Bayer CropScience

Document Title

Tier 2 Summary of the Toxicological Studies and Exposure Data and Information on the Plant Protection Product

Spirotetramat 150 g/L OD
Material No.: 06424376

Submission to RMS Austria as representative use in the EU

Data Requirements

Directive 91/414/EEC
Annex IIIA
Section 3, Point 7
Document M

According to OECD format guidance for industry data submissions on plant protection products and their active substances

Date

2006-09-26

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IIIA1 7 Toxicological Studies and Exposure Data and Information on the Plant Protection Product

IIIA1 7.1 Acute toxicity

Summary of acute toxicity

Type of study	Vehicle	Results	Report No.
acute oral rat	tap water	LD_{50}: ≥ 5,000 mg/kg bw	AT02161
acute dermal rat	--	LD_{50}: > 4,000 mg/kg bw	AT02164
acute inhalation rat	--	LC_{50}: > 1,760 mg/m³ air *	AT02396
skin irritation rabbit		non-irritant	AT02359
eye irritation rabbit	--	non-irritant	AT02358
skin sensitization guinea pig (Buehler Patch Test) (100 % product)	sterile physiological saline solution	skin-sensitization potential	AT01873
skin sensitization guinea pig (Buehler Patch Test) (0.48% product)	Lewatit water	"ready to use" test formulation no skin sensitization	AT02570

--: no vehicle used; * maximum technically attainable concentration

The formulation Spirotetramat 150 OD does not need to be classified on the basis of its acute oral, dermal and inhalative toxicity in rats. The formulation is considered to be non-irritant to skin and to eyes, but exhibits a skin sensitizing potential in the Buehler Patch Test (Xi, R 43 May cause sensitization by skin contact).

The "ready to use" test formulation (0.48% product) was not skin sensitizing under the conditions of the Buehler Patch Test.

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IIIA1 7.1.1 Acute oral toxicity

Report:	**KIIIA1 7.1.1/01, [redacted], M.; 2005**
Title:	BYI 08330 150 OD – Acute toxicity study in the rat after oral administration
Report No &	AT02161
Document No	M-254331-01-1
Guidelines:	OECD 423; EEC Directive 67/548 Annex V-Method B.1 tris; US-EPA OPPTS 870.1100.
Deviation(s):	The test compound is a product known to be stable and homogeneous in both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed. The deviation does not limit the assessment of results.
GLP	Yes (certified laboratory). Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Article no.:	00-06424376
Description:	Light brown suspension
Lot/Batch no.:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

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:	169 g – 189 g
Source:	[redacted], Germany
Acclimatization period:	At least 5 days
Diet:	[redacted] 3883.0.15; [redacted], 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, in ascending group number order. 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, [redacted], Germany.

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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:	2,000 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:	2005-04-21 – 2005-05-11

II. Results and discussion

A. Mortality

Mortality was not observed at 2,000 mg/kg bw.

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Duration of signs	Time of death	Mortality (%)
Females						
2,000 1st	0	0	3	-	--	0
2,000 2nd	0	0	3	--	--	0
acute oral LD_{50}**: > 5,000 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.

C. Body weight

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

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D. Necropsy

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

III. Conclusion

The formulation Spirotetramat 150 OD is non-toxic to rats after acute oral administration.

Classification/labeling according to Commission Directive 1999/45/EEC: None.

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IIIA1 7.1.2 Acute percutaneous (dermal) toxicity

Report:	**KIIIA1 7.1.2/01, [redacted], M.; 2005**
Title:	BYI 08330 150 OD – Acute toxicity in the rat after dermal application
Report No &	AT02164
Document No	M-254642-01-1
Guidelines:	OECD 402; EEC Directive 67/545 Annex V-Method B.3, US- EPA OPPTS 870.1200. Deviation(s): none
GLP	yes (certified laboratory). Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Article no.:	00-06424376
Description:	Light brown suspension
Lot/Batch no.:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

2. Vehicle and/or positive control: None

3. Test animals

Species:	Rat, males and females
Strain:	Wistar (Hsd Cpb:WU)
Age:	9 – 13 weeks approximately
Weight at dosing:	Males: 205 g – 232 g Females: 211 g – 219 g
Source:	[redacted] Germany
Acclimation period:	At least 5 days
Diet:	[redacted] 3883.0.15; [redacted], 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, in ascending group number order. 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, [redacted], Germany. Room temperature: 22 ± 2°C; Air humidity: 55 ± 5%; Ventilation: approx. 10 changes per hour; Light/Dark cycle: 12 hour rhythm.

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B. Study design and methods

1. Animal assignment and treatment

	Dose (mg/kg bw)		Surface area (cm^2)	Range of doses (mg/cm^2)
	males	4,000	14.0	60.9-66.3
	females	4,000	14.0	60.3-62.6
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:	2005-04-21 – 2005-05-05			

II. Results and discussion

A. Mortality

Mortality was not observed at 4,000 mg/kg bw.

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
				Males		
4,000	0	0	5	--	--	0
				Females		
4,000	0	0	5	--	--	0
acute dermal LD_{50}: > 4,000 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. A slight decrease in body weight was observed on day 8 in two females and on day 15 in two other females. This effect is assumed to be caused by the stress of the occlusive dressing, and is not considered test compound related.

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D. Necropsy

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

III. Conclusion

The formulation Spirotetramat 150 OD is non-toxic after acute dermal administration.

Classification/labeling according to Commission Directive 1999/45/EEC: None

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IIIA1 7.1.3 Acute inhalation toxicity to rats

Report:	**KIIIA1 7.1.3/01, [redacted]; 2005**
Title:	BYI 08330 150 OD – Acute inhalation toxicity in rats
Report No &	AT02396
Document No	M-257809-01-1
Guidelines:	OECD 403; EEC Directive 67/545 Annex V-Method B.2, US- EPA OPPTS 870.1300. JMAFF No. 12 Nousan 8147. Deviation(s): none
GLP	yes (certified laboratory). Deviation(s): none

I. Materials and methods

1. Test material: BYI 08330 150 OD

Article no.:	00-06424376
Description:	Light brown suspension
Lot/Batch no.:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

2. Vehicle and/or positive control: None

3. Test animals

Species:	Rat, males and females
Strain:	SPF Wistar (Hsd Cpb:WU)
Age:	Approximately two months
Weight at dosing:	Males: 168.0 g – 199.0 g Females: 168.0 g – 175.0 g
Source:	[redacted], Germany
Acclimation period:	At least 5 days
Diet:	[redacted] 3883 9441 pellets, [redacted], 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 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.

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B. Study design and methods

1. Animal assignment and treatment

Dose:	0 – 1,760 mg/m³ 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:	2005-05-03 – 2005-05-18

2. Generation of the test atmosphere / chamber description

Generation and characterization of chamber atmosphere

	Group 1	Group 2
Target concentration (mg/m³)	Control	5,000
Actual concentration (mg/m³)	--	1,760
Temperature (mean, °C)	22.8	22.5
Relative humidity (mean, %)	47.5	46.8
MMAD (µm)	--	2.21
GSD	--	2.20
Aerosol mass < 3 µm (%)	--	65.2
Mass recovered (mg/m³)	--	1,831

MMAD = Mass Median Aerodynamic Diameter, GSD = Geometric Standard Deviation;
-- not applicable.

II. Results and discussion

A. Mortality

Mortality was not observed at 1,760 mg/m³ air.

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Table 7.1.3-1 Doses, mortality / animals treated

Actual concentration (mg/m³ air)	Toxicological results*			Duration of signs	Time of death	Mortality [%]
Males						
0	0	0	5	--	--	0
1,760	0	5	5	0 d – 3 d	--	0
Females						
0	0	0	5	--	--	0
1,760	0	5	5	0 d – 2 d	--	0
acute inhalative LC_{50}: > 1,760 mg/m³ air						

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

B. Clinical observations
The following clinical signs were observed in the test substance groups:
Males: labored breathing patterns, bradypnea, motility reduced, piloerection, hair-coat ungroomed, high-legged gait, nose: red encrustations, nasal discharge (serous).
Females: labored breathing patterns, bradypnea, piloerection, hair-coat ungroomed, high-legged gait, nose: red encrustations and reddened.

C. Body weight
Comparisons between the control and exposure group revealed mild, although statistically significant decreased body weights.

D. Necropsy
Animals sacrificed at the end of the observation period: Macroscopic findings amongst the groups were indistinguishable.

III. Conclusion
The formulation Spirotetramat 150-OD is of very low toxicity after acute inhalation to rats.

Classification/labeling according to Commission Directive 1999/45/EEC: None

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IIIA1 7.1.4 Skin irritation

Report:	**KIIIA1 7.1.4/01, [redacted], M.; 2005**
Title:	BYI 08330 150 OD – Acute skin irritation/corrosion on rabbits
Report No &	AT02359
Document No	M-256984-01-2
Guidelines:	OECD 404; EEC Directive 67/548 Annex V-Method B.4., US-EPA OPPTS 870.2500. Deviation(s): none
GLP:	Yes (certified laboratory). Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Article no.:	00-06424376
Description:	Light brown suspension
Lot/Batch no:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

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:	2.3 kg - 2.8 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 ([redacted], Germany). The wood granulate was changed at least twice weekly. The water bottles were changed weekly. The animals were regularly transferred to clean cages. The animal room had a standardized climate: Room temperature: 23 ± 3°C; Air humidity: 50 ± 25%; Light/ Dark cycle: 12 hour rhythm.

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B. Study design and methods

1. Animal assignment and treatment

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:	2005-05-10 – 2005-05-17

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted:
Animal no. one: erythema (grade 2) up to 72 hours examination time point.
Animal no. two: erythema (grade 1) up to 72 hours examination time point.
Animal no. three: erythema (grade 1) at 24 and 72 hours examination time points and grade 2 after 48 hours.

There were no systemic intolerance reactions.

Table 7.1.4-1 Summary of irritant effects (Scores)

Animal no.	24h		48h		72h		Mean scores		Response		Reversible (days)	
	E	***O***	***E***	***O***	***E***	***O***	***E***	***O***	***E***	***O***	***E***	***0***
1	2	0	2	0	2	0	2.0	0.0	+	-	7	na
2	1	0	1	0	1	0	1.0	0.0	-	-	7	na
3	1	0	2	0	1	0	1.3	0.0	-	-	7	na

Abbreviation: 0 = no pathological findings, E = Erythema and eschar formation, O = Oedema formation; na = not applicable

III. Conclusion

The formulation Spirotetramat 150 OD is non-irritant to the skin.

Classification/labeling according to Commission Directive 1999/45/EEC: None

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IIIA1 7.1.5 Eye Irritation

Report:	**KIIIA1 7.1.5/01, [redacted], M.; 2005**
Title:	BYI 08330 150 OD – Acute eye irritation on rabbits
Report No &	AT02358
Document No	M-256988-01-1
Guidelines:	OECD 405; EEC Directive 67/548 Annex V-Method B.5., US-EPA OPPTS 870.2400. Deviation(s): none
GLP	Yes (certified laboratory). Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Article no.:	00-06424376
Description:	Light brown suspension
Lot/Batch no:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

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:	2.4 kg - 2.8 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 ([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.

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B. Study design and methods

1. Animal assignment and treatment

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:	2005-05-24 – 2005-06-14

II. Results and discussion

A. Findings

Under the present test conditions the following findings were noted:

Animal no. one: Corneal opacity (grade 2) after 24 hours and grade 1 after 48 and 72 hours. Conjunctival redness (grade 3) after 24 hours, grade 2 after 48 hours and grade 1 after 72 hours. Conjunctival chemosis (grade 2) after 24 hours and grade 1 after 48 hours.

Animal no. two: Corneal opacity (grade 1) after 24 hours and grade 1 up to 72 hours. Conjunctival redness (grade 2) after 24 hours and up to 72 hours. Conjunctival chemosis (grade 2) after 24 hours and up to 72 hours.

Animal no. three: Corneal opacity (grade 2) after 24 hours and grade 1 after 48 and 72 hours. Conjunctival redness (grade 3) after 24 hours and up to 72 hours. Conjunctival chemosis (grade 2) after 24 hours and grade 1 after 48 and 72 hours.

Table 7.1.5-1 Summary of Irritant Effects (Scores)

Animal No.		24 h	48 h	72 h	mean scores	response	reversible [days]
1	corneal opacity	2	1	1	1.3	-	21
	iritis	0	0	0	0.0	-	na
	conjunctivae						
	- redness	3	2	1	2.0	-	14
	- chemosis	2	1	0	1.0	-	3
2	corneal opacity	1	1	1	1.0	-	21
	iritis	0	0	0	0.0	-	na
	conjunctivae						
	- redness	2	2	2	2.0	-	14
	- chemosis	2	2	2	2.0	+	14
3	corneal opacity	2	1	1	1.3	-	21
	iritis	0	0	0	0.0	-	na
	conjunctivae						
	- redness	3	3	3	3.0	+	21
	- chemosis	2	1	1	1.3	-	21

response: corneal opacity: mean scores: <2 = --; ≥ 2<3 = +; ≥3 = ++
iritis: mean scores: <1 = --; ≥ 1<2 = +; =2 = ++
conj. redness: mean scores: <2.5 = --; ≥ 2.5 = +
conj. oedema: mean scores: <2 = --; ≥ 2 = +
na: not applicable

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III. Conclusion

The formulation Spirotetramat 150 OD is non-irritant to the eyes.
Classification/labeling according to Commission Directive 1999/45/EEC: None

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IIIA1 7.1.6 Skin sensitization

Report:	**KIIIA1 7.1.6/01, [redacted], H.-W.; 2005**
Title:	BYI 08330 150 OD (Project: BYI 08330) – Study for the skin sensitization effect in guinea pigs (Buehler Patch Test)
Report No & Document No	AT01873 M-246231-02-1
Guidelines:	OECD 406; EEC Directive 67/548 Method B.6; US-EPA OPPTS 870.2600.
Deviation(s):	The test item contains commercial products known to be stable and homogeneous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of the stability and homogeneity of the formulations in physiological saline solution for administration were not performed. The deviation does not limit the assessment of results.
GLP	Yes (certified laboratory); Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Development no.:	30-00364846
Description:	Brown suspension
Lot/Batch no:	08030/0180(0152)
Content:	144.65 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2005-11-29

2. Vehicle and/or positive control: Sterile physiological saline solution

3. Test animals

Species:	Guinea pig, females
Strain:	SPF-bred (Crl:HA)
Age:	4 -5 weeks
Weight at dosing:	255 g – 351 g
Source:	[redacted] Germany
Acclimation period:	At least 5 days
Diet:	[redacted] 3420, [redacted], Switzerland
Water:	Tap water *ad libitum*
Housing:	During the adaptation and study period the animals were conventionally kept in type IV Makrolon® cages, in groups of five during the adaptation period and in groups of two or three per cage throughout the study period. The cages were exchanged for ones with clean bedding two times per week. Low-dust wood shavings supplied by [redacted], Germany were used as bedding. The wood shavings were spot checked for contaminant levels. Records of these test results are filed at

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Bayer HealthCare AG. Room temperature: 22 +/- 3°C (possibly drifting higher at outdoor temperatures above 24°C); Relative humidity: 40 - 70 %; Light/dark cycle: Twelve hours rhythm; artificial lighting: Air exchange rate: >= 10 times per hour.

B. Study design and methods

1. Animal assignment and treatment

Dose:	
1st to 3rd induction:	100 %
Challenge:	100 %
Application route:	Dermal (challenge; occlusive application)
Application volume:	0.5 ml/animal
Group size:	Test item group: 20 females, control group: 10 females
Observations:	Mortality, clinical signs, skin effects, body weight (at beginning and termination of study)
Grading of the skin reaction:	0 = no reaction; 1 = slight localized redness; 2 = moderate confluent redness; 3 = severe redness and swelling
In life dates:	2005-01-11 – 2005-02-10

II. Results and discussion

A. Findings

There were no skin effects in the animals of the test item group and the control group during the first induction treatment. After the second induction there were skin effects (grade 1) in 11 of 20 animals and after the third induction (grade 1-3) in 20 of 20 animals of the test item group and no skin effects in the animals of the control group. The challenge with the 100 % test item concentration led to skin effects (grade 1-2) in 20 of 20 animals of the test item group (100 %) and no skin effects in the control group.

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Table 7.1.6-1: Number of animals exhibiting skin effects during challenge

	Test item group (20 animals)					Control group (10 animals)				
	Test item patch			Control patch		Test item patch			Control patch	
Hours	30	54	Total	30	54	30	54	Total	30	54
Challenge 100 %	20	20	20	0	0	0	0	0	0	0

III. Conclusion

Under the conditions of the Buehler Patch Test and with respect to the evaluation criteria, the test item therefore exhibits a skin-sensitization potential.

Classification/labeling according to Commission Directive 1999/45/EEC: Xi, R 43 (may cause sensitization by skin contact)

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Report:	**KIIIA1 7.1.6/02, [redacted], H.-W.; 2005**
Title:	BYI 08330 150 OD – Ready to use dilution (Project: BYI 08330) – Study for the skin sensitization effect in guinea pigs (Buehler Patch Test)
Report No & Document No	AT02570 M-260111-01-1
Guidelines:	OECD 406; EEC Directive 67/548 Method B.6., US-EPA OPPTS 870.2600.
Deviation(s):	The test item contains commercial products known to be stable and homogeneous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of the stability and homogeneity of the formulations in physiological saline solution for administration were not performed. The deviation does not limit the assessment of results.
GLP	Yes (certified laboratory); Deviation(s): none

I. Materials and methods

A. Materials

1. Test material: BYI 08330 150 OD

Development no.:	30-00364846
Description:	Light brown liquid
Lot/Batch no:	08030/0189(0152)
Content:	148.89 g/l
Stability of test compound:	Guaranteed for study duration; expiry date: 2006-03-10

2. Vehicle and/or positive control: Lewatit water. A 0.48 % concentration was formulated (ready to use concentration)

3. Test animals

Species:	Guinea pig, females
Strain:	SPF-bred (Crl:HA)
Age:	5 - 6 weeks
Weight at dosing:	290 g – 388 g
Source:	[redacted], Germany
Acclimation period:	At least 5 days
Diet:	[redacted] 3420, [redacted], Switzerland
Water:	Tap water *ad libitum*
Housing:	During the adaptation and study period the animals were conventionally kept in type IV Makrolon® cages, in groups of five during the adaptation period and in groups of two or three per cage throughout the study period. The cages were exchanged for ones with clean bedding two times per week. Low-dust wood shavings supplied by [redacted], Germany were used as bedding. The wood shavings were spot checked for

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contaminant levels. Records of these test results are filed at Bayer HealthCare AG. Room temperature: 22 +/- 3°C (possibly drifting higher at outdoor temperatures above 24°C); Relative humidity: 40 - 70 %; Light/dark cycle: Twelve hours rhythm; artificial lighting: Air exchange rate: >= 10 times per hour.

B. Study design and methods

1. Animal assignment and treatment

Dose:	
1st to 3rd induction:	0.48 %
Challenge:	0.48 %
Application route:	Dermal (challenge: occlusive application)
Application volume:	0.5 ml/animal
Group size:	Test item group: 20 females, control group: 10 females
Observations:	Mortality, clinical signs, skin effects, body weight (at beginning and termination of study)
Grading of the skin reaction:	0 = no reaction; 1 = slight localized redness; 2 = moderate confluent redness; 3 = severe redness and swelling
In life dates:	2005-09-13 - 2005-10-13

II. Results and discussion

A. Findings

There were no skin effects in the animals of the test item group and the control group during the first to third induction treatment. The challenge with the 0.48 % test item concentration led to skin effect (grade 1) in 1 of 20 animals of the test item group (5 %) and to no skin effects in the control group. Single animals showing slight reaction (grade 1) can be detected from time to time not depending on whether they were treated with vehicle or test item. Thus, such skin effects of single animals might appear by chance.

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Table 7.1.6-2: Number of animals exhibiting skin effects during challenge

	Test item group (20 animals)					Control group (10 animals)				
	Test item patch			Control patch		Test item patch			Control patch	
Hours	30	54	Total	30	54	30	54	Total	30	54
Challenge 0.48 %	1	1	1	0	0	0	0	0	0	0

III. Conclusion

Under the conditions of the Buehler Patch Test and with respect to the evaluation criteria, the "ready to use" test formulation exhibits no skin sensitization potential

Classification/labeling according to Commission Directive 1999/45/EEC: None

IIIA1 7.1.7 Supplementary studies for combinations of plant protection products

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

IIIA1 7.2 Short-term toxicity studies

No EC data requirement (the OECD point concerned is not covered by or part of an EC point according to Council Directive 91/414/EEC. Hence, data/documents do not need to be submitted.

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IIIA1 7.3 Operator exposure

'Spirotetramat OD 150' is an oil dispersion formulation containing 150 g/L Spirotetramat. The proposed use is as an insecticide on citrus and lettuce, for the latter both in the field as well as in the greenhouse. Applications of 'Spirotetramat OD 150' will be achieved via field crop sprayers, broadcast air assisted sprayers and hand held sprayers. Hand-held sprayers are used in citrus and in the greenhouse. Water will be the diluent/carrier in all situations. Usage information pertinent to operator exposure is summarised in Table 7.3-1.

Table 7.3-1: Application parameters for 'SPIROTETRAMAT OD 150'

Application technique	Crop(s)	F / G	Dose rate		Spray volume (L/ha)	No of trmt.	Interval betw. trtm. (days)	PHI (days)
			(L/ha product)	(kg a.s./ha)				
BAA	Citrus*, oranges mandarins, lemons, limes, etc.	F	0.64-1.92	0.096-0.288	1000-3000	2	21	14
HHS								
FCS	Lettuce	F	0.48	0.072	500	2	14	7
HHS	Lettuce	G	0.48	0.072	500	2	14	7

FCS = Field crop sprayer, BAA = Broadcast air assisted sprayer, HHS = Hand held sprayer
* In citrus: 0.64 L product and 1000 L water/metre canopy height, max. = 3 m
F = Field use, G = Greenhouse use

Operator exposure estimates are calculated using both the German model[1] and the UK-POEM[2]. Where no model data are available, only the model containing data for the relevant scenario is taken. Exposure calculations are performed without and with protective equipment.

The product is classified with the risk phrase

R 43 May cause sensitization by skin contact

Therefore, in addition to an unprotected operator at least the following personal protective equipment (PPE) is included in the calculation of the risk assessment:

Suitable protective gloves when handling the concentrate.

Dermal absorption data are available from an *in vivo* study performed with the OD 150 formulation and two *vitro* studies applied to human and rat skin - one performed with the OD 150 formulation and another

[1] Lundehn, J.-R.; Westphal, D.; Kiczka, 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)

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one performed with a SC 240 formulation (Annex IIIA1, 7.6). Derived from the results of the studies it is proposed to use 1.19% dermal absorption to calculate systemic exposure to the neat concentration (150 mg/mL), 0.55% to calculate systemic exposure to the medium dose dilution (1.5 mg/mL) and 2.15% to calculate systemic exposure to the low dose dilution (0.05 mg/mL).

Considering the proposed use pattern of 'Spirotetramat OD 150' it is appropriate to compare predicted exposures to an AOEL derived from sub-chronic dosing studies. An Acceptable Operator Exposure Level (AOEL) of 0.1 mg/kg bw/day is established for spirotetramat from the rabbit developmental study (lowest NOAEL: 10 mg/kg bw/day). No correction for oral absorption is made (96% oral absorption). A safety factor of 100 is applied.

IIIA1 7.3.1 Estimation of operator exposure without personal protective equipment

Overall summary on operator exposure

Operator exposure estimates are calculated using both the German model and the UK-POEM. Both, the German Model and the UK-POEM estimates predict that 'Spirotetramat OD 150' can be used safely with field crops sprayers, air assisted sprayers and hand held spray equipment. Exposure estimates based on the greenhouse study also predict that it can be used safely with hand held sprayers in lettuce in greenhouses.

a) Estimation according to the German model

Exposure is calculated for each application technique with the maximum dose rate. Lower doses will be covered by this calculation and separate evaluations are not made. Greenhouse applications are not evaluated with the German model. Exposure for this scenario will be calculated with a separate data set (see c). The following assumptions are made for each scenario:

Broadcast air assisted sprayer (citrus)

Treated area:	8 ha/day
Max. dose rate:	0.288 kg a.s./ha

Hand held sprayer (high pressure spray gun connected to big tank, citrus)

Treated area:	1 ha/day
Max. dose rate:	0.288 kg a.s./ha

Field crop sprayer (outdoor lettuce)

Treated area:	2 ha/day*
Max. dose rate:	0.072 kg a.s./ha

* The default work rate of 20 ha/day is used for industrial crops such as cereals. Lettuce, though, is grown on much smaller areas. A work rate of 2 ha/day and duration of 2 h/day is chosen for the calculation based on recommendations of the French Ministry of Agriculture for risk assessment for this crop[3].

[3] Szilvasi, S. (2001): Guide to the agronomic parameters used in reaching a provisional estimate of the risks associated with the use and application of agricultural antiparasitic products, French Ministry of Agriculture

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Exposure estimates based on the German model and proportions of the systemic AOEL accounted for by the estimates are summarised in the following table. Detailed calculations are presented in the tables 7.3.1-2 to 7.3.1-4.

Table 7.3.1-1: Predicted systemic exposure as a proportion of the AOEL: German model

Active substance	PPE	Systemic exposure [mg/kg bw/day]	AOEL [mg/kg bw/day]	% of AOEL
Tractor-mounted/trailed broadcast air-assisted sprayer				
Spirotetramat	None	0,0097	0,1	10
	With	0,0023		2
Hand-held sprayer: hydraulic nozzles, Outdoor, high level target, M/L big tank.				
Spirotetramat	None	0,0049	0,1	5
	With	0,0027		3
Tractor-mounted/trailed boom sprayer: hydraulic nozzles				
Spirotetramat	None	0,0002	0,1	0,2
	With	0,00003		0,0

* PPE: Gloves during mixing/loading, coverall during application
** Assumes a 70 kg operator, dermal absorption of spirotetramat 1.19% and 2.15% for the concentrate and the diluted spray, respectively. 100 % absorption via the inhalation route.

The German model estimates predict that 'Spirotetramat OD 150' can be used safely with broadcast air assisted sprayers and field crops sprayers without using personal protective equipment. Systemic exposure from the use of 'Spirotetramat OD 150' with broadcast air assisted sprayers in citrus is 10% of the spirotetramat AOEL when no PPE is used (lightly dressed operator wearing short sleeved shirt and short trousers, although a safe use is demonstrated this is not a recommendation according to good occupational practice). When hand-held sprayers are used exposure results in 5% of the spirotetramat AOEL. During the use of field crop sprayers operators are exposed to less than 1% of the AOEL. When wearing gloves during mixing/loading and a coverall during application systemic exposure results in a maximum of 3% of the AOEL.

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Table 7.3.1-2: Calculation of operator exposure to spirotetramat using broadcast air assisted sprayers (German model, without and with PPE)

Operator exposure estimate: German model. Tractor-mounted/trailed broadcast air-assisted sprayer

Product:	Movento OD 150				
Active substance:	Spirotetramat				
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	1,92		Hands:	Gloves	
Work rate [ha/day]:	8	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	1,19	(concentrate)	Body:	Standard protective coverall	
	2,15	(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	2,304	0,00002	1,0	0,00002	I = Inhalation D = Dermal
$D_{M(H)}$ =	2,4	2,304	0,079	0,01	0,0008	M = Mix/Loading
I_A =	0,018	2,304	0,000592	1,0	0,000592	A = Application
$D_{A(C)}$ =	1,2	2,304	0,0395	1,0	0,0395	H = Hands
$D_{A(H)}$ =	0,7	2,304	0,023	1,0	0,023	C = Head
$D_{A(B)}$ =	9,6	2,304	0,316	0,05	0,0158	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	1,2	0,079	0,0009	0,0008	0,0
	Application	2,2	0,3785	0,0081	0,0783	0,0017
Inhalation:	Mix/Loading	100	0,00002	0,00002	0,00002	0,00002
	Application	100	0,000592	0,000592	0,000592	0,000592
		Total =		**0,0097**		**0,0023**

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Table 7.3.1-3: Calculation of operator exposure to spirotetramat using hand held sprayers connected to a big spray tank (German model, without and with PPE)

Operator exposure estimate: German model. Hand-held sprayer: hydraulic nozzles. Outdoor, high level target. M/L big tank.

Product:	Movento OD 150				
Active substance:	Spirotetramat				
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	1,92		Hands:	Gloves	
Work rate [ha/day]:	1	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	1,19	(concentrate)	Body:	Standard protective coverall	
	2,15	(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	0,288	0,000002	1,0	0,000002	D = Dermal
$D_{M(H)}$ =	2,4	0,288	0,0099	0,01	0,0001	M = Mix/Loading
I_A =	0,3	0,288	0,001234	1,0	0,001234	A = Application
$D_{A(C)}$ =	4,8	0,288	0,0197	1,0	0,0197	H = Hands
$D_{A(H)}$ =	10,6	0,288	0,0436	1,0	0,0436	C = Head
$D_{A(B)}$ =	25,0	0,288	0,1029	0,05	0,0051	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	1,2	0,0099	0,0001	0,0001	0,0
	Application	2,2	0,1662	0,0036	0,0685	0,0015
Inhalation:	Mix/Loading	100	0,000002	0,000002	0,000002	0,000002
	Application	100	0,001234	0,001234	0,001234	0,001234
		Total =		**0,0049**		**0,0027**

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Table 7.3.1-4: Calculation of operator exposure to spirotetramat using field crop sprayers (German model, without and with PPE)

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

Product:	Movento OD 150				
Active substance:	Spirotetramat				
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha]:	0,48		Hands:	Gloves	
Work rate [ha/day]:	2	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	None	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	1,19	(concentrate)	Body:	Standard protective coverall	
	2,15	(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	0,144	0,000001	1,0	0,000001	I = Inhalation
$D_{M(H)}$ =	2,4	0,144	0,0049	0,01	0,0	D = Dermal
I_A =	0,001	0,144	0,000002	1,0	0,000002	M = Mix/Loading
$D_{A(C)}$ =	0,06	0,144	0,0001	1,0	0,0001	A = Application
$D_{A(H)}$ =	0,38	0,144	0,0008	1,0	0,0008	H = Hands
$D_{A(B)}$ =	1,6	0,144	0,0033	0,05	0,0002	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	2,2	0,0049	0,0001	0,0	0,0
	Application	2,2	0,0042	0,0001	0,0011	0,0
Inhalation:	Mix/Loading	100	0,000001	0,000001	0,000001	0,000001
	Application	100	0,000002	0,000002	0,000002	0,000002
		Total =		**0,0002**		**0,00003**

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b) Estimation according to the UK-POEM

For comparison with the above German model estimates, the UK POEM is also used to estimate the exposure. 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. Greenhouse applications are not evaluated with the UK-POEM. Exposure for this scenario will be calculated with a separate data set (see c). Exposure calculation for the high level hand held scenario cannot be made with the UK-POEM because the model provides only data for low level target applications. The following assumptions are made for each scenario:

Broadcast air assisted sprayer (citrus)

Work rate:	15 ha/day (500 L/ha model)
Dose:	1.92 L/ha product (citrus)
Spray volume:	3000 L/ha
Duration:	6 h/day

The product is applied in citrus with a concentration of 9.6 g a.s./100 L in a range of (min.) 0.64 L product per 1000 L spray volume up to (max.) 1.92 L product per 3000 L spray volume. The latter results in the highest estimates if the UK-POEM is used for the calculation. Therefore, only this scenario is presented in the detailed calculations and lower dose rate/spray volume calculations are covered by this scenario.

Field crop sprayer (lettuce)

Work rate:	2 ha/day*
Dose:	0.48 L/ha product (lettuce)
Application volume:	500 L/ha
Duration:	2 h/day*

* The default work rate of 50 ha/day is used for industrial crops such as cereals. Lettuce, though, is grown on much smaller areas. A work rate of 2 ha/day and a duration of 2 h/day is chosen for the calculation based on recommendations of the French Ministry of Agriculture for risk assessment for this crop[4].

Calculations are performed for the 5 litre container size.

Exposure estimates based on UK-POEM and proportions of the systemic AOEL accounted for by the estimates are summarised in the following table. Detailed calculations are presented in the tables 7.3.1-6 to 7.3.1-7.

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[4] Szilvasi S. (2001): Guide to the agronomic parameters used in reaching a provisional estimate of the risks associated with the use and application of agricultural antiparasitic products, French Ministry of Agriculture

Table 7.3.1-5: Predicted systemic exposure as a proportion of the AOEL: UK-POEM

Application technique*	Crop type	PPE**	Spirotetramat	
			Total systemic exposure*** (mg/kg bw/day)	% of AOEL (0.1 mg/kg bw/day)
BAA	Citrus	None	0.0064	6
		PPE	0.0036	4
FCS	Lettuce	None	0.0011	1
		PPE	0.0002	1

* FCS = Field crop sprayer, BAA = Broadcast air assisted sprayer

** PPE: Gloves during mixing/loading

*** Assumes a 60 kg operator, dermal absorption of spirotetramat 1.19% and 2.15% for the concentrate and the diluted spray, respectively. 100 % absorption via the inhalation route.

The UK-POEM estimates predict that 'Spirotetramat OD 150' can be used safely with broadcast air assisted sprayers and field crops sprayers. Systemic exposure results in 1% - 6% of the proposed spirotetramat AOEL when no PPE is used. If gloves are used during mixing/loading and during application exposure does not exceed 1% of the AOEL.

It is concluded that an unacceptable risk is not anticipated when handling 'Spirotetramat OD 150'.

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Table 7.3.1-6: Calculation of operator exposure to spirotetramat using broadcast air assisted sprayers (UK-POEM, without and with PPE)

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha		
Product	**Movento OD 150**	Active substance	**Spirotetramat**
Formulation type	organic solvent-based	a.s. concentration	**150** mg/ml
Dermal absorption from product	**1,19** %	Dermal absorption from spray	**2,15** %
Container	5 litres 45 or 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**1,92** l/ha	Work rate/day	**15** ha
Application volume	**3000** l/ha	Duration of spraying	6 h

EXPOSURE DURING MIXING AND LOADING					
Container size	5 litres				
Hand contamination/operation	0,01 ml				
Application dose	1,92 litres product/ha				
Work rate	15 ha/day				
Number of operations	6 /day				
Hand contamination	0,06 ml/day				
Protective clothing	None			Gloves	
Transmission to skin	100 %			10 %	
Dermal exposure to formulation	0,060 ml/day			0,006 ml/day	

DERMAL EXPOSURE DURING SPRAY APPLICATION						
Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha					
Application volume	3000 spray/ha					
Volume of surface contamination	400 ml/h					
Distribution	Hands	Trunk	Legs			
	10 %	65 %	25 %			
Clothing	None	Permeable	Permeable	Gloves	Permeable	Permeable
Penetration	100 %	2 %	5 %	10	2	5 %
Dermal exposure	40	5,2	5 ml/h	4	5,2	5 ml/h
Duration of exposure	6 h			6 h		
Total dermal exposure to spray	121,200 ml/day			85,200 ml/day		

ABSORBED DERMAL DOSE				
	Mix/load	Application	Mix/load	Application
Dermal exposure	0,060	121,200 ml/day	0,006	85,200 ml/day
Concen. of a.s. product or spray	150	0,096 mg/ml	150	0,096 mg/ml
Dermal exposure to a.s.	9,000	11,635 mg/day	0,900	8,179 mg/day
Percent absorbed	1,19	2,15 %	1,19	2,15 %
Absorbed dose	0,107	0,250 mg/day	0,011	0,176 mg/day

INHALATION EXPOSURE DURING SPRAYING	
Inhalation exposure	0,05 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	0,096 mg/ml
Inhalation exposure to a.s.	0,0288 mg/day
Percent absorbed	100 %
Absorbed dose	0,0288 mg/day

PREDICTED EXPOSURE	No PPE	With PPE
Total absorbed dose	0,3861 mg/day	0,2154 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0,0064 mg/kg bw/day	0,0036 mg/kg bw/day

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Table 7.3.1-7: Calculation of operator exposure to spirotetramat using field crop sprayers (UK-POEM, without and with PPE)

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Movento OD 150**	Active substance	**Spirotetramat**
Formulation type	organic solvent-based	a.s. concentration	**150** mg/ml
Dermal absorption from product	**1,19** %	Dermal absorption from spray	**2,15** %
Container	5 litres 45 or 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**0,48** l/ha	Work rate/day	**2** ha
Application volume	**500** l/ha	Duration of spraying	**2** h

EXPOSURE DURING MIXING AND LOADING

Container size	5 litres		
Hand contamination/operation	0,01 ml		
Application dose	0,48 litres product/ha		
Work rate	2 ha/day		
Number of operations	1 /day		
Hand contamination	0,01 ml/day		
Protective clothing	None	Gloves	
Transmission to skin	100 %	10 %	
Dermal exposure to formulation	0,010 ml/day	0,001 ml/day	

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer/hydraulic nozzles						
Application volume	500 spray/ha						
Volume of surface contaminatio	10 ml/h						
Distribution	Hands	Trunk	Legs				
	65 %	10 %	25 %				
Clothing	None	Permeable	Permeable		Gloves	Permeable	Permeable
Penetration	100 %	5 %	15 %		10	5	15 %
Dermal exposure	6,5	0,05	0,375 ml/h		0,65	0,05	0,375 ml/h
Duration of exposure	2 h				2 h		
Total dermal exposure to spray	13,850 ml/day				2,150 ml/day		

ABSORBED DERMAL DOSE

	Mix/load	Application		Mix/load	Application	
Dermal exposure	0,010	13,850	ml/day	0,001	2,150	ml/day
Concen. of a.s. product or spray	150	0,144	mg/ml	150	0,144	mg/ml
Dermal exposure to a.s.	1,500	1,994	mg/day	0,150	0,310	mg/day
Percent absorbed	1,19	2,15	%	1,19	2,15	%
Absorbed dose	0,018	0,043	mg/day	0,002	0,007	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0,01	ml/h
Duration of exposure	2	h
Concentration of a.s. in spray	0,144	mg/ml
Inhalation exposure to a.s.	0,00288	mg/day
Percent absorbed	100	%
Absorbed dose	0,00288	mg/day

PREDICTED EXPOSURE	No PPE	With PPE
Total absorbed dose	0,0636 mg/day	0,0113 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0,0011 mg/kg bw/day	0,0002 mg/kg bw/day

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c) Estimation of exposure in the greenhouse

Summary
Neither the German model nor the UK-POEM provide exposure data to evaluate the "hand held application in greenhouses". Therefore, the exposure of operators during application with hand held sprayers in the greenhouse is evaluated with the study data provided by [redacted] (1996). Detailed considerations and calculations as well as a summary of this greenhouse study will be presented below.

The risk assessment is performed based upon the following assumptions:

Spray equipment:	Spray gun/lance and stationary tank
Work rate/day:	1 ha
Dose rate:	0.072 kg a.s./ha of spirotetramat (0.48 L/ha product)

Exposure estimates and proportions of the systemic AOEL accounted for by the estimates are summarised in the Table 7.3.1-8. Detailed calculations are presented in Table 7.3.1-12.

Table IIIA1 7.3.1-8: Predicted systemic exposure as a proportion of the AOEL (greenhouse)

Application technique*	Crop type	PPE**	Spirotetramat	
			Total systemic exposure*** (mg/kg bw/day)	% of AOEL (0.1 mg/kg bw/day)
HHS	Low crops	None	0.0006	0.6
		PPE	0.0004	0.4

* HHS = Hand held sprayer
** Gloves during mixing/loading and application, coverall during application
*** Assumes a 70 kg operator, dermal absorption of spirotetramat of 1.19% and 2.15% for the concentrate and the diluted spray, 100 % absorption via the inhalation route

Exposure estimates based on the greenhouse study predict that 'Spirotetramat OD 150' can be used safely with hand held sprayers in greenhouses in low crops such as lettuce.
Systemic exposure in low crops results in less than 1% of the proposed spirotetramat AOEL if no PPE is used. It is concluded that an unacceptable risk is not anticipated for the proposed use in greenhouses.

Detailed considerations and calculations
Exposure estimates for the mixing/loading of an oil dispersion formulation are based on model data (German model) because the greenhouse study delivers only data for mixing/loading of a wettable powder (WP).

The mixing/loading step can be performed in two ways:
- Mixing and loading a knapsack sprayer for each application separately
- Mixing and loading a large tank to which the spray equipment is then connected by a hose. This scenario can be compared to the mixing/loading step of tractor-mounted tanks.

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If small plots are treated, the "knapsack procedure" is likely to be performed. However, as soon as large areas are treated, the use of a large tank will be the usual practice. The risk assessment presented herein assumes a work rate of 1 ha/day in the greenhouse. The spray gun/lance connected to a (large) tank will likely be used for this scenario, especially if high water volumes are used. Mixing/loading a liquid into a large tank is therefore considered to calculate the exposure during mixing/loading with the German model.

A summary of the greenhouse study which is used to calculate the exposure during application is presented below.

Report:	**KIIIA1 7.3.1/01, [redacted], 1996**
Title:	Operator exposure in greenhouses during practical use of plant protection products
Report No &	EF 94-02-03
Document No	M-024096-01-1
Dates of work:	July, 1994 – June, 1996
Guidelines:	--
GLP	Yes (certified laboratory)

I Material and methods

Dermal and inhalation exposure were measured with the patch technique, by analysis of whole body underwear, glove and hand rinsing and absorbent air filters during mixing/loading of Euparen® WP 50, Rody® and Saprol® Neu and application to greenhouse ornamentals at 2 sites in Germany. Twelve experienced operators were monitored. The products were applied with commonly used knapsack sprayers at label recommended rates. Samples were analysed for the 3 active substances.

The following scenarios were investigated:
a) Mixing/loading of a Wettable Powder (WP) for knapsack-application
b) Application with knapsack sprayer to low cultures on tables
c) Application with knapsack sprayer to high cultures

II Results and discussion

Results of geometric mean exposure for the three scenarios are given below.

Table IIIA1 7.3.1-9: Specific exposures during <u>mixing/loading a WP</u> for Knapsack application in the greenhouse

Route of exposure during <u>mixing/loading a WP</u>	Exposure (mg/kg as handled)	
	Actual	Potential
Inhalation	0.895	0.895
Dermal (Head)	0.532	0.532
Dermal (Hands)	0.009	41.312
Dermal (Body)	0.146	5.474
Total dermal	0.686	47.318

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Table IIIA1 7.3.1-10: Specific exposures during Knapsack application of greenhouse low crops

Route of exposure during application in low crops	Exposure (mg/kg as handled)	
	Actual	Potential
Inhalation	0.398	0.398
Dermal (Head)	0.439	0.439
Dermal (Hands)	0.009	0.735
Dermal (Body)	0.223	6.350
Total dermal	0.671	7.524

Table IIIA1 7.3.1-11: Specific exposures during Knapsack application of greenhouse high crops

Route of exposure during application in high crops	Exposure (mg/kg as handled)	
	Actual	Potential
Inhalation	0.108	0.108
Dermal (Head)	1.562	1.562
Dermal (Hands)	0.008	13.188
Dermal (Body)	0.228	82.475
Total dermal	1.798	97.325

III Conclusion

The study provides appropriate data for the hand held scenario in greenhouses. Application data may be used for all types of hand held application. Mixing/loading data are only to be used if a Wettable Powder (WP) formulation and a Knapsack sprayer is used. In the absence of available data, the mixing/loading data for formulations other than a Wettable Powder (WP) and for other equipment used (e.g. stationary tank) may be taken from the available exposure models. It is considered that the process of mixing/loading for both indoor and outdoor are similar.

Detailed calculation of exposure based on the greenhouse exposure study:

The following table present the detailed calculations of exposure during the greenhouse use of the formulated product 'Spirotetramat OD 150'. The low crop scenario is chosen to calculate the exposure in lettuce.

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Table IIIA1 7.3.1-12: Calculation of operator exposure to spirotetramat during hand held application in the greenhouse, low crops

Task	Route of exposure	Calculation [potential (actual) exposure x dose rate x work rate]	Exposure estimate [mg a.s./person/day]	
			No PPE	With PPE
Low crops				
Mixing/loading[a]	Inhalation	0.0006x 0.072 x 1	0.00004	0.00004
	Dermal (hands)	2.4 x 0.072 x 1 (x 0.01 [b])	0.1728	0.0017
Application [c]	Inhalation	0.398 x 0.072 x 1	0.0287	0.0287
	Dermal (head)	0.439 x 0.072 x 1	0.0316	0.0316
	Dermal (hands)	0.735 (0.009) x 0.072 x 1	0.0529	0.0006
	Dermal (body)	6.350 (0.223) x 0.072 x 1	0.4572	0.0161
		Systemic exposure[d]	0.0425	0.0298
			[mg/kg bw/day]	
		Systemic exposure[e]	0.0006	0.0004

a Equipment: Large tank; formulation: Liquid (German model)
b Mitigation factor for gloves (German model)
c Greenhouse study ([redacted], 1996); scenario b, see Tables 7.3.1-10
d Dermal absorption: Spirotetramat 1.19% for the concentrate, 2.1% for the diluted spray, Inhalation absorption: 100%
e Body weight: 70 kg

IIIA1 7.3.2 Estimation of operator exposure using personal protective equipment

Estimations of operator exposure using PPE are performed with the respective exposure model. Detailed calculations and summaries are presented in IIIA 7.3.1.

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IIIA1 7.3.3 Measurement of operator exposure

Since the risk assessment carried out indicated that the health-based limit value (AOEL) for spirotetramat will 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.

IIIA1 7.4 Bystander exposure

No official model is available for calculation of bystander exposure. Some proposals were given by the EUROPOEM Bystander Working Group but the report is still a draft and not officially published because slight changes may still be anticipated following comments provided by the members of the working group. Therefore, as long as there is no official guidance on how to calculate bystander exposure an approach is presented in this document that considers both dermal exposure - derived from available drift data - and inhalation exposure - derived from the operator exposure models simulating a bystander who is exposed in a similar way as an unprotected operator spraying in the field.

IIIA1 7.4.1 Estimation of bystander exposure without personal protective equipment

The following definitions and assumptions for bystanders may be applied.

Bystanders are persons:

- who are located within or directly adjacent to the area where pesticide application or treatment is in process or has taken place
- whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of exposure
- who take no action to avoid or control exposure
- that are not wearing protective clothing and/or are wearing light clothing e.g. short sleeved shirt and short trousers.

The dermal exposure is calculated with the following equation:

$$D = \text{Total deposition (mg/m}^2\text{)} \times \text{drift (\%)} \times \text{exposed area (m}^2\text{/person)}$$

Drift data in Table 7.4.1-1 for spraying of arable crops, grapes, orchard trees, hops, etc. are publicly available (Ganzelmeier *et al.*, 1995)[5]. Drift data for fruit trees (2.62%, late stage) are taken to calculate bystander exposure during application in citrus and drift data for field crops (0.14%, early and late stage) are taken to calculate bystander exposure during application in lettuce. A distance of 7.5 m from the spray equipment is assumed.

[5] [redacted]r, H. F.: Studies on the Spray Drift of Plant Protection Products, Federal Biological Research Centre for Agriculture and Forestry; Berlin; No. 305; 1995 (document no.: M-001224-01-1)

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Table 7.4.1-1: Basic drift values proposed for various crop groups

Drift in % of dose rate												
	Mean											
	Field crops		Grapes				Fruit trees				Hops	
	(early + late)		early		late		early		late		late	
Distance (m)	7.5	10	7.5	10	7.5	10	7.5	10	7.5	10	7.5	10
Drift (%)	0.14	0.11	0.39	0.21	1.48	0.91	8.21	5.74	2.62	1.84	5.10	3.65

It is assumed that the bystander is not protected and that only light ordinary clothing is worn i.e. a person wearing a short sleeved shirt and short trousers, the total uncovered area amounts to about 1 m² (i.e. head, back and front of neck, forearms, ½ upper arms, thighs, legs and hands; Lundehn et al. 1992)[6].

The inhalation exposure of a bystander is calculated with the following equation:

$$I_{(bystander)} = I_{(operator, 6\ hours)} \times \frac{\text{Exposure time bystander}}{\text{Exposure time operator}}$$

It is considered that the inhalation exposure of an operator who is located close to the spray equipment is similar to a bystander located at a similar distance from the spray equipment. Therefore, exposure via the inhalation route is calculated with the data measured for an operator (German model). The bystander would not be exposed for the whole 6 hour period as the operator. It is most realistic that it takes one minute for the tractor to pass a bystander i.e. the exposure time is the 360th part of the exposure time of the applicator (spraying 6 hours a day). However, in a conservative approach an exposure duration of max. 5 minutes is assumed.

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

Table 7.4.1-2: Predicted systemic exposure of bystanders as a proportion of the AOEL

Application technique*	Crop type	PPE	Spirotetramat	
			Total systemic exposure** (mg/kg bw/day)	% of AOEL (0.1 mg/kg bw/day)
BAA	High crops	None	0.0003	< 1
FCS	Low crops	None	0.000004	< 1

* BAA = Broadcast air assisted sprayer, FCS = Field crop sprayer

** Assumes a 60 kg bystander, dermal absorption of spirotetramat of 2.15% for the diluted spray and 100 % absorption via the inhalation route.

Based on these data the predicted bystander exposure is less than 1% of the spirotetramat AOEL. It can be concluded that bystanders will not be exposed to critical levels during spray application of 'Spirotetramat OD 150'.

[6] 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, 1992.

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a) Calculation of bystander exposure to spirotetramat during application with broadcast air assisted sprayers

Dermal exposure:

D	=	Total deposition x drift x exposed area
		Calculation of 100 % deposition from spray:
		0.288 kg a.s./ha = 288 000 mg as/10 000 m² =28.8 mg a.s./m²
D	=	28.8 mg a.s./m² x 0.0262 x 1 m²/person/day
D	=	0.755 mg as/person/day
D	=	0.01258 mg as/kg bw/day (60 kg person)

Inhalation exposure:

I	=	I*$_{A\ (tractor)}$ x AT x AR
I*$_{A\ (tractor)}$	=	Spec. exposure during application for broadcast air assisted sprayers in high crop = 0.018 mg/person x kg a.s.
AT	=	Area treated (high crops): 8 ha/day
AR	=	Application Rate: 0.288 kg as/ha
I	=	0.018 x 8 x 0.288
I	=	0.0415 mg as/person/day
		but adapted to 5 minutes (instead of 6 hours for an operator):
I	=	0.0415 [mg as/person/day] : 6 [h/d] : 12 [min/h]
I	=	0.00058 mg as/person/day
I	=	0.00001 mg as/kg bw/day (60 kg person)

The systemic exposure is calculated with

D	=	0.01258 mg as/kg bw/day and
I	=	0.00001 mg as/kg bw/day

and under consideration of 8.45% dermal absorption (for the diluted formulation) as well as 100% absorption via inhalation.

S	=	0.01258 x 0.0215 + 0.00001 x 1
S	=	0.0003 mg/kg bw/day.
% of AOEL $_{(0.1\ mg/kg\ bw/day)}$:		0.1

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b) Calculation of bystander exposure to spirotetramat during application with field crop sprayers

Dermal exposure:

D	=	Total deposition x drift x exposed area
		Calculation of 100 % deposition from spray:
		0.072 kg a.s./ha = 72 000 mg as/10 000 m² = 7.2 mg a.s./m²
D	=	7.2 mg a.s./m² x 0.0014 x 1 m²/person/day
D	=	0.0101 mg as/person/day
D	=	0.00017 mg as/kg bw/day (60 kg person)

Inhalation exposure:

I	=	I*A (Tractor groundboom) x AT x AR
I*A (tractor)	=	Spec. exposure during application for broadcast air assisted sprayers in field crop = 0.001 mg/person x kg a.s.
AT	=	Area treated (high crops): 20 ha/day
AR	=	Application Rate: 0.072 kg as/ha
I	=	0.001 x 20 x 0.072
I	=	0.00144 mg as/person/day
		but adapted to 5 minutes (instead of 6 hours for an operator):
I	=	0.00144 [mg as/person/day] : 6 [h/d] : 12 [min/h]
I	=	0.00002 mg as/person/day
I	=	0.0000003 mg as/kg bw/day (60 kg person)

The systemic exposure is calculated with

D	=	0.00017 mg as/kg bw/day and
I	=	0.0000003 mg as/kg bw/day

and under consideration of 8.45% dermal absorption (for the diluted formulation) as well as 100% absorption via inhalation.

S	=	0.00017 x 0.0215 + 0.0000003 x 1
S	=	0.000004 mg/kg bw/day.

% of AOEL $_{(0.1\ mg/kg\ bw/day)}$: 4

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IIIA1 7.4.2 Measurement of bystander 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 bystander exposure was not necessary and was therefore not carried out.

IIIA1 7.5 Worker exposure

IIIA1 7.5.1 Estimation of worker exposure without personal protective equipment

Summary
'Spirotetramat OD 150' is an insecticide that is applied to citrus, oranges, mandarins, lemon, lime and lettuce, the latter both in the field and in greenhouses. Re-entry into treated crops for maintenance work/harvesting is necessary for farmers usually throughout the growing season. Re-entry exposure is therefore evaluated and compared with the AOEL of spirotetramat. Predicted exposures are calculated from a cumulative foliar deposit based on a maximum number of applications made at the maximum dose, 8 hours contact with foliage per day and a 0.24% dermal absorption for a dried foliar residue. A body weight of 60 kg is calculated for the re-entry worker.
Exposure estimates based on the proportions of the systemic AOEL accounted for by the estimates are summarised in table 7.5.1-1.

Table 7.5.1-1: Summary of predicted worker exposures arising from the use of 'Spirotetramat OD 150' and comparison with the respective AOEL

Active substance	Crop	Total dermal exposure (mg/kg bw/day)	Systemic exposure* (mg/kg bw/day)	% of AOEL**
Spirotetramat	Citrus	0.380	0.0045	5
	Lettuce	0.036	0.0004	<1

* 1.19% dermal absorption for spirotetramat, 60 kg worker
** 0.1 mg/kg bw/day

Exposure of operators entering treated areas is within acceptable levels. Exposure during re-entry in citrus and vegetables results in 5% of the spirotetramat AOEL or less.

Calculations reflect standard work clothing worn by adult workers (shoes, socks, long-legged pants, and long sleeves) working with bare hands. No personal protective equipment is considered to mitigate the exposure.

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Detailed considerations and calculations

A worst case estimate of the theoretical risk to workers entering a newly treated crop has been calculated using the worker re-entry model published by Hoernicke E. *et al*[7]. (1998) together with published transfer coefficient data relating to similar tasks.

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 1 µg as/cm² per kg as/ha according to the following consideration:

  1 kg as/ha = 10 µg/cm²;
  with two sided leaves ⇨ 5 µg/cm²;
  with a LAI (leaf area index) of ca. 3 - 5 ⇨ 1 - 1.66 µg/cm²
  resulting in about 1 µg as/cm² for row crops which do not cover the total sprayed area so that part of the spray is also deposited on the ground.

  This figure is published as a mean value in available literature and was confirmed by [redacted] *et al.*[8] (2001).

- Workers re-enter the treated culture shortly after the spray has dried on plant surfaces.

The exposure calculation is performed according to the following equation:

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

where
- D = Dermal exposure
- 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

It is considered that the evaluation of exposure for a re-entry situation directly after application (spray deposit has dried) and using high end default values for each parameter results in a very conservative approach sufficient to justify the safe use of 'Spirotetramat OD 150'.

---

[7] 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), 267 - 269, 1998 (document no.: M-107544-01-1)

[8] [redacted], D.H.; [redacted], M.; [redacted], 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)

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Furthermore, a potential accumulation of residues after repeated applications is considered in this calculation although it is supposed to be more realistic that in context with resistance prevention strategies the product is used within spray programmes, i.e. alternating with products of other chemical groups with different mode of actions. Scenarios of consecutive applications may thus occur but will be unlikely for most of the cases to be considered. Nevertheless, consecutive sprays are considered in this evaluation.
Considerations on the extent of residues after repeated applications may have an impact on the initial dislodgeable foliar residues (DFR) used in the equation. An estimation of the potential DFR after repeated application is done in the following evaluation.

<u>Considerations on DFR</u>
A maximum of two consecutive sprays per season are considered in this risk assessment. Farmers will only do consecutive treatments if the efficacy of the previous treatment is no longer sufficient. Low efficacy is mainly caused by a decline of residues. Therefore, accumulations of residues on plant surfaces after repeated applications will only occur to a small extent depending on the degree of decline. It is only reasonable to expect some residue decay would occur during a 7 day period (i.e. the required minimum interval between two applications). Otherwise, it would be highly unconceivable for growers to repeat any application when the active substance dislodgeable residues on the foliage could be preserved completely from a single application.

Where no DFR or residue data are available it may be assumed that residues will decline by 50% from the total deposit of the previous application.

An example demonstrates that with this assumption, DFRs will reach an upper maximum level that will not be exceeded.

It may be assumed that:

1. after the <u>first</u> application, DFR will be 1 µg/cm^2 with a following decrease (50%) to 0.5 µg/cm^2 after 14-21 days (= spray interval).
2. after the 2nd application DFR will be 0.5 + 1 = 1.5 µg/cm^2 with a following decrease to 0.75 µg/cm^2
3. after the 3rd application DFR will be 0.75 + 1 = 1.75 µg/cm^2 with a following decrease to 0.875 µg/cm^2
4. directly after the 4th application DFR will be 0.875 + 1 = 1.875 µg/cm^2
5. directly after the 5th application DFR will be 0.938 + 1 = 1.938 µg/cm^2
6. after the xth application DFR will be 1 + 1 = 2 µg/cm^2

With these assumptions, DFRs will not exceed a maximum of 2 µg/cm^2 /kg as handled after multiple applications.

A factor of 1.5 is considered for the DFR calculation <u>directly after the 2nd application</u>.

<u>Considerations on Transfer Coefficients</u>

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Hoernicke *et al.* [9]. (1998) propose in a general approach that a Transfer Coefficient (TC) of 30,000 (cm²/person/h) be used for the transfer of residues from foliage to the clothes or skin of a worker in initial estimates of exposure. This value is considered to represent a worst case for worker exposure, being derived from tasks requiring intensive contact with foliage and representing an unprotected worker. However, where it is considered that less intensive contact with the foliage will occur, the risk assessment may be refined by the use of alternative Transfer Coefficients (TC).

A wide range of TC values associated to various re-entry activities are published in the literature (Krieger *et al.* [10], 1992). It has to be noted that these figures refer to potential transfer coefficients which describe potential dermal exposure. For further estimation of actual dermal exposure, mitigation by ordinary work clothing has to be taken into account. Generally, potential exposure can be assumed to be reduced by 90% when long sleeved shirts and long pants are worn.

Transfer coefficients for work activities in citrus are publicly available and are used in this risk assessment. An unpublished report from TNO with crop/task specific TCs for harvesting cucumber in greenhouses is used for the greenhouse lettuce evaluation.

TC for re-entry in citrus:
TCs for re-entry in citrus are published by Nigg *et al.* [11] (1984) and Stamper *et al.* [12] (1986). An overall of 36 data are recorded for hands and another data set of 36 data are recorded for body. The following statistical results are calculated:

Table IIIA1 7.5.1-2: Transfer coefficients (citrus)

	TC citrus (cm²/hr)	
	Actual body:	Potential hands:
75th percentile:	5800	780

A re-entry worker is assumed to be not protected for his hands but to wear some working clothing. Therefore, the potential hand and the actual body data are used form the study. Hence, the TC for potential hand exposure is 780 cm²/hr (75th percentile) and the TC for actual body exposure is 5800 cm²/hr (75th percentile). The following total actual TC for citrus is:

$$\mathbf{TC_{actual\ citrus} = 6600\ cm^2/hr}$$

Transfer coefficients for re-entry in vegetables:
TCs for re-entry in vegetables are given in an unpublished report by [redacted] *et al.* (1998) for tying-bending and harvesting cucumbers. Details are given in the following:

Report: KIIIA1 7.5.1/01, [redacted], H.J.; [redacted], D.H., [redacted], J.J., 1998

[9] 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)
[10] Krieger, R. I.; Ross, J. H.; Thongsinthusak, T.: Assessing human exposure to pesticides; Rev Environ Contam Toxicol; Vol 128 (1992), 1-15 (document no. M-049968-01-1)
[11] Nigg, H.N.; Stamper, J.H.; Queen, R.M.: The devleopment and use of a univeral model to predict tree crop harvester pesticide exposure; Am. Ind. Hyg. Assoc. J; 45(3), 182 - 186 (1984), (document no.: M-245489-01-1)
[12] Stamper, J.H.; Nigg, H.N.; Queen, M.: Predicted of pesticide dermal exposure and urinary metabolite level of tree crop harvesters from field residues; Bull. Environ. Contam. Toxicol. Vol. 36; 693 - 700 (1986), (document no.: M-245482-01-1)

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Title:	Exposure to pesticides during re-entry activities in greenhouses - Field study in cucumber crop
Report No &	TNO V98.1076
Document No	M-105284-01-1
Dates of work:	1996 - Oct. 1998
Guidelines:	--
GLP	No

I Material and methods

Exposure was measured during re-entry activities in cucumber crop in seven greenhouses, using personal air samplers and cotton coverall, cotton gloves and a T-shirt as dermal dosimeters. The work activities under investigation were harvesting and bending/tying up. Pesticides were applied using high- and low-volume techniques. The period between application and re-entry varied between one and five days. Dislodgeable foliar residues and residues on cucumbers were measured in order to determine a transfer coefficient.

II Results and discussion

An overall of 22 data are recorded for hand exposures (no data for actual hands, all 22 for potential hands) and an overall of 44 data are recorded for body exposure (22 for actual body, all 22 for potential body). The statistical results are calculated as follows:

Table IIIA1 7.5.1-3: Transfer coefficients (vegetables)

		TC vegetables (cm²/hr)	
		Body:	Hands:
Actual exposure:	75th percentile:	174	-
	90th percentile:	242	-
Potential exposure:	75th percentile:	3557	2157
	90th percentile:	4238	2418

III Conclusion

The TC value for hand exposure is 2200 cm^2/hr (75th percentile, potential) and the TC value for body exposure is 3600 cm^2/hr (75th percentile, potential). If the body exposure were to be reduced by a factor of ten (via clothing) the total actual TC value for vegetables would be:

$TC_{actual\ vegetables}$ = 2500 cm^2/hr

Calculations:

Based on the published TCs detailed calculations of re-entry exposure are presented in the following:

Detailed calculations of worker exposure during re-entry in citrus:

D	=	DFR	x	TC	x	WR	x	AR	x	P
D	=	1.5	x	6600	x	8	x	0.288	x	1
D	=	22810 µg a.s./person/day								
	=	22.81 mg a.s./person/day								
	=	0.38 mg/kg bw/day (60 kg person)								

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Detailed calculations of worker exposure during re-entry in lettuce:

D	=	DFR	x	TC	x	WR	x	AR	x	P
D	=	1.5	x	2500	x	8	x	0.072	x	1
D	=	2160 µg a.s./person/day								
	=	2.16 mg a.s./person/day								
	=	0.036 mg/kg bw/day (60 kg person)								

IIIA1 7.5.2 Estimation of worker exposure using personal protective equipment

Estimations of worker exposure using PPE as an additional layer of clothing and/or gloves are not performed because the exposure of workers without using PPE is acceptable. Detailed calculations are are presented in MIIIA 7.5.1.

IIIA1 7.5.3 Estimation of worker exposure using data on dislogeable residues

Dislodgeable foliar residue studies were not performed because the estimation of worker exposure is acceptable for re-entry directly after the application when the spray deposit has dried. Detailed calculations are presented in MIIIA 7.5.1.

IIIA1 7.5.4 Measurement of worker 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 worker exposure was not necessary and was therefore not carried out.

IIIA1 7.6 Dermal absorption

Summary and conclusion on dermal absorption

The extend of dermal absorption of BYI 08330 was investigated *in vivo* in rats and *in vitro* on human and rat skin. The *in vivo* study was performed with [^{14}C]-BYI 08330 in an OD 150 formulation. *In vitro* data are available from two studies , one performed with the SC 240 formulation and another one performed with the OD 150 formulation.

The results of the *in vivo* study performed with the OD 150 formulation together with the results of the *in vitro* study performed with the OD 150 formulation are used to determine the dermal absorption to be used for risk assessment for the OD 150 formulation.

The *in vitro* studies demonstrate that no significant difference in dermal absorption is detected between both the SC 240 and the OD 150 formulations. The same is expected for the *in vivo* results. Therefore, the results of the *in vivo* study performed with the OD 150 formulation together with the results of the

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in vitro study performed with the SC 240 formulation are used to develop a proposal for dermal absorption of BYI 08330 in the SC 240 formulation.

A summary of the studies and conclusion on dermal absorption is given below.

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***In vitro* results**

The percentage of [^{14}C]-BYI 08330 considered to be potentially absorbable from the neat OD 150 formulation (150 mg/mL), the medium dose (1.5 mg/mL) dilution and the low dose (0.05 mg/mL) dilution was 0.24%, 2.74% and 8.45% through human skin and 2.14%, 23.21% and 22.71% through rat skin.

BYI 08330 in the OD 150 formulation is more absorbed by rat than by human skin. Dermal absorption is a factor of 8.9 times higher in rat skin than in human skin when skin is exposed to the concentrate (150 mg/mL), a factor of 8.5 when the skin is exposed to the medium dose (1.5 mg/mL) dilution and a factor of 2.7 when the skin is exposed to the low dose (0.05 mg/mL) dilution.

Table 7.6-1 Recovery of systemic radioactivity *in vitro* in human/rat skin, OD 150 formulation

BYI 8330 OD 150						
Compartment	**High dose (150 mg/mL)**		**Medium dose (1.5 mg/mL)**		**Low dose (0.05 mg/mL)**	
	Human	**Rat**	**Human**	**Rat**	**Human**	**Rat**
Skin (%)	0.23	1.88	2.32	19.96	7.89	10.49
Receptor fluid (%)	0.01	0.26	0.41	3.25	0.56	12.22
Total absorbed *in vitro* (%)	0.24	2.14	2.74	23.21	8.45	22.71
Factor of difference	8.9		8.5		2.7	

The percentage of [^{14}C]-BYI 08330 considered to be potentially absorbable from the neat SC 240 formulation (240 mg/mL), the medium dose (1.5 mg/mL) dilution and the low dose (0.05 mg/mL) dilution was 0.41%, 1.41% and 11.47% through human skin and 2.90%, 11.76% and 16.32% through rat skin. Both the dilutions were tested by adding 0.15% of the adjuvant Mero® (0.3% product) which will be sold in a Twin Pack.

BYI 08330 in the SC 240 formulation is more absorbed by rat than by human skin. Dermal absorption is a factor of 7.1 times higher in rat skin than in human skin when skin is exposed to the undiluted concentrate (240 mg/mL), a factor of 8.3 when the skin is exposed to the medium dose (1.5 mg/mL) dilution and a factor of 1.4 when the skin is exposed to the low dose (0.05 mg/mL) dilution.

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Table 7.6-2 Recovery of systemic radioactivity in vitro in human/rat skin, SC 240 formulation

BYI 8330 SC 240						
Compartment	**High dose (240 mg/mL)**		**Medium dose (1.5 mg/mL)**		**Low dose (0.05 mg/mL)**	
	Human	**Rat**	**Human**	**Rat**	**Human**	**Rat**
Skin (%)	0.31	2.61	1.34	10.27	11.23	9.33
Receptor fluid (%)	0.10	0.29	0.07	1.49	0.24	6.99
Total absorbed *in vitro* (%)	0.41	2.90	1.41	11.76	11.47	16.32
Factor of difference	7.1		8.3		1.4	

***In vivo* results**

After an exposure time of 10 hours and a period of 168 hours post application the directly absorbed amounts of [^{14}C]-BYI 08330 in three different concentrations of an OD 150 formulation were 7.69%, 2.99% and 3.99% of the dose applied in the high (10 mg/mL), intermediate (1.5 mg/mL) and low dose (0.5 mg/mL) group, respectively. As low amounts of radioactivity were still found after that period in urine and faeces the percentage of [^{14}C]-BYI 08330 found in the skin and stratum corneum were also considered to be potentially absorbable (indirectly absorbed) resulting in 10.57%, 4.71% and 5.81% for the high, intermediate and low dose, respectively. Results are shown in the following table.

Table 7.6-3 Recovery of systemic radioactivity in rat in vivo (10 h exposure, 168 h post application)

	[^{14}C]-BYI 08330 (% of applied dose)		
	High dose (10 mg/mL)	**Intermediate dose (1.5 mg/mL)**	**Low dose (0.5 mg/mL)**
Surface compartment	84.30	87.10	87.62
Skin compartment	2.87	1.72	1.82
Systemic compartment			
Total directly absorbed	7.69	2.99	3.99
Total indirectly absorbed	10.57	4.71	5.81
Overall recovery	94.87	91.81	93.43

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The high dose concentration (10 mg/mL) used in the study is somewhat lower than the concentration of a.s. in the concentrate OD 150 formulation (150 mg/mL). However, as relative dermal absorption is usually higher for a lower concentration the results from the high dose can be considered as a sufficiently conservative estimate for the concentrate product.

Conclusion:

The *in vitro* results demonstrate that [^{14}C]-BYI 08330 is more absorbed by rat than by human skin. The *in vivo* results on rat skin are therefore corrected by the factor of difference between human and rat skin found in the *in vitro* studies. The calculation of human *in vivo* dermal absorption from rat *in vivo* and human/rat *in vitro* data is presented in the following table.

Table 7.6-4 Conclusion on human dermal absorption in vivo

		[^{14}C]-BYI 08330 (% of applied dose)		
		High dose	**Intermediate dose**	**Low dose**
In vivo rat (% absorbed)		10.57	4.71	5.81
In vitro factor of difference rat/human skin	**OD 150**	8.9	8.3	2.7
	SC 240	7.1	8.3	1.4
In vivo human (% absorbable)	**OD 150**	10.57/8.9 = **1.19**	4.71/8.5 = **0.55**	5.81/2.7 = **2.15**
	SC 240	10.57/7.1 = **1.49**	4.71/8.3 = **0.57**	5.81/1.4 = **4.15**

The calculation of human dermal absorption of BYI 08330 *in vivo* to be used in risk assessment present similar results for both the OD 150 formulation and the SC 240 formulation. Dermal absorption of BYI 08330 from the OD 150 formulation is 1.19% for the concentrate product (150 mg/mL), 0.55% for the intermediate dose (1.5 mg/mL) and 2.15% for the low dose (0.05 mg/mL). Dermal absorption of BYI 08330 from the SC 240 formulation is 1.49% for the concentrate product (240 mg/mL), 0.57% for the intermediate dose (1.5 mg/mL) and 4.15% for the low dose (0.05 mg/mL).

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IIIA1 7.6.1 Dermal absorption, in vivo in the rat

Report:	**KIIIA1 7.6.1/01, [redacted] (2006)**
Title:	[^{14}C]-BYI 08330 in OD150 formulation: In vivo Dermal Absorption Study in the Male Rat
Report No & Document No	S -06009 M-276579-01-2
Dates of work:	July 27, 2006
Guidelines:	US-EPA, Prevention, Pesticides, and Toxic Substances (7101), Health Effects Test Guidelines, OPPTS 870.7600 Dermal Penetration, August 1998.
GLP	Yes (certified laboratory)

I Material and methods:

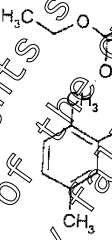
1. Test Material: BYI 08330 150 OD Formulation (150 g as/L) containing radiolabeled active [^{14}C]-BYI 08330

Description: technical is a white powder

Storage before use: freezer at –20°C

CAS # of TGAI: 203313-25-1

Name / Structure (as): Carbonic acid, cis-3-(2,5-dimethylphenyl)-8-methoxy-2-oxo-1-azaspiro[4.5]dec-3-en-4-yl-ethyl ester



*: denotes position of label

initial specific activity was 3.67 MBq/mg (99.1 µCi/mg)

> 99%

Bayer CropScience AG, Product Technology, Isotope, [redacted], Germany

Vehicle/Solvent used: water

2. Test animals:

Species: Rats (males only)

Strain: Wistar Rj. WI (IOPS HAN) strain

Age/weight at study initiation: 182.3 – 302 g

Source: [redacted], France

Housing: Individual metabolism units (Jencon's Metabowls Mk III or Radleys) equipped with metabowl unit with separator and flasks for the quantitative collection of urine and faeces.

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Diet:	Certified rodent pelleted and irradiated diet A04C-10 (from [redacted], France), ad libitum	
Water:	Filtered and softened water from the municipal water supply, ad libitum	
Environmental conditions:	Temperature:	22 ± 2°C
	Humidity:	55 ± 15%
	Air changes:	10-15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	14 days	

In a 2006 GLP study, the dermal absorption of [^{14}C]-BYI 08330 in an OD 150 formulation was studied in male rats using three dose concentrations. The test substance was applied with 60 µL onto each shaved area of 6 cm^2 (10 µL/cm^2) at rates of 10 mg/mL (high dose: 100 µL/cm^2), 1.5 mg/mL (intermediate dose: 15 µL/cm^2) and 0.5 mg/mL (low dose: 5 µL/ cm^2). Exposure times were 1, 10, and 24 hours. The exposure time of the formulation on the skin was identical with the time of sacrifice except for one group of rats at each dose. For this group at each dose, 4 male rats were exposed for 10 hours, then the dose site was washed and the animals left individually in the metabolism cages for up to 168 hours post dose application.

Table 7.6.1-1: Dose administration (dermal absorption in vivo, rats)

Dose Level	Dose Applied (mg/mL)	Group No.	No. male rats	Time of exposure (hours)
Low-Dose	0.5	1	4	1
		2	4	10
		3	4	24
		4	4	10 (168)*
Mid-Dose	1.5	5	4	1
		6	4	10
		7	4	24
		8	4	10 (168)*
High-Dose	10	9	4	1
		10	4	10
		11	4	24
		12	4	10 (168)*

*For these groups the time of exposure = 10 hrs and the time of sacrifice = 168 hrs post-application

At termination, the skin was swabbed with a freshly prepared mild liquid soap solution. The skin was shaved, if necessary, prior to tape-stripping to remove the stratum corneum. The dressings (saddle, gauze, cover, and tape) were removed and kept for analysis. For group 4, 8 and 12, urine and faeces were collected separately into receivers at 24-hour intervals up to sacrifice (168 hours). At the end of each collection period all debris was removed from the metabolism cage and retained. The cages were washed with distilled water. At termination each cage was washed with water and an appropriate organic

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solvent, retaining the washings for measurement of radioactivity. The treated area of skin was removed and taken for analysis. The residual carcass was also retained for analysis.

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II Results and discussion

A representative exposure time for farmers in the fields would be a period of 6-8 hours. Therefore, the results of the rat groups 4, 8 and 12 which were exposed for 10 hours and sacrificed after 168 hours is presented in this summary. The long period of 168 hours allows monitoring whether the amount of active substance still bound to the skin would be potentially available.

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Table 7.6.1-2: Summary of the mean distribution of radioactivity 168 hours after a single topical application of [^{14}C]-BYI 08330 at the high, intermediate and low dose concentrations (Groups 4, 8 and 12)

Results expressed in terms of % of applied dose.

	[^{14}C]-BYI 08330					
	High dose		Intermediate dose		Low dose	
	Male Wistar Rat					
Groups	**4**		**8**		**12**	
Exposure time	**10h**					
Times of sacrifice	**168h**					
Samples	Mean	SD	Mean	SD	Mean	SD
Surface compartment						
Swabs X, Y, Z (10h)	0.05	0.04	0.17	0.13	0.19	0.11
Swabs X, Y, Z (168h)	0.07	0.05	0.13	0.13	0.12	0.05
Swabs (10h & 168h)	79.59	2.67	83.89	4.93	82.33	2.35
Swabs surrounding[a]	0.03	0.02	0.02	0.04	0.06	0.05
Total % swabs	**79.74**	**2.64**	**84.21**	**4.76**	**82.71**	**2.37**
Fur (dose site)	2.13	0.82	1.64	0.84	1.99	0.99
Dressing	1.85	0.51	1.25	0.82	2.22	1.17
Surface dose[b]	0.58	0.31	0.41	0.15	0.71	0.43
Total % non-absorbed	**84.30**	**1.57**	**87.10**	**3.16**	**87.62**	**1.54**
Skin compartment						
Stratum corneum[c]	2.60	1.58	1.53	0.80	1.53	0.45
Treated skin[d]	0.28	0.17	0.19	0.13	0.30	0.30
Total % at dose site	**2.87**	**1.75**	**1.72**	**0.88**	**1.82**	**0.59**
Systemic compartment						
Urine	2.06	0.90	1.83	0.45	1.49	0.56
Faeces	0.18	0.05	0.16	0.03	0.20	0.08
Cage Wash	4.01	2.68	0.44	0.10	0.78	0.21
Total % excreted	***6.25***	***3.39***	***2.42***	***0.35***	***2.47***	***0.81***
Blood	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.13	0.03	0.14	0.01	0.51	0.11
Non treated skin	0.24	0.12	0.18	0.07	0.35	0.12
Surrounding skin	1.07	0.24	0.39	0.28	0.66	0.36
Total % directly absorbed	**7.69**	**3.41**	**2.99**	**0.41**	**3.99**	**1.36**
Total % indirect absorbed[e]	**10.57**	**4.68**	**4.71**	**0.96**	**5.81**	**1.92**
Overall % recovery*	**94.87**	**4.22**	**91.81**	**2.33**	**93.43**	**2.68**

[a]: two swabs were used for the surrounding skin
[b]: Tape-strips 1 & 2
[c]: Tape-strips 3 to the last tape-strip
[d]: Skin after tape-stripping procedure
[e]: Total % indirect absorbed = Total % at dose site + Total % directly absorbed

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*: overall recovery is derived from Debra 5.2 software calculations; SD: Standard Deviation; h: hour(s)

In all groups, the vast majority of the applied radioactivity was found to be non-absorbed which accounted for means of 84.30%, 87.10% and 87.62% of the dose applied in the high, intermediate and low dose formulation group, respectively.
The data indicate a low potential for direct absorption resulting in 7.69%, 2.99% and 3.99% of the dose applied in the high, intermediate and low dose formulation group, respectively. Seven days (168 hours) after application small amounts of radioactivity could still be found in the skin and stratum corneum (2.87%, 1.72% and 1.82% of the dose applied in the high, intermediate and low dose formulation group, respectively) resulting in total recoveries of 94.87%, 91.81% and 93.43% for each group, respectively.

III Conclusion

It may be argued that the amount still found in the skin and stratum corneum after 168 hours will not be bio-available indicating that this amount is potentially not absorbable. However, although very low, some quantities of radioactivity (no serial non-detects) could still be found in urine and faeces after the 168 hours period. Therefore, a total % indirect absorbed was calculated from the sum of the %age directly absorbed (urine, faeces, cage wash, blood, carcass, non treated skin, surrounding skin) and the %age found in the stratum corneum and treated skin resulting in 10.57%, 4.71% and 5.81% of the dose applied in the high, intermediate and low dose formulation group, respectively.

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IIIA1 7.6.2 Comparative dermal absorption, in vitro using rat and human skin

OD 150 formulation

Report:	**KIIA 7.6.2/01, [redacted]; 2006**
Title:	[^{14}C]-BYI 08330 in OD150 formulation: Comparative *In vitro* Dermal Absorption Study using Human and Rat skin.
Report No & Document No	SA 05254 M-269449-01-1
Guidelines:	OECD Guideline for Testing of Chemicals; Skin Absorption: In Vitro Method. Guideline 428 (April 2004) OECD Environmental Health and Safety Publications Series on testing and Assessment N° 28. Guidance Document for the Conduct of Skin Absorption Studies (March 2004) **European Commission Guidance Document on Dermal Absorption – Sanco/222/2000 rev. 7, (March 2004)**
GLP	**Yes**

Material and Methods:

Species, strain:	Rat, Wistar Rj: WI (IOPS HAN).
Source:	[redacted] France.
Number and sex:	10 males.
Age:	6-8 weeks
Acclimatisation:	At least 5 days
Housing:	Wire-mesh bottomed stainless steel cage
Environmental conditions:	Temperature: 20°C - 24°C Humidity: 54-70% Ventilation: 10 - 15 air changes per hour Photoperiod: 12 hour light & 12 hour dark
Food:	Certified rodent diet A04C-10, obtained from [redacted], France.
Water:	Filtered and softened water obtained from the municipal supply that was routinely analysed to ensuring that no contaminants were present that could affect the outcome of the study.

Test Material:

Non-radiolabelled:	Batch: n°M26802.
Radiolabelled:	[^{14}C]-BYI 08330
Batch:	KML 2978-2
Specific activity:	3.67 MBq/mg.
Radiopurity:	>99% by HPLC
Formulation:	The formulation used in this experiment was an BYI 08330 OD150 formulation prepared at three concentrations: neat, 150 g/L BYI 08330 and two representative spray dilutions of 1.5 g/L and 0.05 g/L).
Skin preparation:	After the acclimatisation period each animal was killed by cervical dislocation and a dorsal area of the skin was clipped and this area removed for use in the study. The skin was

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dermatomed by use of a mini-dermatome (Decadermatome microsystem motor, Thackray Surgery, Leeds, UK) to obtain samples of 420 – 510 µm in thickness.

Human

Source:	[redacted], France
Number:	13 donors

Test system

The flow-through diffusion cell (Franz 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 (pH 7.4) supplemented by 5% bovine serum albumin and gentamycin (50 mg/L). The receptor fluid in contact with the skin was warmed in order to maintain the skin at 32°C ± 2°C (close to the normal skin temperature) using a water-heated manifold. The receptor chamber contents were stirred continuously with the aid of a magnetic bar (400 rpm), and pumped at a flow rate of 1.5 ml/h.

Skin integrity

The integrity of the selected skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Dermalab, Cortex Technology, Hadsund, Denmark) was placed securely on the top of the receptor cell and the amount of water diffusing through the skin was measured.

Treatment:

The dose preparations were applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µl/cm^2 exposed skin area for both concentrations. Human and rat skin preparations were tested simultaneously.

Sampling:

The receptor fluid passing through the receptor chamber was collected in plastic vials held in a fraction collector. The fraction collector was started after dose application for each group was complete. 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 buffered 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 cell was swabbed prior to the tape-stripping. The tape-stripping procedure 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 viable epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials. The remaining skin was removed and taken for analysis. The receptor fluid remaining in the cell and outlet tubing at the end of the experiment was retained for analysis. The diffusion cell components were also retained and washed with the washings analysed for mass balance.

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Radioassay:
The amounts of radioactivity in the various samples were determined by liquid scintillation counting. 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 in which quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail type 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:

<u>High dose</u>
Following the application of the high dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 95.98%. The radioactivity recovered in skin swabs at 8 and 24 hours were 91.07% and 0.95% respectively, and the amount retrieved from the donor chamber was 0.51% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 1.32% whilst the radioactivity remaining in the skin after tape stripping and in the stratum corneum were 0.75% and 1.14%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 0.26% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.24%) and at termination (0.02%) and the dose retrieved in the receptor chamber (< 0.005%).

Following the application of the high dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 96.21 %. The doses recovered in skin swabs at 8 and 24 hours were 95.01 % and 0.53 % respectively and the amount retrieved from the donor chamber was 0.14 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 0.29% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 0.11% and 0.12%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.01% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.01%) and at termination (<0.005%).

For the high dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.01% and 0.26% in the human and rat skin for the high dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the high dose treatment, the total absorbable was 0.24% through human skin and 2.14% through the rat skin.

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Table 7.6.2-1: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of the BYI 08330 at the high dose in OD150 formulation to human and rat dermatomed skin preparations

	High dose formulation (SYP12801)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 5)		Rat Skin (n = 5)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	0.29	0.48	1.32	0.77
Skin Swabs (8h)	95.01	3.60	91.07	2.32
Skin swabs (24h)	0.53	0.74	0.95	0.56
Skin Swabs (8h + 24h)	95.54	3.07	92.02	2.08
Dose remaining in donor chamber	0.14	0.10	0.51	0.61
Total % non-absorbed	95.97	2.80	93.84	1.49
Skin[a]	0.11	0.13	0.75	0.53
Stratum Corneum[b]	0.12	0.15	1.14	0.28
Total % at dose site	0.23	0.28	1.88	0.79
Receptor fluid (0 - 24h)	0.01	0.01	0.24	0.10
Receptor fluid terminal	<0.005	<0.005	0.02	0.01
Receptor chamber	<0.005	<0.005	<0.005	<0.005
Total % directly absorbed	0.01	0.01	0.26	0.10
Total % potentially absorbable	0.24	0.28	2.14	0.82
Total % recovery	**96.21**	**2.65**	**95.98**	**0.82**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
a: skin after tape-stripping procedure
b: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Medium dose

Following the application of the medium dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 97.44%. The radioactivity recovered in skin swabs at 8 and 24 hours were 61.94% and 3.21% respectively, and the amount retrieved from the donor chamber was 0.56% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 8.52% whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 4.34% and 15.62%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 3.25% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (2.94%) and at termination (0.31%) and the dose retrieved in the receptor chamber (< 0.005%).

Following the application of the medium dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 98.98 %. The doses recovered in skin swabs at 8 and 24 hours were 91.56 % and 1.45 % respectively and the amount retrieved from the donor chamber was 2.55 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 0.68% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum

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corneum were 0.67% and 1.66%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.41% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.36%) and at termination (0.05%).

For the medium dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.41% and 3.25% in the human and rat skin for the medium dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the medium dose treatment, the total absorbable was 2.74% through human skin and 23.21% through the rat skin.

Table 7.6.2-2: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of the BYI 08330 at the medium dose in OD150 formulation to human and rat dermatomed skin preparations

	Medium dose formulation (SYP12803)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 4)		Rat Skin (n = 5)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	0.68	0.46	8.52	6.08
Skin Swabs (8h)	91.56	4.69	61.94	11.48
Skin swabs (24h)	1.45	1.14	3.21	3.55
Skin Swabs (8h + 24h)	93.01	4.64	65.15	8.83
Dose remaining in donor chamber	2.55	3.16	0.56	0.24
Total % non-absorbed	96.24	4.27	74.23	13.99
Skin[a]	0.67	0.25	4.34	4.70
Stratum Corneum[b]	1.66	1.94	15.62	7.11
Total % at dose site	2.32	2.13	19.96	8.40
Receptor fluid (0 - 24h)	0.36	0.29	2.94	0.82
Receptor fluid terminal	0.05	0.09	0.31	0.17
Receptor chamber	<0.005	<0.005	<0.005	<0.005
Total % directly absorbed	0.41	0.36	3.25	0.96
Total % potentially absorbable	2.74	1.87	23.21	8.31
Total % recovery	**98.98**	**2.54**	**97.44**	**6.60**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
a: skin after tape-stripping procedure
b: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Low dose

Following the application of the low dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 100.06%. The radioactivity recovered in skin swabs at 8 and 24 hours were 68.59% and 1.53% respectively, and the amount retrieved from the donor chamber was 1.66% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 5.57%

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whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 1.26% and 9.22%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 12.22% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (10.45%) and at termination (0.22%) and the dose retrieved in the receptor chamber (1.55%).

Following the application of the low dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 96.04 %. The doses recovered in skin swabs at 8 and 24 hours were 83.83 % and 0.89 % respectively and the amount retrieved from the donor chamber was 0.41 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 2.46% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 3.24% and 4.65%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.56% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.56%) and at termination (<0.005%).

For the low dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.56% and 12.22% in the human and rat skin for the low dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the low dose treatment, the total absorbable was 8.45% through human skin and 22.71% through the rat skin.

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Table 7.6.2-3: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of BYI 08330 at the low dose in OD150 formulation to human and rat dermatomed skin preparations

	Low dose formulation (SYP12804)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 5)		Rat Skin (n = 7)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	2.46	1.47	5.57	5.05
Skin Swabs (8h)	83.83	8.63	68.59	9.70
Skin swabs (24h)	0.89	1.34	1.53	1.01
Skin Swabs (8h + 24h)	84.72	7.64	70.12	9.46
Dose remaining in donor chamber	0.41	0.58	1.66	1.82
Total % non-absorbed	87.59	6.09	77.35	4.84
Skin[a]	3.24	3.12	1.26	1.22
Stratum Corneum[b]	4.65	3.29	9.22	4.22
Total % at dose site	7.89	5.68	10.49	4.62
Receptor fluid (0 - 24h)	0.56	0.67	10.45	5.07
Receptor fluid terminal	0.005	0.005	0.22	0.12
Receptor chamber	<0.005	<0.005	1.55	2.66
Total % directly absorbed	0.56	0.67	12.22	6.04
Total % potentially absorbable	8.45	6.05	22.71	6.25
Total % recovery	**96.04**	**3.79**	**100.06**	**4.95**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
[a]: skin after tape-stripping procedure
[b]: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Conclusion:
The mean percentage of [^{14}C]-BYI 08330 considered to be potentially absorbable over a period of 24 hours from the high dose OD 150 formulation was 0.24% and 2.14% for the human and rat skin, respectively, yielding a factor difference of 8.9 between the two species for the neat product.

For the medium dose formulation, the mean percentage total potentially absorbable was 2.74% and 23.21% for the human and rat skin, respectively yielding a factor difference of 8.5 between the two species for the spray dilution.

For the low dose formulation, the mean percentage total potentially absorbable was 8.45% and 22.71% for the human and rat skin, respectively yielding a factor difference of 2.7 between the two species for the spray dilution.

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SC 240 formulation

Report:	**KIIA 7.6.2/02, [redacted]; 2006**
Title:	[^{14}C]-BYI 08330 in SC 240 formulation: Comparative *In vitro* Dermal Absorption Study using Human and Rat skin.
Report No & Document No	SA 05255 M-269195-01-2
Guidelines:	OECD Guideline for Testing of Chemicals; Skin Absorption: In Vitro Method Guideline 428 (April 2004) OECD Environmental Health and Safety Publications Series on testing and Assessment N° 28. Guidance Document for the Conduct of Skin Absorption Studies (March 2004) **European Commission Guidance Document on Dermal Absorption – Sanco/222/2000 rev. 7, (March 2004)**
GLP	**Yes**

Material and Methods:

Species, strain:	Rat, Wistar Rj: WI (IOPS HAN).
Source:	[redacted], France.
Number and sex:	11 males.
Age:	6-8 weeks
Acclimatisation:	At least 5 days
Housing:	Wire-mesh bottomed stainless steel cage
Environmental conditions:	Temperature: 20°C - 24°C Humidity: 54-70% Ventilation: 10 - 15 air changes per hour Photoperiod: 12 hour light & 12 hour dark
Food:	Certified rodent diet A04C-10, obtained from [redacted], France.
Water:	Filtered and softened water obtained from the municipal supply that was routinely analysed to ensuring that no contaminants were present that could affect the outcome of the study.

Test Material:

Non-radiolabelled:	Batch: n°M26802.
Radiolabelled:	[^{14}C]-BYI 08330
Batch:	KML 2978-2
Specific activity:	3.67 MBq/mg.
Radiopurity:	>99% by HPLC
Formulation:	The formulation used in this experiment was a BYI 08330 SC 240 formulation prepared at three concentrations: neat, 240 g/L BYI 08330 and two representative spray dilutions of 1.5 g/L and 0.05 g/L), the dilutions containing 0.15% of the adjuvant Mero® (0.3% product).
Ski Preparation:	After the acclimatisation period each animal was killed by cervical dislocation and a dorsal area of the skin was clipped and this area removed for use in the study. The skin was

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dermatomed by use of a mini-dermatome (Decadermatome microsystem motor, Thackray Surgery, Leeds, UK) to obtain samples of 420 – 510 µm in thickness.

Human

Source:	[redacted], France
Number:	13 donors

Test system

The flow-through diffusion cell (Franz 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 (pH 7.4) supplemented by 5% bovine serum albumin and gentamycin (50 mg/L). The receptor fluid in contact with the skin was warmed in order to maintain the skin at 32°C ± 2°C (close to the normal skin temperature) using a water-heated manifold. The receptor chamber contents were stirred continuously with the aid of a magnetic bar (400 rpm), and pumped at a flow rate of 1.5 ml/h.

Skin integrity

The integrity of the selected skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Dermalab, Cortex Technology, Hadsund, Denmark) was placed securely on the top of the receptor cell and the amount of water diffusing through the skin was measured.

Treatment:

The dose preparations were applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µl/cm^2 exposed skin area for both concentrations. Human and rat skin preparations were tested simultaneously.

Sampling:

The receptor fluid passing through the receptor chamber was collected in plastic vials held in a fraction collector. The fraction collector was started after dose application for each group was complete. 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 buffered 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 cell was swabbed prior to the tape-stripping. The tape-stripping procedure 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 viable epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials. The remaining skin was removed and taken for analysis. The receptor fluid remaining in the cell and outlet tubing at the end of the experiment was retained for analysis. The diffusion cell components were also retained and washed with the washings analysed for mass balance.

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Radioassay:
The amounts of radioactivity in the various samples were determined by liquid scintillation counting. 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 in which quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail type 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:

<u>High dose</u>
Following the application of the high dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 92.88%. The radioactivity recovered in skin swabs at 8 and 24 hours were 87.69% and 0.28% respectively, and the amount retrieved from the donor chamber was 0.18% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 1.84% whilst the radioactivity remaining in the skin after tape stripping and in the stratum corneum were 0.07% and 2.54%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 0.29% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.29%) and at termination (<0.005%) and the dose retrieved in the receptor chamber (< 0.005%).

Following the application of the high dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 92.08 %. The doses recovered in skin swabs at 8 and 24 hours were 91.28 % and 0.09 % respectively and the amount retrieved from the donor chamber was 0.05 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 0.25% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 0.20% and 0.11%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.10% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.08%) and at termination (0.02%).

For the high dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.10% and 0.29% in the human and rat skin for the high dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the high dose treatment, the total absorbable was 0.41% through human skin and 2.90% through the rat skin.

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Table 7.6.2-4: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of the BYI 08330 at the high dose in SC 240 formulation to human and rat dermatomed skin preparations

	High dose formulation (SYP12806)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 5)		Rat Skin (n = 5)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	0.25	0.22	1.84	0.58
Skin Swabs (8h)	91.28	1.30	87.69	1.99
Skin swabs (24h)	0.09	0.05	0.28	0.19
Skin Swabs (8h + 24h)	91.37	1.33	87.97	2.13
Dose remaining in donor chamber	0.05	0.04	0.18	0.24
Total % non-absorbed	91.67	1.13	89.98	1.75
Skin[a]	0.20	0.28	0.07	0.07
Stratum Corneum[b]	0.11	0.13	2.54	1.09
Total % at dose site	0.31	0.41	2.61	1.16
Receptor fluid (0 - 24h)	0.08	0.13	0.29	0.45
Receptor fluid terminal	0.02	0.05	<0.005	<0.005
Receptor chamber	0.005	<0.005	<0.005	<0.005
Total % directly absorbed	0.10	0.14	0.29	0.45
Total % potentially absorbable	0.41	0.39	2.90	1.60
Total % recovery	**92.08**	**0.80**	**92.88**	**1.12**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
[a]: skin after tape-stripping procedure
[b]: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Medium dose

Following the application of the medium dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 99.46%. The radioactivity recovered in skin swabs at 8 and 24 hours were 71.75% and 6.74% respectively and the amount retrieved from the donor chamber was 0.15% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 9.06% whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 0.95% and 9.33%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 1.49% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (1.07%) and at termination (0.26%) and the dose retrieved in the receptor chamber (0.16%).

Following the application of the medium dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 94.73 %. The doses recovered in skin swabs at 8 and 24 hours were 90.46 % and 1.16 % respectively and the amount retrieved from the donor chamber was 0.11 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was

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1.60% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 0.47% and 0.87%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.07% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.07%), at termination (<0.005%) and the dose retrieved in the receptor chamber (<0.005%).

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For the medium dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.07% and 1.49% in the human and rat skin for the medium dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the medium dose treatment, the total absorbable was 1.41% through human skin and 11.76% through the rat skin.

Table 7.6.2-5: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of the BYI 08330 at the medium dose in SC 240 formulation to human and rat dermatomed skin preparations

	Medium dose formulation (SYP12808)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 4)		Rat Skin (n = 5)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	1.60	3.39	9.06	12.25
Skin Swabs (8h)	90.46	8.06	71.75	26.92
Skin swabs (24h)	1.16	2.41	6.74	8.82
Skin Swabs (8h + 24h)	91.62	6.28	78.49	19.44
Dose remaining in donor chamber	0.11	0.17	0.15	0.14
Total % non-absorbed	93.33	4.77	87.70	17.65
Skin[a]	0.47	0.42	0.95	0.84
Stratum Corneum[b]	0.87	1.43	9.33	18.54
Total % at dose site	1.34	1.79	10.27	18.24
Receptor fluid (0 - 24h)	0.07	0.04	1.07	0.99
Receptor fluid terminal	<0.005	<0.005	0.26	0.51
Receptor chamber	<0.005	<0.005	0.16	0.31
Total % directly absorbed	0.07	0.04	1.49	0.84
Total % potentially absorbable	1.41	1.77	11.76	17.96
Total % recovery	**94.73**	**4.70**	**99.46**	**7.34**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
[a]: skin after tape-stripping procedure
[b]: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Low dose

Following the application of the low dose formulation of [^{14}C]-BYI 08330 to rat skin the overall mean recovery of the dose was 94.15%. The radioactivity recovered in skin swabs at 8 and 24 hours were

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73.57% and 0.76% respectively, and the amount retrieved from the donor chamber was 0.29% dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 3.22% whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 2.60% and 6.73%, respectively. The total amount of radioactivity directly absorbed through rat skin accounted for 6.99% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (6.70%) and at termination (0.29%) and the dose retrieved in the receptor chamber (<0.005%).

Following the application of the low dose formulation of [^{14}C]-BYI 08330 to human skin the overall mean recovery of the dose was 94.90 %. The doses recovered in skin swabs at 8 and 24 hours were 78.67 % and 0.92 % respectively and the amount retrieved from the donor chamber was 0.20 % dose. In the two first tape-strips of the stratum corneum corresponding to the surface dose the amount was 3.64% of the dose whilst the radioactivity remaining in the skin after tape-stripping and in the stratum corneum were 3.41% and 7.82%, respectively. The total amount of radioactivity directly absorbed through human skin accounted for 0.24% of the applied dose, corresponding to the sum of the dose recovered in the receptor fluid between 0 and 24 hours (0.24%), at termination (<0.005%) and the dose retrieved in the receptor chamber (<0.005%).

For the low dose concentration the overall amount of [^{14}C]-BYI 08330 considered to be directly absorbed was represented by the radioactivity present in the receptor fluid (including receptor fluid at termination and receptor chamber). This accounted for 0.24% and 6.99% in the human and rat skin for the low dose formulation. The radioactivity retained in the stratum corneum (excluding tape-strips 1 & 2) and in the treated skin is considered as absorbable. Therefore, following dermal application of the low dose treatment the total absorbable was 11.47% through human skin and 16.32% through the rat skin.

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Table 7.6.2-6: [^{14}C]-BYI 08330: Recovery of radioactivity following a single topical application of BYI 08330 at the low dose in SC 240 formulation to human and rat dermatomed skin preparations

	Low dose formulation (SYP12809)			
	Distribution of radioactivity (% dose)			
	Human skin (n = 5)		Rat Skin (n = 7)	
	Mean	SD	Mean	SD
Surface dose (Tape-strips 1 & 2)	3.64	1.64	3.22	1.66
Skin Swabs (8h)	78.67	2.00	73.57	4.08
Skin swabs (24h)	0.92	0.53	0.76	0.25
Skin Swabs (8h + 24h)	79.59	2.27	74.33	4.24
Dose remaining in donor chamber	0.20	0.27	0.29	0.58
Total % non-absorbed	83.43	1.44	77.83	3.45
Skin[a]	3.41	1.30	2.60	1.05
Stratum Corneum[b]	7.82	2.19	6.73	2.18
Total % at dose site	11.23	1.89	9.33	1.47
Receptor fluid (0 - 24h)	0.24	0.14	6.70	3.27
Receptor fluid terminal	0.005	0.005	0.29	0.05
Receptor chamber	<0.005	<0.005	<0.005	<0.005
Total % directly absorbed	0.24	0.17	6.99	3.29
Total % potentially absorbable	11.47	1.93	16.32	3.29
Total % recovery	**94.90**	**1.68**	**94.15**	**2.18**

SD: standard deviation
N.D.: not detected
n: number of skin cells used for calculation
[a]: skin after tape-stripping procedure
[b]: tape-strips excluding number 1 & 2 which are considered to be non-absorbed dose.

Conclusion:
The mean percentage of [^{14}C]-BYI 08330 considered to be potentially absorbable over a period of 24 hours from the high dose SC 240 formulation was 0.41% and 2.90% for the human and rat skin, respectively, yielding a factor difference of 7.1 between the two species for the neat product.

For the medium dose formulation, the mean percentage total potentially absorbable was 1.41% and 11.76% for the human and rat skin, respectively, yielding a factor difference of 8.3 between the two species for the spray dilution.

For the low dose formulation, the mean percentage total potentially absorbable was 11.47% and 16.32% for the human and rat skin, respectively, yielding a factor difference of 1.4 between the two species for the spray dilution.

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IIIA1 7.7 Dislodgeable residues

IIIA1 7.7.1 Dislodgeable residues - foliar

Dislodgeable foliar residue studies were not performed because the estimation of worker exposure is acceptable for re-entry directly after the application when the spray deposit has dried. Detailed calculations are presented in section IIIA 7.5.1

IIIA1 7.7.2 Dislodgeable residues - soil

No EC data requirement (the OECD point concerned is not covered by or part of an EC point according to Council Directive 91/414/EEC. Hence, data/documents do not need to be submitted.

IIIA1 7.7.3 Dislodgeable residues - indoor surface re-volatization

No EC data requirement (the OECD point concerned is not covered by or part of an EC point according to Council Directive 91/414/EEC. Hence, data/documents do not need to be submitted.

IIIA1 7.8 Epidemiology

No EC data requirement (the OECD point concerned is not covered by or part of an EC point according to Council Directive 91/414/EEC. Hence, data/documents do not need to be submitted.

IIIA1 7.9 Data on formulants

The available toxicological data for each formulant are presented in the safety data sheets and they are included in the 'Confidential information'.

IIIA1 7.9.1 Material safety data sheet for each formulant

Safety data sheets are included in the 'Confidential information'.

IIIA1 7.9.2 Available toxicological data for each formulant

All information relating to the composition of the formulation is confidential. Therefore, it is submitted separately in the 'Confidential information'.

IIIA1 7.10 Domestic animal/livestock safety

No EC data requirement (the OECD point concerned is not covered by or part of an EC point according to Council Directive 91/414/EEC. Hence, data/documents do not need to be submitted.

IIIA1 7.11 Other/special studies

No other or special studies have been considered necessary or have been conducted.

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