Document Title

Summary of the toxicological studies
Methiocarb FS 500 (500 g/L)

Data Requirements

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

According to the guidance document SANCO 10181/2013

for preparing dossiers for the approval of a chemical active substance

Date

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number
2015-12-18	Original document	M-542840-01-1
2016-03-04	Inclusion of additional information on request of CRD	M-542840-02-1
2017-07-25	Dose-level justification added for CP 7.1.6/03 Revised risk assessments for operators, bystander and worker (CP 7.2)	M-542840-03-1

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

Table of Contents

CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Methiocarb is an insecticide and repellent active substance and was included into Annex I of Directive 91/414 on 1st October 2007 (Directive 2007/5/EC).

This Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of methiocarb under Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer CropScience (BCS) for the Annex I inclusion under Directive 91/414/EEC are contained in the DAR, its Addenda and are included in the Baseline Dossier provided by BCS. These data are only mentioned in the Supplementary Dossier for the sake of completeness and only general information (e.g. author, reference etc.) is available for these data. In order to facilitate discrimination between new data and data submitted during the Annex I inclusion process under Directive 91/414/EEC, the old data are written in grey typeface. For all new studies, detailed summaries are provided within this Supplementary Dossier.

The presented and submitted studies used different synonyms and codes for the active substance Methiocarb.

INTRODUCTION

This document summarizes the information related to the toxicological studies and exposure (operators, workers and bystanders) for the plant protection product Methiocarb FS 500 G (Specification No. 102000007167) which contains the active substance methiocarb.

Methiocarb FS 500 G was a representative formulation during the Annex I inclusion of methiocarb and has thus been evaluated according to uniform principles.

A full risk assessment according to the Uniform principles is provided which demonstrates that the product is safe for operators, workers and bystanders.

Methiocarb was included into Annex I of Directive 91/414/EEC on 1 October 2007 (Commission Directive 2007/5/EC).
Where appropriate this document refers to the conclusions of the EU review of the active substance. 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 methiocarb, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 29 September 2006 shall be taken into account.

The EFSA conclusion (EFSA Scientific Report (2006) 79, 1-82) for methiocarb is considered to provide the relevant scientific information for the review of the product.

In the Annex I Inclusion Directive for methiocarb 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 30-04-1984.

CP 7.1 Acute toxicity

The product Methiocarb FS 500 G (Specification No. 102000007167, Material No. 04411935) was tested for skin sensitisation in a Local Lymph Node Assay but not for its acute toxicity as well as skin and eye irritation. However, studies on acute oral, dermal and inhalation toxicity as well as skin and eye irritation exist with the very similar product Methiocarb SC 500 (Specification No. 102000006871, Material No. 04212746). Methiocarb SC 500 differs from Methiocarb FS 500 only slightly, so that the toxicological properties resulting from the aforementioned toxicological studies on Methiocarb SC 500 also apply to Methiocarb FS 500. The differences in composition between both products and the rationale why the acute toxicity and irritating properties of Methiocarb FS 500 can be derived from Methiocarb SC 500 are discussed in detail in the respective confidential bridging statement enclosed in the document JCP (M-542436-02-1).
Synonymous names for both products used in the following are Methiocarb 500 g/L FS for Methiocarb FS 500 as well as H 321 500 SC and Mesurol SC 500 for Methiocarb SC 500.

For the Annex I inclusion of methiocarb, two representative formulation were supported, i.e. “Mesurol FS 500” and “Mesurol RB 4”. For the Annex I renewal of methiocarb, only the Methiocarb FS 500 formulation will be supported as representative formulation. Therefore, study data regarding the “Mesurol RB 4” formulation are not presented in this dossier.
Furthermore, in the baseline dossier the data for acute oral, dermal, inhalation toxicity, as well as skin and eye irritation based on an old specification for Methiocarb SC 500. Due to a change of the composition, new studies on the Methiocarb SC 500 formulation were conducted. Since the new composition of methiocarb SC 500 is more similar to the current Methiocarb FS 500 formulation, only the results of the new studies with Methiocarb SC 500 are presented here.
For toxicity information of the RB 4 and previously supported FS 500 formulation, please refer to the baseline dossier.

Summary of acute toxicity

Study	Results	Reference
Methiocarb SC 500 (Spec. 102000006871, Batch No. PF90060209)		
Acute oral rat	LD_{50} > 50 < 300 mg/kg bw	[redacted]. (2005) CP 7.1.1/3 Report AT02669 [M-261963-01-1]
Acute dermal rat	LD_{50} > 2000 mg/kg bw	[redacted]. (2005) CP 7.1.2/3 Report AT02668 [M-261936-01-1]
Acute inhalation rat	LC_{50} > 1571 mg/m^3 air*	[redacted]. (2005) CP 7.1.3/2 Report AT02749 [M-262830-01-1]
Acute skin irritation rabbit	Not irritating	[redacted]. (2005) CP 7.1.4/3 Report AT02694 [M-262050-01-1]
Acute eye irritation rabbit	Not irritating	[redacted]. (2005) CP 7.1.5/3 Report AT02695 [M-262054-01-1]
Methiocarb FS 500 (Spec. 102000007167; Batch No. PF90117711)		
Skin sensitisation mouse – (Local Lymph node Assay)	Not sensitising	[redacted]. (2005) CP 7.1.6/3 Report AT02977 [M-269882-01-1]

*: maximum technically attainable concentration

The results of the toxicological studies indicate that Methiocarb FS 500 G is toxic after acute oral administration, but of low to moderate toxicity after acute inhalation and of no toxicity after acute dermal application. It is not irritating to the skin and eyes of rabbits and does not show skin sensitising properties in the Local Lymph Node Assay in mice.

According to the study results the following classification/labelling is triggered for methiocarb FS 500 G:
- Regulation (EC) No 1272/2008 (CLP): Acute Tox. Cat. 3, H301 (Toxic if swallowed)

CP 7.1.1 Oral toxicity

Report:	[redacted]:;[redacted]; 2005; M-261963-01-1
Title:	H 321 500 SC - Acute toxicity in the rat after oral administration
Report No.:	AT02669
Document No.:	M-261963-01-1
Guideline(s):	OECD 423; Directive 67/548/EEC, Annex V, Method B.1.tris; US-EPA 712-C-98-190, OPPTS 870.1100
Guideline deviation(s):	The test compound 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: H 321 500 SC

Synonym	Mesurol SC 500, Methiocarb SC 500
Specification no.:	102000006871
Description:	white suspension
Lot/Batch no:	PF90060209
Content:	504 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2006-08-22

2. Vehicle: tap water

3. Test animals:

Species:	Rat
Strain:	Wistar rat, HsdCpb:Wu
Age:	approx. 10 – 12 weeks
Weight at dosing:	153 g – 170 g
Source:	[redacted]
Acclimatisation period:	at least 5 days
Diet:	standard diet [redacted] 3883.0.15 Maus/Ratte Haltung, [redacted] Switzerland, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	group caged conventionally in polycarbonate cages, bedding: low dust wood granulate ([redacted], [redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	50 – 300 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) 50	0	3	3	10' – 2 h	--	0
(2nd) 50	0	3	3	10' – 2h	--	0
300	3	3	3	5'-15 '	10' – 15'	100
LD_{50}: > 50 < 300 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 50 mg/kg bw: decreased motility, spasmodic state, tremor, chromodacryorrhea

In animals dosed with 300 mg/kg bw: decreased motility, spasmodic state, tremor, chromodacryorrhea.

C. Body weight

There were no toxicologically effects on body weight or body weight gain in rats treated with 50 mg/kg body weight.

D. Necropsy

The gross pathological investigations revealed no treatment-related findings neither in the animals which died during the observation period nor in the animals which were sacrificed at the end of the study.

III. Conclusion

Methiocarb SC 500 is toxic after acute oral administration to rats.

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

- Regulation (EC) No 1272/2008 (CLP): Acute Tox. Cat.3
  H301 (Toxic if swallowed)

CP 7.1.2 Dermal toxicity

Report:	[redacted]; [redacted]; 2005; M-261936-01-1
Title:	H 321 500 SC - Acute toxicity in the rat after dermal application
Report No.:	AT02668
Document No.:	M-261936-01-1
Guideline(s):	OECD 402; Directive 67/548/EEC, Annex V, Method B.3; US-EPA 712-C-98-192, OPPTS 870.1200
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: H 321 500 SC

Synonym(s):	Mesural SC 500, methiocarb SC 500
Specification no.:	102000006871
Description:	White suspension
Lot/Batch no:	PF90060209
Content:	504 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2006-08-22

2. Vehicle: none

3. Test animals:

Species:	rat
Strain:	Wistar rat, Crl: (Wi)WU BR
Age:	approx. 9 – 13 weeks
Weight at dosing:	males: 240 g – 270 g; females: 200 g – 214 g
Source:	[redacted]
Acclimatisation period:	at least 5 days
Diet:	Standard diet [redacted] 3883.0.15 Maus/Ratte Haltung, [redacted] Switzerland, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	Individually in polycarbonate cages; bedding: low dust wood granulate ([redacted], [redacted], Germany).

B. Study design and methods

1. Animal assignment and treatment:

Dose:

Dose (mg/kg bw)		Surface area (cm²)	Range (mg/cm²)
males	2000	12.0	40.0 – 45.0
females	2000	9.0	44.4 -47.6

Application route:	dermal, semi-occlusive dressing
Exposure duration:	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

No mortalities occurred at 2000 mg/kg bw

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	0	5	-	-	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

A dermally applied dose of 2000 mg/kg bw was tolerated by male and female rats without toxicologically relevant clinical signs or mortality.

Locally, a partial yellowish discoloration of the treatment area was observed. The most plausible interpretation is a discoloration by the test compound, which has a yellowish appearance after the 24 h exposure period.

C. Body weight

There were no toxicological effects on body weight or body weight development in males. In one female a distinct decrease in body weight gain in the first week was observed.

D. Necropsy

No gross pathological changes were observed in animals that died during the observation period or in animals sacrificed at the end of the study period.

III. Conclusion

Methiocarb SC 500 is non-toxic after acute dermal application to rats.

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

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

CP 7.1.3 Inhalation toxicity

Report: [redacted],,[redacted]; 2005; M-262830-01-1
Title: H 321 500 SC - Acute inhalation toxicity in rats
Report No.: AT02749
Document No: M-262830-01-1
Guideline(s): OECD 403; Directive 92/69/EEC, Annex V, Method B.2.; US-EPA 712C-98-193, OPPTS 870.1300; JMAFF Notification no. 12 Nousan-8147
Guideline deviation(s): none
GLP/GEP: **yes**

I. Materials and methods

A. Materials

1. Test material:	H 321 500 SC
Synonym	Mesurol SC 500
Specification no.:	102000006871
Description:	white suspension
Lot/Batch no:	PF90060209
Content:	504 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2006-08-22
2. Vehicle:	demineralized water
3. Test animals:	
Species:	Rat
Strain:	Wistar rat, HsdCpb:Wu (SPF)
Age:	approx. 2 month
Weight at dosing:	Males: 185 g – 205 g; females: 169 g – 185 g
Source:	[redacted], [redacted], Netherlands
Acclimatisation period:	at least 5 days
Diet:	standard fixed-formula diet ([redacted] 3883 = NAFAG 9441 pellets maintenance diet for rats and mice; [redacted] SA, [redacted], Switzerland, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	individually in conventional Makrolon® Type IIIH cages, bedding: type BK8/15 low-dust wood granulate ([redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment:	
Dose:	0 – 1571 mg/m³ (maximum technically attainable concentration)
Application route:	Inhalation, nose-only exposure
Exposure duration:	4 hours
Group size:	5 rats/sex/dose
Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, body weight, rectal temperature, reflex measurements, gross necropsy

2. Generation of the test atmosphere / chamber description

Generation and characterization of chamber atmosphere

	Group 1	Group 2
Target concentration (mg/m³)	0	1500
Nominal concentration (mg/m³)	control (water)	13037.5
Gravimetric concentration (mg/m³)	--	955
Actual concentration (mg/m³)[1)]	--	1571
Recovery (%)	--	12
Temperature (mean, °C)	22.9	22.6
Relative humidity (mean, %)	>95	>94.3
MMAD (µm) GSD Aerosol mass < 3 µm (%) Mass recovered (mg/m³)	-- -- --	3.76 2.31 39.9 890.69

Recovery = Actual concentration x 100/Nominal concentration; MMAD = Mass Median Aerodynamic Diameter, GSD = Geometric Standard Deviation; - = not applicable, 1) Actual concentration: Conversion to test substance, gravimetric concentration x 100 / 100-39.2).

II. Results and discussion

A. Mortality

Mortality was observed in two male and one female rat at 1571 mg/m³ air.

Table 7.1.3-1 Doses, mortality / animals treated

Actual concentration (mg/m³)	Toxicological result*			Occurrence of signs	Time of death	Rectal temperature (°C)
Male rats						
0	0	0	5	--	--	37.9
1571	2	3	5	Day 0 – day 6	4 h	32.0
Female rats						
0	0	0	5	--	--	38.2
1571	1	4	5	Day 0 – day 8	4 h	28.3
LC_{50} > 1571 mg/m³ (maximum technically attainable concentration)						

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

B. Clinical observations

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

1571 mg/m³ air: Bradypnea, laboured breathing patterns, breathing irregular, piloerection, hair-coat ungroomed, tremor, limp, high-legged gait, motility reduced, abdominal position, non-specific behavioral changes, miosis, corneal opacity, red tears, salivation, exophthalmus, reddened nose, nose, nostrils and eyelids with red encrustations, emaciation, convulsions, head area with swellings, vocalization: sneezing sounds. All signs subsided towards the beginning of the second post-exposure week.

Reflex measurements

A battery of reflex measurements was made on the first post-exposure day. The rats exposed to the test substance show reduced grip strength and tonus, miosis at light reflex and an impaired righting response. Further observations with lower incidence during reflex measurement were bizarre reaction for sound and/or touch startle reflex, and freezing after tail-pinch. All rats of the control group tolerated the test without abnormal reflexes.

C. Body weight

Animals treated with Methiocarb SC 500 exhibited a statistically significant decrease of body weights in comparison to control animals.

D. Necropsy

Animals which died after exposure had a colorless discharge in the nose, less collapsed lungs and pale spleens. One male that was sacrificed at the end of the observation period showed isolated dark-red foci in the lungs.

III. Conclusion

Methiocarb SC 500 (liquid aerosol) has a low to moderate acute inhalation toxicity to rats.

The study result triggers the following classification/labelling:

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

CP 7.1.4 Skin irritation

Report:	[redacted], 2005, M-262050-01-1
Title:	H 321 500 SC - Acute skin irritation/corrosion on rabbits
Report No.:	AT02694
Document No.:	M-262050-01-1
Guideline(s):	OECD 404, Directive 67/548/EEC, Annex V, Method B.4., US-EPA 712-C-98-196, OPPTS 870.2500
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material:

Synonym(s):	Mesurol SC 500, Methiocarb SC 500
Specification no.:	02000006871
Description:	White suspension
Lot/Batch no.:	PF90060209
Content:	504 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2006-08-22

2. Vehicle: none

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White rabbit, HsdIf:NZW
Age:	young adult
Weight at dosing:	2.4 kg – 2.5 kg
Source:	[redacted]

Acclimatisation period:	at least 5 days
Diet:	standard diet "[redacted]" 4mm ([redacted], Germany), approximately 100 g/animal/day
Water:	tap water, *ad libitum*
Housing:	individually in cage units Metall/[redacted] on low dust wood granulate bedding ([redacted], [redacted], Germany)

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

There were no systemic intolerance reactions.

Table 7.1.4-1 Summary of irritant effects (Scores)

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)
		<2.3	(Regulation (EC) No 1272/2008)
	(+) = mild irritant for mean scores	≥1.5 - <2.3	(GHS category 3)
		≥2.3	(Regulation (EC) No 1272/2008 and GHS category 2)

III. Conclusion

Methiocarb SC 500 is not irritating to the skin of rabbits.

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

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

CP 7.1.5 Eye irritation

Report:	[redacted]g; [redacted]; 2005; M-262054-01-1
Title:	H 321 500 SC - Acute eye irritation on rabbits
Report No.:	AT02695
Document No.:	M-262054-01-1
Guideline(s):	OECD 405; Directive 67/548/EEC, Annex V, Method B.5; US-EPA 712-C-98-195; OPPTS 870.2400
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: H 321 500 SC

Synonym(s):	Mesurol SC 500, Methiocarb SC 500
Specification no.:	102000006871
Description:	White suspension
Lot/Batch no:	PF90060209
Content:	504 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2006-08-22

2. Vehicle: none

3. Test animals:

Species:	Rabbit
Strain:	New Zealand White rabbit, Crl:KBL(NZW)BR
Age:	young adult
Weight at dosing:	2.0 kg – 2.7 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "[redacted]" 4mm ([redacted], Germany), approximately 100g/animal/day
Water:	tap water, *ad libitum*
Housing:	individually in cage units Metall/[redacted]

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0.1 mL/animal
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

There were no systemic intolerance reactions.

Table 7.1.5-1 Summary of Irritant Effects (Score)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	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	--	na
	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)
(+)	= 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)
++	= irreversible effects/ serious damage	≥3	>2.5			(Regulation (EC) No. 1272/2008 and GHS category 1)
na :	not applicable,					

III. Conclusion

Methiocarb SC 500 is not irritating to the eyes of rabbits.

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

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

CP 7.1.6 Skin sensitization

Report: [redacted]; 2006; M-269882-01-1

Title: Methiocarb 500 g/L FS (Project: Methiocarb (H 321)) - Local lymph node assay in mice (LLNA/IMDS)

Report No.: AT02977

Document No.: M-269882-01-1

Guideline(s): OECD 406, OECD 429; Guideline 96/54/EC, Method B.6., B.42.; US-EPA 712-C-03-197, OPPTS 8702600

Guideline deviation(s): 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 results.

GLP/GEP: **yes**

I. Materials and methods

A. Materials

1. Test material:	Methiocarb FS 500
Synonym(s):	Methiocarb 500 g/L FS
Specification no.:	102000007167
Description:	Red suspension
Lot/Batch no:	PF90117711
Content:	495 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2007-03-31
2. Vehicle:	Pluronic PE 9200 / 0.9% NaCl solution, 1% v/v
3. Test animals:	
Species:	mouse
Strain:	NMRI mouse, Hsd Win:NMRI (SPF)
Age:	10 weeks
Weight at dosing:	24 g – 31 g
Source:	[redacted]
Acclimatisation period:	at least 7 days
Diet:	[redacted] SA 3883 maintenance diet for rats and mice ([redacted] SA, [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 Makrolon® type II cages; bedding: low-dust wood granulate ([redacted] Füllstoff-Fabriken, [redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0 (vehicle control) - 3% - 10% - 30% The justification for the dose level selection is provided in Document M-570817-01-1 and summarised below: Taken into account the toxicity of the test item (oral LD_{50} value between 50 mg/kg and 300 mg/kg in rats), as well as the systemic availability after dermal exposure, the 3%, 10% and 30% concentration series had been selected for the study. Application of 50% test item formulation would have increased the risk to meet systemic toxicity in the mice without adding valuable information regarding the endpoint tested by the study. Thus, the chosen concentrations of 0%, 3%, 10% and 30% considered to cover maximum exposure while avoiding systemic toxicity
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 any treatment.

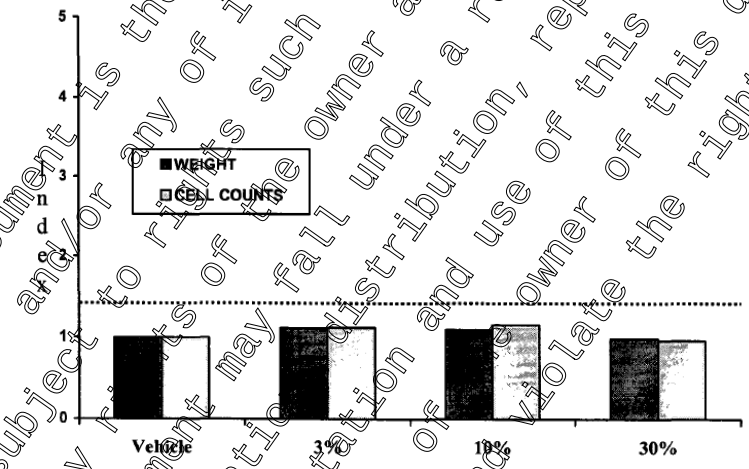
The NMRI mice did not show an increase in the stimulation indices for cell counts or for weights of the draining lymph nodes after application of Methiocarb 500 g/L FS.

The "positive level" which is 1.4 for the cell count index (which is calculated by dividing the mean cell count from the animals of a treatment group by the respective value from 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, has not been exceeded or reached in any dose group.

For ear weights no substance specific effects were determined, too.

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 Methiocarb FS 500



III. Conclusion

The results show that Methiocarb FS 500 has neither an irritating nor a sensitizing potential in mice after dermal application. No activation of the cells of the immune system via dermal route was determined after application of up to and including 30 % Methiocarb 500 g/L FS. The concentration of 30 % turned out to be the NOEL for the parameters investigated in this study

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

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

CP 7.1.7 Supplementary studies on the plant protection product

No supplementary studies were performed.

CP 7.1.8 Supplementary studies for combinations of plant protection products

Not applicable. This plant protection product is not planned to be combined with other plant protection products.

CP 7.2 Data on exposure

CP 7.2.1 Operator exposure

Methiocarb FS 500 is a flowable concentrate for seed treatment (water based seed dressing liquid) containing 500 g/L of the insecticidal active substance (a.s.) methiocarb. Use instructions and information related to operator exposure are summarized in **Table 7.2.1-1**.

Table 7.2.1-1. Application parameters of Methiocarb FS 500.

Crop	Formulation	Application				Application rate per treatment			Remark
		Method	BBCH Stage	Number	Interval	kg a.s./unit seed	mL product/unit of seed	kg a.s./ha	
Corn	**Methiocarb FS 500** g/L	Seed treatment	0 (pre-seeding)	1	n.a.	0.075	150	0.090-0.150	Sowing rate from 1.2-2 units/ha

Methiocarb FS 500 is applied to corn seeds at the dose rate of 150 mL/seed unit (1 seed unit = 50000 grains), equivalent to 0.075 kg (75 g) a.s./seed unit or 1.5 mg a.s./seed.

The sowing rate ranges from 1.2-2 units/ha corresponding to 0.09-0.150 kg (90-150 g) a.s./ha. During treatment the product is diluted to final slurry volume of 177.5 to 270 mL/unit of seeds corresponding to a dilution factor of 1.2 to 1.8.

In this assessment, as a risk envelope approach, the occupational exposure to **Methiocarb FS 500** during **seed treatment** (i.e. mixing/loading, calibration, cleaning and bagging, stacking) and **seed sowing** (i.e. loading and sowing of treated seeds) will be estimated for the worst case scenario (i.e. 150 mL product (75 g a.s.)/seed unit and 2 units/ha, respectively).

<u>Consideration on Dermal Absorption</u>

The extent of dermal absorption of methiocarb formulated as an FS 500 (methiocarb FS 500) formulation was investigated *in vitro* using human skin according to the *2012 EFSA Guidance on Dermal Absorption*[1]. Since <u>no significant dilution is likely to occur</u> in a given **seed treatment** plant facility (including during all cleaning activities), the penetration of the neat formulation is considered to be applicable to all exposure scenarios during seed treatment. In the same way the dermal exposure to grain dust during seed treatment and seed sowing will also be subjected to the same penetration extension, considered here to be the worst case scenario. However, the RMS proposed a pro-rata correction of for the 1:1.2 and 1:1.8 dilutions of Mesurol FS 500. Inhalation absorption is considered to be 100%.

- Dermal absorption (neat formulation, possible minor dilutions, grain dust): 0.9%
- Dermal absorption (dilution factor 1.2, *pro-rata* corrected): 1%

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

- Dermal absorption (dilution factor 1.8, *pro-rata* corrected): 2%
- Inhalation absorption: 100%

Consideration on AOEL

The Acceptable Operator Exposure Level (AOEL) of 0.013 mg/kg bw/day is established for methiocarb from a 90-day dietary study in dogs based on a NOAEL of 1.3 mg/kg bw/day and a safety factor of 100[2].

Consideration on AAOEL

An Acute Acceptable Operator Exposure Level (AAOEL) of 0.017 mg/kg bw/day is proposed by the RMS for methiocarb from a 21-day inhalative study in rats based on a NOAEL of 6 mg/m^3 and a safety factor of 100. This AAOEL is proposed and elucidated by the RMS in Volume 1 of the RAR, and is therefore used in this dossier in chapter CP 7.2 for the acute assessment of operators, workers and bystander. However, the RMS used an AAOEL of 0.016 mg/kg bw/day instead of 0.017 mg/kg bw/day for the acute assessments throughout Volume 3CP Section 7 of the RAR, which is not comprehensible for us, and we think this is a mistake. Unfortunately, we did not notice this mistake earlier, but as already stated, we now use the correctly calculated AAOEL of 0.017 mg/kg bw/day for all following acute exposure assessments.

Consideration on estimation of operator exposure with *SeedTROPEX*

As a first tier assessment for **seed treatment** and **seed sowing**, the *SeedTROPEX* model was applied. The results of the exposure estimations are summarized in **Table 7.2.1-2**.

- ***SeedTROPEX***

Table 7.2.1-2. Seed*TROPEX* predicted systemic operator exposure to Methiocarb as a proportion of the AOEL.

Task	Total systemic exposure (mg/kg bw/day)	% of AOEL*	MoS
Seed Treatment			
All tasks	0.0298	229	44
Loading/Sowing			
Loading/Sowing	0.0044	33.8	295

Standard clothing of the operators is one layer of work clothing during all tasks and in addition protective gloves except for bagging; exposure during bagging mg/h; * AOEL 0.013 mg/kg bw/day; MoS: Margin of Safety.

[2] EFSA Scientific Report, 2006, (79), 1-82.

Assessment

SeedTROPEX calculations indicate that the intended uses of **Methiocarb FS 500** are favorable for operators while **sowing treated corn seeds**, accounting for 33.8% (MoS 295) of the respective systemic AOEL (0.013 mg/kg bw/day).

Additionally, calculations figures indicate that further refinement become necessary to better address the exposure while **treating corn seeds** with **Methiocarb FS 500**, accounting initially for 229% (MoS 44) of the AOEL (0.013 mg/kg bw/day).
The RMS considered the process of loading and sowing of treated seeds as a worker re-entry scenario. Therefore, this point is now individually addressed in chapter CP 7.2.3 along with an acute exposure assessment due to the proposal of an AAOEL.

- **Measurement of Exposure during Seed Treatment**

Operator exposure estimations during **seed treatment** are also calculated using measured data generated in crop and product-specific study in Germany (see CP 7.2.1.2).
Results are presented in **Table 7.2.1-3 and Table 7.2.1-4**.

Table 7.2.1-3. Predicted longer term systemic operator exposure to methiocarb during corn seed treatment as a proportion of the AOEL based on the measured exposure values of a product and crop-specific study.

Task	Data type	Total systemic exposure[4]	% AOEL[5]
Handling of the product[1]	Parametric 75th percentile	0.002572	20
Handling treated seeds[2]	Parametric 75th percentile	0.002086[6]	16
Cleaning[3]	Parametric 75th percentile	0.001932	15

[1] The task of these operators included the short term activity *Loading & Calibration* and "*Additional activities*" like operation of the seed treater, seed supply, printing of labels, etc.; in plant II the operators controlled additionally controlled the automated bagging and stacking; [2] The operators conducted the bagging of the treated seeds and stacking of the filled bags either fully manual or semi-automated; [3] Cleaning of the treatment machinery; [4] Total systemic exposure = (Actual dermal exposure x Dermal absorption + Inhalation Exposure)/Individual body weight kg; Dermal absorption 2.0%; Inhalation absorption 100%; [5] as a proportion of the AOEL of 0.013 mg/kg bw/day. [6]Calculated considering an FFP2 RPE.

Table 7.2.1-4. Predicted acute systemic operator exposure to methiocarb during corn seed treatment as a proportion of the AOEL based on the measured exposure values of a product and crop-specific study.

Task	Data type	Total systemic exposure[4]	% AAOEL[5]
Handling of the product[1]	Parametric 95^{th} percentile	0.008462	50
Handling treated seeds[2]	Maximum	0.003673[6]	22
Cleaning[3]	Parametric 95^{th} percentile	0.009911	58

[1] The task of these operators included the short term activity *Loading & Calibration* and "*Additional activities*" like operation of the seed treater, seed supply, printing of labels, etc., in plant II the operators controlled additionally controlled the automated bagging and stacking; [2] The operators conducted the bagging of the treated seeds and stacking of the filled bags either fully manual or semi-automated; [3] Cleaning of the treatment machinery; [4] Total systemic exposure = (Actual dermal exposure x Dermal absorption + Inhalation Exposure)/Individual body weight kg; Dermal absorption 2.0%; Inhalation absorption 100%; [5] as a proportion of the AAOEL of 0.017 mg/kg bw/day.[6] Calculated considering an FFP2 RPE.

Assessment

According to the estimates calculated with the measured exposure values from a product and crop-specific operator exposure study (see CP 7.2.1.2) the predicted longer term systemic operator exposure to methiocarb is always below the systemic AOEL (0.013 mg/kg bw/day) when the operators wear adequate work clothing (e.g. work jacket and trousers or coverall), in addition gloves and an impermeable coverall (e.g. Tyvek type) during Cleaning and when handling the concentrate (**Methiocarb FS 500**) and a dust mask (FFP2 RPE) when handling treated seeds. Even if an operator performs additionally to his long term task a short term task (e.g. Cleaning) the calculated systemic operator exposure is still below the systemic AOEL. A dust mask (e.g. FFP S2) should be worn when activities in a dusty environment have to be performed (e.g. during cleaning with compressed air or during manual bagging or other whole day activities performed close to sources for dust emission).

Based on the parametric 75^{th} percentile values operator exposure to methiocarb in professional corn seed treatment plants during the long term tasks handling of the product and handling of treated seeds is 20% and 16% of the systemic AOEL, respectively. During the short term task of cleaning operator exposure to methiocarb is lower (15% of the AOEL) when the operators wear adequate work clothing and personal protective equipment (e.g. an impermeable coverall, gloves). Even when considering that operators perform cleaning activities additionally to a long term activity, operator exposure does not exceed the AOEL.

According to the estimates calculated with the measured exposure values from a product and crop-specific operator exposure study (see CP 7.2.1.2) the predicted acute systemic operator exposure to methiocarb is always below the systemic AAOEL (0.017 mg/kg bw/day) when the operators wear adequate work clothing (e.g. work jacket and trousers or coverall), in addition gloves and an impermeable coverall (e.g. Tyvek type) during Cleaning and when handling the concentrate (**Methiocarb FS 500**) and a dust mask (FFP2 RPE) when handling treated seeds.

Based on the parametric 95^{th} percentile values or the maximum, respectively, operator exposure to methiocarb in professional corn seed treatment plants during the long term tasks handling of the product and handling of treated seeds is 50% and 22% of the systemic AAOEL, respectively, when the

operators wear adequate work clothing and personal protective equipment as described earlier. During the short term task of cleaning operator exposure to methiocarb is 58% the AAOEL.

Conclusion

Based on the exposure estimates presented, there is no unacceptable risk anticipated for a given operator performing activities related ~~either~~ to seed treatment ~~or seed sowing~~ with the intended use of **Methiocarb FS 500** if adequate work clothing is worn (e.g. work jacket and trousers or coverall and in addition gloves when direct contact to treated seeds or contaminated surfaces is given).
During *Cleaning,* and *Loading & Calibration* an impermeable coverall and protective gloves must be worn. Respiratory equipment (e.g. mask FFP2 S2) has to be used when activities in a dusty environment have to be performed (e.g. during *Cleaning* or during manual *Bagging* in small rooms with limited air aspiration).

It must be considered, that the study results are representing an unrealistic worst case due to several reasons. In the formulation (and the prepared slurry) no sticker agents were used – not a common practice during the period the study was conducted, season 2004/2005. The confirmation of low dust content in the treated seeds was not required at that time.
The current requirements predict the use of dust reducing seed coatings or treatment technologies which lead to a dust reduced work environment and lower inhalation and dermal exposure values (must be also highlighted the very low penetration potential of the diluted formulation, 2%). Coating substances (e.g. *Peridian*®), when not already present in seed treatment formulations, must be intentionally added to promote better product adherence with consequent lower dust generation.

Therefore, it is expected that all operator exposure levels related to the exposure of grain dust containing methiocarb is extensively reduced at present due to such practices. Also the exposure results generated in the high tier study are considered to overestimate the exposure expected under current conditions during corn seed treatment activities.

Detailed information regarding the operator exposure estimates and exposure studies are presented in the following sections.

CP 7.2.1.1 Estimation of operator exposure

Exposure estimates for **seed treatment** and for **seed sowing** using the *SeedTROPEX* model were initially applied. Exposure estimates assume one layer of work clothing during all tasks while treating seeds (calibration, mixing/loading, bagging and cleaning) and protective gloves (except for bagging). Additionally mask was considered while executing cleaning activities in a given seed treatment facility.

In general, it is not the aim of operator exposure studies to generate data for **unprotected operators**. In these studies the operators wear their usual work clothes and dependent on the activities they have to perform additional personal protective equipment (PPE). Therefore, the option to differentiate between exposure with or without personal protective equipment **is not given**. But study results include data for total potential dermal exposure which correspond to the exposure that impinges on a given operator. However, this rather reflects the exposure of a naked operator as opposed to an operator without personal protective equipment. Therefore, exposure estimates are calculated **only for operators wearing usual work clothes** and dependent on the working activities they are wearing additional personal protective equipment.

Consideration on estimation of operator exposure with *SeedTROPEX*

Operator exposure estimation for **seed treatment** and **seed sowing** using the *SeedTROPEX* model was initially applied. The following the assumptions were used for the calculations:

Body weight:	60 kg
Seed treatment capacity:	2500 units/day (=50000 corn grains/unit)
Seed sowing capacity:	15 ha/day
Dilution factor:	1.2 (lowest dilution)
Personal protective equipment (PPE):	Standard clothing of the operators is one layer of work clothing during all tasks and in addition protective gloves except for bagging. Mask during cleaning related activities.

Detailed calculations with the *SeedTROPEX* model for **seed treatment** and **seed sowing** are presented in **Table 7.2.1.1-1** and **Table 7.2.1.1-2**, respectively.

Table 7.2.1.1-1. Predicted systemic exposure to Seed Treatment with Methiocarb FS 500 according to the *SeedTROPEX* model.

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	13.57	5.93	0.575	*1*	13.3656	5.9253	0.5754
Mixing / Loading	2.5961	2.596	0.064	*1*	2.5961	2.5961	0.0640
Bagging (mg/hr)	1.84	0.698	0.0054	*8*	14.7200	5.5840	0.0432
Cleaning	363	34.74	0.666666667	*1*	363.2320	34.7351	0.6667
Total route specific exposure (mg/person/day)					**394**	**48.8**	**1.35**
Dermal absorption/Inhaltion absorption (incl RPE reduction)					n/a	0.90%	100%
Route specific absorbed dose (mg/kg bw/day)						**0.0073**	**0.022**
Total absorbed dose (mg/kg bw/day)							**0.0298**

* exposure during bagging mg/hour

** frequency during bagging in hours/day

% of AOEL	229	0.013	mg/kg bw/day
MoS	44	1.3	mg/kg bw/day

SCENARIO VARIABLES		
Given a.i. concentration =	*308*	g/l
Given dilution factor =	*1.2*	
Given average bodyweight =	*60*	kg
Given Dermal absorption	*09*	%
Given Inhalation absorption =	*100*	%

Table 7.2.1.1-2. Predicted systemic exposure to Seed Sowing with Methiocarb FS 500 according to the *SeedTROPEX* model.

Route of exposure	Specific exposure [mg a.s./hour]		Working duration per day		Exposure result [mg/person/day]	Exposure result** [mg/kg bw/day]	Absorbed dose* [mg/kg bw/day]
Total Dermal	1.48	x	10 hours	=	14.8	0.247	*not applicable*
Actual Dermal	0.73	x	10 hours	=	7.3	0.122	0.0011
Total Inhalation	0.02	x	10 hours	=	0.20	0.0033	0.0033
Total systemic exposure							**0.0044**

*Dermal absorption: 0.9%; inhalation absorption 100%; body weight: 60 kg.

CP 7.2.1.2 Measurement of operator exposure

- **Measurement of operator exposure during seed treatment of corn seed**

The operator exposure study performed during seed treatment of corn with **Methiocarb FS 500** in professional seed treatment plants is summarised in the following. The study was conducted in compliance with the current OECD Principles of Good Laboratory Practice (GLP).

Report:	KCP 7.2.1.2/06 [redacted]; [redacted]; 2010; M-261386-02-1
Title:	Determination of operator exposure to methiocarb during seed treatment of maize with Mesurol® (FS 500) in Germany
Report No.:	MR-110/05
Document No.:	M-261386-02-1
Guideline(s):	not specified
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Material and methods

The purpose of the study was the determination of the dermal and inhalation exposure of operators to methiocarb during treatment of corn seeds with liquid dressing formulations in three different facilities during the season of 2004-2005. Previously in 2001, a similar study protocol was established in the same seed treatment plants. Evidences clearly show that improvements in the working environment and technical progress in the treatment equipment were performed in all three plants between periods. These progresses in the treatment equipment, improvements in the working environment and a better training of the working staff consequently lead to a decline of all operator exposure figures when compared to previous determinations. Therefore, as a representative of the **most up-to-date data**, regarding product and use specific exposure situation in a seed treatment facility, the 2005 study outcomes were taken into account for exposure estimation and assessment of risks.

In general the plants monitored are characterised by low to high level of automation. A low level of automation was given in the first plant monitored. In this plant *Bagging* and *Stacking* of the treated seeds was done manually as separate tasks. The *Bagging* activity included the preparation of the bags for the stitching station and was performed by two operators. One further operator (machinist) was responsible for running of the treatment line. This operator performed activities like operation of the seed treatment machinery/process, supply of dressing formulation and seed, printing of labels, etc. The supply of ready-to-use dressing formulation included agitation of the dressing liquid with an electrical stirrer, connecting the dressing container via a hose with the delivery pumps of the twin batch seed treater and calibration of the delivery pumps (i.e. *Loading & Calibration*).

The third plant monitored was equipped with an automated bagging station. However, still one operator was needed to run the bagging station (e.g. providing bags and labels). In addition this operator controlled the stitching station. Stacking of the bagged seed was still done manually. Again as in the first plant one additional operator (machinist) was responsible for running of the seed treatment machinery/process, and performing the *Loading & Calibration* as well as the seed supply.

The highest level of automation was given in the second plant where the whole bagging and stacking process was automated. Accordingly only one operator (machinist) was needed to run the whole seed

treatment process including *Bagging* and *Stacking*. This operator also performed the *Loading* activity. The *Calibration* of the metering pump was automated and regulated by the computerised control unit of the seed treater. The respective plant characteristics as well as the activities monitored are summarised in **Table 7.2.1.2-1**.

Table 7.2.1.2-1. Characteristics of the plants and tasks monitored.

	Plant I	**Plant II**	**Plant III**
Type of treater	Twin batch treater	Batch treater	Batch treater
Bagging	Manual	Automated	Automated
Stacking	Manual	Automated	Manual
Separate monitored tasks:			
- Treatment (machinist)	3 replicates OT1, OT2, OT3	3 replicates OM1, OM2, OM3	3 replicates OT4, OT5, OT6
- Bagging/stitching (bagger)	6 replicates OB1, OB2, OB3, OB4, OB5, OB6	n.a.	3 replicates OB7, OB8, OB9
- Stacking (stacker)	3 replicates OS1, OS2, OS3	n.a.	3 replicates OS4, OS5, OS6
- Cleaning	3 replicates OC1, OC2, OC3	3 replicates OC4, OC5, OC6	3 replicates OC7, OC8, OC9
Range of seed treated per monitored shift	26 – 35 tonnes	39 – 44 tonnes	31 – 37 tonnes
Treatment rate [kg a.s./ tonne of seed]	≈ 4	≈ 4.6	≈ 5

Operator exposure was determined for a usual working shift in the actual treatment season of corn seed. In this context it has to be noted that the short term task *Loading & Calibration* was one of the activities performed by the respective machinist operator except for the second plant where the *Calibration* of the metering pump was automated. In addition at all plants, operator exposure during the short term activity *Cleaning* was determined as a separate task.

Measurement of exposure

Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analysing a long sleeved shirt (cotton), work jacket and a pair of trousers (both cotton/polyester) as outer garments. For the working activities *Loading & Calibration* and *Cleaning* the operators were additionally provided with disposable coveralls. Exposure to the head was determined by a cap and face neck wipes. Exposure to the hands was determined via rinsing of the protective gloves (nitrile gloves) and hand washings. The results of the outer garments, the protective coverall, the gloves rinsing and the cap together with the results of the face/neck wipes, the underwear and the hand washings correspond to potential dermal exposure whereas the results of the underwear, the cap, the face/neck wipes and the hand washings are regarded as actual dermal exposure.
With regard to the machinist operators being responsible for *Treatment* and '*Additional activities'* (e.g. seed supply, bag and label supply) as well as for *Loading & Calibration*, exposure of the gloves (if used) and the hands were determined separately for the tasks *Additional activities* and *Loading & Calibration*. In addition, the cap worn when performing the *Additional activities* was replaced by the hood of the protective coverall worn when performing the *Loading & Calibration* task.

Inhalation exposure was measured via an IOM-sampler equipped with a glass fibre filter fixed to the garments at the breathing zone of the operator and connected to a personal powered air pump. The pump ran for the duration of the respective working task, except for operators OM1 (430 min duration of working task and 285 min of monitoring), OB3 (388 min duration of workings task and 333 min of monitoring) and OC4 (25 min duration of workings task and 20 min of monitoring). Results of inhalation exposure for these operators were corrected for the difference in task duration and sampling time. Moreover, field recovery values for IOM filters were at average 87%, which is below 95%. Therefore, according to the OECD Guidance for the conduct of studies of occupation exposure to pesticides during agricultural application (OECD/GD(97)148), IOM dosimeter results were corrected for the average field recovery.

For analysis the samples were extracted and the methiocarb residues in the extracts were determined by liquid chromatography with electrospray MS/MS-detection.

II. Findings

The exposure results of the study are summarised in the **Table 7.2.1.2-2**. The operators are grouped according to their main activities into three categories:

- **Handling of the product:** Treatment, Machinist;
- **Handling of treated seeds:** Bagger, Stacker;
- **Cleaning of the treatment equipment:** Cleaner.

Moreover, the operators of the three different plants are pooled in their respective categories due to the fact that the range of technical equipment, technical standard and working conditions in the monitored plant represents a realistic variety in the EU. In particular, activities of treatment operators and machinists are comparable in all plant and are not affected by the level of automation. The same is true for the cleaning operators. All plants used more or less the same techniques for cleaning the batch treaters, and in all three plants this was a manual process. The process of bagging and stacking was fully automated in plant II. In plant III, an automated bagging station was used, but stitching of the bags was controlled by one operator and stacking was done manually. In plant I, the bagging and stacking process was done manually. However, the different levels of automation for the process of bagging and stacking reflect a realistic variety of seed treatment plants found in the EU at present. Therefore, pooling the operators of the different plants accounts for all possible scenarios in the EU and therefore gives a realist estimate of exposure during seed treatment.

<u>Handling of the product</u>

For the treatment and machinists actual dermal exposure was in a very close range of 0.244 to 2.32 mg a.s./day. The corresponding figures for potential inhalation exposure amount to 0.0261 – 0.322 mg a.s./day.

The activities of the machinist and treatment operators in all plants was comparative and unaffected by the different level of automation. All operators performed a combination of short activities with a higher potential for contamination e.g. calibration or mixing/loading and operation of the machinery. The operation of the automated bagging and stacking equipment performed in plant II by the operators

OM1, OM2, OM3 is supposed not to contribute significantly to the overall exposure since this activity required no contact to contaminated surfaces or seeds.

Handling of treated seeds

Operators performing the bagging and stacking are classified into the same group. Activities performed by these operators include all steps following the treatment of the seeds, i.e. filling the bags, closing and labelling of bags, palletizing of full bags. The activities are performed usually by one person or by a team of operators who will change their positions during the day. In the study the operators were fixed to one task during the whole working day which reflects a highly conservative situation since the potential for exposure varies between the positions.

Nevertheless, even when considering the differences in the activities for the bagging and stacking operators actual dermal exposure was in a range of 0.535 to 7.021 mg a.s./day corresponding to a factor of about 14. The corresponding figures for potential inhalation exposure amount to 0.0561 – 2.382 mg a.s./day. The inhalation exposure range amounts to a factor of 42. Nevertheless, exposure results between the tasks and plants are overlapping and therefore the definition sub-classes is not indicated for the operators handling the treated seeds (i.e. baggers, stackers).

It has to be noted that within plant I *Bagging* (Operators OB1, OB2, OB3, OB4, OB5, OB6) was performed in a small and separated bagging room (about 2.5 m x 6 m x 3 m). As the supply of fresh air was very limited, dust content in the air was high. Therefore, potential inhalation exposure was higher in plant I (mean: 1.03 mg a.s./day) than in plant III (mean: 0.537 mg a.s./day). It can be stated that it is not good occupational practice to conduct fully manual bagging of the treated seeds in a small room with limited aspiration.

In accordance to the unfavourable working conditions, it was common practice in plant I that bagging operators in charge of the bagging process used respiratory protection equipment "*(...) during the whole working day.*" (i.e. RPE FFP 2 complying with European Standard EN 149:2001. See report p.18, lines 2-3). According to common seed treatment practice, evidenced by the present study, operators must use RPE during their entire shift, whenever a working environment with high dust content can be expected. Such protection minimizes the respiratory contamination to the corn seed dust in general and in particular to the contaminants derived from their treatment. Additionally, professional seed treatment facilities are foreseen to be equipped with exhaustion systems responsible to dramatically reduce the levels of seed dust contamination in the air.

RPE FFP 2 masks are individual devices most commonly disposable (single shift), available as needed to operators, especially in professional seed treatment facilities. These devices have in general a long shelf-life[3] and are manufactured to last during one full work shift and to be duly replaced with the start of a new one. Another class of RPE FFP 2 individual devices declared as re-usable demand some additional maintenance practices to ensure the respiratory protection yield. The best practices, irrespectively if a disposable or a non-disposable RPE FFP 2 is worn are also expected to be provided regularly to operators throughout training of safety procedures in professional seed treatment facilities. Therefore an operator whilst undertaking bagging/stacking activities on a dusty environment is requested and trained to keep his/her RPE FFP 2 device always functional. The criteria to use and maintain a RPE FFP 2, both disposable and non-disposable, follows the European Standard

[3] Technical Datasheet. 3M 8300 Series Particulate Respirators. http://solutions.3m.com/3MContentRetrievalAPI/BlobServlet?locale=en_WW&lmd=1256655532000&assetId=1180620493566&assetType=MMM_Image&blobAttribute=ImageFile

EN149:2001. They are indicated by manufactures in the product's use directions and are to be followed to ensure full yield of respiratory protection by[3,4]

- ensuring good storage and transportation conditions of RPEs;
- always ensuring the RPE is suitable of its application (i.e. is indeed an FFP 2 RPE); fits correctly; is worn during all periods of exposure and replaced when necessary;
- not using them with beards or other facial hair that may inhibit contact between the face and the product thus preventing a good seal;
- not altering, modifying, cleaning (not applicable to disposable devices which must be replaced after the end of every work shift. Non-disposable RPEs must be clean accordingly after every work shift) or repairing the mask;
- executing every time it is worn a *Fit Check*, normally composed by the correct positioning of the RPE and the airflow verification before entering a contaminated area;
- leaving the contaminated area (dusty environment) immediately if breathing becomes difficult; dizziness or other distress occurs; the mask becomes damaged; a taste or smell of contaminants is felt; an irritation occurs.

It is worth mentioning that potential inhalation exposure of the operators performing the *Stacking* task was significantly higher in plant III, especially on the first monitoring day. This finding is most likely attributable to the fact that on this day methiocarb treated seeds from the previous year was unpacked at another facility located next to the stacking operator.

Cleaning

The Cleaning task was performed in all plants in the same way independent of the level of automation. All plants were equipped with batch treaters. The cleaning task included the removal of solid residues and seeds out of the treatment chamber and the removal of treated seeds out of the transport unit for treated seeds. More or less the same techniques and tools e.g. scraper, vacuum cleaner were used by all operators. The similarity of the activities of all operators within the three plants is reflected in the close range of the measured actual dermal and potential inhalation exposure values. For the operators performing the Cleaning task actual dermal exposure was in the range from 0.0511 to 0.675 mg a.s./day and potential inhalation exposure covered a range from 0.0101 to 0.364 mg a.s./day.

[4]3M 8822 Dust/Mist Respirator (Valved) Fitting Instructions.
http://multimedia.3m.com/mws/media/531303O/3mtm-8822-fitting-poster.pdf

Table 7.2.1.2-2. Measured exposure to methiocarb.

Operator category	Operator ID	Protective clothing (ug/day)	Outer garments (ug/day)	Outer garments (shirt) (µg/day)	Inner garments (ug/day)	Hand washings (ug/day)	Gloves (ug/day)	Head exposure (ug/day)	Inhalation exposure (2L/min)*
Handling the product	OT1	325.9	1302	34.21	32.15	135.3	15920	41.98	2.511
	OT2	2239	3809	59.26	61.86	1105	4790	110.51	3.805
	OT3	3291	5317	94.4	60.59	303.1	29060	68.09	4.298
	OM1	2420	1442	22.42	52.68	428.5	158033	50.27	4.578#
	OM2	8227	1905	37.81	65.93	170.2	199255	69.94	5.999
	OM3	1154	3293	73.80	152.4	407.1	110935	126.0	7.279
	OT4	3177	15179	303.8	717.1	991.7	26860	304.2	18.22
	OT5	5609	8728	306.7	278.7	295.1	33690	213.2	30.44
	OT6	2644	14509	198.2	284.6	350.7	20673	168.2	30.94
Handling treated seeds	OB1		3612	134.9	70.77	957.7		170.0	16.63
	OB2		14662	666.2	107.6	252.8	4644	1539	142.4
	OB3		10056	518.2	122.8	1448	644.0	514.8	48.39#
	OB4		19780	1008	141.2	284.1	8303	1667	172.9
	OB5		5643	171.3	663.0	784.7		237.2	23.13
	OB6		16721	1017	182.1	426.8	4661	2505	189.0
	OB7		22365	470.4	784.5	2410	5452	445.1	90.16
	OB8		15059	306.1	467.8	1922	1917	316.0	29.38
	OB9		17101	341.6	219.4	2121	2119	333.1	35.47
	OS1		5356	292.5	641.7	141.4		209.7	10.78
	OS2		9011	319.1	374.6	188.2		344.6	24.23
	OS3		7943	206.1	94.00	102.6		132.5	5.394
	OS4		33082	2430	1014	573.4		3004	229.1
	OS5		19977	1316	418.0	682.8		907.9	57.28
	OS6		17916	1076	379.1	559.5		604.3	65.31
Cleaner	OC1	5097	88.93	3.770	19.83	54.68	53680	0.8936	3.345
	OC2	413826	303.6	17.94	56.14	85.98	68000	6.984	35.00
	OC3	33952	137.8	18.99	74.88	221.3	33080	9.222	14.60
	OC4	10312	54.07	3.530	14.05	28.26	32330	2.296	1.341#
	OC5	8024	20.00	3.640	15.56	42.92	34500	1.218	0.9747
	OC6	12330	25.30	4.420	14.35	31.78	15880	0.5999	0.9805
	OC7	17659	222.7	48.53	277.2	337.3	14830	11.89	9.118
	OC8	8133	177.1	33.18	149.0	419.4	15470	6.484	9.713
	OC9	7823	81.52	34.59	99.15	274.7	21350	9.879	19.93

* Inhalation exposure has been corrected for low average field recovery (87%).
# For operators OM1, OB3 and OC4 inhalation exposure results have been corrected due to the duration of air samples being less than the duration of activity monitored.

III. Conclusion

The study results represent the exposure data from use of corn seed treatment in professional plants in Germany. The different levels of automation in the observed plants cover the range of the equipment used currently in the EU. In 2005 when the study was conducted a restriction of the dust content in the treated maize seed was not prescribed and stickers were not used to reduce the dust content. The study data generated in the study therefore cover work conditions that are not relevant anymore in the EU during treatment of maize seed since it can be expected that the higher dust abrasion from the seed leads to higher dust concentration in the air and higher inhalation exposure results of the operators.

Thus, it can be concluded that the study conditions (i.e. the selected plants, the work tasks, the work rate, the work conditions, etc.) and subsequently the determined exposure figures are conservative measurements for the considered exposure scenario for the **Methiocarb FS 500** use.

Calculation of operator exposure during corn seed treatment based on measured data

For the calculation of the operator exposure during corn seed treatment the measured exposure data of a product and crop specific study was used. This covers a wide range of technical equipment, technical standards and working conditions and includes a suitable number of replicates. Therefore, based on the measured exposure data the use of the 75th percentile values is regarded as a reasonable approach for calculation of longer term operator exposure during corn seed treatment in professional plants. As the RMS proposed an AAOEL for methiocarb, an acute exposure assessment will be conducted in addition which either uses the parametric estimate of the 95th percentile or the maximum, depending on the sample size and whichever value is higher. This is in accordance to EFSA's recommendation for the statistical analysis of exposure study data. Moreover, the range of technical equipment, technical standard and working conditions in the monitored plant represents a realistic variety in the EU, and therefore, the results of the three plants are combined for statistical analysis.

For some of the operators performing bagging and stacking (handling of treated seeds) high potential inhalation exposure values were observed as a result of their work activities performed in a very dusty work environment. Grain dust itself, independent if it is contaminated with the plant protection product or not, can cause critical health effects due to sensitising properties. It should be ensured that exposure to airborne grain dust is as low as is reasonably practicable and should not exceed 10 mg dust/m3 averaged over eight hours[5]. Hence concerning inhalation exposure, the use of RPE has to be considered for those operators who are working in a dusty environment (i.e. bagging in plant I, stacking in plant III) due to the rules for occupational hygiene and worker protection. Accordingly, an estimate of actual inhalation exposure with the use of FFP2 RPE assuming a mitigation factor of 0.1 has been calculated for all operators undertaking bagging and stacking tasks.

[5] UK HSE: Control of exposure to grain dust. Available at: http://www.hse.gov.uk/pubns/indg140.pdf

Assumptions for calculation of operator exposure to methiocarb during seed treatment:

The following assumptions have been made in calculating operator exposure to methiocarb during seed treatment in professional plants:

- Potential dermal exposure (PDE) is the sum of outer garments, gloves, inner garments, hand wash, face/neck wipe (including caps, if worn) and represents the dermal exposure to which an operator would be subject to wearing no clothing.

- Actual dermal exposure (ADE) is the sum of inner garments, hand wash and face/neck wipes and represents dermal exposure to which an operator would be subject to the following PPE:

  1. Wear suitable protective clothing (coveralls), suitable protective gloves when handling the concentrate, handling contaminated surfaces, or handling treated seed.
  2. Wear suitable protective clothing (coveralls, coveralls worn beneath a second, disposable coverall) when cleaning machinery and when handling the concentrate during mixing/loading and calibration.
  3. Wear suitable protective clothing (coveralls) when bagging treated seed.

- Potential inhalation exposure (PIE) is equivalent to the results for air filters corrected for a default breathing rate of 20.8 liters/minute according to the EFSA Guidance.
- Actual inhalation exposure (AIE) was calculated for ~~those~~ operators who are working in a dusty environment where the grain dust alone may cause critical health effects. Therefore it is appropriate to assume a dust mask for all baggers and stackers. In this case RPE (dust mask 90% protection) is considered for calculation.
- Dermal absorption of the highest dilution ~~0.9~~ 2 %
- Inhalation absorption 100 %
- Operator body weight: Individual body weights

It is worth mentioning that an AAOEL of 0.017 mg/kg bw/day is used for the acute assessment, which in our opinion is the correctly calculated AAOEL as described in Volume 1 of the RAR.

The estimated values of systemic operator exposure to methiocarb are summarised in **Table 7.2.1.2-3**. The statistic summary is presented in **Table 7.2.1.2-4.**

Table 7.2.1.2-3. Predicted systemic exposure to methiocarb.

Operator ID	Body weight (kg)	PDE (µg/day)	ADE (µg/day)	PIE (µg/day at 16.7 L/min)	AIE (µg/day at 16.7 L/min)	Total systemic PDE (mg/kg bw/day)	Total systemic ADE (mg/kg bw/day)	Total systemic ADE and AIE (mg/kg bw/day)	% AOEL PDE	% AOEL ADE	% AOEL ADE and AIE
OT1	90.5	17750	209.5	18.24		0.00197	0.00022		15	2	
OT2	90.5	12063	1277	27.64		0.00151	0.00043		12	3	
OT3	90.5	38126	431.8	31.22		0.00417	0.00039		32	3	
OM1	86.0	162399	531.5	22.05		0.01735	0.00031		133	2	
OM2	86.0	209661	306.1	43.58		0.02245	0.00084		173	4	
OM3	86.0	116016	685.6	52.88		0.01276	0.00069		98	5	
OT4	70.5	47229	2013	132.1		0.00790	0.00213		61	14	
OT5	70.5	48907	787.0	221.1		0.00938	0.00324		72	25	
OT6	70.5	38659	803.4	224.8		0.00812	0.00329		62	25	
OB1	72.5	4775	1199	120.79	12.08	0.00226	0.00181	0.00032	17	14	2
OB2	76.0	20333	1899	1034.3	103.5	0.01602	0.01383	0.00159	123	106	12
OB3	68.0	12789	2085	301.67	30.17	0.00613	0.00471	0.00072	47	36	6
OB4	76.0	29516	2092	1255.7	125.6	0.02002	0.01677	0.00190	154	129	15
OB5	75.5	7262	1685	168.6	16.8	0.00309	0.00243	0.00042	24	19	3
OB6	76.0	23008	3114	1373	137.3	0.02079	0.01844	0.00218	160	142	17
OB7	80.0	31482	3640	655.0		0.01173	0.00860	0.00860	90	66	66
OB8	80.0	19673	2706	213.4		0.00488	0.00297	0.00297	38	23	23
OB9	80.0	21902	2673	257.7		0.00568	0.00352	0.00352	44	27	27
OS1	68.0	6431	992.8	78.30		0.00200	0.00128	0.00128	15	10	10
OS2	75.5	9893	907.5	176.0		0.00351	0.00244	0.00244	27	19	19
OS3	68.0	8346	329.2	39.19		0.00168	0.00062	0.00062	13	5	5
OS4	125.0	37099	4591	1664.4	166.4	0.01399	0.01365	0.00166	123	105	13
OS5	125.0	22303	2009	416.1		0.00494	0.00347	0.00347	38	27	27
OS6	125.0	19931	1543	476.5		0.00523	0.00391	0.00391	40	30	30
OC1	72.5	58944	75.40	24.30		0.00765	0.00034		59	3	
OC2	75.0	482289	149.1	254.3		0.06126	0.00341		471	26	
OC3	75.0	67485	305.4	106.0		0.00951	0.00145		73	11	
OC4	73.0	42742	44.61	7.79		0.00538	0.00011		41	1	
OC5	92.0	42606	59.69	7.08		0.00424	0.00008		33	1	
OC6	92.0	28286	46.72	7.71		0.00284	0.00008		22	1	
OC7	97.5	33375	626.4	66.24		0.00376	0.00074		29	6	
OC8	97.5	24381	574.9	70.56		0.00297	0.00078		23	6	
OC9	97.5	29663	383.8	144.8		0.00422	0.00152		32	12	

Table 7.2.1.2-3. Predicted systemic exposure to methiocarb.

Operator ID	Body weight (kg)	ADE mg/day)	PIE (mg/day)	AIE (mg/day)	Total systemic exposure (mg/kg bw/day)	% AOEL	% AAOEL	Total systemic exposure (mg/kg bw/day) with FFP2RPE	% AOEL	% AAOEL
OT1	90.5	0.2436	0.02612		0.0003424	2.6	2.0			
OT2	90.5	1.336	0.03957		0.0007325	5.6	4.3			
OT3	90.5	0.5262	0.04470		0.0006102	4.7	3.6			
OM1	86.0	0.5539	0.04761		0.0006825	5.2	4.0			
OM2	86.0	0.3439	0.06239		0.0008054	6.2	4.7			
OM3	86.0	0.7594	0.07570		0.001057	8.1	6.2			
OT4	70.5	2.317	0.1895		0.003345	26	20			
OT5	70.5	1.094	0.3165		0.0048003	37	28			
OT6	70.5	1.002	0.3218		0.004849	37	29			
OB1	75.5	1.333	0.1730	0.01730	0.002644	20	16	0.0003822	4.5	3.4
OB2	76.0	2.566	1.481	0.1481	0.02016	155	119	0.0026241	20	15
OB3	68.0	2.603	0.5032	0.05032	0.008166	63	48	0.0015856	12	8.9
OB4	76.0	3.1	1.798	0.1798	0.02447	188	144	0.0021814	24	19
OB5	75.5	1.856	0.2405	0.02405	0.003677	28	22	0.0008102	6.2	4.8
OB6	76.0	4.131	1.965	0.1965	0.02695	207	159	0.0036729	28	22
OB7	80.0	4.11	0.9377	0.09377	0.01273	98	75	0.0021996	17	13
OB8	80.0	3.012	0.3055	0.03055	0.004572	35	27	0.0011349	8.7	6.7
OB9	80.0	3.015	0.3689	0.03689	0.005365	41	32	0.0012149	9.3	7.1
OS1	68.0	1.285	0.1121	0.01121	0.002026	16	12	0.0005428	4.2	3.2
OS2	75.5	1.227	0.2520	0.02520	0.003663	28	22	0.0006588	5.1	3.9
OS3	68.0	0.5322	0.05610	0.00561	0.0009824	8	5.8	0.0002399	1.8	1.4
OS4	129.0	7.021	2.382	0.2382	0.01956	150	115	0.0029354	23	17
OS5	129.0	3.324	0.5957	0.05957	0.005133	40	30	0.0009771	7.5	5.7
OS6	129.0	2.649	0.6792	0.06792	0.005671	44	34	0.0009326	7.2	5.5
OC1	72.5	0.07917	0.03479		0.0005016	3.9	3.0			
OC2	75.0	0.16708	0.3640		0.004898	38	29			
OC3	75.0	0.32439	0.1518		0.002111	16	12			
OC4	73.0	0.04814	0.01394		0.0002042	1.6	1.2			
OC5	92.0	0.06333	0.01014		0.0001240	1.0	0.73			
OC6	92.0	0.05114	0.01020		0.0001226	0.97	0.72			
OC7	97.5	0.6749	0.09483		0.001112	8.5	6.5			
OC8	97.5	0.608	0.1010		0.001161	8.9	6.8			
OC9	97.5	0.4184	0.2073		0.002212	17	13			

Table 7.2.1.2-4. Statistic summary.

Activity	Statistic	Without PPE		With PPE		With PPE and RPE	
		mg/kg bw/d	% of AOEL	mg/kg bw/d	% of AOEL	mg/kg bw/d	% of AOEL
Handling of the product	Empirical 75th percentile	0.0128	98	0.00213	16	n.a.	n.a.
	Empirical 95th percentile	0.0204	157	0.00327	25	n.a.	n.a.
	Maximum	0.0224	173	0.00329	25	n.a.	n.a.
	Parametric 75th percentile	0.0138	106	0.00166	13	n.a.	n.a.
	Log normal?	yes		yes			
Handling of treated seeds	Empirical 75th percentile	0.0139	107	0.0171	86	0.00322	25
	Empirical 95th percentile	0.0202	156	0.0173	133	0.00534	41
	Maximum	0.0208	160	0.0184	142	0.00860	66
	Parametric 75th percentile	0.0109	84	0.00873	67	0.00322	25
	Log normal?	yes		yes		yes	
Cleaning	Empirical 75th percentile	0.00765	59	0.00145	11	n.a.	n.a.
	Empirical 95th percentile	0.0406	312	0.00265	20	n.a.	n.a.
	Maximum	0.0613	471	0.00340	26	n.a.	n.a.
	Parametric 75th percentile	0.0126	97	0.00130	10	n.a.	n.a.
	Log normal?	no		yes			

Table 7.2.1.2-4. Statistical summary.

Activity	Statistic	Total systemic exposure			Total systemic exposure with FFP2 RPE.		
		mg/kg bw/d	% AOEL	% AAOEL	mg/kg bw/d	% AOEL	% AAOEL
Handling of the product	Empirical 75th percentile	0.003345	26%	20%	n.a.	n.a.	n.a.
	Empirical 95th percentile	0.004829	37%	28%	n.a.	n.a.	n.a.
	Maximum	0.004849	37%	29%	n.a.	n.a.	n.a.
	Parametric 75th percentile	0.002572	20%	15%	n.a.	n.a.	n.a.
	Parametric 95th percentile	0.008462	65%	50%	n.a.	n.a.	n.a.
	Log normal?	Yes			n.a.		
Handling of treated seeds	Empirical 75th percentile	0.01615	124%	95%	0.002412	19%	14%
	Empirical 95th percentile	0.02521	194%	148%	0.003329	26%	20%
	Maximum	0.02695	207%	159%	0.003673	28%	22%
	Parametric 75th percentile	0.01297	100%	76%	0.002086	16%	12%
	Parametric 95th percentile	0.03821	294%	225%	0.004905	38%	29%
	Log normal?	Yes			Yes		
Cleaning	Empirical 75th percentile	0.002111	16%	12%	n.a.	n.a.	n.a.
	Empirical 95th percentile	0.003824	29%	22%	n.a.	n.a.	n.a.
	Maximum	0.004898	38%	29%	n.a.	n.a.	n.a.
	Parametric 75th percentile	0.001932	15%	11%	n.a.	n.a.	n.a.
	Parametric 95th percentile	0.009971	76%	58%	n.a.	n.a.	n.a.
	Log normal?	Yes			No		

~~Summary of longer term operator exposure form the proposed uses of Methiocarb FS 500~~

~~Activity~~	~~Total ADE systemic exposure* (mg/kg bw/day)~~	~~% AOEL~~
~~Handling the product~~	~~0.00166~~	~~13~~
~~Handling of treated seeds~~	~~0.00873~~	~~67~~
~~Cleaning~~	~~0.00130~~	~~10~~

~~*parametric 75th percentile; ** 0.013 mg/kg bw/day~~

Summary of longer term operator exposure from the proposed uses of Mesurol FS 500

Activity	Total systemic exposure (mg/kg bw/day)	% AOEL	Total systemic exposure (mg/kg bw/day) with FFP2 RPE	% AOEL
Handling the product	0.002572	20%	n.a.	n.a.
Handling of treated seeds	0.01297	100%	0.002086	16%
Cleaning	0.001932	15%	n.a.	n.a.

Summary of acute operator exposure from the proposed uses of Mesurol FS 500

Activity	Total systemic exposure (mg/kg bw/day)	% AAOEL	Total systemic exposure (mg/kg bw/day) with FFP2 RPE	% AAOEL
Handling the product	0.008462	50%	n.a.	n.a.
Handling of treated seeds	0.02695	159%	0.003673	22%
Cleaning	0.009911	58%	n.a.	n.a.

CP 7.2.2 Bystander and resident exposure

Treatment of corn seeds with **Methiocarb FS 500** is usually performed in professional plants where no person is around whose presence is quite incidental and unrelated to the work. Further, no other (not involved) persons are allowed to enter into a given plant. Therefore, bystander exposure to **Methiocarb FS 500** during seed treatment is not relevant or unlikely to occur. During loading of the seed treated with **Methiocarb FS 500** it is highly unlikely that bystander exposure will occur. However, even in the theoretical case it is unlikely that bystander exposure is higher than that of an operator.

~~Therefore, a detailed calculation or even measurement of bystander exposure is considered to be not necessary for the intended use of **Methiocarb FS 500**.~~

However, the RMS is of the opinion that a forklift truck driver is a person, who works in the plant but is not directly involved in the seed treatment process, and therefore represents a bystander in a seed treatment plant. The SeedTROPEX study data included the exposure of three forklift truck drivers operating in a seed treatment plant, which should be used generically to assess the bystander exposure in a seed treatment plant.

The applicant does not agree with the opinion of the RMS, because the applicants understanding of a forklift truck driver is a regular employee of the plant with a regular working day within the treatment facility. Such a person takes action to avoid or control exposure and is therefore equipped with safety/protection measures as needed. This is underpinned by the fact that often a forklift truck driver is also involved in other activities of the seed treatment process and thereby needs to be a trained person. Therefore, the forklift truck driver does not represent a bystander as defined in the EFSA guidance on assessment of non-dietary exposure in the applicant's opinion.

Despite the disagreement between the applicant and the RMS in the definition of a bystander in a seed treatment plant, the applicant is willing to address this point by providing exposure calculations according to the following considerations and assumptions:

The SeedTROPEX model underlying dataset comprises two seed treatment studies. The report of the study conducted in the UK includes exposure data generated for forklift truck drivers. These data could be used to represent a so called "background contamination", which a person whose presence is quite incidental and unrelated to work involving pesticides might be exposed to. It is clear that each person belonging to the plant's staff even if the work is restricted mainly to e.g. office work must know about the safety regulations in the plants and therefore is protected accordingly. Also persons who are not staff members but performing activities in the plant e.g. truck drivers loading or unloading the truck or people maintaining the equipment must be instructed to follow the safety rules of the plant. Nevertheless, those people might ignore the rules and might be exposed to the background contamination in the plant. Anyhow, those people are not exposed for whole working days. Considering this it can be concluded, that this group of persons is exposed not higher than the operators.

CP 7.2.2.1 Estimation of bystander and resident exposure

~~Considered to be not necessary (see CP 7.2.2)~~

According to the opinion of the RMS, the forklift truck driver is considered as a bystander in a seed treatment plant. Therefore, the SeedTROPEX model underlying study conducted in the UK, which

includes exposure data for three forklift truck drivers, will be used in the following to assess the bystander exposure during seed treatment of maize with Mesurol FS 500.

The RMS considered the potential dermal exposure of the forklift truck drivers without assuming any clothing, calculated the potential inhalation exposure with a breathing rate of 29 L/min as proposed in the respective study report and assumed duration of exposure of 8 hours for the calculation of systemic exposure. Moreover, the RMS set a dermal absorption value of 2%, which refers to the highest possible product dilution, against a concentration of Methiocarb in the formulation of 500 g/L, which refers to the concentration of Methiocarb in an undiluted product and therefore introduces additional conservatism into the exposure calculation.

The applicant is of the opinion that these assumptions highly overestimate the exposure of a bystander. Therefore, there are different options how the original SeedTROPEX data can be evaluated to describe a bystander exposure in a more realistic manner:

a) The dermal exposure will be calculated as a worst case with a concentration of Methiocarb in the treatment slurry of 278 g/L (1:1.8 dilution) and the corresponding dermal absorption value of 2% (*pro rata* corrected for 1:1.8 dilution).

b) The dermal exposure of the forklift truck driver will be calculated assuming light clothing (t-shirt and shorts) because it is very unlikely that the forklift truck driver will not wear any clothing.

c) A breathing rate of 20.8 L/min will be assumed for the forklift truck driver. This is also in accordance with the breathing rate which is proposed for operators and workers for a whole working day in the EFSA Guidance on pesticide exposure assessment of operators, workers, residents and bystanders. A breathing rate of 29 L/min for a whole working day is unlikely high and would typically not occur while driving a forklift truck.

d) Exposure duration of 2 hours will be assumed for the bystander because it is not very probable that a person whose presence is quite incidental and unrelated to the work would be in a seed treatment plant for a whole working day. Therefore, exposure duration of 2 hours is considered as sufficiently conservative.

In the following, the four options listed above will be evaluated to assess the bystander exposure during seed treatment of maize grains with Mesurol FS 500. The longer term exposure to methiocarb for bystanders during the seed treatment process is calculated using the geometric mean and the parametric 75th percentile of data supporting the Seed-TROPEX model. Due to the small sample size (3 forklift truck drivers) it is considered that the parametric 95th percentile should be used to calculate acute exposure to bystanders rather than the sample maximum due to the uncertainty of the underlying population.

It is worth mentioning that an AAOEL of 0.017 mg/kg bw/day is used for the acute assessment, which in our opinion is the correctly calculated AAOEL as described in Volume 1 of the RAR.

Bystander exposure assessment considering the dermal exposure and a.s. concentration of the treatment slurry, light clothing of the forklift truck driver, a breathing rate of 20.8 L/min and 2h exposure duration

Table 7.2.2.1-1: Statistical analysis of exposure to bystanders using UK data of SeedTROPEX model

Worker Number	Potential Dermal Exposure (ml formulation/h)	Actual Dermal Exposure (ml formulation/h)	Inhalation exposure (ml formulation/h)
Worker No. 1	0.001302	0.001036	0.0000049
Worker No. 7	0.000579	0.000492	0.0000034
Worker No. 13	0.000592	0.000584	0.0000175
Geometric mean	0.000764	0.000668	0.0000066
Empirical 75th percentile	0.000947	0.000840	0.0000112
Parametric 75th percentile	0.001181	0.000964	0.0000149
Empirical 95th percentile	0.001231	0.000990	0.0000163
Parametric 95th percentile	0.003623	0.002483	0.0001223
Maximum	0.001302	0.001036	0.0000175

The systemic exposure of the bystander is calculated using the following equation:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(ADE \times DA + PIE) \times d \times c}{BW}$$

ADE = Actual dermal exposure in mL/hr
PIE = Potential inhalation exposure in mL/hr
DA = Dermal Absorption of 1:1.8 diluted Mesurol FS 500 (=2%)
d = Exposure duration in hours (= 2 hrs)
c = Concentration of active ingredient in the treatement slurry in g/L (=278 g/L)
BW = Body weight in kg (= 60 kg)

Longer term exposure to bystanders using geometric mean exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(0.000668 \times 2\% + 0.0000066) \times 2 \times 278}{60}$$

= 0.00018 mg/kg bw/day = 1.4% of the AOEL

Longer term exposure to bystanders using the parametric 75th percentil exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(0.000964 \times 2\% + 0.0000149) \times 2 \times 278}{60}$$

= 0.00032 mg/kg bw/day = 2.4% of the AOEL

The longer term exposure to methiocarb for bystanders during the seed treatment process calculated using the geometric mean and the parametric 75th percentile of data supporting the Seed-TROPEX

model are both within acceptable limits, when systemic exposure is calculated assuming the active substance concentration of the treatment slurry together with the dermal absorption value of the diluted product, light clothing of the forklift truck driver, a breathing rat of 20.8 L/min and 2 hours working duration.

Acute exposure to bystanders using the parametric 95th percentil exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(0.002483 \times 2\% + 0.0001223) \times 8 \times 278}{60}$$

$$= 0.0016 \text{ mg/kg bw/day} = 9.4\% \text{ of the AAOEL}$$

The estimated acute exposure to bystanders based on the parametric 95th percentile of forklift truck driver exposure data supporting the Seed-TROPEX model is within acceptable limits, when systemic exposure is calculated assuming the active substance concentration of the treatment slurry together with the dermal absorption value of the diluted product, light clothing of the forklift truck driver, a breathing rat of 20.8 L/min and 2 hours working duration.

CP 7.2.2.2 Measurement of bystander and resident exposure

Considered to be not necessary (see CP 7.2.2)

CP 7.2.3 Worker exposure

The only intended use of **Methiocarb FS 500** is treating seeds prior to sowing. Consequently no re-entry scenario is given. ~~Therefore, worker exposure to **Methiocarb FS 500** is not applicable.~~

However, the RMS defines the worker exposure as an exposure during loading and sowing of treated seed. The applicant is of the opinion that a person handling treated seeds for sowing activities mandatory has to be an experienced person. For such people a general awareness of handling seeds that are treated according to the seed bag label information can be assumed. This involves the understanding on how to protect during handling appropriately. The awareness and information level might not necessarily be comparable for a "worker per definition" (EFSA), that is to say "persons who, as part of their employment, enter an area that has been treated previously with a PPP or who handle a crop that has been treated with a PPP." Such people might not be mandatory informed about details of the PPP, application measures or further aspects.

Nevertheless, the applicant is willing to address the RMS`s request for an exposure assessment of workers and therefore provides exposure estimations for loading/sowing of treated seeds with the SeedTROPEX model. Moreover, as a refinement option, exposure estimations during loading and sowing of treated seeds are also calculated using measured data generated in a crop specific exposure study in Germany and Italy.

CP 7.2.3.1 Estimation of worker exposure

~~Considered to be not applicable (see CP 7.2.3)~~

The estimated exposures based on the loading and sowing studies supporting the SeedTROPEX model are given in the below table.

Table 7.2.3.1-1: Statistical analysis of exposure to workers loading and sowing using Seed-TROPEX data

Subject Number		Total Potential Dermal exposure (mg/hr)	Estimated Actual Dermal exposure (mg/hr)	Potential Inhalation exposure (mg/hr)
UK Data	Worker No. 1	1.9400	1.3800	0.0120
	Worker No. 2	0.1300	0.0670	0.0070
	Worker No. 3	1.2700	0.7800	0.0140
	Worker No. 4	2.0600	1.3700	0.0050
	Worker No. 5	1.5300	1.0500	0.0070
	Worker No. 6	4.5300	0.6950	0.1440
	Worker No. 11	0.4330	0.1720	0.0900
	Worker No. 12	1.3200	0.8000	0.0220
	Worker No. 13	1.7200	1.4400	0.0030
	Worker No. 14	0.3460	0.2250	0.0020
	Worker No. 15	1.6300	1.2900	0.0250
	Worker No. 16	4.1600	2.8900	0.0660
	Worker No. 17	1.8000	1.2200	0.0560
French Data	Farm No 1	2.5400	0.8640	0.0250
	Farm No 2	0.9400	0.3080	0.0360
	Farm No 3	3.2200	1.2700	0.0190
	Farm No 4	0.7400	0.3410	0.0320
	Farm No 5	4.7700	1.1300	0.0140
	Farm No 6	3.2800	1.4400	0.0260
Geometric mean		1.4787	0.7331	0.0186
Empirical 75th percentile		2.8800	1.3300	0.0340
Parametric 75th percentile		2.8619	1.4083	0.0412
Empirical 95th percentile		4.5540	1.5850	0.0954
Parametric 95th percentile		7.8033	3.7968	0.1378
Maximum		4.7700	2.8900	0.1440

The estimated actual dermal exposure is based on the clothing/PPE worn in the Seed-TROPEX studies. Workers monitored in the studies wore cotton trousers and jacket, over inner dosimeter clothing. It is considered that protective coveralls are suitable to represent the clothing worn in the study. Workers in the study were also supplied with protective gloves if normally worn.

Systemic exposure is calculated with the following equation:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(ADE \times DA + PIE) \times d}{BW}$$

ADE = Actual dermal exposure in mg/hr
PIE = Potential inhalation exposure in mg/hr
DA = Dermal Absorption of 1:1.8 diluted Mesurol FS 500 (= 2%)
d = Exposure duration in hours (= 10 hrs)
BW = Body weight in kg (= 60 kg)

Longer term exposure to workers during loading and sowing of treated seeds using geometric mean exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(0.7331 \times 2\% + 0.0186) \times 10}{60}$$

$$= 0.00554 \text{mg/kg bw/day} = 42.3\% \text{ of the AOEL}$$

Longer term exposure to workers during loading and sowing of treated seeds using the parametric 75th percentil exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(1.4083 \times 2\% + 0.0412) \times 10}{60}$$

$$= 0.0116 \text{ mg/kg bw/day} = 88.9\% \text{ of the AOEL}$$

The longer term exposure to methiocarb for workers during loading and sowing of treated seeds calculated using the geometric mean and the parametric 75th percentile of data supporting the Seed-TROPEX model are both within acceptable limits.

For calculating the potential and actual dermal exposure to workers the parametric 95th percentile of the exposure data from the Seed-TROPEX studies is greater than the sample maximum. The sample size of the data set is 19, therefore it is considered that the sample maximum should be used to estimate acute exposure in line with the EFSA guidance. For the inhalation exposure to workers the parametric 95th percentile of the exposure data from the Seed-TROPEX studies is below the sample maximum, therefore the parametric 95th percentile has been used to calculate acute exposure during loading and sowing seed.

Again, it is worth mentioning that an AAOEL of 0.017 mg/kg bw/day is used for the acute assessment, which in our opinion is the correctly calculated AAOEL as described in Volume 1 of the RAR.

Acute exposure to workers during loading and sowing of treated seeds using the parametric 95th percentil exposure value is calculated to be:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(2.8900 \times 2\% + 0.1378) \times 10}{60}$$

$$= 0.0326 \text{ mg/kg bw/day} = 192\% \text{ of the AAOEL}$$

The estimated acute exposure to workers loading and sowing seed treated with 'Mesurol FS 500' is above acceptable limits based on the clothing/PPE worn in the study.

An estimate of acute exposure to workers with the use of FFP2 RPE during the loading and sowing process with mitigation factor of 0.1 is provided below.

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(2.8900 \times 2\% + 0.1378 \times 0.1) \times 10}{60}$$

$$= 0.01193 \text{ mg/kg bw/day} = 70\% \text{ of the AAOEL}$$

The estimated acute exposure to workers during loading and sowing of treated seed is within acceptable limits when assuming the use of FFP2 RPE.

The RMS proposes that a closed cab with suitable in-cab dust filtration system should be used in preference to FFP2 RPE during a whole working day. However the applicant cannot assume that a closed cab with suitable in-cab dust filtration system is available to all farmers in the EU, and wearing a FFP2 RPE during a whole working day is very inconvenient for the operator and should be avoided if possible. Moreover, higher exposure values are expected during loading of the treated seeds as the operator come into contact with the treated seed via the dermal and the inhalative route. Exposure during seed sowing is expected to be lower. However, the underlying study of the SeedTROPEX model does not allow distinguishing between exposure during loading and sowing of treated seed. Moreover, the data used in the SeedTROPEX model refer to seed sowing of cereals, but the techniques used for sowing cereals and maize are substantially different, and therefore, exposure data derived from cereals sowing do not necessarily give a realistic estimate of the exposure during loading and sowing of maize.
Therefore, to address the above mentioned issues, the applicant presents a crop specific study for loading and sowing of treated seeds to refine the worker exposure assessment.

CP 7.2.3.2 Measurement of worker exposure

~~Considered to be not applicable (see CP 7.2.3)~~

The worker exposure study performed during loading and sowing of Gaucho® treated corn seeds in Italy and Germany is summarised in the following. The study was conducted in compliance with the current OECD Principles of Good Laboratory Practice (GLP). Exposure estimates will be used generically to calculate the exposure during loading and sowing of Mesurol FS 500 treated corn seeds.

Report:	KCP 7.2.3.2/01 [redacted],; 2008; M-274182-03-1
Title:	Determination of operator exposure to Imidacloprid during loading/sowing of Gaucho-treated maize seeds under realistic field conditions in Germany and Italy
Report No.:	IF-05/00328969
Document No.:	M-274182-03-1
Guideline(s):	OECD Environmental Health and Safety Publications, Series on Testing and Assessment, No. 9, OECD/GD(97)148, Paris, France US EPA OPPTS 875.1600
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Materials and methods

The study was conducted to determine the dermal and inhalation exposure of operators to imidacloprid when loading and sowing Gaucho® treated corn seeds with pneumatic sowing machines on farms in Italy and Germany. In total 16 operators were monitored, four in Italy and twelve in different regions of Germany (three in Bavaria, four in Saxony-Anhalt and Brandenburg, and finally five in the [redacted] and [redacted] region). The farms were selected with respect to many different types of pneumatic sowing machines and many various local modes of corn sowing. Therefore, the data of this study cover a broad range of sowing aspects and can be considered as representative for corn drilling in Europe.

The monitoring began in Italy within the typical local season for corn sowing on 4th April 2005 and ended in [redacted]land on 24th May 2005. The loading of seed hoppers and the drilling phase were monitored separately. Depending on local requirements the hoppers were filled two to six times and one to three different corn varieties were sown by one operator. The daily acreage of sowing corn seeds ranged from 5.5 ha to 41.2 ha (mean 15.4 ha). The total working times ranged from 333 minutes to 502 minutes and the daily phases of seed loading lasted from 12 to 47 minutes. During their daily working times the operators handled with the treated seeds on average 1.12 kg of imidacloprid (range 0.644 to 3.544 kg of imidacloprid).

Each variety of corn seed was treated with Gaucho® FS 350 (Italy) or Gaucho® FS 600 (Germany) containing 350 g/L or 600 g/L of imidacloprid as active substance (a.s.). The target seed loading rate is 1.0 mg a.s./seed. All seeds were commercial brands and purchased by the farmers from the local market. To determine the actual amount of imidacloprid handled by the operator during the working day the amount of loaded and remaining seed was recorded. Furthermore, a sample of each seed variety was taken when the kernels were poured into the hopper. The specimens were kept at room temperature until being analysed for the content of imidacloprid on the seed kernels by HPLC and UV detection at 294 nm. The average loading rate of the corn seeds used in the study was 0.94 mg imidacloprid per kernel.

Each operator was equipped with the same components of passive dosimeters consisting of long-sleeved undershirt and long underpants as inner dosimeters (simulating the skin) and a long-sleeved shirt, working jacket and working trousers as outer dosimeters.

The dermal exposure was further investigated by wiping the face and the neck at the end of the working day and by washing the hands with an aqueous detergent solution before the working day started, after each loading or sowing phase and finally after having taken off the outer dosimeter garments. Each hand wash solution was analysed separately.

During the loading phase the operators could wear protective gloves but were also allowed to load the corn seeds with bare hands. They were asked in each case to wear protective gloves if they had to adjust, maintain or repair the sowing machine, which was considered as a part of the drilling phase. Also filling of fertiliser into the hoppers was considered as a part of the drilling phase. That is why all operators wore protective gloves during loading of fertiliser. All protective gloves were washed with 2-propanol after collection of all other specimens and the wash solutions were analysed separately.

To determine the potential inhalation exposure the operator was additionally equipped with a personal IOM air sampler system consisting of a small membrane pump and a filter cassette with a glass fibre filter (IOM filter). The inhalation exposure during the loading phases and the drilling phases was monitored separately.

At the end of the monitoring day the operators were undressed and the dosimeters collected as specimens for analysis. The sleeves and legs were cut from the respective torsi and taken as a separate specimen. Except for the liquid specimens hand wash solutions, face/neck wipes and glove washing solutions, the textile specimens and the IOM filter cassettes were wrapped into aluminium foil before packed into bags and labelled. All specimens were kept deep-frozen at -18 °C or below until analysis.

To verify the stability of imidacloprid during the exposure time and subsequent shipment and storage of the specimens each type of dosimeter material was fortified with the a.s. and exposed under a roof to the ambient conditions for a time period that corresponded to the exposure time of the respective dosimeter (field fortifications). Thereafter the specimens were retrieved and kept deep-frozen together with the dosimeter specimens under identical conditions. Field fortification experiments were conducted in parallel to the monitoring on eight farms at least once in each region.

II. Findings

The work clothes, hands and gloves were the most exposed parts of the body, as it could be expected from the nature of the working process. Typically, the paper bag with the corn seeds was lifted and supported by the right hand and led to the opening of the hopper with the other hand. Sometimes the paper bag was pressed against the hip (corresponding to the torso of the work jacket) or against the upper part of the thigh (corresponding to the legs of the work trousers). This behaviour explained the typical contamination of these body parts.

The hands were highly exposed, in particular if no gloves were worn and the operator smoothed the top of the seeds within the hopper with his bare hands. Another typical source of contamination was touching the lids of the hoppers, for instance to close them, and the attitude to put a tear-off from the paper bag back into the bag while the hands grabbed into the empty but very dusty paper bag.

Although the operators were asked to wear protective gloves if they wanted to adjust something at the sowing machine or to eliminate malfunctions many spots for contamination could be possible as for instance dust on handles inside and outside of the tractor cabin or part of the sowing machine which might be touched incidentally. Contamination could also happen if the operator handled the gloves inappropriately and touched them from outside when taking them off.

The extreme potential dermal exposure value of 59.08 mg/day of imidacloprid (operator OC) might be explained by the frequent operation with smeary hydraulic tubes. These tubes were attached to the hydraulic motor of the auger conveyor of the trailer with fertiliser and had to be connected to the hydraulic pump of the tractor each time when fertiliser had to be loaded. Therefore, the working jacket and working trousers and in particular the protective gloves were heavily contaminated with hydraulic

oil. About 22 % of the potential dermal exposure was caused by the pair of gloves which the operator wore during the loading phase of fertiliser. In addition, it is most probable that dust of imidacloprid stuck at that oil at a much higher amount than it normally adhered at the cotton/polyester fabric of the working clothing.

The actual dermal exposure ranged from 0.0820 mg/day of imidacloprid to 7.22 mg/day. The maximum value was allocated to operator OL. The extreme contamination of his hands is explainable because operator OL did not wear protection gloves during the loading phases, grabbed into the inside of the open bag when he lifted it, held the dusty tear-off in his other hand and put it back into the emptied bag. Finally he closed the dusty lids of the seed hoppers with his palm.

The two most obvious reasons for the contamination of the hands were not wearing gloves when the operator handled treated corn seeds or when the operator mishandled the gloves during taking them off and transfer to an interim storage place. On the opposite, the operators, who distinguished themselves by showing a low actual dermal exposure did wear protection gloves and used them in a correct manner.

The results from the IOM air monitors indicate that usually the exposure to dust was clearly less during the drilling phase than during the loading procedure. Although the drilling phases lasted much longer (approximately 6 to 8 hours versus 12 to 47 minutes) the spreading of dust was significantly higher during the loading phases. This result could be expected since the dust was mainly formed for instance by abrasion from the corn kernels while handling the paper bags or while pouring the seeds into the hoppers. The results of the operator exposure study are summarised in Table 7.2.3.2-1.

Table 7.2.3.2-1 Exposure (mg a.s./day) to imidacloprid during loading and sowing of Gaucho® treated maize seed

Operator Code[a]	Operator exposure to imidacloprid (mg a.s./day)							
	Potential dermal exposure			Actual dermal exposure			Potential inhalation exposure[b]	
	Body	Hands loading	Hands sowing	Body	Hands loading	Hands sowing	Loading	Sowing
OA	4.466	0.369	4.079	0.075	0.369	0.207	0.0456	0.0052
OB	11.23	0.959	1.144	0.281	0.408	0.730	0.0529	0.0198
OC	40.47	3.315	15.30	0.249	0.383	2.146	0.1572	0.0691
OR	7.558	1.833	0.567	0.202	0.196	0.542	0.0242	0.0348
OE	5.213	0.553	0.231	0.110	0.0540	0.154	0.0715	0.0048
OF	1.350	0.217	0.408	0.048	0.0130	0.0210	0.0229	0.0016
OH	3.532	0.776	0.223	0.096	0.0370	0.0840	0.0591	0.0040
OJ	1.453	0.392	0.228	0.063	0.0560	0.0740	0.0147	0.0076
OK	2.780	0.856	0.156	0.042	0.856	0.129	0.0120	0.0135
OM	1.662	0.460	0.287	0.069	0.460	0.193	0.1631	0.0067
OL	5.116	9.199	0.765	0.168	6.466	0.586	0.1572	0.0371
ON	0.811	0.127	0.044	0.062	0.0160	0.0230	0.0309	0.0013
OO	0.900	0.906	0.075	0.032	0.906	0.0700	0.0288	0.0006
OP	13.45	0.220	1.290	0.113	0.018	0.366	0.0153	0.0924
OQ	5.585	2.129	0.331	0.171	0.143	0.101	0.2086	0.0582

[a] Operator OG was not considered due to the very low content of imidacloprid on the maize seed.

[b] The inhalation rate was calculated with 20.8 L/min.

III. Conclusion

In the study the operator exposure during loading and sowing of treated corn seeds was analysed in a large number of replicates under realistic field conditions on farms in Italy and Germany. A wide variety of different currently available sowing equipment was used.

It can be concluded that the study conditions (i.e. the selected farms, the equipment used, the work tasks, the work rate, the work conditions, etc.) and subsequently the determined exposure figures are representative for the considered exposure scenario. In this context it can be concluded that:

- Contaminated dust is the main source of operator exposure during loading and sowing of treated corn seeds.
- The amount of active substance(s) in the dust depends on the treatment (loading) rate.

Thus with respect to a generic use of the study results, the measured exposure values were normalised to the amount of active substance handled (mg a.s./kg a.s. handled). This type of normalisation reflects at best exposure in relation to the respective amount of active substance loaded to the seed. Hence using this type of normalisation the most realistic operator exposure estimate for the respective amount of active substance loaded to the seed can be provided. Based on the study results the normalised exposure figures (mg a.s./kg a.s. handled) are presented in Table 7.2.3.2.-2.

Table 7.2.3.2-2 Normalized Exposure (mg a.s./kg a.s.) to imidacloprid during loading and sowing of Gaucho® treated maize seed

Operator Code[a]	Operator exposure to imidacloprid (mg a.s./kg a.s.)							
	Potential dermal exposure			Actual dermal exposure			Potential inhalation exposure[b]	
	Body	Hands loading	Hands sowing	Body	Hands loading	Hands sowing	Loading	Sowing
OA	6.510	0.538	5.946	0.109	0.538	0.302	0.0665	0.0076
OB	13.662	1.167	1.392	0.342	0.496	0.888	0.0643	0.0240
OC	59.602	4.882	22.533	0.367	0.564	3.161	0.2315	0.1017
OR	11.736	2.846	0.880	0.314	0.304	0.842	0.0376	0.0540
OE	1.471	0.156	0.065	0.031	0.015	0.043	0.0202	0.0013
OF	1.071	0.172	0.324	0.038	0.010	0.017	0.0182	0.0013
OH	1.897	0.417	0.120	0.052	0.020	0.045	1.7392	0.1180
OJ	1.597	0.431	0.251	0.069	0.062	0.081	0.0079	0.0041
OK	2.079	0.640	0.117	0.031	0.640	0.096	0.0132	0.0149
OM	1.187	0.329	0.205	0.049	0.329	0.138	0.1220	0.0050
OL	2.777	4.994	0.415	0.091	3.510	0.318	0.1123	0.0265
ON	0.699	0.109	0.038	0.053	0.014	0.020	0.0168	0.0007
OO	0.604	0.608	0.050	0.024	0.608	0.047	0.0248	0.0005
OP	15.545	0.254	1.491	0.131	0.021	0.423	0.0103	0.0620
OQ	3.978	1.516	0.236	0.122	0.102	0.072	0.2411	0.0673

[a] Operator OG was not considered due to the very low content of imidacloprid on the maize seed.
[b] The inhalation rate was calculated with 20.8 L/min.

Calculation of operator exposure during seed loading and sowing based on measurements

Exposure to methiocarb during loading and sowing of corn seed treated with Mesurol FS 500 will be assessed taking into account exposure figures normalised to the amount of active substance handled. Exposure will be calculated for each operator individually. The following assumptions and requirements were made for the estimate of operator exposure during loading and sowing of treated seeds:

Seed handled:	Corn
Seed treatment (loading) rate:	75 g methiocarb/unit of seed
Sowing rate per ha:	1.2 – 2 units/ha (i.e. 60 000 – 100 000 seeds/ha)
Amount of a.s. handled per ha:	90 – 150 g methiocarb/ha
Area to be sown in one day:	15 ha
Amount of a.s. handled per day:	1.35 – 2.25 kg methiocarb/day
Dermal absorption highest dilution:	2 %
Inhalation absorption:	100 %
Operator body weight:	Individual operator body weights from the study are considered
Operator clothing:	Operators do wear adequate working clothes (e.g. a work jacket or a long sleeved shirt and long trousers or a coverall). In addition gloves are worn when direct contact to treated seed or contaminated surfaces is given.

Considering the normalised exposure to imidacloprid as presented in table 7.2.3.2-2, total systemic exposure to methiocarb during loading and sowing of Mesurol FS 500 treated seeds is calculated using the following equation:

$$\textbf{Systemic exposure [mg/kg bw/day]} = \frac{\textbf{(ADE x DA + PIE) x LR}}{\textbf{BW}}$$

ADE = Actual dermal exposure in mg a.s./kg a.s. (= actual dermal exposure hands during sowing + actual dermal exposure hands during loading + actual dermal exposure body)

PIE = Potential inhalation exposure in mg a.s./kg a.s. (= potential inhalation exposure during sowing + potential inhalation exposure during loading)

DA = Dermal Absorption of 1:1.8 diluted Mesurol FS 500 (= 2%)

BW = Body weight in kg (individual operator body weights from study)

LR = Loading rate of methiocarb with 15 ha/day working rate (= 2.25 kg methiocarb/day)

Again, it is worth mentioning that an AAOEL of 0.017 mg/kg bw/day is used for the acute assessment, which in our opinion is the correctly calculated AAOEL as described in Volume 1 of the RAR.

In the following table, systemic exposure for the individual study operators is presented.

Table 7.2.3.2-3 Calculation of total systemic exposure to methiocarb during loading and sowing of Mesurol FS 500 treated corn seeds

Operator Code[a]	Total systemic exposure (mg/kg bw/day)	%AOEL	%AAOEL
OA	0.0018861	15	11
OB	0.0038417	30	23
OC	0.0113900	87	67
OR	0.0029856	23	18
OE	0.0006169	4.7	3.6
OF	0.0005912	4.5	3.5
OH	0.0597688	460	352
OJ	0.0005003	3.8	2.9
OK	0.0012862	9.9	7.6
OM	0.0040656	31	24
OL	0.0044027	34	26
ON	0.0004047	3.1	2.4
OO	0.0009726	7.5	5.7
OP	0.0022712	17	13
OQ	0.0076889	59	45
Empirical 75th percentile	**0.004234**	**33**	**25**
Empirical 95th percentile	**0.025904**	**199**	**152**
Parametric estimate of 75th percentile	**0.006256**	**48**	**37**
Parametric estimate of 95th percentile	**0.027944**	**215**	**164**
Maximum	**0.059769**	**460**	**352**

[a] Operator OG was not considered due to the very low content of imidacloprid on the maize seed.

Longer term exposure using the parametric estimate of the 75th percentile is calculated to be 48% of the AOEL.

Acute exposure using the parametric estimated of the 95th percentile is calculated to be 164% of the AAOEL.

Hence, the longer term exposure to methiocarb for workers during the loading and sowing process calculated using the parametric 75th percentile of study data is within acceptable limits. However, the acute exposure to methiocarb following loading and sowing methiocarb treated maize seeds exceeds the AAOEL when assuming the clothing/PPE worn in the study.

An estimate of acute exposure to workers with the use of FFP2 RPE during the loading process with a mitigation factor of 0.1 is provided below.

Table 7.2.3.2-3 Calculation of total systemic exposure to methiocarb during loading and sowing of Mesurol FS 500 treated corn seeds when assuming FFP2 RPE during loading

Operator Code[a]	Total systemic exposure (mg/kg bw/day)	%AOEL	%AAOEL
OA	0.0006731	5.2	4.0
OB	0.0020320	16	12
OC	0.0056731	44	33
OR	0.0021488	17	13
OE	0.0001365	1.1	0.8
OF	0.0001257	1.0	0.7
OH	0.0094574	73	56
OJ	0.0002812	2.2	1.7
OK	0.0009338	7.2	5.5
OM	0.0008146	6.3	4.8
OL	0.0023544	18	14
ON	0.0000872	0.7	0.5
OO	0.0004135	3.2	2.4
OP	0.0020206	16	12
OQ	0.0023810	18	14
Empirical 75th percentile	**0.002252**	**17**	**13**
Empirical 95th percentile	**0.006808**	**52**	**40**
Parametric estimate of 75th percentile	**0.002488**	**19**	**15**
Parametric estimate of 95th percentile	**0.011790**	**91**	**69**
Maximum	**0.009457**	**73**	**56**

Longer term exposure using the parametric estimate of the 75th percentile is calculated to be 19% of the AOEL.

For calculating the acute exposure, the maximum is used as the parametric estimate of the 95th percentile is higher than the maximum. According to the EFSA Guidance, the maximum can be used instead if the sample size is sufficiently high (n=15). The acute exposure is calculated to be 56% of the AAOEL.

Hence, the longer term exposure to methiocarb for workers during the loading and sowing process calculated using the parametric 75th percentile of study data is within acceptable limits. The acute exposure to methiocarb following loading and sowing methiocarb treated maize seeds is within acceptable limits when FFP2 RPE is worn only during the loading process.

CP 7.3 Dermal adsorption

Summary and conclusion on dermal absorption

The extent of dermal absorption of methiocarb formulated as an FS 500 (Methiocarb FS 500) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following section along with the mean values based on the study results and following application of the new EFSA[6] guidance rules. A conclusion and recommendation regarding the dermal absorption of methiocarb formulated as an FS 500 is given below.

Study results

The mean percentage of methiocarb in the FS 500 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.3% for the human skin. Applying the new EFSA guidance this value adjusts to 0.9%.

According to the new EFSA guidance[7] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-methiocarb in the Methiocarb FS 500 formulation:

- 0.9% for the neat formulation (500 g/L)

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

Report:	KCP 7.3/04[redacted]; 2015; M-536332-01-1
Title:	Methiocarb (formulated as Mesurol FS): In vitro dermal absorption study using human skin
Report No.:	TMR0097
Document No.:	M-536332-01-1
Guideline(s):	Section 7.3 of Annex III of the EU Directive 91/414/EEC (OECD Guideline 417) using the OECD Test Guideline 428 (April 2004) and the corresponding OECD Guidance Document for the conduct of in vitro skin absorption studies (March 2004); Guidance on Dermal Absorption, EFSA Journal 2012; 10(4):2665
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods

Human skin: [redacted].

Number and sex: 5 donors, female.
Anatomical region: Abdomen.
Thickness: 200 to 400 µm.

Test Material:

Non-radiolabelled: Batch: AE F082618 00 1B09 0001
Purity = 99.6% w/w.

Radiolabelled: [phenyl-1-4-^{14}C]-methiocarb.
Batch: KML 9968
Specific activity: 4.1 MBq/mg.
Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the Methiocarb FS 500 formulation (specification number 10200007167) containing methiocarb (500 g/L). It was used at one nominal concentration of 500 g/L.

Test system: An automated flow-through diffusion cell apparatus (Scott/Dick, University of Newcastle-upon-Tyne, UK) was used. The flow-through diffusion cells were placed in a manifold heated *via* a circulating water bath set to maintain the skin surface temperature at approximately 32°C. The cells were connected to multi-channel peristaltic pumps from their afferent ports with the receptor fluid effluent dropping *via* fine bore tubing into scintillation vials on a fraction collector. The surface area of exposed skin within the cells was 0.64 cm^2. The peristaltic pumps were adjusted to maintain a flow-rate of 1.5 mL/h.

The receptor fluid used physiological phosphate-buffered saline, supplemented with 5% bovine serum albumin, adjusted to pH 7.4.

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

The receptor fluid samples were measured by LSC to determine the radioactivity content. The absorption profile was constructed by plotting the

amount of radioactivity absorbed per unit area skin (dpm/cm^2) against time (hr), and the absorption rate of ^3H_2O through the skin membrane calculated from the gradient at steady-state (dpm/cm^2/hr). Steady-state absorption was regarded as the linear portion of the absorption profile. The permeability coefficient (Kp) for ^3H_2O (cm/hr) was then calculated by dividing the absorption rate by the applied concentration of radioactivity (dpm/mL).

A Kp value of $\leq 3.5 \times 10^{-3}$ cm/hr was generally considered acceptable, but if Kp values were higher, then the percentage absorption radioactivity and absorption profile of the skin were compared to donors with acceptable membrane integrity to assess their suitability. Cells with Kp values > 3.5×10^{-3} cm/hr were shown to have similar absorption profiles to those within the same group that had Kp values $\leq 3.5 \times 10^{-3}$ cm/hr, therefore the data from these cells were accepted

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

The dose formulation was applied to the skin membrane with a calibrated positive displacement pipette at the rate of approximately 10 µL/cm^2 exposed skin area (6.4 µL dose, unoccluded). The actual amount of [^{14}C]-Methiocarb applied to the skin was determined from aliquots (6.4 µL) of each dose formulation (homogeneity checks) taken prior to dosing each group of cells.

Sampling: The receptor fluid passing through the receptor chamber was collected into glass vials held in a fraction collector. Samples were then collected at hourly intervals for the duration of the experiment (24 hours).

After 8 hours, the skin was swabbed with 1% v/v Tween 80 in distilled water on cotton wool buds until no further radioactivity was removed (confirmed by monitoring the swabs with a radiation monitor). A dry cotton wool bud was then used to remove any residual swabbing solution.

After 24 hours exposure, the skin membranes were tape-stripped using 3 M Scotch 'Magic' tape. The initial tape strips (1-2) were collected into a glass vial separately and represented material that was associated with surface residues. Subsequent tape strips containing the stratum corneum were analysed individually. The remaining skin was retained and analysed separately.

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

All samples that were not analysed immediately after collection were stored at approximately < -15°C as soon as possible after collection.

Radioassay: Radioactivity was measured by liquid scintillation counting (LSC). Generally radioactivity in gross amounts of less than twice background (4 minute counts) was considered to be below the limit of detection.

Aliquots of liquid samples were mixed with Ultima Gold scintillator (PerkinElmer Life and Analytical Sciences, Boston, USA) for measurement of radioactivity.

Solid samples were combusted in oxygen using a Packard sample oxidiser. The efficiency of the oxidiser was determined using aliquots of Spec-Chec-^{14}C check source for sample oxidisers (Packard BioScience) and was greater

than 95%. Measurements of radioactivity were corrected for oxidiser efficiency.

Findings:

The solubility of [^{14}C]-Methiocarb at a mean concentration of 84.6 µg/mL (target concentration of 88.9 µg/mL) in the selected receptor fluid, 5% w/v bovine serum albumin in 0.01M phosphate buffered saline at pH 7.4, was demonstrated after incubation for approximately 24 hours at ca 32°C. The solubility of the test substance in the receptor fluid was therefore demonstrated to be adequate and not to be rate limiting to the absorption process.

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

The study results are presented in Table 7.6.2-1.

Table 7.6.2-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- methiocarb in an FS 500 formulation at the rate of 500 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)	
Dose Levels	500 g/L	
Species	Human (n=12)	
	Mean	SD
SURFACE COMPARTMENT		
Skin swabs (8h)[a]	103.4	2.9
Surface Dose (1st two tape-strips)	0.5	0.4
Donor chamber	0.4	0.5
Total % non-absorbed	104.2	2.6
SKIN COMPARTMENT		
Skin[b]	0.15	0.4
Stratum corneum[c]	0.08	0.2
Total % at dose site	***0.23***	***0.5***
RECEPTOR COMPARTMENT		
Total % directly absorbed[d]	***0.04***	***0.1***
STUDY: Total % Potentially Absorbable[e]	0.3	0.6
TOTAL % RECOVERY	104.5	2.5
Evaluation according to EFSA Guidance		
absorption >75% within half of study duration	No	
standard deviation >25%	Yes	
recovery <95%	No	
adjusted: Total % Potentially Absorbable[f]	**0.9**	

[a]: sum of radioactivity found in swabs at 8h.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
[f]: values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***

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

Conclusion:
The extent of dermal absorption of methiocarb formulated as an FS 500 (Methiocarb FS 500) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following section along with the mean values based on the study results and following application of the new EFSA[8] guidance rules. A conclusion and recommendation regarding the dermal absorption of methiocarb formulated as an FS 500 is given below.

The mean percentage of methiocarb in the FS 500 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.3% for the human skin. Applying the new EFSA guidance this value adjusts to 0.9%.

According to the new EFSA guidance[9] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-methiocarb in the Methiocarb FS 500 formulation:

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

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately in Document JCA.