Bayer CropScience

Document Title

Summary of the toxicological studies

Isoxaflutole + Cyprosulfamide SC 480 (240+240) g/L

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013

Document MCP

Section 7: Toxicological studies

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

Date

2013-10-30

Author(s)

[redacted]

Bayer CropScience

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying licenseagreement.

M-472502-01-3

OWNERSHIP STATEMENT

This document, the data contained in it and copyright therein are owned by Bayer CropScience. No part of the document or any information contained therein may be disclosed to any third party without the prior written authorisation of Bayer CropScience.

The summaries and evaluations contained in this document are based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority. Other registration authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this document unless they have received the data on which the summaries and evaluation are based, either:

- **From Bayer CropScience; or**
- **From other applicants once the period of data protection has expired.**

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[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

This document is copyright protected
Any distribution, reproduction or publication requires
the consent of Bayer AG (or its respective affiliate).
Any use of the document or its content for regulatory or
any other commercial purpose is prohibited and constitutes
a violation of the underlying license agreement.

Table of Contents

Page

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

This document summarises the information related to the toxicological studies for the plant protection product isoxaflutole + cyprosulfamide SC 480 (also known as IFT+CSA SC 480, IFT+CSA SC 240 + 240 and Merlin® Flexx) which contains the active substance isoxaflutole and the safener cyprosulfamide. This document has been prepared for the formulation specification N° 102000016788.

CP 7.1 Acute toxicity

Isoxaflutole & cyprosulfamide SC 480 is a suspension concentrate formulation containing 240 g/L isoxaflutole and 240 g/L cyprosulfamide (safener). The toxicology studies were performed with the formulated product Isoxaflutole & cyprosulfamide SC 480 (global recipe – 102000014305). The recipe to be as part of the AIR 3 process (102000016788) has a slightly different composition due to differences in the formulants available in the different regions. The differences between the two formulations have been assessed in a bridging document (document number M-284787-01-1) and it was concluded that the acute toxicology studies performed with the global recipe are applicable for the EU recipe.

The results of all the acute toxicology studies performed on this formulation are summarized in the Table CP 7.1-1.

Table CP 7.1-1 Summary of acute toxicity studies

Study/Parameter	Species (sex)	Results	Reference
Acute oral / LD_{50} (mg/kg)	Female	No mortality at highest tested dose of 2000 mg/kg LD_{50} cut-off > 5000 mg/kg bw	CP 7.1.1/01 [redacted] M. (2006) M-275632-01-2
Acute dermal / LD_{50} (mg/kg)	Male & Female	LD_{50} > 2000 mg/kg bw	CP 7.1.2/01 [redacted] M. (2006) M-275614-01-2
Acute inhalation / LC_{50} (mg/L)	Male & Female	LC_{50} > 2.674 mg/L	CP 7.1.3/01 [redacted] J. (2006) M-280036-01-2
Acute skin irritation	Female	Not irritant	CP 7.1.4/01 [redacted] C. (2006) M-283854-02-2
Acute eye irritation	Female	Not irritant	CP 7.1.5/01 [redacted] M. (2006) M-279246-01-2
Skin sensitization test, LLNA in mice	Female	Not sensitising	CP 7.1.6/01 [redacted] G. (2006) M-278552-01-2

Therefore, according to the EC classification criteria (2001/59/EC Directive), the formulation Isoxaflutole & cyprosulfamide SC 480 is not classified and should be labelled as follows:

Symbols of danger **None**
Risk phrases **None**

This document is copyrighted. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate) for its content for regulatory purposes. Any use of the document for its content for regulatory purposes is prohibited and constitutes any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7.1.1 Oral toxicity

Report:	[redacted]6; [redacted];2006;M-275632-01
Title:	Isoxaflutole + AE 0001789 SC 480 - Acute toxicity in the rat after oral administration.
Report No & Document No	AT03188 M-275632-01-2
Guidelines:	OECD Guidelines N° 423, (2001) EEC Directive 67/548 Annex V, Method B1 tris (1967, in its current version) EPA (OPPTS 870.1100 – 712-C-98-190), (1998)
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 the results.
GLP	Yes

Any distribution, reproduction or publication of this document is copyright protected. Any use of the document or its content for regulatory or any other commercial purposes is prohibited and constitutes a violation of the underlying license agreement without the consent of Bayer AG (or its respective affiliate).

I. Materials and methods

A. Materials

1. Test material: Isoxaflutole + AE 0001789 SC 480

Specification no.: 102000014305

Description: Beige liquid

Lot/Batch no.: 2006-001042 (EFHM000580)

Content: Isoxaflutole: 240 g/L, cyprosulfamide: 240 g/L (Nominal values)
Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)

Stability of test compound: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: Tap water

3. Test animals

Species: Rat, females

Strain: Wistar (Hsd CpPb:WU)

Age: 10-12 weeks approximately

Weight at dosing: 164 g – 174 g

Source: [redacted], Germany

Acclimatization period: At least 5 days

Diet: Provimi Kliba 3883.0.15; Kaiseraugst, Switzerland

Water: Tap water *ad libitum*

Housing: The animals were group caged conventionally in polycarbonate cages on low dust wood granulate bedding ([redacted], Germany). The cages of the animals were placed on racks. The wood granulate was randomly checked for

contaminants at regular intervals and the results have been stored at the Department for Laboratory Animal Services, Bayer HealthCare AG, Wuppertal, Germany.
Room temperature: 22 ± 2°C; Air humidity: 55 ± 5%; Ventilation: approx. 10 changes per hour;
Light/ Dark cycle : 12 hour rhythm

B. Study design and methods

1. Animal assignment and treatment

Dose:	2000 mg/kg bw
Application route:	Oral by gavage
Application volume:	10 mL/kg bw
Fasting time:	For administration, food was withheld from the animals for approximately 16 - 24 h before administration of the test compound, and they were fed again approximately 2-4 h after administration
Group size:	3 rats/dose group
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weight, gross necropsy
In life dates:	10th May 2006 to 31st May 2006

The test compound was formulated in tap water; and the test material was administered per os in a single dose (2000 mg/kg) by gavage to 3 fasted female Wistar rats. As no mortality occurred, three additional animals were treated with the same dose.

II. Results and discussion

A. Mortality

Mortality was not observed at 2000 mg/kg bw.

Table CP 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality (%)
Females						
2000 1st	0	0	3	--	--	0
2000 2nd	0	0	3	--	--	0
Acute oral LD_{50}**: ≥ 5000 mg/kg bw						

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

** according to the principles of OECD Guideline 423

B. Clinical observations

No clinical signs were observed.

This document is copyrighted. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

C. Body weight

Body weight and body-weight gain were not affected by the treatment.

D. Necropsy

No particular gross pathological changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

According to the OECD Guideline 423 the acute oral LD_{50} cut-off of Isoxaflutole + cyprosulfamide SC 480 formulation in rats is ≥ 5000 mg/kg and as a result is a category 5 product (i.e. unclassified according to the Globally Harmonised Classification System).

According to the EC classification criteria (2001/59/EC Directive) the formulation Isoxaflutole + AE 0001789 SC 480 is labelled as follows:

Symbols of danger	:	None
Risk phrases	:	None

CP 7.1.2 Dermal toxicity

Report:	[redacted]k;[redacted];2006;M-275614-01
Title:	Isoxaflutole + AE 0001789 SC 480 - Acute toxicity in the rat after dermal application.
Report No & Document No	AT03187 M-275614-01-2
Guidelines:	OECD Guidelines N° 402, (1987) EEC Directive 67/548 Annex V, Method B3 (1967 in its current version) EPA (OPPTS 870.1200 – 712-C-98-192, (1998)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material: Isoxaflutole + cyprosulfamide SC 480

Specification no.: 102000014305

Description: Beige liquid

Lot/Batch no.: 2006-001042 (EFIM000580)

Content: Isoxaflutole: 240 g/L, cyprosulfamide: 240 g/L (Nominal values)
Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)

Stability of test compound: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: None

3. Test animals

This document is copyright protected. Any distribution or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Species:	Rat, males and females
Strain:	Wistar (Hsd Cpb:WU)
Age:	9 – 13 weeks approximately
Weight at dosing:	Males: 240 g – 250 g Females: 203 g – 220 g
Source:	[redacted], Germany
Acclimation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15; Kaiseraugst, Switzerland
Water:	Tap water *ad libitum*
Housing:	The animals were caged individually in polycarbonate cages on low dust wood granulate bedding ([redacted], Germany). The cages of the animals were placed on racks. The wood granulate was randomly checked for contaminants at regular intervals and the results have been stored at the Department for Laboratory Animal Services, Bayer HealthCare AG, Wuppertal, Germany. Room temperature: 22 ± 2°C; Air humidity: 55 ± 5%; Ventilation: approx. 10 changes per hour; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

One day before the start of the treatment the back and flanks of 5 male and 5 female Wistar rats were shorn (~ 10% of body area). They received a single dermal dose of 2000 mg/kg bw of the pure liquid test compound applied semi-occlusively. After an exposure time of 24 hours, the dressings were removed and the treated area was rinsed with tepid water using soap and gently patting the area dry.

Dose (mg/kg bw)		Surface area (cm²)	Range of doses (mg/cm²)
males	2000	16.0	30.0-31.3
females	2000	15.75	25.8-27.9

Application route:	Dermal, semi-occlusive dressing
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
In life dates:	10th May 2006 to 24th May 2006

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its affiliate). Any use of the document for its specified purpose is prohibited and any other commercial purpose is subject to regulatory a violation of the underlying licensing agreement.

II. Results and discussion

A. Mortality

Mortality was not observed at 2000 mg/kg bw.

Table CP 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
2000	0	0	5	--	--	0
Females						
2000	0	0	5	--	--	0
Acute dermal 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

B. Clinical observations

No clinical signs were observed.

C. Body weight

Body weight and body weight gain was not affected by treatment in males. In four females there was a slight decrease of body weight in the first week after treatment.

D. Necropsy

No particular gross pathological changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

The dermal LD_{50} of the formulation Isoxaflutole + cyprosulfamide SC 480 was greater than 2000 mg/kg bw for rats.

According to the EC classification criteria (2001/59/EC Directive), the formulation BYH 18636 + AE 0001789 SC 480 is labelled as follows:

Symbols of danger: None
Risk phrases: None

Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.
This document is copyright protected.

CP 7.1.3 Inhalation toxicity

Report:	[redacted]x; [redacted];2006;M-280036-01
Title:	Isoxaflutole & AE 0001789 SC480 - Acute inhalation toxicity in rats
Report No.: Document No.:	AT03351 M-280036-01-2
Guidelines:	OECD Guidelines N° 403 (12 May 1981) EEC Directive 92/69/EEC Annex V – Method B2 (1992) EPA: OPPTS 870.1300 (1998) Japan MAFF: N-12 Nousan-8147 (2000)
GLP	Yes

I. Materials and methods

1. Test material: Isoxaflutole + cyprosulfamide SC 480

Specification no.: 102000014305

Description: Beige liquid

Lot/Batch no.: 2006-001042 (EFIM000580)

Content: Isoxaflutole: 240 g/L, AE 0001789: 240 g/L (Nominal values)

Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)

Stability of test compound: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: The test article was aerosolised as aqueous solution.

3. Test animals

Species: Rat, males and females

Strain: SPF Wistar (Hsd Cpb:WU)

Age: Approximately two months

Weight at dosing: Males: 190 g – 197 g
Females: 171 g – 176 g

Source: [redacted], Germany

Acclimation period: At least 5 days

Diet: Provimi Kliba 3883 9441 pellets, Kaiseraugst, Switzerland

Water: tap water *ad libitum*

Housing: During the acclimation and study periods, the animals were housed singly in conventional Makrolon® Type III cages (based on A. Spiegel and R. Gönnert, Zschr. Versuchstierkunde, 1, 38 (1961) and G. Meister, Zschr. Versuchstierkunde, 7, 144-153 (1965)). Cages were changed twice a week while unconsumed feed and water bottles were changed once per week. The legal requirements for housing experimental animals (Directive 86/609 EEC) were followed. Bedding consisted of type

This document is copyright protected and Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

BK8/15 low-dust wood granulate from [redacted], Germany. The wood granulate was randomly checked for harmful constituents at the request of the Laboratory Animal Services, Bayer Healthcare AG. Room temperature: 22 ± 2°C; Air humidity: 40-60%; Ventilation: approx. 10 changes per hour; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

One group of 10 Wistar rats (5 animals/sex) was exposed to mean aerosol concentration of 2.674 mg/L for up to 4 hours using nose only exposure system. Attempts were made so that liquid aerosol generated was respirable to rats. The test item was aerosolised undiluted.

Dose:	0 – 2.674 mg/L air (maximum technically attainable concentration)
Application route:	Inhalation (nose-only exposure)
Duration:	4 hours
Group size:	5 rats/dose/sex
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weights, rectal temperature, reflex measurements, gross necropsy
In life dates:	22nd May 2006 to 6th June 2006

2. Generation of the test atmosphere / chamber description

Generation and characterization of chamber atmosphere

Target concentration (mg/L)	Nominal concentration (mg/L)	Mean achieved concentration (mg/L)	Mean mass Aerodynamic Diameter (µm)	Geometric standard deviation (µm)	Respirable fraction (% < 3 µm)
5.0	17.471	2.674	3.48	2.25	43.1

II. Results and discussion

A. Mortality

Mortality was not observed at 2.674 mg/L air.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Table CP 7.1.3-1 Doses, mortality / animals treated

Actual concentration (mg/L air)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
0	0	0	5	--	--	0
2.674	0	0	5	--	--	0
Females						
0	0	0	5	--	--	0
2.674	0	0	5	--	--	0
Acute inhalative LC_{50}: > 2.674 mg/L air						

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

B. Clinical observations
All rats tolerated the exposure without specific signs.
Reflex measurements: no exposed rats exhibited changes in reflexes.
Rectal temperature: comparisons between the control and the exposure group revealed a significant hypothermia.

C. Body weight
Body weights: no significant changes.

D. Necropsy
Effects on organs: necropsy findings were unremarkable in rats sacrificed at the end of the observation period.

III. Conclusion
The inhalation LC_{50} of the formulation Isoxaflutole + cyprosulfamide SC 480 for male and female Wistar rats was higher than 2.674 mg/L, the highest attainable concentration.

According to the EC classification criteria (2001/59/EC Directive), the formulation Isoxaflutole + cyprosulfamide SC 480 is labelled as follows:

Symbols of danger : None
Risk phrases None

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7.1.4 Skin irritation

Report:	[redacted]3; [redacted];2006;M-283854-02; Amended: 2007-02-16
Title:	Isoxaflutole + AE 0001789 SC 480 - Acute skin irritation/corrosion on rabbits
Report No & Document No	AT03299 M-283854-02-2
Guidelines:	OECD Guidelines N° 404 (2002) EEC Directive 67/548 Annex V-, Method B.4. (1967 in its current version) EPA (OPPTS 870.2500 – 712-C-98-196)(1998)
GLP	Yes

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

I. Materials and methods

A. Materials

1. Test material: Isoxaflutole + cyprosulfamide SC 480

Article no.: 102000011430S

Description: Beige liquid

Lot/Batch no: 2006-001042 (LFIM000580)

Content: Isoxaflutole: 240 g/L, cyprosulfamide: 240 g/L (Nominal values)

Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)

Stability of test compound: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: None

3. Test animals

Species: Rabbit, females

Strain: Albino (Crl:KBL(NZW)BR)

Age: Young adult animals

Weight at dosing: 2.9 kg – 3.0 kg

Source: [redacted] Germany

Acclimation period: At least 5 days

Diet: [redacted], Germany

Water: Tap water *ad libitum*

Housing: The animals were housed individually in cage units Metall/Noryl by EBECO. Excrement trays below the cages contained low dust wood granulate bedding (J[redacted], Germany). The wood granulate was changed at least twice weekly.
The animals were regularly transferred to clean cages. The animal room had a standardized climate: Room temperature: 20 ± 3°C; Air humidity: 50 ± 25%; Light/ Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

One day before the test, the 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 to the shorn skin of 3 females albino rabbits of 0.5 mL of the pure liquid test item/animal was applied. The treated skin area was approximately of 2.5 cm by 2.5 cm. Doses of 0.5 mL of the undiluted test item were placed on a dry gauze pad which was then applied to the clipped, intact skin of three rabbits for 4 hours. After an exposure period of 4 hours, the dressing and patch were removed and the treated area was carefully cleaned with water. The treatment site was observed shortly after the end of the exposure period then daily for up to 72 h.

Dose:	0.5 mL pure liquid test substance/animal
Application route:	Dermal (semi occlusive procedure)
Duration:	4 hours
Group size:	3 rabbits
Observations:	Clinical signs, skin effects, body weight (at beginning of study)
In life dates:	30th May 2006 to 2nd June 2006

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted: no systemic intolerance reactions.

Table CP 7.1.4-1 Summary of irritant effects (Scores)

Animal		24 hours	48 hours	72 hours	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	-	1*
	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

*the score was 1 at 1h

Abbreviations: No positive response: mean scores <2 = -
Positive response: mean scores ≥2 = +
na : not applicable

Any distribution, reproduction or publication of this document is copyright protected and requires the consent of Bayer AG or its respective affiliate(s) for regulatory use of the document or its content for regulatory purposes. Any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

III. Conclusion

It was concluded that Isoxaflutole + cyprosulfamide SC 480 was not irritating to the rabbit skin.

According to the criteria for classification defined in the Directive 2001/59/EC, the formulation Isoxaflutole + cyprosulfamide SC 480 is labelled as follows:

Symbols of danger : None
Risk phrases : None

CP 7.1.5 Eye irritation

Report:	[redacted] §; [redacted]; 2006; M-279246-01
Title:	Isoxaflutole + AE 0001789 SC 480 - Acute eye irritation on rabbits
Report No & Document No	AT03287 M-279246-01-2
Guidelines:	OECD Guidelines N° 405 (2002) EEC Directive 67/548 annex V Part B, Method B5 (1967 in its current version) EPA (OPPTS 870.2400 - 712-C-98-195) (1998)
GLP	Yes

I. Materials and methods

A. Materials

1. Test material: Isoxaflutole + cyprosulfamide SC 480

Specification no.: 10200001430S
Description: Beige liquid
Lot/Batch no: 2005-001042 (EFM000580)
Content: Isoxaflutole: 240 g/L, cyprosulfamide: 240 g/L (Nominal values)
Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)
Stability of test compound: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: None

3. Test animals

Species: Rabbit, females
Strain: Albino (Crl:KBL(NZW)BR)
Age: Young adult animals
Weight at dosing: 2.2 kg – 2.5 kg
Source: [redacted] Germany
Acclimation period: At least 5 days
Diet: [redacted], Germany
Water: Tap water *ad libitum*

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its affiliate), document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Housing:	The animals were housed individually in cage units Metall/Noryl by EBECO. Excrement trays below the cages contained low dust wood granulate bedding ([redacted] Germany). The wood granulate was changed at least twice weekly. The animal room had a standardized climate: Room temperature: 20 ± 3°C; Air humidity: 50 ± 25%; Light/Dark cycle: 12 hour rhythm.

B. Study design and methods

1. Animal assignment and treatment

A single dose of 0.1 mL of the undiluted test item was placed into the conjunctival sac of one eye 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 right eye was untreated and served as the control. The eyes were not rinsed for at least 24 hours after administration of the test item. Since the test item was not severely irritant on the first animal, it was then evaluated in two other animals. Ocular reactions were observed approximately 1 hour, 24, 48 and 72 hours after instillation.

Dose:	0.1 mL pure liquid test substance/animal
Application route:	instillation into the conjunctival sac of one eye. The eye was not rinsed for at least 24 hours following instillation.
Group size:	3 rabbits
Observations:	Clinical signs, eye effects, body weight (at beginning of study)
In life dates:	7th June 2006 to 10th June 2006

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted:

The individual findings of the treated eyes at the various observation times are summarized in Table CP 7.1.5-1. The control eyes did not show any abnormal findings and are not listed in the Table CP 7.1.5-1.

For all animals the test compound adhered to cornea and conjunctiva at 1h post application. At 24h the test compound adhered to conjunctiva and the eye was rinsed with 0.9% saline solution for animals 2 and 3.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purposes is prohibited and constitutes a violation of the underlying licence agreement.

Table CP 7.1.5-1 Summary of Irritant Effects (Scores)

Observations Animal 1	**1h**	**24h**	**48h**	**72h**	**Mean scores (24-48-72h)**	**Reversible (days)**
Degree of cornea opacity	0	0	0	0	0.0 (-)	na
Iris	0	0	0	0	0.0 (-)	na
Redness conjunctivae	2	3	0	0	1.0 (-)	2
Chemosis conjunctivae	1	1	0	0	0.3 (-)	2
Observations Animal 2	**1h**	**24h**	**48h**	**72h**	**Mean scores (24-48-72h)**	**Reversible (days)**
Degree of cornea opacity	0	0	0	0	0.0 (-)	na
Iris	0	0	0	0	0.0 (-)	na
Redness conjunctivae	2	3	1	0	1.3 (-)	3
Chemosis conjunctivae	1	1	0	0	0.3 (-)	2
Observations Animal 3	**1h**	**24h**	**48h**	**72h**	**Mean scores (24-48-72h)**	**Reversible (days)**
Degree of cornea opacity	0	0	0	0	0.0 (-)	na
Iris	0	0	0	0	0.0 (-)	na
Redness conjunctivae	2	3	3	0	2.0 (-)	3
Chemosis conjunctivae	2	2	1	0	1.0 (-)	3

na = not applicable

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

III. Conclusion

It was concluded that Isoxaflutole + cyprosulfamide SC 480 was not irritating to the rabbit eye.

According to the criteria for classification defined in the Directive 2001/59/EC, the formulation is labelled as follows:

Symbols of danger : None
Risk phrases : None

According to OECD classification criteria, Isoxaflutole + cyprosulfamide SC 480 is not irritating to eyes.

Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of this document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7.1.6 Skin sensitization

Report:	[redacted]2;[redacted];2006;M-278552-01
Title:	Isoxaflutole + AE 0001789 SC 480 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No. & Document No.	SA06149 M-278552-01-2
Guidelines:	O.E.C.D. Guideline 429 (2002) US EPA OPPTS 870.2600
GLP	Yes

I. Materials and methods

A. Materials

1. Test material: Isoxaflutole + cyprosulfamide SC 480

Specification no.: 10200001/4305

Description: Beige liquid

Lot/Batch no: 2005-001042 (EFIM000580)

Content: Isoxaflutole: 240 g/L, cyprosulfamide: 240 g/L (Nominal values)
Isoxaflutole: 246 g/L, cyprosulfamide: 245 g/L (Certified by analysis)

Stability of test compounds: Guaranteed for study duration; expiry date: 27th March 2007

2. Vehicle and/or positive control: Vehicle: Water containing 1% Pluronic Acid was selected to ensure compatibility with the test substance and maximum wetting of the mouse ears with the maximum possibility of skin penetration of the various formulation ingredients.

A positive control group received 0.25% p-benzoquinone in 10% Isoxaflutole+cyprosulfamide SC 480 and 90% Pluronic acid at 1% in water. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive control.

3. Test animals

Species: Mice, females

Strain: CBA/J

Age: At least 8 weeks old

Source: [redacted]France

Acclimation period: At least 5 days

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Diet:	Certified rodent pellet diet: AO4C-10, S.A.F.E. (Scientific Animal Food and Engineering, Route de Saint Bris, Augy, France)
Water:	Tap water *ad libitum*
Housing:	During the study period the animals were individually housed in suspended, stainless steel, wire mesh cages. Room temperature: 20-24°C Humidity: 40 - 70 %; Light/dark cycle: Twelve hours rhythm Air exchange rate: 10-15 times per hour.

B. Study design and methods

1. Animal assignment and treatment

Twenty-four female CBA/J mice were allocated to 6 groups of four animals each.

- Four groups received the test substance at a concentration of 1, 2.5, 5 and 10% in vehicle,
- A positive control group received 0.25% p-Benzoquinone in 10% Isoxaflutole + cyprosulfamide SC480 and 90% of aqueous Pluronic Acid at 1%. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive controls.
- A control group received the vehicle, 1% pluronic acid in water.
-

Observations:	Mortality, clinical signs, skin effects, body weight (at beginning and termination of study)
In life dates:	20th June 2006 to 29th June 2006

The test substance, positive control or the vehicle were applied on external surfaces of each ear (25 µL/animal) for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations. On Day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices and auricular weight.

II. Results and discussion

A. Findings

Mortality and clinical signs - No mortality and no clinical signs were observed during the study. No cutaneous reactions and no irritation were observed at the treated site for the negative control, positive control or Isoxaflutole + Cyprosulfamide SC480 treated groups.

Body weights - No significant body weight changes were observed during the study either in the control or in the treated groups.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliated) or any use of the document or its content for regulatory or commercial purposes is prohibited and constitutes a violation of the underlying license agreement.

Proliferation Index

The results are presented in Table 7.1.6-1.

The proliferation index values of the test substance were 1.3, 1.1, 1.8 and 1.2 at treatment concentrations of 1, 2.5, 5 and 10% respectively.

The proliferation index value of the positive control was 4.5 at a treatment concentration of 0.25% of p-Benzoquinone in 10% Isoxaflutole + Cyprosulfamide SC480 and 90% aqueous Pluronic Acid at 1%.

Negative lymphoproliferative responses (SI<3) was noted for Isoxaflutole + cyprosulfamide SC480 at all concentrations tested.

In the positive control group given p-Benzoquinone, a SI value > 3 was noted.

Table CP 7.6.1-1: Proliferation Index

GROUP	TEST SUBSTANCE(S)	# OF ANIMALS	CONCENTRATION % DAYS 0-2	DPM/NODE	STIMULATION INDEX (SI)
1	Vehicle control*	4	0	327	
2	Isoxaflutole + cyprosulfamide SC480	4	1.0	416	1.3
3		4	2.5	370	1.1
4		4	5.0	576	1.8
5		4	10.0	389	1.2
6	p-Benzoquinone**	4	0.25	1475	4.5

* 1% aqueous pluronic acid

** 0.25% p-Benzoquinone in 10% Isoxaflutole + Cyprosulfamide SC480 and 90% of aqueous Pluronic Acid at 1%.

Negative lympho-proliferative responses (SI<3) were noted for Isoxaflutole + Cyprosulfamide SC480 at all concentrations tested. In the positive control group given p-Benzoquinone, a SI value >3 was noted. This positive response to p-Benzoquinone demonstrates the validity of this assay under the current condition using the specific test formulation.

III. Conclusion

As no stimulation index value was over 3 for treated group and as no dose-related effect was noticed, Isoxaflutole + cyprosulfamide SC480 was found not to be a sensitizing formulation in the Local Lymph Node Assay.

According to the Commission Directive 2001/59/EC, the test substance Isoxaflutole + Cyprosulfamide SC480 is labelled as follows:

Symbols of danger : None
Risk phrases : None

CP 7.1.7 Supplementary studies on the plant protection product

None.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No short-term toxicity studies are required by the EU Directive 91/414/EEC.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliates) or its representative for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7.2 Data on exposure

Isoxaflutole & cyprosulfamide SC 480 is a suspension concentrate containing 240 g/L isoxaflutole and 240 g/L cyprosulfamide. The proposed representative use is as an herbicide in maize and sweet corn. Applications of isoxaflutole & cyprosulfamide SC 480 will be achieved via field crop sprayers. Usage information pertinent to operator exposure is summarised in Table CP 7.2-1.

Table CP 7.2-1: Application parameters for isoxaflutole & cyprosulfamide SC 480

Crop(s)	Product Name	F / G	Application	Growth stage BBCH	N° of applications	Maximum Application rate		Spray volume (L/ha)	PHI
						(kg product/ha)	(kg IFT/ha)		
Maize/corn	Merlin® Flexx	F	FCS	00-13	1	0.417	0.1	150-400	NA
Sweet corn				00-09					

* IFT is the abbreviation for isoxaflutole, F = Field use, FCS = Field crop sprayer, NA = Not applicable.

CP 7.2.1 Operator exposure

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 maize/corn was used for exposure calculations.

It should be noted that "no PPE" in the German Model considers a lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes. Such an unprotected operator should never handle plant protection products as this clothing is not in accordance with good occupational practice. Therefore, a coverall or alternatively, work trousers, a work jacket and sturdy footwear should be regarded as basic working clothing for operators handling plant protection products. This scenario is in line with the UK POEM, if "no PPE" is considered (i.e. an operator wearing typical (long sleeved) working clothing). Both models allow estimates for protected operators wearing additional PPE, if necessary.

It should be noted that this selection of protective measures is not intended to be a recommendation for the minimum PPE necessary when handling IFT+CSA 480. It does not consider specific requirements, which may exist in individual Member States. Additional PPE can be used to further reduce the exposure of the operator.

This document is Copyright protected. Any distribution or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purposes is prohibited and constitutes a violation of the underlying license agreement.

[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 Protections); 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)

Dermal absorption

Dermal absorption data are available for isoxaflutole from *in vitro* studies with human/rat skin Details regarding how the dermal absorption values were derived are provided in Section 7.3. The values used in the following risk assessments were:

Isoxaflutole:

Concentrate: 0.7%.
Spray dilution: 6%.

The current EU AOEL for isoxaflutole was derived from a 90 day oral rat study (60% oral absorption and a safety factor of 100) resulting in an AOEL of **0.02** mg/kg bw/day.

The results of the exposure calculations are summarized 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 0.417 L product/ha,70 kg operator				
Isoxaflutole	No PPE 1)	0.00403	0.02	20
	With PPE 2)	0.00094		4.7
UK POEM				
Field crop sprayer application to cereals, 50 ha/day at a rate of 0.41 L product/ha,60 kg operator				
Isoxaflutole	No PPE 3)	0.032589	0.02	163
	With PPE 4)	0.005181		26

1) No PPE = lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes but no gloves.
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 and application.

*Dermal absorption values of 0.7% (neat formulation) and 6% (spray). Inhalation absorption was taken as 100%.

Overall conclusion

Exposure estimates using both models predict acceptable risks for the intended use when appropriate PPE is worn. The BBA model predicts a safe use without the use of PPE.

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.

This document is copyright protected. Any distribution or reproduction requires the consent of Bayer AG (or its affiliate). Any use of the document for commercial purposes is prohibited and constitutes any other violation of the underlying license agreement.

CP 7.2.1.1 Estimation of operator exposure

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: 0.1 kg a.s./ha isoxaflutole i.e. 0.417 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 during application.

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:	IFT+CSA SC 480				
Active substance:	IFT	a.s. concentration:	240	[g/l or kg]	
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	0.417		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 [%]	0.7 (concentrate)		Body:	Standard protective coverall	
	6.0 (dilution)				

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
I_{M} =	0.0006	2.0016	0.000017	1.0	0.000017	I = Inhalation
$D_{M(H)}$ =	2.4	2.0016	0.0686	0.01	0.000686	D = Dermal
I_{A} =	0.001	2.0016	0.000029	1.0	0.000029	M = Mix/Loading
$D_{A(C)}$ =	0.06	2.0016	0.0017	1.0	0.001716	A = Application
$D_{A(H)}$ =	0.38	2.0016	0.0109	1.0	0.010866	H = Hands
$D_{A(B)}$ =	1.6	2.0016	0.0458	0.05	0.002288	C = Head
						B = Body

Absorbed dose:

Route		Absorption [%]	No PPE: Estimated route exposure [mg/kg bw/day]	No PPE: Systemic exposure [mg/kg bw/day]	With PPE: Estimated route exposure [mg/kg bw/day]	With PPE: Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	0.7	0.068626	0.00048	0.000686	0.000005
	Application	6.0	0.058332	0.0035	0.014869	0.000892
Inhalation:	Mix/Loading	100	0.000017	0.000017	0.000017	0.000017
	Application	100	0.000029	0.000029	0.000029	0.000029
		Total =		**0.004026**		**0.000943**

Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement. This document is copyright protected.

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 (maize/corn)

Treated area:	50 ha per day.
Max. dose rate:	0.417 L product/ha corresponding to 0.1 kg a.s./ha IFT.
Minimum Applied volume:	150 L/ha.
Duration of work:	6 hours.
Container size:	10 L, wide neck (reasonable worst case for a 50 ha application).

Exposure estimates based on the UK POEM (with and without PPE) and proportions of the systemic AOEL are summarised in Table CP 7.2.1-1.

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

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Table CP 7.2.1.1-2: Calculation of exposure to IFT of operators using IFT+CSA SC 480 at 0.417 L/ha; application with field crop sprayer (UK POEM, with and without PPE) in 50 ha cereal fields

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Product	**IFT+CSA SC 480**		Active substance	**IFT**	
Formulation type	water-based		a.s. concentration	**240**	mg/ml
Dermal absorption from product	**0.7**	%	Dermal absorption from spray	**6**	%
Container	10 litres 63 mm closure				
PPE during mix/loading	Gloves		PPE during application	Gloves	
Dose	**0.417**	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	0.417	litres product/ha							
Work rate	50	ha/day							
Number of operations	3	/day							
Hand contamination	0.15	ml/day							
Protective clothing	None					Gloves			
Transmission to skin	100	%				5	%		
Dermal exposure to formulation	0.150	ml/day				0.008	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	Gloves		Permeable	Permeable
Penetration	100%		5%		15%	10%		5%	15%
Dermal exposure	0.65		0.05		0.375	0.65		0.05	0.375 ml/h
Duration of exposure	6	h				6	h		
Total dermal exposure to spray	41.550	ml/day				6.450	ml/day		
ABSORBED DERMAL DOSE									
	Mix/load			Application		Mix/load			Application
Dermal exposure	0.15	ml/day		41.55	ml/day	0.0075	ml/day		6.45 ml/day
Concen. of a.s. product or spray	240	mg/ml		0.6672	mg/ml	240	mg/ml		0.6672 mg/ml
Dermal exposure to a.s.	36	mg/day		27.722	mg/day	1.8	mg/day		4.30344 mg/day
Percent absorbed	0.7			6	%	0.7	%		6 %
Absorbed dose	0.252	mg/day		1.663	mg/day	0.0126	mg/day		0.258 mg/day
INHALATION EXPOSURE DURING SPRAYING									
Inhalation exposure	0.01	ml/h							
Duration of exposure	6	h							
Concentration of a.s. in spray	0.6672	mg/ml							
Inhalation exposure to a.s.	0.040032	mg/day							
Percent absorbed	100	%							
Absorbed dose	0.040032	mg/day							
PREDICTED EXPOSURE	No PPE					With PPE			
Total absorbed dose	1.955	mg/day				0.311	mg/day		
Operator body weight	60	kg				60	kg		
Operator exposure	0.03258930	mg/kg bw/day				0.005181	mg/kg bw/day		
AOEL	0.020	mg/kg bw/day							
%AOEL	162.9	%				25.9 %			

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

CP 7.2.1.2 Measurement of operator exposure

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

CP 7.2.2 Bystander and resident exposure

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 EU level 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 AOELs 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)				
Isoxaflutole	Bystander: adult	0.000035	0.02	**0.173**
	Bystander: child	0.000034		**0.172**
Residential Exposure				
Isoxaflutole	Resident: adult	0.0000021	0.02	**0.011**
	Resident: child	0.0000055		**0.028**

*Assumes a 60 kg bystander for an adult and 16.15 kg for a child.
*Dermal absorption value of 6% for IFT. 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 IFT+CSA SC 480.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its affiliate) in respect of its content or regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement. Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

[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)

CP 7.2.2.1 Estimation of bystander and resident exposure

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

Bystanders and residents are not involved in application or handling plant protection products or the professional handling of treated crops. The question arises whether it is necessary to distinguish between bystanders and residents in terms of the potential for exposure and health risks. However, because the circumstances of this exposure could differ with respect to amount, frequency and duration, this seems to be reasonable.

Bystanders may inadvertently be present within or directly adjacent to an area for a short period of time, typically a matter of minutes, where application of a plant protection product is in progress or has recently taken place. They may be exposed to plant protection products mainly *via* the dermal route from spray drift and by inhalation of drifting spray droplets. 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 > 50 cm	 0.29 1.23

Exposure calculations are performed according to the following equations:

a) Bystander exposure to isoxaflutole

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

SDE_B = (AR x D x BSA x DA) / BW

Where:

SDE_B	= Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)	
AR	= Application Rate (mg/m^2)	0.1 kg a.s./ha = 10 mg/m^2
D	= Drift (%)	0.29% (10 m distance) for 1 application
BSA	= Exposed Body Surface Area (m^2)	1 m^2 (adult), 0.21 m^2 (child)
DA	= Dermal Absorption (%)	6%
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child)

This document is copyright protected. Any distribution or reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

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) 0.1 kg a.s./ha.
A = Area Treated (ha/day) 20 ha (field crop sprayer).
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 isoxaflutole

Adults			**Children**		
Bystander of Field Crop Sprayer					
Dermal exposure:			Dermal exposure:		
$SDE_B = (AR \times D \times BSA \times DA) / BW$			$SDE_B = (AR \times D \times BSA \times DA) / BW$		
(10 x 0.29% x 1 x 6%) / 60			(10 x 0.29% x 0.21 x 6%) / 16.15		
Absorbed dose:	0.000029	mg/kg bw/day	Absorbed dose:	0.000023	mg/kg bw/day
Inhalation exposure:			Inhalation exposure:		
$SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$			$SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$		
(0.001 x 0.1 x 20 x 5/360 x 100%) / 60			(0.000575 x 0.1 x 20 x 5/360 x 100%) / 16.15		
Absorbed dose:	0.00000556	mg/kg bw/day	Absorbed dose:	0.00001186	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:	**0.000035**	**mg/kg bw/d**	**Total absorbed dose:**	**0.000034**	**mg/kg bw/d**
% of AOEL:	**0.173**		**% of AOEL:**	**0.172**	

b) Residential exposure to isoxaflutole

Dermal exposure *via* deposits caused by spray drift

$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$

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

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG or its respective affiliates. Any use of the document for regulatory or any other commercial purposes is prohibited and constitutes a violation of the underlying License agreement.

AR	= Application Rate (mg/cm^2)	0.1 kg a.s./ha = 0.001 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 (%)	6%.
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/m^3): 0 mg/m^3 (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 isoxaflutole is 1.0×10^{-5} 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/cm^2)	0.1 kg a.s./ha = 0.001 mg/cm^2.
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 (cm^2)	20 cm^2.
Freq	= Frequency of Hand to Mouth (events/hour)	20 events/h.
H	= Exposure Duration (hours)	2 h.
OA	= Oral Absorption (%)	60%.
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/cm^2)	0.1 kg a.s./ha = 0.001 mg/cm^2.
D	= Drift (%)	0.29% (10 m) for 1 application.
DFR	= Dislodgeable Foliar Residues (%)	20%.
IgR	= Ingestion Rate for Mouthing of Grass/Day (cm^2)	25 cm^2/day.
OA	= Oral Absorption (%)	60%.
BW	= Body Weight (kg/person)	16.15 kg (child)

Any distribution, reproduction or publication requires the consent of the Bayer AG (or its respective affiliated). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Total systemic exposure of residents is then estimated for

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

Where:
SE_R = Systemic Exposure of Residents (mg/kg bw/day)
SDE_R = Systemic Dermal Exposure of Residents (mg/kg bw/day)
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 isoxaflutole

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		
(0.001 x 0.29% x 5% x 7300 x 2 x 6%) / 60			(0.001 x 0.29% x 5% x 2600 x 2 x 6%) / 16.15		
Absorbed dose:	0.00000212	mg/kg/day	Absorbed dose:	0.00000280	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		
			(0.001 x 0.29% x 5% x 50% x 20 x 20 x 2 x 60%) / 16.15		
			Absorbed dose	0.00000215	mg/kg/day
			Oral exposure (object-to-mouth transfer):		
			SOE_O = (AR x D x DFR x IgR x OA) / BW		
			(0.001 x 0.29% x 20% x 25 x 60%) / 16.15		
			Absorbed dose	0.00000054	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:	**0.00000212**	**mg/kg/day**	**Total absorbed dose:**	**0.00000549**	**mg/kg/day**
% of AOEL	**0.011**		**% of AOEL:**	**0.0275**	

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

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

According to the use pattern the product is applied in the EU at BBCH growth stage 00 – 13 i.e. at pre-emergence or early post emergence (3 leaf stage). Therefore it is reasonable to conclude that there is either no need for farmers to re-enter the treated corn field and to come into contact with the crop or that any contact is going to be negligible. The control of the crops shortly after spray application ("scouting") can be performed visually, i.e. without having contact to the treated weeds (which have a size of approx. 10 cm) which would not normally be expected to lead to exposure. However, in order to demonstrate that even if the farmer were to touch the crop there would be no unacceptable levels of exposure, a risk assessment for scouting is provided.

Risk assessment for worker

CP 7.2.3.1 Estimation of worker exposure

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

This document is copyright protected. Any distribution, reproduction, publication requires the consent of Bayer AG or its respective affiliated companies. Any use of the document for its contents for regulatory or other commercial purposes is prohibited and constitutes any other violation of the underlying licence agreement.

[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)

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

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 isoxaflutole. 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.

Table CP 7.2.3.1-1: Summary of predicted worker exposures arising from the use of IFT+CSA SC 480and comparison with the AOEL

Active substance	Systemic exposure (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
IFT	0.001500	0.02	7.5

*Dermal absorption value of 6% for IFT.
Inhalation absorption was taken as 100% for all compounds.

Assessment

The exposure of workers entering treated areas is well within acceptable limits for IFT+CSA SC 480.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG or its respective affiliated. Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

Detailed calculations of worker exposure during re-entry:

Re-entry exposure to isoxaflutole:

Product Name: IFT+CSA SC 480
Active substance: IFT

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	0.1	x	1	
D	=	1500 µg a.s./pers/day									
	=	1.5 mg a.s./pers/day									
	=	0.025 mg/kg bw/day									
using		6.00% dermal absorption (highest value)									
S	=	0.025	x	0.0600							
	=	0.001500 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

Isoxaflutole

The extent of dermal absorption of isoxaflutole formulated in the IFT+CSA SC 480 formulation was investigated *in vitro* using human and rat skin. A summary of the study is given below. A conclusion and recommendation regarding the dermal absorption of isoxaflutole formulated in the SC 480 formulation is given below.

The *in vitro* study indicated that the mean percentage of [^{14}C]-isoxaflutole considered to be potentially absorbable over a period of 24 hours from the neat formulation was 0.36% and 1.15% for the human and rat skin, respectively. The mean percentage of [^{14}C]-isoxaflutole considered to be potentially absorbable from the intermediate concentration (44 g/L) was 0.91% and 5.6% for the human and rat skin respectively. The mean percentage of [^{14}C]-isoxaflutole considered to be potentially absorbable from the low concentration (0.3 g/L) was 2.6% and 17.4% for the human and rat skin respectively.

In the absence of an appropriate *in vivo* rat study the *in vitro* human skin values were used alone.

According to the new EFSA guidance[7] 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

[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.

Any distribution, reproduction or publication requires the consent of Layer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

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 isoxaflutole in the Merlin® Flexx formulation (IFT+CSA SC 240+240):

- 0.7% for the neat formulation (240 g/L)
- 1.2% for the intermediate dose (44 g/L)
- 5.7% for the low dose (0.3 g/L).

Dermal absorption, in vivo in the rat

No study using the appropriate formulation is available.

Comparative dermal absorption, in vitro using rat and human skin

Report:	CP 7.3/01, [redacted], M., (2008)
Title:	Cyprosulfamide + Isoxaflutole, (240 + 240) [^{14}C]-isoxaflutole: Comparative *in vitro* dermal absorption study using human and rat skin.
Document N°:	M-391215-01-1
Guidelines:	O.E.C.D. guideline for the testing of chemicals; skin absorption: *in vitro* Method 428 (April 2004), O.E.C.D. Environmental health and safety publications series on testing and assessment N°28, Guidance document for the conduct of skin absorption studies (March 2004), European Commission guidance document on dermal absorption-Sanco/222/2000 rev. 7, (March 2004).
GLP	Yes

Material and methods

Rat skin:

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

Source: [redacted] (France).

Sex: Male (6).

Anatomical site: Dorsal.

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

Human skin: Source: [redacted] France.
Number and sex: 6 donors, female.
Anatomical region: Abdomen.
Thickness: 416 to 554 µm.

Test Material:

Non-radiolabelled: Batch: ABJ1704PFI.
Purity = 98.5% w/w.

Radiolabelled: [phenyl-^{14}C]-isoxaflutole

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document or its content for regulatory or any other commercial purposes is prohibited and constitutes any violation of the underlying license agreement.

Batch: KATH 6183.
Specific activity: 4.35 MBq/mg.
Radiopurity of the formulation: 99%.

Formulation: The formulation used in this experiment was the Cyprosulfamide + Isoxaflutole SC 480 formulation used at three nominal concentrations: 240 g a.s./L, 44 g a.s./L and 0.3 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 (Dermalab, Cortex Technology, Denmark) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 40 g/hm^2 were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

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

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

Radioassay: The amounts of radioactivity in the various samples were determined by liquid

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliate). Any use of the document for regulatory or any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

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:

Isoxaflutole was demonstrated to be soluble in the receptor fluid up to the concentration of 0.8 mg/mL of receptor fluid. This corresponds to having the maximum amount of IFT applied to the cell diffusing into the receptor fluid instantaneously. Therefore the solubility in the receptor fluid was deemed to be sufficient to have reduced 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 90.7% to 102.4% of the applied dose. The study results are presented in Table 7.6.2-1.

This document is copyright protected. Any distribution, reproduction or publication requires the consent of Bayer AG (or its respective affiliates/ Any use of the document or its content for regulatory/ any other commercial purpose is prohibited and constitutes a violation of the underlying license agreements.

Table CP 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-isoxaflutole in an SC 480 formulation at the rates of 240 g/L, 44 g/L and 0.3 g/L to human and rat skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)											
Dose Levels	Neat formulation: High dose (SYP13304, 240 g/L)				Dilution: Intermediate dose (SYP13307, 44 g/L)				Dilution: Low dose (SYP13309, 0.3 g/L)			
Species	Human (n=6)		Rat (n=6)		Human (n=5)		Rat (n=5)		Human (n=4)		Rat (n=5)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT												
Skin swabs (8h)	99.99	2.26	98.48	1.62	94.00	2.11	87.69	5.53	87.67	3.11	66.21	15.46
Skin swabs (24h)[a]	0.11	0.13	0.94	0.88	0.75	0.27	2.74	1.72	1.58	1.19	8.51	7.41
Surface Dose (1st two tape-strips)	0.33	0.28	1.76	0.70	0.87	0.26	2.94	2.14	0.82	0.39	4.57	4.16
Donor chamber	0.11	0.09	0.12	0.07	0.49	0.27	0.10	0.04	0.19	0.22	0.26	0.25
Total % non-absorbed	***100.5***	***2.04***	***101.3***	***1.17***	***96.11***	***1.79***	***93.47***	***3.01***	***90.27***	***1.76***	***79.54***	***7.61***
SKIN COMPARTMENT												
Skin [b]	0.12	0.08	0.21	0.20	0.22	0.09	0.78	1.06	1.42	1.51	2.28	2.22
Stratum corneum [c]	0.24	0.24	0.87	0.67	0.66	0.24	4.72	2.73	1.40	0.77	13.18	8.51
Total % at dose site	***0.35***	***0.31***	***1.08***	***0.85***	***0.89***	***0.31***	***5.50***	***2.42***	***2.82***	***2.12***	***15.45***	***7.24***
RECEPTOR COMPARTMENT												
Receptor fluid (0-24h)	0.004	0.009	0.06	0.03	0.03	0.02	0.09	0.01	0.24	0.12	1.77	0.47
Receptor fluid terminal	n.d.	n.a.	0.005	0.007	n.d.	n.a.	0.01	0.01	n.d.	n.a.	0.10	0.08
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	0.09	0.20
Total % directly absorbed [d]	***0.004***	***0.01***	***0.06***	***0.03***	***0.03***	***0.02***	***0.10***	***0.02***	***0.24***	***0.12***	***1.95***	***0.50***
Total % Potentially Absorbable	***0.36***	***0.32***	***1.15***	***0.86***	***0.91***	***0.31***	***5.61***	***2.42***	***3.06***	***2.23***	***17.40***	***7.40***
TOTAL % RECOVERY	**100.9**	**1.88**	**102.4**	**1.36**	**97.03**	**1.61**	**99.08**	**3.49**	**93.33**	**1.34**	**96.95**	**3.56**

[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
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.

This document is copyright protected or published for regulatory or public disclosure purposes. Any distribution, reproduction or transmission for any other purpose is prohibited without the consent of Bayer AG or its affiliate). Any use of the document for regulatory or any other commercial purpose constitutes a violation of the underlying License agreement.

Conclusion:
The dermal penetration of [^{14}C]-isoxaflutole through human and rat dermatomed skin from the SC 480 formulation was investigated at three concentrations corresponding to the neat product (240 g /L) and to two representative dilutions (44 and 0.3 g/L), respectively.

Overall, the dermal penetration of [^{14}C]-isoxaflutole in the SC 480 formulation was low at all concentrations used. There was a significant species difference in the absorption levels at all three concentrations tested with the human skin being up to 6.7 times less permeable that the rat skin.

The mean percentage of isoxaflutole in the SC 480 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 0.4% and 1.2% for the human and rat skin, respectively.

The mean percentage of isoxaflutole in the SC 480 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 0.9% and 5.6% for the human and rat skin respectively.

The mean percentage of isoxaflutole in the SC 480 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 3.1% and 17.4% for the human and rat skin respectively.

According to the new EFSA guidance[8] 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 isoxaflutole in the Merlin® Flexx formulation (IFT+CSA SC 240+240):

- 0.7% for the neat formulation (240 g/L)
- 1.2% for the intermediate dose (44 g/L)
- 5.7% for the low dose (0.3 g/L).

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

Any distribution, reproduction or publication requires the consent of Bayer AG (or its concerned affiliate) Any use of the document for its respective regulatory purpose is prohibited and constitutes any other commercial purpose is prohibited and constitutes a violation of the underlying license agreement.

[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.