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Document Title

Summary of the toxicological studies iodosulfuron-methyl-sodium + mefenpyr-diethyl OD 400 (100+300 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013

Document MCP

Section 7: Toxicological studies

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

Date

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Bayer CropScience

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Version history

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

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

HUSSAR®OD is an Oil Dispersion formulation (OD) containing iodosulfuron-methyl-sodium (100 g/L) and mefenpyr-diethyl (300 g/L). It is an herbicide used on cereals.

The formulation can be considered as an Emulsion Concentrate (EC). The maximum recommended dose rate in Europe is **0.1 L/ha**, corresponding to **10 g** active substance **iodosulfuron-methyl-sodium** per ha.

CP 7.1 Acute toxicity

The following tests were performed on the formulated product:
- LD_{50} oral, rat
- LD_{50} dermal, rat
- Skin irritation, rabbit
- Eye irritation, rabbit
- Sensitisation of the skin according to Modified Buehler test: 9 applications, Guinea pigs

All acute studies have been conducted with the formulated product HUSSAR®OD
The results were as follows:

Study/Parameter	Species (sex)	Results	Reference
Acute oral / LD_{50} (mg/kg)	Rat (F)	> 5000 mg/kg	M-226073-01-1 [redacted]., 2003,
Acute dermal / LD_{50} (mg/kg)	Rat (M+F)	> 4000 mg/kg	M-226076-01-1 [redacted] 2003,
Acute skin irritation	Rabbit (M+F)	Non Irritant	M-227098-01-1 [redacted] 2004,
Acute eye irritation	Rabbit (M+F)	Moderately Irritant Not classified/	M-227099-01-1 [redacted] 2004,
Acute eye irritation	Rabbit (F)	Irritating to eyes	M-247898-01-1 [redacted] 2005
Skin sensitisation (Buehler 9 applications)	Guinea pig	Not a skin sensitiser	M-227097-01-1 [redacted] 2004,

Therefore, according to the EC classification criteria the classification of the Plant Protection Product Iodosulfuron-methyl-sodium + mefenpyr-diethyl OD 400 (100 +300g/L) is classified and should be labelled as follows:

- **EC classification criteria (2001/59/EC):**
  - **Xi, R36 "irritating to eyes".**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **Eye Irritation Category 2; Warning: H319 "Causes serious eye irritation".**

CP 7.1.1 Oral toxicity

Report:	[redacted]; [redacted];2003;M-226073-01
Title:	Iodosulfuron-methyl-sodium & mefenpyr-diethyl OD 100 + 300 (Hussar liquide) Acute toxicity in the rat after oral administration
Report No:	C038943
Document No(s):	M-226073-01-1
Guidelines:	**EU (=EEC): 67/548/EEC; OECD: 423; USEPA (=EPA): OPPTS 870.1100;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods
The formulation iodosulfuron-methyl-sodium & mefenpyr-diethyl OD 100 + 300 - HUSSAR Liquid (batch number: 193/03) contained iodosulfuron-methyl-sodium (nominal 100 g/L; measured 96.7 g/L) and mefenpyr-diethyl (nominal 300 g/L, measured 289.6 g/L).

The test material, a beige brown liquid was formulated in demineralized water. The administration volume was 10 mL/kg b.w. The test material was administered as a single gavage dose (2000 mg/kg) to 3 fasted female Wistar rats. Three additional animals were treated with the same dose.

Table CP 7.1.1-1: Acute oral toxicity in female rats

Dose (mg/kg)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} (mg/kg) (14 days)
(1st) 2000	0/3/3	5 min – 5 h	--	≥ 5000
(2nd) 2000	0/3/3	10 min – 2 h	--	≥ 5000

*number of dead animals/number of animals with clinical signs/number of animals tested.

Findings
- Clinical signs: decreased motility, digging and cleaning gestures, bradypnea, laboured breathing, increased salivation, temporarily narrowed palpebral fissures.
- Body weights: there were no toxicological effects on body weights or on body weight gain.
- Necropsy: no gross pathologic changes were observed in animals sacrificed at the end of the study period.

Conclusion
The oral LD_{50} of HUSSAR® OD was found to be higher than 5000 mg/kg b.w. in female Wistar rats.
According to the EC classification criteria the formulation is labeled as follows:
- **EC classification criteria (2001/59/EC):**
  - **None**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **None**

CP 7.1.2 Dermal toxicity

Report:	[redacted]; [redacted];2003;M-226076-01
Title:	Iodosulfuron-methyl-sodium & mefenpyr-diethyl OD 100 + 300 (Hussar liquide) Acute toxicity in the rat after dermal application
Report No:	C038945
Document No(s):	M-226076-01-1
Guidelines:	**EU (=EEC): 67/548/EEC; OECD: 402; USEPA (=EPA): OPPTS 870.1200;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods
The formulation iodosulfuron-methyl-sodium & mefenpyr-diethyl OD 100 + 300 - HUSSAR Liquid (batch number: 193/03) contained the active ingredients iodosulfuron-methyl-sodium (nominal 100 g/L; measured 96.7 g/L) and mefenpyr-diethyl (nominal 300 g/L; measured 289.6 g/L).
One day before the start of the treatment the back and flanks of 5 male and 5 female Wistar rats were shorn. They received a single dermal dose of 4000 mg/kg b.w. of the pure liquid test compound applied semi-occlusively. After an exposure time of 24 hours, the fixing bandage and the gauze strip were removed and the treated area was cleaned with soap and water.

Table CP 7.1.2-1: Acute dermal toxicity in rats

	Dose (mg/kg)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} (mg/kg) (14 days)
Males	4000	0/5/5	2d – 12d	--	> 4000
Females	4000	0/5/5	2d – 15d	--	> 4000

* number of dead animals/number of animals with clinical signs/number of animals in the group

Findings
- Mortality: no deaths occurred during the study.
- Body weights and body weight gain: they were unaffected in males. A clear decrease in body weight was observed on day 8 of the study in two females.
- Clinical signs: local skin reactions were observed at the treatment area: partly reddening, partly formation of scale, partly encrustation, partly induration, partly swelling, chapped in place.
- Effects on organs: No particular findings were found.

Conclusion
The dermal LD_{50} of HUSSAR®OD was greater than 4000 mg/kg b.w. for male and female Wistar rats.
According to the EC classification criteria the formulation is labeled as follows:
- **EC classification criteria (2001/59/EC):**
  - **None**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **None**

CP 7.1.3 Inhalation toxicity

Inhalation exposure to the formulated product is very unlikely due to the physico-chemical properties of the formulated product and due to its indicated use.

Inhalation testing is not triggered according to 94/79/EEC because HUSSAR®OD is a liquid formulation and is not:
- a gas or liquefied gas,

- a smoke generating formulation or fumigant,
- to be used with fogging equipment,
- a vapour releasing preparation,
- an aerosol,
- a powder, is dust-free, and hence does not contain a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis),
- to be applied from aircraft,
- an active substances with a vapour pressure > 1×10^{-2} Pa and
- to be used in enclosed spaces such as warehouses or glasshouses,
- is a liquid concentrate that does contain a significant proportion of particles or droplets of diameter < 50 µm (> 1 % on a weight basis).

According to the EC classification criteria the formulation is labeled as follows:

- **EC classification criteria (2001/59/EC):**
  - **None**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **None**

CP 7.1.4 Skin irritation

Report:	[redacted]; [redacted]; 2004; M-227098-01
Title:	Acute skin irritation corrosion on rabbits - Hussar liquid Iodosulfuron-methyl-sodium & mefenpyr-diethyl, OD 100 + 300
Report No:	C039662
Document No(s):	M-227098-01-1
Guidelines:	**EU (=EEC): 67/548/EEC, Part B, B.4; OECD; 404;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods

HUSSAR® OD (batch number: 193/03) contained the active ingredients iodosulfuron-methyl-sodium (nominal 100 g/L; measured 96.7 g/L) and mefenpyr-diethyl (nominal 300 g/L; measured 289.6 g/L).

Approximately one day before the start of the treatment, fur was shorn on the right and left side from the dorso-lateral area of the trunk of each of the rabbits. A single application of 0.5 mL of the pure liquid test item was performed onto the shorn skin of 3 female KBL(NZW)BR White rabbits. The treated skin area was approximately 6 cm². After an exposure time of 4 hours, the dressing and patch were removed and the treated area was cleaned with water.

The individual findings of the treated skin areas at the various observation times are summarized in Table CP 7.1.4-1 and 7.1.4-2.

Table CP 7.1.4-1: Irritant effects on the skin – one animal – undiluted test substance

	DRAIZE grade after					
Exposure	3 minutes		1 hour		4 hours	
Observation	Immediately after patch removed					
Animal No.	E	O	E	O	E	O
2549	0	0	0	0	0	0

Abbreviations: E = Erythema (redness) and Eschar formation, O = Oedema formation

Table CP 7.1.4-2: Irritant Effects on the skin – Undiluted Test Substance (Exposure: 4 hours)

		DRAIZE grade after									
Exposure		4 hours									
Observation after patch removed		1 hour		24 hours		48 hours		72 hours		Irritation Mean value 24-48-72h	
Animal No.	Body weight	E	O	E	O	E	O	E	O	E	O
2549	2503 g	0	0	0	0	0	0	0	0	0.00	0.00
2530	2227 g	0	0	0	0	0	0	0	0	0.00	0.00
2538	2390 g	0	0	0	0	0	0	0	0	0.00	0.00

Abbreviations: E = Erythema (redness) and Eschar formation, O = Oedema Formation

Findings
No symptoms.

Conclusion
HUSSAR®OD is not irritating to the skin.

According to the EC classification criteria the formulation is labeled as follows:

- **EC classification criteria (2001/59/EC):**
  - **None**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **None**

CP 7.1.5 Eye irritation

Report:	[redacted];2004;M-227099-01
Title:	Acute eye irritation/corrosion on rabbits - Hussar liquid Iodosulfuron-methyl-sodium & mefenpyr-diethyl, OD 100 + 300
Report No:	C039664
Document No(s):	M-227099-01-1
Guidelines:	**EU (=EEC): 67/548/EEC, Part B, B.5; OECD: 405;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods
HUSSAR®OD (AE F115008 02 OD35 A1) (batch number: 193/03) contained iodosulfuron-methyl-sodium (nominal 100 g/L; measured 96.7 g/L) and mefenpyr-diethyl (nominal 300 g/L; measured 289.6 g/L). The test was started with one of three rabbits. 100 µL of the pure liquid test substance was placed into the conjunctival sac of one eye of the first animal after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order to prevent loss of the test compound. The other eye, which remains untreated, served as control. The eyes were not washed for at least 24 hours following instillation.

The individual findings of the treated eyes at the various observation times are summarized in Tables CP 7.1.5-1 and 7.1.5-2.

Table CP 7.1.5-1: Test on three rabbits for irritation effects on the eye

Animal (1) – No. 2526, Body Weight 2759 g										
Observation	1 h	24 h	48 h	72 h	day 4	day 5	day 6	day 7	day 14	Mean value 24-48-72h
Degree of Cornea opacity	2	2	1	1	1	1	1	1	0	1.33 (-)
Area of Cornea opacity	1	2	2	2	1	1	1	1	0	2.00
Iris	0	0	0	0	0	0	0	0	0	0 (-)
Aqueous humor opacity	0	0	0	0	0	0	0	0	0	0
Redness Conjunctivae	2	2	2	1	0	0	0	0	0	0.67 (-)
Chemosis Conjunctivae	1	1	1	0	0	0	0	0	0	0.67 (-)
Lacrimation	2	1	0	0	0	0	0	0	0	0.33

Abbreviations: g = gram h = hour(s)

Animal (2) – No. 2528, Body Weight 2643 g										
Observation	1 h	24 h	48 h	72 h	day 4	day 5	day 6	day 7	day 14	Mean value 24-48-72h
Degree of Cornea opacity	2	2	2	2	2	1	1	1	0	2.00 (+)
Area of Cornea opacity	2	4	3	3	1	1	1	1	0	3.33
Iris	0	0	0	0	0	0	0	0	0	0 (-)
Aqueous humor opacity	0	0	0	0	0	0	0	0	0	0
Redness Conjunctivae	2	1	1	1	1	1	1	1	0	1.00 (-)
Chemosis Conjunctivae	1	1	1	0	0	0	0	0	0	0.67 (-)
Lacrimation	1	1	0	1	0	0	0	0	0	0.67

Abbreviations: g = gram h = hour(s) * = grading not possible

Animal (3) – No. 2531, Body Weight 3072 g										
Observation	1 h	24 h	48 h	72 h	day 4	day 5	day 6	day 7	day 14	Mean value 24-48-72h
Degree of Cornea opacity	2	1	1	1	1	1	1	1	0	1.00 (-)
Area of Cornea opacity	1	3	3	3	1	1	1	1	0	3.00
Iris	0	0	0	0	0	0	0	0	0	0 (-)
Aqueous humor opacity	*	0	0	0	0	0	0	0	0	0
Redness Conjunctivae	2	1	1	1	1	1	1	0	0	1.00 (-)
Chemosis Conjunctivae	2	1	1	0	0	0	0	0	0	0.67 (-)
Lacrimation	2	1	0	1	0	0	0	0	0	0.67

Abbreviations: g = gram h = hour(s) * = grading not possible

Conclusion

The formulation iodosulfuron-methyl-sodium and mefenpyr-diethyl 100 + 300 (HUSSAR®OD) is moderately irritating to the eye with full reversibility within 14 days. According to the criteria for classification in Commission Directive 2001/59/EC, this formulation is not classified.

Two tests were carried out with HUSSAR®OD, because of minor formulation changes. The current formulation which will be sold has the code AE F115008 02 OD35 A2 and can contain two inerts that were not present in the original formulation. Whilst one of them (the antifoam) is unclassified the dispersing agent has been classified as an eye and skin irritant by calculation. Given the concentration of the dispersing agent component in the formulation and the results from the original skin and eye irritation studies, where absolutely no effect was seen for skin irritation and moderate irritation was seen for the eye, it was decided that a second eye irritation study would be the prudent course of action. It was also decided that the amount of the dispersing agent would be very unlikely to produce a classifiable skin irritation in the new formulation.
Details on the formulation changes and a bridging statement are included in Document JCP of this dossier.

Report:	[redacted];[redacted];2005;M-247898-01
Title:	AE F115008 02 OD35 A2 - Acute eye irritation on rabbits
Report No:	C047212
Document No(s):	M-247898-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Material and Methods

The formulation HUSSAR®OD (AE F115008 02 OD35 A2) (batch number: AAIM01665) contained iodosulfuron-methyl-sodium (nominal 100 g/L; measured 8.82% w/w) and mefenpyr-diethyl (nominal 300 g/L; measured 26.0% w/w).

The test was started with one of three rabbits. 100 µL of the pure liquid test substance was placed into the conjunctival sac of one eye of the first animal after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order to prevent loss of the test compound. The other eye, which remained untreated, served as control. The eyes were not washed for at least 24 hours following instillation. As one hour after treatment a severe irritation was not observed, two further rabbits were treated as described. The individual findings of the treated eyes at the various observation times are summarized in Table CP 7.1.5-2.

Table CP 7.1.5-2: Test on three Rabbits for Irritation Effects on the eye

Animal 1, Body Weight 2.9 kg								
Observations	**1h**	**24h**	**48h**	**72h**	**day 7**	**day 14**	**day 21**	**Mean scores (24-48-72h)**
Degree of cornea opacity	0	2	2	2	0	-	-	2.00 (+)
Iris	0	0	0	0	0	-	-	0.00 (-)
Redness conjunctivae	3	3	3	3	0	-	-	3.00 (+)
Chemosis conjunctivae	2	4	2	2	0	-	-	2.67 (+)

Animal 2, Body Weight 2.7 kg								
Observations	**1h**	**24h**	**48h**	**72h**	**day 7**	**day 14**	**day 21**	**Mean scores (24-48-72h)**
Degree of cornea opacity	0	2	2	2	1	0	-	2.00 (+)
Iris	0	0	0	0	0	0	-	0.00 (-)
Redness conjunctivae	3	3	3	3	0	0	-	3.00 (+)
Chemosis conjunctivae	2	3	2	1	0	0	-	2.00 (+)

Animal 3, Body Weight 3.0 kg								
Observations	**1h**	**24h**	**48h**	**72h**	**day 7**	**day 14**	**day 21**	**Mean scores (24-48-72h)**
Degree of cornea opacity	0	2	2	2	0	0	-	2.00 (+)
Iris	0	0	0	0	0	0	-	0.00 (-)
Redness conjunctivae	3	3	3	3	1	0	-	3.00 (+)
Chemosis conjunctivae	2	4	3	2	0	0	-	3.00 (+)

Abbreviations: - : no further examination

Response: Corneal opacity: mean scores <2 = (-), ≥2<3 = (+), ≥3 = (++)
Iritis: mean scores <1 = (-), ≥1<2 = (+), ≥2 = (++)
Conjunctival redness: mean scores <2.5 = (-), ≥2.5 = +
Conjunctival oedema: mean scores <2 = (-), ≥ 2 = +

Conclusion

HUSSAR®OD is irritating to eyes with full reversibility within 14 days.

According to the EC classification criteria the formulation is labeled as follows:

- **EC classification criteria (2001/59/EC):**
  - **Xi, R36 "Irritating to eyes".**
- **Regulation (EC) No 1272/2008 (CLP):**
  - **Eye Irritation Category 2; Warning H319.**

CP 7.1.6 Skin sensitization

Report:	[redacted];[redacted];2004;M-227097-01
Title:	Study for the skin sensitization effect in guinea pigs (Buehler patch test) Code: AE F115008 02 OD35 A103
Report No:	C039661
Document No(s):	M-227097-01-1
Guidelines:	**EU (=EEC): 96/54/EC; OECD: 406; USEPA (=EPA): OPPTS 870.2600;Deviation not specified**
GLP/GEP:	**yes**

Material and Methods:

HUSSAR®OD (AE F115008 02 OD35 A103) (batch number: 193/03) contained 100 g/l (measured 96.7 g/L) of the active ingredient iodosulfuron-methyl-sodium, and 300 g/L (measured: 289.6 g/L) of the active ingredient mefenpyr-diethyl.

The test was performed on 30 female guinea pigs (20 animals for the test item group and 10 control animals). Two animals were used for dose-finding, where the test compound was formulated in physiological saline solution.

Induction: the animals were dermally treated with the test item nine times over 3 weeks. The 1st to 9th inductions were performed with the 12% test item concentration. The volume applied per animal was 0.5 mL on the left flank of animals.

The occlusive patches were removed after an exposure period of 6 hours. The treatment areas were visually assessed 30 hours after initiation of exposure.

Challenge: the challenge was performed four weeks after the first dermal induction. The backs and the flanks of the animals were shorn one day prior to challenge. A patch, loaded with 0.5 mL of the 6% test compound was applied and fixed to the right flank of the animals for an exposure period of 6 hours. The skin reactions were assessed 30 and 54 hours after the beginning of the challenge.

Table CP 7.1.6-1: Skin sensitization test in guinea pigs

Sex	Animal number	Control group			
		Test item patch		Control patch	
		30 hours*	54 hours*	30 hours*	54 hours*
Male	01	0	0	0	0
	02	0	0	0	0
	03	0	0	0	0
	04	+	+	+	+
	05	0	0	0	0
	06	0	0	0	0
	07	0	0	0	0
	08	0	0	0	0
	09	0	0	0	0
	10	0	0	0	0
		Treated group			
Male	11	0	0	0	0
	12	0	0	0	0
	13	0	0	0	0
	14	0	0	0	0
	15	0	0	0	0
	16	0	0	0	0
	17	0	0	0	0
	18	0	0	0	0
	19	0	0	0	0
	20	0	0	0	0
	21	0	0	0	0
	22	0	0	0	0
	23	+	+	+	+
	24	0	0	0	0
	25	0	0	0	0
	26	0	0	0	0
	27	0	0	0	0
	28	0	0	0	0
	29	0	0	0	0
	30	0	0	0	0

* : finding made 30 and 54 hours after start of exposure,
\+ : animal died

Findings
Mortality: Animal no 4 of the control item group died at day 25 of the study, and animal no 23 of the test item group died at day 19 of the study.

Clinical signs:
Animal no 6 of the control group showed from day 23 to the end of study: labored breathing, piloerection, pale
Animal 23 of the treated group showed clinical signs from day 18 to death at day 19: labored breathing, piloerection, pale
Animal 16 of the treated group showed clinical signs from day 26 to the end of study: labored breathing, piloerection, pale
No clinical signs were recorded for other animals
Body weights: no difference was observed between the control group and the treated group.

Dermal observations: no skin effects were recorded during the challenge phase with the 6% test item formulation.

Conclusion
HUSSAR®OD (AE F115008 02 OD35 A103) formulation, under the conditions of this test is not considered to be a dermal sensitiser.

According to the EC classification criteria the formulation is labeled as follows:

- **EC classification criteria (2001/59/EC):**
    - **None**
- **Regulation (EC) No 1272/2008 (CLP):**
    - **None**

CP 7.1.7 Supplementary studies on the plant protection product

Not relevant: the formulation is not recommended to be combined with other plant protection products.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies have been conducted because HUSSAR®OD will not be registered as a tank-mixture partner with other plant protection products for the intended uses.

CP 7.2 Data on exposure

IMS+MPR OD 400 (or HUSSAR® OD) is an Oil Dispersion (OD) formulation containing 100 g/L iodosulfuron-methyl-sodium and the safener mefenpyr-diethyl (300 g/L).

The critical GAP for the re-approval of Iodosulfuron-methyl-sodium is based on the use of the representative formulation Hussar OD. Hussar OD is used is intended to be used as a selective post-emergence herbicide in cereals (wheat, rye, barley, triticale, spelt, durum wheat). Its use pattern consists, depending on the country, in a single application varying from 2.5 to 10 g a.i. /ha, between BBCH 13-32. In the dossier two critical GAPs are defined as a single application at 7.5 -10 g/ha per hectare (see in the table below). Water will be the diluent/carrier in all situations. Usage information pertinent to operator exposure is summarised in Table CP 7.2-1.

For modelling purposes the OD will be treated as an Emulsion Concentrate formulation (EC).

Table CP 7.2-1: Application parameters for IMS+MPR OD 400

Crop(s)	Appl. Techn.	Growth stage (BBCH)	N° of applications	Maximum dose rate			Spray volume (L/ha)
				(L/ha product)	g a.s./ha		
					IMS	MPR	
Winter wheat	FCS	13-32	1	0.1	10	30	150 - 400
Winter Barley	FCS	20-32	1	0.075	7.5	22.5	150 - 400

FCS = Field crop sprayer. , IMS = iodosulfuron-methyl-sodium, MPR = mefenpyr-diethyl.

CP 7.2.1 Operator exposure

Risk assessment for operator

Dermal Absorption

Dermal absorption data are available for iodosulfuron-methyl-sodium (IMS) from an *in vitro* study with human/rat skin (CP 7.6). The formulation tested is the representative one described in this dossier. Derived from the results of this study it is proposed to use respectively for concentrate and spray mixture:

- 0.4% for the neat (non-diluted) formulation.
- 5% for the spray dilution (lowest concentration tested was 0.01 g/L and lowest expected in-use concentration is 0.02 g/L).

Acceptable Operator Exposure Level

The AOEL for iodosulfuron-methyl-sodium was set during the Annex I inclusion process. It was derived from a 90 day and a 1 year dog study (NOAEL of 7 mg/kg/day, 70% oral absorption and a safety factor of 100) resulting in an AOEL of 0.05 mg/kg bw/day.

Operator exposure estimates

Operator exposure estimates were calculated using both the German model[1] and the UK-POEM[2]. Exposure calculations are performed without and with protective equipment. The application to winter cereals will be used for exposure calculations as it represents the highest application rate and thus the worst case scenario.

The results of the exposure calculations are summarised in Table CP 7.2.1-1.

Table CP 7.2.1-1: Predicted systemic exposure as a proportion of the AOEL

Substance	PPE	Total systemic exposure (mg/kg bw/day)*	AOEL (mg/kg/day)	% of AOEL
German model Field crop sprayer application to cereals, 20 ha/day at a rate of 0.1 L product/ha,70 kg operator				
IMS	No PPE 1)	0.00032	0.05	0.6
	With PPE 2)	0.00008		0.2
UK POEM Field crop sprayer application to cereals, 50 ha/day at a rate of 0.1 L product/ha, 150 L/ha. 60 kg operator				
IMS	No PPE 3)	0.002708	0.05	5.4
	With PPE 4)	0.002408		4.8

1) No PPE = lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes.
2) With PPE = Gloves during mixing/loading and a coverall during application.
3) No PPE UK POEM = operator wearing long sleeved shirt and long trousers.
4) With PPE UK POEM: operator wearing long sleeved shirt, long trousers and gloves during Mixing/Loading.
*Dermal absorption values of 0.4% (neat formulation) and 5% (spray). Inhalation absorption was taken as 100%.

[1] Lundehn, J.-R.; Westphal, D.; Kieczka, H.; Krebs, B.; Löcher-Bolz, S.; Maasfeld, W.; Pick, E.-D. (1992): Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, n° 277, 1 - 112 (1992); (M-001230-02-1)

[2] Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) – A User's Guide (UK MAFF); 1992, revised model 2003; (M-054618-01-1)

The BBA model estimates predict that IMS+MPR OD 400 can be used safely with Field Crop Sprayers even without the use of any personal protective equipment. Systemic exposure from the use of IMS+MPR OD 400 with Field Crop Sprayer without protection results in 0.6% of the iodosulfuron-methyl-sodium AOEL.

The UK POEM estimates predict that IMS+MPR OD 400 can be used safely with Field Crop Sprayers even without the use of any personal protective equipment. Systemic exposure from the use of IMS+MPR OD 400 with Field Crop Sprayer without protection results in 5.4% of the iodosulfuron-methyl-sodium AOEL.

Overall conclusion
Exposure estimates predict acceptable risks for the intended use even without the use of personal protective equipment. To be consistent with good agricultural practices when handling pesticides, it is recommended that gloves be worn during mixing/loading and when handling contaminated surfaces.

CP 7.2.1.1 Estimation of operator exposure

a) Estimation according to the German model
Exposure is calculated with the maximum dose rate. Lower doses will be covered by this calculation and separate evaluations are not made. The following assumptions are made:

Field crop sprayer

Treated area:	20 ha/day
Max. dose rate:	0.01 kg a.s./ha IMS i.e. 0.1 L/ha product
Personal protective equipment (PPE):	
	No PPE: lightly dressed operator (short sleeved shirt and short trouser)
	PPE: Gloves for mixing/loading, standard coverall).

Detailed calculations with the BBA model are presented in Table CP 7.2.1.1-1.

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

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

Product:	HUSSAR OD				
Active substance:	IMS	a.s. concentration:	100	[g/l or kg]	
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	0.1		Hands:	Gloves	
Work rate [ha/day]:	20	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	0.4	(concentrate)	Body:	Standard protective coverall	
	5.0	(dilution)			

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
						I = Inhalation
I_M =	0.0006	0.2	0.000002	1.0	0.000002	D = Dermal
$D_{M(H)}$ =	2.4	0.2	0.0069	0.01	0.000069	M = Mix/Loading
I_A =	0.001	0.2	0.000003	1.0	0.000003	A = Application
$D_{A(C)}$ =	0.06	0.2	0.0002	1.0	0.000171	H = Hands
$D_{A(H)}$ =	0.38	0.2	0.0011	1.0	0.001086	C = Head
$D_{A(B)}$ =	1.6	0.2	0.0046	0.05	0.000229	B = Body

Absorbed dose:

Route		Absorption [%]	No PPE Estimated route exposure [mg/kg bw/day]	No PPE Systemic exposure [mg/kg bw/day]	With PPE Estimated route exposure [mg/kg bw/day]	With PPE Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.4	0.006857	0.000027	0.000069	0.0
	Application	5.0	0.005829	0.000291	0.001486	0.000074
Inhalation:	Mix/Loading	100	0.000002	0.000002	0.000002	0.000002
	Application	100	0.000003	0.000003	0.000003	0.000003
			Total =	**0.000323**		**0.000079**

b) Estimation according to the UK-POEM

Using the UK-POEM, the highest exposure for each application type is calculated if the maximum dose rates and the minimum spray volumes are used. Lower dose rates and higher spray volumes for crops which are treated with the same application type will be covered by this calculation and separate evaluations are not made. The following assumptions have been made:

Field Crop Sprayer application (cereals)

Treated area: 50 ha per day.

Max. dose rate: 0.1 L/ha plant protection product corresponding to 0.010 kg a.s./ha iodosulfuron-methyl-sodium.

Applied volume: 150 L/ha

Duration of work: 6 hours

Container size: 10 L, 63 mm closure.

Detailed calculations with the UK POEM are presented in Table CP 7.2.1.1-2.

Table CP 7.2.1.1-2: Calculation of exposure to Iodosulfuron-methyl-sodium (IMS) of operators using IMS+MPR OD 400 at 0.1 L/ha; application with field crop sprayer (UK POEM, with and without PPE) to 50 ha cereal fields.

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**HUSSAR OD**	Active substance	**IMS**
Formulation type	organic solvent-based	a.s. concentration	**100** mg/ml
Dermal absorption from product	**0.4** %	Dermal absorption from spray	**5** %
Container	10 litres 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	None
Dose	**0.1** L/ha	Work rate/day	**50** ha
Application volume	**150** L/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING								
Container size	10	litres						
Hand contamination/operation	0.05	ml						
Application dose	0.1	litres product/ha						
Work rate	50	ha/day						
Number of operations	1	/day						
Hand contamination	0.05	ml/day						
Protective clothing	None					Gloves		
Transmission to skin	100	%				10	%	
Dermal exposure to formulation	0.050	ml/day				0.005	ml/day	

DERMAL EXPOSURE DURING SPRAY APPLICATION								
Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles							
Application volume	150	spray/ha						
Volume of surface contamination	10	ml/h						
Distribution	Hands		Trunk		Legs			
	65%		10%		25%			
Clothing	None	Permeable	Permeable		None	Permeable	Permeable	
Penetration	100%	5%	15%		100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h	6.5	0.05	0.375	ml/h
Duration of exposure	6	h			6	h		
Total dermal exposure to spray	41.550	ml/day			41.260	ml/day		

ABSORBED DERMAL DOSE								
	Mix/load		Application			Mix/load		Application	
Dermal exposure	0.05	ml/day	41.55	ml/day		0.005	ml/day	41.55	ml/day
Concen. of a.s. product or spray	100	mg/ml	0.066666667	mg/ml		100	mg/ml	0.066667	mg/ml
Dermal exposure to a.s.	5	mg/day	2.770	mg/day		0.5	mg/day	2.77	mg/day
Percent absorbed	0.4	%	5	%		0.4	%	5	%
Absorbed dose	0.02	mg/day	0.139	mg/day		0.002	mg/day	0.139	mg/day

INHALATION EXPOSURE DURING SPRAYING		
Inhalation exposure	0.01	m³/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.066666667	mg/ml
Inhalation exposure to a.s.	0.004	mg/day
Percent absorbed	100	%
Absorbed dose	0.004	mg/day

PREDICTED EXPOSURE	No PPE		With PPE	
Total absorbed dose	0.163	mg/day	0.145	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.002708333	mg/kg bw/day	0.002408	mg/kg bw/day
AOEL	0.050	mg/kg bw/day		
%AOEL	5.4	%	4.8	%

CP 7.2.1.2 Measurement of operator exposure

Since the exposure estimate carried out indicated that the health-based limit values (AOEL) will not be exceeded under practical conditions of use, a study to provide a measure of operator exposure was not necessary and was therefore not carried out.

CP 7.2.2 Bystander and resident exposure

Risk assessment for bystander and resident
Currently no official and implemented EU model is available for calculation of bystander or residential exposure.

Therefore, as long as there is no official guidance on how to estimate bystander exposure an approach is presented in this document that considers both dermal exposure – derived from available drift data – and inhalation exposure – derived from an operator exposure model simulating a bystander who is exposed in a similar way as an unprotected operator spraying in the field. Additionally, exposure to residents is assessed as well.

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

Exposure estimates and proportions of the systemic AOEL accounted for by the estimates are summarised in the following table.

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

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Low crop application (tractor-mounted)				
IMS	Bystander: adult	0.000003	0.05	**0.006**
	Bystander: child	0.000003		**0.006**
Residential Exposure				
IMS	Resident: adult	0.0000002	0.05	**0.0004**
	Resident: child	0.0000005		**0.0011**

* Assumes a 60 kg bystander for an adult and 16.15 kg for a child.
*Dermal absorption value of 5%. Inhalation absorption was taken as 100%.

Assessment
The results of the calculations reveal that the situation with respect to bystander and resident exposure is favourable for the intended use of IMS+MPR OD 400.

CP 7.2.2.1 Estimation of bystander and resident exposure

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

Bystanders and residents are not involved in application or handling plant protection products or the professional handling of treated crops. The question arises whether it is necessary to distinguish between bystanders and residents in terms of the potential for exposure and health risks. However,

3 Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G.; Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application, Journal für Verbraucherschutz und Lebensmittelsicherheit *Journal of Consumer Protection and Food Safety* (2008, in preparation)

because the circumstances of this exposure could differ with respect to amount, frequency and duration, this seems to be reasonable.

Bystanders may inadvertently be present within or directly adjacent to an area for a short period of time, typically a matter of minutes, where application of a plant protection product is in progress or has recently taken place. They may be exposed to plant protection products mainly *via* the dermal route from spray drift and by inhalation of drifting spray droplets. Hand held application is considered to be worse case compared to field crop sprayer.

Residents may live or work near areas of the application of plant protection products (e.g. standing, working or sitting in a garden in the vicinity of the application). They may be exposed to plant protection products mainly *via* the dermal route from spray drift deposits and by inhalation of vapour drift (depending on the vapour pressure of the active substance). For infants and toddlers exposure might also occur orally (e.g. through hand-to-mouth transfer and/or object-to-mouth transfer).

Table CP 7.2.2.1-1: Percent Drift Values for Different Crops (Rautmann *et al.* 2001, current version 27.03.2006) – 1 application only

Crop, Distance 10 m	Percent Drift (1 application) (90^{th} percentile values)
Field crops	0.29
Fruit crops, early	11.81
Fruit crops, late	3.60
Grapes	1.23
Hops	5.77
Vegetables, ornamentals & small fruit:	
< 50 cm	0.20
> 50 cm	1.23

Exposure calculations are performed according to the following equations:

a) Bystander exposure to iodosulfuron-methyl-sodium

- Dermal exposure due to spray drift following 1 low crop application using a tractor mounted sprayer

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

Where:

SDE_B	= Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)	
AR	= Application Rate (mg/m²)	0.01 kg a.s./ha = 1 mg/m²
D	= Drift (%)	0.29% (10 m distance) for 1 application
BSA	= Exposed Body Surface Area (m²)	1 m² (adult), 0.21 m² (child)
DA	= Dermal Absorption (%)	5%
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child)

- Inhalation exposure due to spray drift

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

Where:

SIE_B	= Systemic Exposure of Bystanders via the Inhalation Route (mg/kg bw/day).	
I_A^*	= Specific Inhalation Exposure (mg/kg a.s. handled per day)	0.001 mg/kg a.s. (FCS).

AR	= Application Rate (kg a.s./ha)	0.01 kg a.s./ha.
A	= Area Treated (ha/day)	20 ha (FCS).
T	= Time [Duration] (min)	5 min.
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

Total Systemic Exposure of Bystanders

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

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

Table CP 7.2.2.1-2: Calculations for bystander exposure to iodosulfuron-methyl-sodium

Adults			**Children**		
Bystander of Field Crop Sprayer					
Dermal exposure:			Dermal exposure:		
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(1 x 0.29% x 1 x 5%) / 60			(1 x 0.29% x 0.21 x 5%) / 16.15		
Absorbed dose:	0.000002	mg/kg bw/day	Absorbed dose:	0.000002	mg/kg bw/day
Inhalation exposure:			Inhalation exposure:		
SIE_B = (I_A* x AR x A x T x IA) / BW			SIE_B = (I_A* x AR x A x T x IA) / BW		
(0.001 x 0.01 x 20 x 5/360 x 100%) / 60			(0.000575** x 0.01 x 20 x 5/360 x 100%) / 16.15		
Absorbed dose:	0.00000056	mg/kg bw/day	Absorbed dose:	0.00000119	mg/kg bw/day
Total systemic exposure:			**Total systemic exposure:**		
$SE_B = SDE_B + SIE_B$			$SE_B = SDE_B + SIE_B$		
Total absorbed dose:	**0.000003**	**mg/kg bw/d**	**Total absorbed dose:**	**0.000003**	**mg/kg bw/d**
% of AOEL:	**0.0059**		**% of AOEL:**	**0.0061**	

** Specific Inhalation Exposure divided by 1.74, according to Martin et al (reference 3)

b) Residential exposure to iodosulfuron-methyl-sodium

- Dermal exposure *via* deposits caused by spray drift

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

Where:
SDE_R = Systemic Exposure of Residents via the Dermal Route (mg/kg bw/day).

AR	= Application Rate (mg/cm^2)	0.01 kg a.s./ha = 0.0001 mg/cm^2.
D	= Drift (%)	0.29% (10 m distance) for 1 application.
TTR	= Turf Transferable Residues (%)	5%.
TC	= Transfer Coefficient (cm^2/hour)	7300 cm^2/h (adult), 2600 cm^2/h (child).
H	= Exposure Duration (hours)	2 h.

DA	= Dermal Absorption (%)	5%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

- Inhalation exposure due to vapour drift.

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

Where:

SIE_R	= Systemic Exposure of Residents via the Inhalation Route (mg/kg bw/day)	
AC_V	= Airborne Concentration of Vapour (mg/m³): 0 mg/m³ (vapour pressure of a.s. < 10^{-5} Pa).	
IR	= Inhalation Rate (m^3/day)	16.57 m^3/day (adult), 8.31 m^3/day (child).
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

As the vapour pressure of iodosulfuron-methyl-sodium is 2.6 x 10^{-9} Pa @ 20°C the product is considered as non-volatile and therefore $AC_V = 0$ and $SIE_R = 0$.

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

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

Where:

SOE_H	= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day).	
AR	= Application Rate (mg/cm²)	0.01 kg a.s./ha = 0.0001 mg/cm².
D	= Drift (%)	0.29% (10 m) for 1 application.
TTR	= Turf Transferable Residues (%)	5%.
SE	= Saliva Extraction Factor (%)	50% (EPA default value).
SA	= Surface Area of Hands (cm²)	20 cm².
Freq	= Frequency of Hand to Mouth (events/hour)	20 events/h.
H	= Exposure Duration (hours)	2 h.
OA	= Oral Absorption (%)	70%.
BW	= Body Weight (kg/person)	16.15 kg (child).

- Children's object-to-mouth transfer

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

Where:

SOE_O	= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day).	
AR	= Application Rate (mg/cm²)	0.01 kg a.s./ha = 0.0001 mg/cm².
D	= Drift (%)	0.29% (10 m) for 1 application.
DFR	= Dislodgeable Foliar Residues (%)	20%.
IgR	= Ingestion Rate for Mouthing of Grass/Day (cm²)	25 cm²/day.
OA	= Oral Absorption (%)	70%.
BW	= Body Weight (kg/person)	16.15 kg (child)

<u>Total systemic exposure of residents is then estimated for</u>

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

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

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

Table CP 7.2.2.1-3: Calculations for resident exposure to iodosulfuron-methyl-sodium

Adults			**Children**		
Resident: Exposure after application with Field Crop, tractor mounted/trailed					
Dermal exposure:			Dermal exposure:		
SDE_R = (AR x D x TTR x TC x H x DA) / BW			SDE_R = (AR x D x TTR x TC x H x DA) / BW		
(0.0001 x 0.29% x 5% x 7300 x 2 x 5%) / 60			(0.0001 x 0.29% x 5% x 2600 x 2 x 5%) / 16.15		
Absorbed dose:	0.00000018	mg/kg/day	Absorbed dose:	0.00000023	mg/kg/day
Inhalation exposure:			Inhalation exposure:		
SIE_R = (AC_V x IR x IA) / 1000 x BW			SIE_R = (AC_V x IR x IA) / BW		
(0 x 16.57 x 100%) / 60			(0 x 8.31 x 100%) / 16.15		
Absorbed dose:	0.0	mg/kg/day	Absorbed dose:	0.0	mg/kg/day
			Oral exposure (hand-to-mouth transfer):		
			SOE_H = (AR x D x TTR x SE x SA x Freq x H x OA) / BW		
			(0.0001 x 0.29% x 5% x 50% x 20 x 20 x 2 x 70%) / 16.15		
			Absorbed dose	0.00000025	mg/kg/day
			Oral exposure (object-to-mouth transfer):		
			SOE_O = (AR x D x DFR x IgR x OA) / BW		
			(0.0001 x 0.29% x 20% x 25 x 70%) / 16.15		
			Absorbed dose	0.00000006	mg/kg/day
Total systemic exposure:			**Total systemic exposure:**		
SE_R = SDE_R + SIE_R			**SE_R = SDE_R + SIE_R + SOE_H + SOE_O**		
Total absorbed dose:	**0.00000018**	**mg/kg/day**	**Total absorbed dose:**	**0.00000055**	**mg/kg/day**
% of AOEL:	**0.0004**		**% of AOEL:**	**0.0011**	

CP 7.2.2.2 Measurement of bystander and resident exposure

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

CP 7.2.3 Worker exposure

Risk assessment for worker

The greatest potential for worker exposure following re-entry will be contamination *via* the skin. Risk of inhalation exposure during re-entry is generally confined to a brief period after application, while the product is drying, which will be rapid under outdoor conditions and would generally be avoided according to good agricultural practices. Exposure to workers entering treated areas are predicted

using an exposure model proposed by Hoenicke *et al*,[4] (1998) and Krebs *et al.* [5](2001). The following assumptions are made;

- Re-entry exposure is predominantly *via* the dermal route (contact with the foliage)
- Residues on the foliage depend on:
  - i) application rate
  - ii) extent of remaining residues from previous applications
  - iii) the Leaf Area Index (LAI) [total size of foliage compared to surface area]
- Transfer of residues from foliage to the clothes or skin of workers depends mainly on the intensity of contact with the foliage.
- Activities with a similar pattern can be grouped and a generic Transfer Coefficient (TC) applied
- Dislodgeable Foliar Residue (DFR) is calculated using a default value of 3 µg as/cm² per kg as/ha. This figure is based Brouwer *et al*.[6] (2001)
- Workers re-enter the treated culture shortly after the spray has dried on plant surfaces, nevertheless it is now recommended to use the higher dermal absorption values amongst neat and diluted values.

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

$$D = DFR \times TC \times WR \times AR \times P$$

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

DFR levels:

A single application is considered in this risk assessment resulting in an assumed DFR of 3 µg as/cm² per kg as/ha.

Transfer Coefficients:

As no specific TCs are available in Europe to assess re-entry activities performed in cereals a reasonable value of 2500 cm²/person/h has been used in this risk assessment. This value was obtained from the Europoem II data for handling vegetables and is considered to be conservative with regards to scouting activities.

Predicted exposures are compared with the AOEL of iodosulfuron-methyl-sodium. Systemic exposure values assume the highest dermal absorption values. A body weight of 60 kg is assumed for the re-entry worker. Exposure estimates based proportions of the systemic AOELs accounted for by the estimates are summarised in the following Table. Detailed calculations are presented below.

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

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

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

Table CP 7.2.3-1: Summary of predicted worker exposures arising from the use of IMS in the HUSSAR®OD formulation and comparison with the AOEL

Active substance	Systemic exposure (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
IMS	0.000125	0.05	0.25

*Dermal absorption value of 5%.
Inhalation absorption was taken as 100% for all compounds.

Assessment

The exposure of workers entering treated areas is well within acceptable limits for IMS+MPR OD 400.

CP 7.2.3.1 Estimation of worker exposure

Detailed calculations of worker exposure during re-entry:

Re-entry exposure to iodosulfuron-methyl-sodium:

Product Name: Hussar OD
Active substance: Iodosulfuron-methyl-Na

D	=	DFR	x	TC	x	WR	x	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
D	=	3	x	2500	x	2	x	0.01	x	1
D	=	150 µg a.s./pers/day								
	=	0.15 mg a.s./pers/day								
	=	0.0025 mg/kg bw/day								

using 5.00% dermal absorption (for a dried foliar residue)

S	=	0.0025	x	0.0500
		0.000125 mg/kg bw/day		

CP 7.2.3.2 Measurement of worker exposure

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

CP 7.3 Dermal adsorption

<u>Summary and conclusion on dermal absorption</u>

The extent of dermal absorption of iodosulfuron-methyl-sodium formulated as an OD 400 (HUSSAR® OD) formulation (IMS+MPR OD 100+300) was investigated in vitro using human and rat 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[7] guidance rules. A conclusion and recommendation regarding the dermal absorption of iodosulfuron-methyl-sodium formulated as an OD 400 is given below.

<u>Study results</u>

The mean percentage of iodosulfuron-methyl-sodium in the OD 400 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 0.23% for the human skin and 2.63% for the rat skin.
The mean percentage of iodosulfuron-methyl-sodium in the OD 400 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 1.75% for human skin and 4.99% for the rat skin.
The mean percentage of iodosulfuron-methyl-sodium in the OD 400 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 2.40% for human skin and 6.78% for the rat skin.

<u>Application of the EFSA guidance rules</u>

According to the new EFSA guidance 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 met for the intermediate dose group for the human skin samples and the high and low dose groups for the rat skin samples 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 84^{th} 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, these values have been considered. The application of the guidance then results in the following values for $[^{14}C]$-iodosulfuron-methyl-sodium in the HUSSAR®OD formulation for use in the occupational and residential risk assessments:
<u>Human skin:</u>

- 0.4% for the neat formulation (100 g/L)
- 1% for the intermediate dose (0.1 g/L)
- 5% for the low dose (0.01 g/L).

[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:	[redacted]:[redacted];2010;M-366373-01
Title:	Hussar OD 400: (^{14}C)-Iodosulfuron.methyl-sodium - Comparative in vitro dermal absorption study using human and rat skin
Report No:	SA 09209
Document No:	M-366373-01-1
Guidelines:	**O.E.C.D. Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004); O.E.C.D. Environmental Health and Safety Publication Series on testing and Assessment No 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004); European Commission Guidance Document on Dermal Absorption- Sanco/222/2000-rev. 7, (March 2004);not specified**
GLP/GEP:	**yes**

Material and methods

Rat skin:

Species, strain: Rat, Wistar Rj:WI (IOPS HAN).
Source: [redacted] (France).
Sex: Male.
Number: 14
Anatomical site: Dorsal
Rat Skin Preparation: Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of *ca* 400 to 570 µm in thickness.

Human skin: Source: [redacted], France.
Number and sex: 8 donors, female.
Anatomical region: Abdomen.
Thickness: 451 to 590 µm.

Test Material:

Non-radiolabelled: Batch: JV 233505/2.
Purity = 97.3%.
Radiolabelled: [triazinyl-2-^{14}C]-iodosulfuron-methyl-sodium
Batch: KATH 6364.
Specific activity: 3.95 MBq/mg.
Radiopurity of the formulation: >98%.

Formulation: The formulation used in this experiment was the Hussar OD 400 formulation (specification number 102000011563) of iodosulfuron-methyl-sodium used at three nominal concentrations: 100 g a.s./L, 0.1 g a.s./L and 0.01 g a.s./L.

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

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment: The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm² exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

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

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

Findings:

Iodosulfuron-methyl-sodium was demonstrated to be soluble in the receptor fluid up to the maximum amount applied of 100 mg/cell. The solubility in the receptor fluid was deemed to be sufficient to reduce any risk of back diffusion.

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

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 97% to 111% of the applied dose.

These study results are presented in Table CP 7.3-1 and Table CP 7.3-2 for human and rat skin respectively.

Table CP 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-iodosulfuron-methyl-sodium in an OD formulation at the rates of 100 g/L, 0.1 g/L and 0.01 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)					
Dose Levels	Neat formulation: High dose (100 g/L)		Dilution: Intermediate dose (0.1 g/L)		Dilution: Low dose (0.01 g/L)	
Species	Human (n=6)		Human (n=6)		Human (n=6)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (8h)	96.46	2.53	99.91	2.60	104.6	1.53
Skin swabs (24h)[a]	0.05	0.03	0.70	0.61	0.25	0.11
Surface Dose (1st two tape-strips)	0.07	0.06	1.18	0.98	0.68	0.33
Donor chamber	0.19	0.14	1.32	1.19	2.79	2.36
Total % non-absorbed	**96.77**	**2.39**	**103.1**	**1.28**	**108.4**	**2.11**
SKIN COMPARTMENT						
Skin [b]	0.07	0.07	***0.41***	***0.30***	1.32	1.13
Stratum corneum [c]	0.15	0.12	1.18	0.48	1.08	1.22
Total % at dose site	***0.22***	***0.17***	1.59	0.60	***2.40***	***2.29***
RECEPTOR COMPARTMENT						
Receptor fluid (0-24h)	0.01	0.01	0.16	0.15	n.d.	n.a.
Receptor fluid terminal	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total % directly absorbed [d]	***0.01***	***0.01***	***0.16***	***0.15***	***n.d.***	***n.a.***
STUDY: Total % Potentially Absorbable [e]	**0.23**	**0.17**	**1.75**	**0.63**	**2.40**	**2.29**
TOTAL % RECOVERY	96.99	2.28	104.9	1.23	110.8	3.07
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	No		Yes		No	
standard deviation >25%	Yes		Yes		Yes	
recovery <95%	No		No		No	
adjusted: Total % Potentially Absorbable [f]	**0.4**		**1**		**5**	

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

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

Table CP 7.3-2: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-iodosulfuron-methyl-sodium in an OD formulation at the rates of 100 g/L, 0.1 g/L and 0.01 g/L to rat skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)					
Dose Levels	Neat formulation: High dose (100 g/L)		Dilution: Intermediate dose (0.1 g/L)		Dilution: Low dose (0.01 g/L)	
Species	Rat (n=6)		Rat (n=5)		Rat (n=5)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (8h)	92.79	3.39	94.19	6.70	91.79	4.24
Skin swabs (24h)[a]	0.11	0.09	2.93	1.64	1.04	0.59
Surface Dose (1st two tape-strips)	0.48	0.56	1.18	0.34	3.57	4.38
Donor chamber	0.80	0.78	n.d.	n.a.	3.52	2.46
Total % non-absorbed	**94.18**	**2.40**	**98.29**	**7.27**	**99.92**	**5.32**
SKIN COMPARTMENT						
Skin [b]	***0.78***	***0.49***	2.34	1.87	***2.54***	***2.03***
Stratum corneum [c]	0.95	1.28	2.24	3.04	0.98	1.43
Total % at dose site	1.73	1.61	***4.58***	***4.63***	3.52	3.44
RECEPTOR COMPARTMENT						
Receptor fluid (0-24h)	0.90	1.01	0.40	0.18	3.26	3.32
Receptor fluid terminal	0.01	0.01	n.d.	n.a.	n.d.	n.a.
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total % directly absorbed [d]	***0.90***	***1.02***	***0.40***	***0.18***	***3.26***	***3.32***
STUDY: Total % Potentially Absorbable [e]	**2.63**	**1.84**	**4.99**	**4.70**	**6.78**	**6.72**
TOTAL % RECOVERY	96.81	1.18	103.3	2.91	106.7	5.53
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	Yes		No		Yes	
standard deviation >25%	Yes		Yes		Yes	
recovery <95%	No		No		No	
adjusted: Total % Potentially Absorbable [f]	**3**		**10**		**10**	

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

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

Conclusion:

The dermal penetration through human dermatomed skin of [^{14}C]-iodosulfuron-methyl-sodium in the OD 400 formulation was investigated at three concentrations corresponding to the neat product (100 g /L) and to two representative dilutions (0.1 and 0.01 g/L), respectively.

The mean percentage of iodosulfuron-methyl-sodium in the OD 400 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 0.23% for the human skin and 2.63% for the rat skin.

The mean percentage of iodosulfuron-methyl-sodium in the OD 400 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 1.75% for human skin and 4.99% for the rat skin.

The mean percentage of iodosulfuron-methyl-sodium in the OD 400 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 2.40% for human skin and 6.78% for the rat skin.

According to the new EFSA guidance 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 met for the intermediate dose group for the human skin samples and the high and low dose groups for the rat skin samples 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, these values have been considered. The application of the guidance then results in the following values for [^{14}C]-iodosulfuron-methyl-sodium in the HUSSAR®OD formulation:

Human skin:

- 0.4% for the neat formulation (100 g/L)
- 1% for the intermediate dose (0.1 g/L)
- 5% for the low dose (0.01 g/L).

Rat skin:

- 3% for the neat formulation (100 g/L)
- 10% for the intermediate dose (0.1 g/L)
- 10% for the low dose (0.01 g/L)

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document JCP)