE = (3D x SA_A x (100%-AF)) x DA)/BW_A+ C x BR_A

= (0.0150 x 0.48 x (100%-18%) x 0.2%)/10 + 0.0000454 x 0.0019 = 1.1×10^{-6} + 8.6×10^{-8} mg/kg bw/day = 1.186×10^{-6} mg/kg bw/day	= (0.0150 x 1.637 x (100%-18%) x 0.2%)/60 + 0.0000454 x 0.0004 = 6×10^{-7} + 1.8×10^{-9} = 6.02×10^{-7} mg/kg bw/day
Mean: $SE = (3D \times SA_{CH} \times (100\%-AF) \times DA)/BW_{Ch} + C \times BR_{Ch}$ = (0.0130 x 0.48 x (100%-18%) x 0.2%)/10 + 0.000 039 3 x 0.0019 = 0.000 001 020 + 0.000 000 075 mg/kg bw/day = 1.10×10^{-6} mg/kg bw/day	Mean: $SE = (3D \times SA_{A} \times (100\%-AF) \times DA)/BW_{A} + C \times BR_{A}$ = (0.0130 x 1.637 x (100%-18%) x 0.2%)/60 + 0.0000393 x 0.0004 = 5.8×10^{-7} + 1.6×10^{-9} mg/kg bw/day = 5.82×10^{-7} mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
3-D	*= 3-D dust deposition [mg a.s./m²]*
$SA_{CH/A}$	*= Surface area – Child/Adult [m²]*
AF	*= Light clothing adjustment factor [%]*
C	*= Concentration of a.s. in air [mg/m³]*
BR	*= Breathing rate [m³/kg]*
DA	*= Dermal absorption [%]*
$BW_{Ch/A}$	*= Body weight – Child/Adult [kg/person]*

2. Vapour (after the PPP has been applied)

The vapour pressure of thiacloprid is 3×10^{-10} Pa at 20°C. Therefore, thiacloprid is practically non-volatile. The treated maize grain is also buried in the soil. Exposure via vapour is therefore not expected after sowing.

3. Surface deposits

Exposure from surface deposits is calculated based on the experimentally determined ground dust drift deposition (2D: 0.0257 g a.s./ha, 75th perc., and 0.0209 g a.s./ha, mean). Deposition is estimated for a 3 m distance from field edge of the sowing area. The evaluation is performed for sowing equipment classified as pneumatic suction drillers equipped with deflectors.

Exposure of adult and child bystander/residents is calculated as the sum of the exposure via the dermal, hand-to-mouth and object to mouth routes.

- Dermal

Child	Adult
Parametric 75th perc.: $SE = (GD \times TTR \times TTC_{Ch} \times D \times DA)/BW_{Ch}$	Parametric 75th perc.: $SE = (GD \times TTR \times TTC_{A} \times D \times DA)/ BW_{A}$

= (0.000 000 26 x 5% x 5200 x 2 x 0.2%)/10	= (0.000 000 26 x 5% x 14500 x 2 x 0.2%)/60
= 0.000 000 027 mg/kg bw/day	= 0.000 000 013 mg/kg bw/day
Mean:	Mean:
$SE = (GD \times TTR \times TTC_{Ch} \times D \times DA)/BW_{Ch}$	$SE = (GD \times TTR \times TTC_{A} \times D \times DA)/BW_{A}$
= (0.000 000 21 x 5% x 5200 x 2 x 0.2%)/10	= (0.000 000 21 x 5% x 14500 x 2 x 0.2%)/60
= 0.000 000 022 mg/kg bw/day	= 0.000 000 010 mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
TTR	*= Turf Transferable Residue [%]*
$TTC_{Ch/A}$	*= Transfer coefficient of surface deposits – Child (1-3 year old)/Adult [cm²/hour]*
D	*= Exposure duration [hours]*
DA	*= Dermal absorption [%]*
$BW_{Ch/A}$	*= Body weight – Child/Adult [kg/person]*

- Hand-to-mouth:

Child
Parametric 75th perc.:
$SE = (GD \times TTR \times SE \times SA \times Freq \times D \times OA)/BW_{Ch}$
= (0.000 000 26 x 5% x 50% x 20 x 20 x 2 x 100%)/10
= 0.000 000 540 mg/kg bw/day
Mean:
$SE = (GD \times TTR \times SE \times SA \times Freq \times D \times OA)/BW_{Ch}$
= (0.000 000 21 x 5% x 50% x 20 x 20 x 2 x 100%)/10
= 0.000 000 420 mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
TTR	*= Turf Transferable Residue [%]*
SE	*= Saliva Extraction Factor (%)*
SA	*= Surface Area of Hands (cm²)*
Freq	*= Frequency of Hand-to-Mouth (events/hour)*
D	*= Exposure Duration (hours)*
OA	*= Oral Absorption (%)*
BW	*= Body Weight (kg/person)*

- Object-to-mouth:

Child
Parametric 75th perc.:
SE = (GD x DFR x IgR x OA)/BW_{Ch}
= (0.000 000 26 x 20% x 25 x 100%)/10
= 0.000 000 130 mg/kg bw/day
Mean:
SE = (GD x DFR x IgR x OA)/BW_{Ch}
= (0.000 000 21 x 20% x 25 x 100%)/10
= 0.000 000 110 mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
DFR	*= Dislodgeable Foliar Residues (%)*
IgR	*= Ingestion Rate for Mouthing of Grass/Day (cm²)*
OA	*= Oral Absorption (%)*
BW	*= Body Weight (kg/person)*

- Total systemic exposure from surface deposits

Child	Adult
Parametric 75th perc.:	Parametric 75th perc.:
SE = 0.000 000 027 + 0.000 000 540 + 0.000 000 130	SE = 0.000 000 013 mg/kg bw/day
= 0.000 000 697 mg/kg bw/day	
Mean:	Mean:
SE = 0.000 000 022 + 0.000 000 420 + 0.000 000 110	SE = 0.000 000 010 mg/kg bw/day
= 0.000 000 552 mg/kg bw/day	

4. Entry into treated crops

Thiacloprid FS 400 is only used as a seed treatment product in maize. Dislodgeable foliar residues on maize leaves will not be available. A re-entry scenario therefore does not exist.

Bystander exposure

1. Dust drift (at the time of sowing)

Dermal exposure

Dermal exposure of adult and child bystander is calculated using the experimental three dimensional (3D) dust deposition value (maximum value 0.1740 g a.s./ha equivalent to 0.0174 mg a.s./m^2) on child/adult body surface of 4800 cm^2 (child) and 16370 cm^2 (adult) and adjustment for light clothing (EFSA Guidance, reduction of 18%).

Inhalation exposure

Guidance to calculate inhalation exposure from dust drift deposition is not available. Therefore, an expert judgment is made in the following.

Inhalation exposure is calculated based on air concentration and breathing rate.

Air concentration:

The concentration of the a.s. in the air during the experimental study is determined assuming that the total amount measured in the gauze netting (3D deposition) was deposited during a single pass. The deposition was measured with 12 sowing passes for duration of 30 minutes of drilling of about 1 ha (each single pass 2.5 min). The calculation of inhalation exposure from dust drift is aligned with the BREAM approach in which it was observed that the majority of spray drift occurred following the first pass of the sprayer and therefore the exposure values used for the bystander assessment is based on the 95th percentile value from a single pass (and therefore the volume of air inhaled during a single pass). The concentration is furthermore determined by the air volume that has passed during the exposure time of 2.5 min (single pass). The average wind speed in the study was 2.2 m/sec. Therefore, the total deposited amount (maximum value 0.0174 mg a.s./m^2) was deposited from an air volume of 330 m^3 (150 x 2.2) passing one square meter deposition area. The concentration of thiacloprid in the air was therefore

- 0.0000527 mg a.s./m^3 (maximum value 0.0174 mg a.s./330 m^3)

Breathing rate:

Based on the daily bystander inhalation rates of 0.19 m^3/h/kg for a child and 0.04 m^3/h/kg for an adult the respiration volumes during the exposure period of 2.5 min are

- Child: 0.0079 m^3/kg (0.19 m^3/h/kg : 60 min. x 2.5 min)
- Adult: 0.0017 m^3/kg (0.04 m^3/day/kg : 60 min. x 2.5 min).

Dermal and inhalation exposure of residents from dust drift is calculated as follows.

Child	Adult
Parametric 75th perc.:	Parametric ^{75th} perc.:
SE = (3D x SA_{CH} x (100%-AF))xDA)/BW_{Ch} + C x BR_{Ch}	SE = (3D x SA_A x (100%-AF)) x DA)/BW_A+ C x BR_A
= (0.0174 x 0.48 x (100%-18%) x 0.2%)/10 +	= (0.0174 x 1.637 x (100%-18%) x 0.2%)/60 +
0.0000527 x 0.0079	0.0000527 x 0.0017
= 13.6 x 10^{-7} + 4.16 x 10^{-7}	= 7.7 x 10^{-7} + 0.89 x 10^{-7}
= 17.76 x 10^{-7} mg/kg bw/day	= 8.59 x 10^{-7} mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
3-D	*= 3-D dust deposition [mg a.s./m²]*
$SA_{CH/A}$	*= Surface area – Child/Adult [m²]*
AF	*= Light clothing adjustment factor [%]*
C	*= Concentration of a.s. in air [mg/m³]*
BR	*= Breathing rate [m³/kg]*
DA	*= Dermal absorption [%]*
$BW_{Ch/A}$	*= Body weight – Child/Adult [kg/person]*

2. Vapour (after the PPP has been applied)

The vapour pressure of thiacloprid is 3×10^{-10} Pa at 20°C. Therefore, thiacloprid is practically non-volatile. The treated maize grain is buried in the soil. Exposure via vapour is therefore not expected after sowing.

3. Surface deposits

Exposure from surface deposits is calculated based on the ground dust drift deposition (2D: 0.0543 g a.s./ha, parametric 95th perc. equivalent to 0.000005 4 mg a.s./cm²). Deposition is estimated for a 3 m distance from field edge of the sowing area. The evaluation is performed for sowing equipment classified as pneumatic suction drillers equipped with deflectors.

Exposure of adult and child bystander/residents is calculated as the sum of the exposure via the dermal, hand-to-mouth and object to mouth routes.

- Dermal:

Child	Adult
Parametric 95th perc.:	Parametric 95th perc.:
$SE = (GD \times TTR \times TTC_{Ch} \times D \times DA)/BW_{Ch}$	$SE = (GD \times TTR \times TTC_{A} \times D \times DA)/ BW_{A}$
$= (0.000\,000\,54 \times 5\% \times 5200 \times 2 \times 0.2\%)/10$	$= (0.000\,000\,54 \times 5\% \times 14500 \times 2 \times 0.2\%)/60$
$= 0.56 \times 10^{-7}$ mg/kg bw/day	$= 0.26 \times 10^{-7}$ mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
TTR	*= Turf Transferable Residue [%]*
$TTC_{Ch/A}$	*= Transfer coefficient of surface deposits – Child (1-3 year old)/Adult [cm²/hour]*
D	*= Exposure duration [hours]*
DA	*= Dermal absorption [%]*
$BW_{Ch/A}$	*= Body weight – Child/Adult [kg/person]*

- Hand-to-mouth:

Child

Parametric 95th perc.:
SE = (GD x TTR x SE x SA x Freq x D x OA)/BW_{Ch}
= (0.000 000 54 x 5% x 50% x 20 x 20 x 2 x 100%)/10
= 10.8 x 10^{-7} mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
TTR	*= Turf Transferable Residue [%]*
SE	*= Saliva Extraction Factor (%)*
SA	*= Surface Area of Hands (cm²)*
Freq	*= Frequency of Hand-to-Mouth (events/hour)*
D	*= Exposure Duration (hours)*
OA	*= Oral Absorption (%)*
BW	*= Body Weight (kg/person)*

- Object-to-mouth:

Child
Parametric 95th perc.:
SE = (GD x DFR x IgR x OA)/BW_{Ch}
= (0.000 000 54 x 20% x 25 x 100%)/10
= 2.7 x 10^{-7} mg/kg bw/day

Where:

SE	*= Systemic exposure [mg/kg bw/day]*
GD	*= Dust ground deposition [mg a.s./cm²]*
DFR	*= Dislodgeable Foliar Residues (%)*
IgR	*= Ingestion Rate for Mouthing of Grass/Day (cm²)*
OA	*= Oral Absorption (%)*
BW	*= Body Weight (kg/person)*

- Total systemic exposure from surface deposits

Child	Adult
Parametric 95th perc.:	Parametric 95th perc.:
SE = (0.56 + 10.8 + 2.7) x 10^{-7}	SE = 0.26 x 10^{-7} mg/kg bw/day
= 14.06 x 10^{-7} mg/kg bw/day	

4. Entry into treated crops

Thiacloprid FS 400 is only used as a seed treatment product in maize. Dislodgeable foliar residues on maize leaves will not be available. A re-entry scenario therefore does not exist.

CP 7.2.3 Worker exposure

The loading and sowing of treated maize grain may be considered as relevant for worker exposure. This exposure was measured in an experimental seed sowing study. Outcome of the risk assessment is presented in the operator evaluation KCP 7.2.1.

Re-entry into maize fields that are grown from treated seeds will not result in exposure to thiacloprid because no dislodgeable foliar residue will be available after sowing of the treated maize seed. Therefore, a re-entry scenario does not exist and it is reasonable to assume that there will be no undue risk for workers.

CP 7.2.3.1 Estimation of worker exposure

Not necessary.

CP 7.2.3.2 Measurement of worker exposure

Not necessary.

Overall conclusions on non-dietary exposure

BCS has made considerable progress on dust reduction and thus on non-dietary exposure to active substances in the seed treatment formulations. For thiacloprid in the Sonido FS 400 formulation, stewardship measures such as optimisation of formulation, use of deflectors in drilling equipment, certification schemes for seed treatment facilities have already been implemented.

In the area of Formulations & Coatings:

> BCS have screened various components for replacing ingredients from today's seed treatment formulations and film-coatings, leading to lower dust abrasion (measured with Heubach test). Combinations of wetting agents, polymers, dispersants, oils and surfactants have shown great dust reduction properties.
>
> By measuring physico-chemical properties, such as surface tension of the seed surface, improvements were achieved to increase the seed coverage and the adherence of the treatment product on the seed.

New technologies/procedures are under development to further minimize the formation of dust.

During seed treatment:

- drying during the treatment,
- sequential coating (to first apply formulation with the active ingredient, then shortly afterwards the film-coating),
- increased film-coating rates, and
- drying and/or air cleaning of seeds after treatment

> BCS have developed technologies to measure the optimal point in time when to stop the treatment process, in order to avoid too long treatment times which lead to more dust originating from the treated seeds.

During seed sowing:

Machines for corn planting in Europe often use a vacuum-fan in order to plant seeds individually. BCS have developed two technologies that reduce the unwanted dust release to the environment with the exhaust air.

- BCS have invented a cyclone that cleans the air from dust particles, in combination with burying the separated dust in the ground (so-called SweepAir technology).
- With the AirWasher technology a water atomizer is placed close to the air release of the vacuum-fan (the so-called deflector) so that small water droplets can capture dust particles.

It has been demonstrated that exposure to thiacloprid established by the already implemented stewardship/mitigation measures both during seed treatment and during seed sowing is already very low and considered to be negligible.

The current projects under development will further contribute to the minimization of exposure as far as technically possible.

CP 7.3 Dermal adsorption

The extent of dermal absorption of thiacloprid formulated as an FS 400 formulation has been investigated in an *in vitro* comparative study using human and rat skin and an *in vivo* rat study. A summary of the studies is given in the following section along with a conclusion and recommendation regarding the dermal absorption of thiacloprid formulated as an FS 400.

The results from the *in vivo* rat study provided dermal absorption values for thiacloprid FS 400 of **1%** for the neat formulation (400 g/L) and **2%** for the representative dilution of 100 g/L.

The human/rat comparative *in vitro* study indicated that the mean percentage of [^{14}C]-thiacloprid considered to be absorbable over a period of 24 hours for the neat formulation was **0.1%** and **1%** for the human and rat skin, respectively. The mean percentage of [^{14}C]-thiacloprid considered to be potentially absorbable at the low dose was **0.1%** and **1%** for the human and rat skin respectively.

Taking a so-called triple pack approach to estimate the human *in vivo* dermal values we get:

Test material	Rat *in vivo* dermal absorption	Human *in vitro* dermal absorption	Rat *in vitro* dermal absorption	Ratio/factor between man and rat *in vitro*	Estimated human *in vivo* dermal absorption
Neat formulation	1%	0.1%	1%	0.1	0.1%
Spray dilution	2%	0.1%	1%	0.1	0.2%

Hence the human *in vivo* dermal absorption values that can be used for exposure assessments are:

- 0.1% for the neat formulation (400 g/L)
- 0.2% for the low dose (100 g/L).

Report:	[redacted]g; [redacted]; 2012; M-428935-01-1
Title:	Thiacloprid FS 400: [14C]-thiacloprid - In vivo dermal absorption study in the male rat
Report No.:	SA 11108
Document No.:	M-428935-01-1
Guidelines:	**OECD Guideline for the Testing of Chemicals, 427: Skin Absorption: In Vivo Method for the conduct of skin absorption studies and associated Draft Guidance Documents, (April 2004).** **OECD Environmental Health and Safety Publications Series on testing and Assessment N° 28. Guidance Document for the Conduct of Skin Absorption Studies (March 2004)** **European Commission Guidance Document on Dermal Absorption- Sanco/222/2000 rev. 7,** **(March 2004); not specified**
GLP/GEP:	**yes**

Material and Methods:

Rat:

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

Source: [redacted], France

Sex: Male

Body weights: 247 to 369 g.

Age: 7 to 9 weeks old.

Acclimatisation & Housing: Test animals were acclimatized in the room to be used for the experiment for six days prior to the starting day. The cages were suspended, stainless steel and wire mesh. Test animals were acclimatized in the room and in the metabolism cage to be used for the experiment 24 hours prior applications. The cages were either Jencon's metabowls Mk III or Radleys.

Animal identification: Ear tags.

Environmental conditions:

Temperature:	22 ± 2°C
Humidity:	55 ± 15%
Air changes	10-15 per hour
Photoperiod:	12 hour light/dark cycles (7am – 7pm)

Food: Certified rodent pelleted and irradiated diet A04C-10 (from [redacted], France), *ad libitum.* Feed was stored in an identified room controlled for temperature and humidity. Diet was used only until the date of expiry.

Water: Filtered and softened tap water from the municipal water supply, *ad libitum*. Routine analyses of feed and water indicated that there was no contamination which could have compromised the study. Certificates of water analysis were

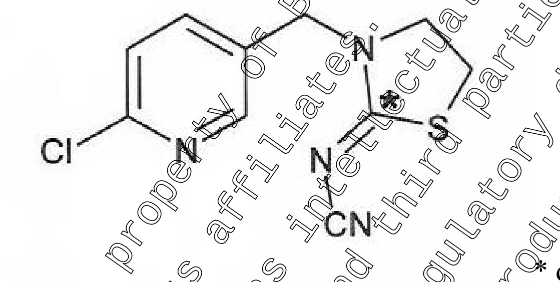
provided by the "Laboratoire de l'Environnement Nice Côte d'Azur" (France) and "Institut Scientifique d'Hygiène et d'Analyse" (Longjumeau, France).

Test Material:

Non-radiolabelled: Batch: KATH4852-1-3.
Purity = 99.0% w/w.

Radiolabelled: [thiazolidine-2-^{14}C]-thiacloprid
Batch: KATH 6747.
Specific activity: 4.12 MBq/mg.
Radiopurity of the formulation: >99%.

Structural formula:



* denotes position of radiolabel

Formulation: The formulation used in this experiment was the thiacloprid FS 400 formulation (specification number 102000022825 01) used at two nominal concentrations: 400 and 100 g thiacloprid/L.

Treatment: An area of dorsal skin was shaved approximately 24 hours prior to dosing. Just prior to dosing the animals were lightly anaesthetized and two plastic protective saddles were secured in place using Cyanoacrylate adhesive to define the site for application of the test substance (approximately ≈ 2 x 6 cm^2). Approximately 120 µL (2 x 60 µL) of each dose formulation was applied to the shaved area. This amount of formulation corresponded to approximately 450 kBq/rat for the high dose formulation and 496 kBq/rat for the low dose formulation, according the nominal concentrations of radioactivity in the formulations. When dose application was complete, the skin was semi-occluded with a perforated plastic cover (to allow ventilation) held in place over the plastic saddle with surgical tape (approximately 3 x 4 cm). The cover prevented loss of test substance but permitted air circulation over the application site. The cover was not in direct contact with the test material on the skin. Immediately after dose application the rats were housed individually in metabolism cages.

Treatment Groups There were 4 treatment groups per dose level.
Groups 1 to 4 were treated at the rate of 400 g/L and sacrificed at 8, 24, 72 and 168 hours post application.
Groups 5 to 8 were treated at the rate of 100 g/L and sacrificed at 8, 24, 72 and 168 hours post application.

Sampling: After the 8-hour exposure time, the filter paper cover was removed. The cover and application site were then swabbed with freshly prepared 2% v/v soap solution using a gauze pad followed by a gauze pad moistened with water and a dry gauze pad. The swabs were retained for analysis. Animals that were

required to provide samples beyond 8 hours were then fitted with a clean cover to capture any radioactivity lost by desquamation and replaced in the metabolism cage.

Urine and faeces were collected separately into receivers at 0 to 8, 8 to 24 and at 24-hour intervals up to sacrifice. At the end of each collection period all debris was removed from the metabolism cage and retained. At each sampling, the cage was carefully washed with distilled water. At termination each cage was washed with water and appropriate organic solvent. These washings were retained for measurement of radioactivity.

At termination, the rats were exsanguinated whilst under "Isoflurane" anaesthesia and a blood sample was withdrawn by cardiac puncture and placed into vials containing lithium heparin.
The treated skin was swabbed following sacrifice prior to removal. The skin was then shaved (shavings retained), if necessary, prior to tape-stripping to remove the stratum corneum. This procedure involved the application of an adhesive tape (CILS, France) for 5 seconds before the tape was carefully removed against the direction of hair growth. This process was continued until a ‘shiny’ appearance of the epidermis was evident, indicating that the stratum corneum had been removed.

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

Findings:
There were no treatment related clinical signs observed during the study. After a single topical application of the [^{14}C]-thiacloprid at 400 g/L, the mean total recoveries of radioactivity were 101.6%, 99.6%, 101.8% and 99.4% for the 8, 24, 72 and 168 hour groups respectively.

After a single topical application of the [^{14}C]-thiacloprid at 100 g/L, the mean total recoveries of radioactivity were 102.0%, 102.5%, 102.5% and 100.6% for the 8, 24, 72 and 168 hour groups respectively.

The results are presented in Tables 7.6.1-1. to 7.6.1-2.

Table 7.3-1.: The mean distribution of radioactivity 8, 24, 72 and 168 hours after a single topical application of [^{14}C]-thiacloprid from a 400 g/L FS 400 formulation

Dose Group 400 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	8		24		72		168	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8 hr & terminal)	99.34	1.56	95.11	1.10	99.57	1.40	94.04	2.43
Surface dose (tape strips 1 & 2)	0.15	0.06	0.20	0.04	0.10	0.02	0.30	0.13
Fur	n.s.	n.s.	0.04	0.07	n.s.	n.s.	1.24	0.41
Dressings	0.07	0.07	1.07	0.88	0.55	0.15	1.65	0.92
Total % non-absorbed	99.56	1.56	97.04	0.63	100.87	1.23	97.73	0.66
SKIN COMPARTMENT								
Stratum corneum [a]	0.65	0.48	1.28	0.630	0.19	0.06	0.42	0.24
Treated skin [b]	0.50	0.28	0.53	0.31	0.09	0.08	0.26	0.10
Surrounding skin [c]	0.29	0.17	0.50	0.48	0.20	0.14	0.50	0.55
Total % at dose site	1.44	0.70	2.32	0.68	0.48	0.21	1.18	0.59
SYSTEMIC COMPARTMENT								
Urine	0.01	0.00	0.02	0.00	0.03	0.01	0.11	0.03
Faeces	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cage wash	n.d.	n.d.	n.d.	n.d.	0.01	0.01	0.02	0.02
Cardiac blood	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Non-treated skin	0.23	0.10	0.06	0.01	0.12	0.07	0.10	0.01
Carcass	0.36	0.11	0.16	0.01	0.28	0.06	0.20	0.03
Total % directly absorbed	0.60	0.15	0.24	0.01	0.43	0.07	0.44	0.04
Total Recovered	101.6	1.01	99.60	0.46	101.8	1.34	99.35	0.94

[a] = tape strips excluding surface dose strips 1 & 2, [b] = skin at dose site after tape-stripping procedure, [c] = skin immediately outside the dose application area, SD = standard deviation, n.d. = not detected, less than limit of quantification, n.a. = not applicable, n.s. = no sample.

At both treatments levels, the majority of the radioactivity was not absorbed and was recovered from the skin by swabbing. This mean proportion of the applied dose considered to be non-absorbed was relatively similar for groups exposed the high and low dose formulations (from 97.73% to 100.9% for the high dose formulation and from 97.31% to 100.4% for the low dose formulation).

Percentage recoveries measured in the surface dose (tape-strips 1 and 2) were low and stable for the high dose. For the low dose, the amount of radioactivity measured in the surface dose remained stable over time but was slightly higher than those measured in the groups exposed to the neat product.

Percentage recoveries measured in the dressing (including saddle, gauze, cover and tape strips) were low for all groups. For the two dose formulations, the relatively high variability in these results can be due to technical problem during application or swabbing process, the highest value of radioactivity measured in the dressing being in relation with lowest amount of radioactivity in swabs at 8 hours post-dose (see groups 2, 4 and 8).

For the high dose formulation, the percentages of recovery measured in the stratum corneum did not seem to be affected by time: from 0.65% after 8 hours of application to 0.42% after 168 hours post-application. For the groups exposed to the low dose formulation, a slight decrease between 8 and 24 hours can be observed (from 2.03% to 0.61% after 8 and 168 hours post-dose respectively).

Table 7.3-2: The mean distribution of radioactivity 8, 24, 72 and 168 hours after a single topical application of [14C]-thiacloprid from a 100 g/L FS 400 formulation.

Dose Group 100 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	8		24		72		168	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8 hr & terminal)	96.56	3.03	99.72	2.45	99.30	1.60	95.42	1.63
Surface dose (tape strips 1 & 2)	0.42	0.12	0.38	0.29	0.37	0.29	0.34	0.24
Fur	0.29	0.58	n.s.	n.s.	0.03	0.04	0.41	0.27
Dressings	0.05	0.01	0.29	0.19	0.54	0.22	1.97	0.65
Total % non-absorbed	97.31	2.37	100.39	2.00	100.24	1.22	98.15	1.45
SKIN COMPARTMENT								
Stratum corneum [a]	2.03	1.03	1.11	0.99	1.29	1.06	0.61	0.17
Treated skin [b]	1.61	0.69	0.21	0.16	0.15	0.03	0.37	0.09
Surrounding skin [c]	0.52	0.28	0.24	0.14	0.19	0.13	0.31	0.08
Total % at dose site	4.16	1.54	1.56	1.29	1.62	1.18	1.30	0.25
SYSTEMIC COMPARTMENT								
Urine	0.01	0.00	0.02	0.02	0.07	0.03	0.27	0.13
Faeces	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.15	0.07
Cage wash	0.03	0.00	0.01	0.01	0.01	0.02	0.16	0.17
Cardiac blood	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.02	0.03
Non-treated skin	0.27	0.12	0.12	0.02	0.15	0.13	0.21	0.09
Carcass	0.23	0.06	0.41	0.22	0.37	0.06	0.30	0.15
Total % directly absorbed	0.53	0.16	0.55	0.23	0.60	0.21	1.13	0.49
Total Recovered	102.0	1.22	102.5	0.73	102.5	0.75	100.6	1.26

[a] = tape strips excluding surface dose strips 1 & 2, [b] = skin at dose site after tape-stripping procedure, [c] = skin immediately outside the dose application area, SD = standard deviation, n.d. = not detected, less than limit of quantification, n.a. = not applicable, n.s. = no sample.

Taking into account the inter-variability, the fraction of test chemical present in the treated skin following removal of the residual dose appeared to be relatively stable for the high treatment formulation. This same tendency was observed for skin taken from around the application site (so called "surrounding skin). For the low dose formulation, a decrease of radioactivity in the treated skin can be observed between 8 and 24 hours, followed by a stable tendency until 168 hours post-dose. The measurement of radioactivity in the surrounding skin gave rise to a similar observation with percentages of 0.52% to 0.24% of radioactivity at 8 and 24 hours post-dose respectively followed by stable levels until 168 hours post-dose.

Therefore, the total of radioactivity located at the dose site appeared to be stable for the high dose formulation. The variability of these results between each group can be linked to the percentages of radioactivity considered as non-absorbed, the amount of radioactivity considered as directly absorbed didn't change with time (see following paragraph). For the low dose groups, the percentage of radioactivity located at the dose site appeared to slightly decrease from 8 hours (4.16%) to 24 hours (1.56%) and remained stable thereafter (1.30% at 168 hours post-dose).

The amounts of radioactivity found in the tissues (carcass, cardiac blood and non-treated skin) and eliminated in the excreta (urine, faeces and cage wash) were considered as directly absorbed by the male rats. For the neat product and the low dose formulation, a small portion of radioactivity was directly absorbed, as 0.36% and 0.23% of the dose applied appeared in the carcass after 8 hours post-application. After that, taking into account the inter-individual variability, the level of radioactivity measured in the carcass of male rats exposed to the high and low dose formulations appeared to be

relatively stable. No radioactivity (or percentage below the detection limit) was detected in the cardiac blood and in the non-treated skin for the two dose formulations.

For the two dose formulations, percentages of radioactivity measured in excreta indicated that the urine was the route of elimination following dermal application. The total amount of radioactivity excreted was very low for the two dose formulations. For the high dose groups, the percentages of radioactivity remained stable until 72 hours post-dose (from 0.01% to 0.02% at 8 hours and 72 hours post-dose, respectively) and thereafter slightly increased (0.13% at 168 hours post-dose). For the low dose formulation, a stability of excreted amount of radioactivity was observed until 24 hours post-dose following by a small increase until 168 hours post-dose: 0.03%, 0.03%, 0.08% and 0.59% at 8, 24, 72 and 168 hours post-dose, respectively.

For the high dose formulation, time under the experimental conditions of the study seems to have no impact on the direct dermal absorption of thiacloprid. Each time point produced similar results regarding the percentages of radioactivity measured in the dose site and in the systemic compartment. For the low dose formulation, the total percentage of radioactivity directly absorbed seems to be stable between 8 hours and 72 hours post-dose and slightly increased thereafter, probably in relation to the small decrease observed in the total amount of radioactivity detected at the dose site.

With a sampling time of 168 hours, half the study sampling period corresponds to 84 hours post dose application. For the neat formulation the amount of radioactivity recovered by 72 hours (i.e. before half way through the study) was >75% and therefore the stratum corneum does not need to be included in the absorbed fraction of the dose. For the 100 g/L dilution only *ca.* 53% of the applied radioactivity has been recovered by 72 hours and therefore the stratum corneum does need to be included in the absorbed fraction.

Conclusion:
The dermal absorption value for the thiacloprid FS 400 neat formulation (based on the results from the human skin samples) is 1% and the dermal absorption from the 100 g/L dilution is 2%.

Report:	[redacted]i; [redacted]; 2012; M-420411-01-1
Title:	Thiacloprid FS 400: [14C]-thiacloprid - Comparative in vitro dermal absorption study using human and rat skin
Report No.:	SA 11107
Document No.:	M-420411-01-1
Guidelines:	**O.E.C.D. Guideline for the testing of Chemicals** **Skin Absorption In Vitro Method Guideline 428 (April 2004).** **O.E.C.D. Environmental Health and Safety Publication Series on testing and Assessment N° 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004).** **European Commission Guidance Document on Dermal Absorption- Sanco/222/2000 rev. 7, (March 2004).; not specified**
GLP/GEP:	**yes**

Material and methods

Rat skin:

Species, strain:	Rat, Wistar Rj: WI (IOPS HAN).
Source:	[redacted] (France).
Sex:	Male.
Number:	6
Anatomical site:	Dorsal.
Rat Skin Preparation:	Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of *ca* 460 to 540 µm in thickness.

Human skin: Source: [redacted], France.
Number and sex: 9 donors, female.
Anatomical region: Abdomen.
Thickness: 420 to 586 µm.

Test Material:

Non-radiolabelled:	Batch: KATH4852-1-3. Purity = 99.0%.
Radiolabelled:	[thiazolidine-^{14}C]-thiacloprid Batch: KATH 6747. Specific activity: 4.12 MBq/mg. Radiopurity of the formulation: >99%.
Formulation:	The formulation used in this experiment was the thiacloprid FS 400 formulation (specification number 102000022825 01) which was used at two nominal concentrations: 400 g a.s./L, 0.05 g a.s./L and 100 g a.s./L.
Test system:	A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped

through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm^2 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 $\mu L/cm^2$ 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 levels of radioactivity in the 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 liquid scintillation counter. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. An efficiency correlation curve was prepared for each scintillation cocktail that was regularly checked by the use of $[^{14}C]$-n-hexadecane standards. The scintillation counter was recalibrated when a deviation of greater than 2% was observed when counting quality control standards. The limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails.

Findings:
Thiacloprid was demonstrated to be soluble in the receptor fluid up to a concentration of 0.8 mg/mL. During the study the maximum achieved concentration was 1.03 µg/mL. The achieved concentrations were at least 777 times lower than the determined solubility concentration, therefore the solubility in the receptor fluid was deemed to be sufficient to reduce any risk of back diffusion.

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable according to in-house SOPs.

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 98.50% to 99.98% of the applied dose. These study results are presented in Table IIIA 7.6.2-3.

Table 7.3-3: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-thiacloprid in an FS 400 formulation at the rates of 400 g/L and 100 g/L to human and rat skin samples.

Results expressed in terms of percentage of applied radioactivity.

Distribution of radioactivity (mean % dose ± Standard deviation)				
Dose levels	Neat formulation (SYP13685, 400 g/L)		Dilution: Low dose (SYP13688, 100 g/L)	
	Human (n=5)	Rat (n=6)	Human (n=6)	Rat (n=6)
SURFACE COMPARTMENT				
Skin swabs (8h)	99.75 (±3.51)	97.28 (±1.33)	97.65 (±2.08)	95.58 (±2.56)
Skin swabs (24h)[a]	0.04 (±0.02)	0.18 (±0.10)	0.11 (±0.11)	0.59 (±0.35)
Total % in skin swabs	***99.79 (±3.50)***	***97.46 (±1.30)***	***97.76 (±2.04)***	***96.16 (±2.35)***
Surface Dose (tape-strips 1 & 2)	0.03 (±0.06)	0.32 (±0.32)	0.37 (±0.83)	1.85 (±1.37)
Donor chamber	0.12 (±0.25)	0.21 (±0.23)	0.28 (±0.33)	0.10 (±0.13)
Total % non-absorbed	**99.94 (±3.65)**	**97.98 (±1.22)**	**98.41 (±2.01)**	**98.11 (±1.85)**
SKIN COMPARTMENT				
Skin [b]	0.03 (±0.02)	0.12 (±0.07)	0.04 (±0.03)	0.08 (±0.07)
Stratum corneum [c]	0.01 (±0.01)	0.36 (±0.72)	0.03 (±0.04)	1.17 (±0.54)
Total % at dose site	**0.04 (±0.03)**	**0.48 (±0.69)**	**0.07 (±0.07)**	**1.26 (±0.57)**
RECEPTOR COMPARTMENT				
Receptor fluid (0-24h)	< LOQ	0.14 (±0.15)	0.02 (±0.03)	0.09 (±0.06)
Residual Receptor Fluid	< LOQ	0.02 (±0.02)	< LOQ	0.01 (±0.01)
Receptor chamber	< LOQ	0.25 (±0.28)	< LOQ	< LOQ
Total % directly absorbed [d]	< LOQ	**0.41 (±0.40)**	**0.02 (±0.03)**	**0.09 (±0.07)**
Total % potentially absorbable [e]	**0.04 (±0.03)**	**0.89 (±0.64)**	**0.09 (±0.08)**	**1.35 (±0.51)**
Total % Recovery	**99.98 (±3.66)**	**98.87 (±1.09)**	**98.50 (±2.01)**	**99.46 (±1.94)**

[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 number 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]: sum of radioactivity in Total % directly absorbed and Total % of dose site.

< LOQ.: below the limit of quantification (< 0.005%)

n: number of skin cells used for calculation

Recovery of radioactivity in the receptor fluid was not >75% by 12 hours post dose and therefore the stratum corneum was included in the absorbed fraction.

Conclusion:

The dermal penetration of [^{14}C]-thiacloprid through human and rat dermatomed skin from the FS 400 formulation was investigated at two concentrations corresponding to the neat product (400 g /L) and one representative dilution (100 g/L), respectively.

Overall, the dermal penetration of [^{14}C]-thiacloprid from the FS 400 formulation was very low for both concentrations used. In addition, the absorption was lower in human skin compared to rat skin.

The mean percentage of thiacloprid that was considered to be absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.1% and 1% for the human and rat skin, respectively, yielding a factor difference of 10 between the two species for the neat product.

The mean percentage of thiacloprid that was considered to be absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 0.1% and 1% for the human and rat skin respectively, yielding a factor difference of 10 between the two species for the low dose formulation.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

Appendix 1: 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], 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 Toxicology in Stilwell 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 (F/F1)**	300 **23/22 (F/F1)**	600 **43/43 (F/F1)**	**Historical control data 1992 - 1997[A]**
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

[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-309754-01-2 ([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*** *(-17.9% 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 [redacted], 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 (day 4): 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]	0	2	10	50	Historical control data 1992-1999[A]
No. of dams on study	*35*	*35*	*35*	*35*	
No. of dams with implantations	*28*	*31*	*32*	*30*	
No. of dams with viable fetuses	*28*	*31*	*32*	*29*	
Post-implantation loss (%)					
mean per dam with implantations	0.9	0.9	0.5	**2.8****	0.5 - 4.6
mean per dam with viable fetuses	0.9	0.9	0.5	**2.5**	0.5 - 4.4

[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], Germany

Dose [mg/kg bw]	0	2	10	45	Historical control data 1992-1998[A]
No. of dams on study	*24*	*24*	*24*	*24*	
No. of dams with implantations	*22*	*21*	*24*	*22*	
No. of dams with viable fetuses	*22*	*20*	*24*	*19*	
Post-implantation loss (%)					
mean per dam with implantations	0.9	1.1	0.3	**1.8**[B]	0.1-1.3
mean per dam with viable fetuses	0.9	0.8	0.3	1.0[B]	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 22.3 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]** *No. of dams P-generation* *No. of dams F1-generation*	0 **0** *30* *30*	50 **3.8/3.6 (P/F1)** *30* *30*	300 **23/22 (P/F1)** *30* *30*	600 **43/43 (P/F1)** *30* *30*	**Historical control data 1992 –1997[A]**
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], 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	107	73	81	97	170 - 389
stillborn	6	1	1	3	0 - 6
found dead (PND 0-4)	3	2	0	**16**	1 - 15
No indication for missing & cannibalized pups					
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 (4) / 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	337	292	291	198	86 - 383
stillborn	15	5	**15**	**15**	0 - 13
found dead	4	3	9	**14**	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 [redacted], 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	351	349	340	338	No data
stillborn	5	0	4	1	
found dead or presumed cannibalized (PND 1-5)	4	5	9	4	
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** *29* *(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 3 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^**
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	

^: 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], U.; 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: [redacted], 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], 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] & [redacted] (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.**