Document Title

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

BYI 02960 (Flupyradifurone) SL 200

Specification number 102000021884

Data Requirements

Regulation (EC) No 1107/2009

Regulatory Directive 2003-01/Canada/PMRA
OPPTS guidelines/US/EPA

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

2012-02-29

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OWNERSHIP STATEMENT

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

IIIA1 7.1 Acute toxicity

BYI 0260 SL 200 g/L (spec N° 102000021884) is a soluble concentrate containing 200 g/L BYI 02960.

The toxicological results were as follows:

Study/Parameter	Species (sex)	Results	References
Acute oral / LD_{50} (mg/kg)	Rat (Female)	$LD_{50\ cut\ off} \geq 5000$ mg/kg bw	[redacted] U. (2010) M-385422-01-1
Acute dermal / LD_{50} (mg/kg)	Rat (Male & Female)	$LD_{50} > 2000$ mg/kg bw	[redacted] U. (2010) M-385421-01-1
Acute inhalation/LC_{50}	Rat (M+F)	LC_{50} male = 4.483; LC_{50} female = 3.496	[redacted] A. (2010) M-392826-01-1
Acute skin irritation	Rabbit (Female)	Not irritant	[redacted] C. (2010) M-370381-01-1
Acute eye irritation	Rabbit (Female)	Not irritant	[redacted] C. (2010) M-364511-01-1
Skin sensitization test, LLNA in mice	Mouse (Female)	Sensitising	[redacted] M. (2010) M-3368808-01-1

Therefore, according to the EC classification criteria (2001/59/EC Directive), the formulation BYI 02960 SL 200 g/L is classified and should be labelled as follows:

Symbols of danger: Xn, Harmful
Xi, Irritant

Risk phrases: R20, Harmful by inhalation
R43, May cause sensitization by skin contact

IIIA1 7.1.1 Acute oral toxicity

Report:	**KIIIA1 7.1.1/01; [redacted] U., 2010**
Title:	BYI 02960 SL 200 g/L - Acute toxicity in the rat after oral administration.
Report No & Document No	AT05943 M-385422-01-1
Dates of work	February 03, 2010 to March 03, 2010
Guidelines:	Regulation (EC) No 1907/2006 (Reach) OECD Guidelines N° 423, (2001) EEC Directive 440/2008 Method B1.tris EPA OPPTS 870.1100 – 712-C-98-190, (1998)
GLP	Yes

Material and Methods

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The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

The test compound was formulated in tap water; the administration volume was 10 mL/kg bw. The test material was administered first at a single dose (2000 mg/kg) by gavage to 3 fasted female Wistar rats. As no compound mortality occurred three additional animals were treated with the same dose.

Table 7.1.1-1: Acute oral toxicity in female rats

Dose (mg/kg bw)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} cut-off (mg/kg bw)
(1st) 2000	0/3/3	3h - 5h	-	≥ 5000
(2nd) 2000	0/3/3	3h - 4h	--	

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

Findings

- Mortality: no death occurred.
- Clinical signs: decreased motility and temporary tremor were observed.
- Body weights: there were no toxicological effects on body weights or body weight gain.
- Necropsy: no particular findings.

Conclusion

The acute oral LD_{50} cut off of the formulation BYI 02960 SL 200 g/L in rats was greater or equal to 5000 mg/kg bw.

According to the EC classification criteria (2001/59/EC Directive), the formulation is labeled as follows:
Symbol of danger: None
Risk phrase: None

According the GHS criteria, the formulation BYI 02960 SL 200 g/L should be ranked as "Category 5" or "Unclassified".

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IIIA1 7.1.2 Acute percutaneous (dermal) toxicity

Report:	**KIIIA1 7.1.2/01; [redacted] U., 2010**
Title:	BYI 02960 SL 200 g/L – Acute toxicity in the rat after dermal application.
Report No & Document No	AT 05944 M-385421-01-1
Dates of work	February 03, 2010 to February 17, 2010
Guidelines:	Regulation (EC) No 1907/2006 (REACH) OECD Guidelines N° 402, (1987) EEC Directive 440/2008, Method B3 EPA (OPPTS 870.1200 – 712-C-98-192, (1998))
GLP	Yes

Material and Methods

The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

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

Table 7.1.2-1: Acute dermal toxicity in rats

	Dose (mg/kg bw)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} (mg/kg bw)
Male	2000	0/0/5	--	--	> 2000
Female	2000	0/0/5	--	--	> 2000

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

Findings

- Mortality: no death occurred.
- Clinical signs: no clinical signs were observed.
- Body weights: there were no toxicological effects on body weights or body weight gain related to the test compound.
- Necropsy: no particular findings at the end of the study.

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Conclusion

The dermal LD_{50} of the formulation BYI 02960 SL 200 g/L was greater than 2000 mg/kg bw in rats.

According to the EC classification criteria (2001/59/EC Directive), the formulation is labeled as follows:
Symbol of danger: None
Risk phrase: None

According the GHS criteria, the formulation BYI 02960 SL 200 g/L should be ranked as "Category 5" or "Unclassified".

IIIA1 7.1.3 Acute inhalation toxicity to rats

Report:	**KIIIA1 7.1.3/01; [redacted], 2010**
Title:	BYI 02960 SL 200 g/L - Acute inhalation toxicity in rats
Report No & Document No	AT06016 M-392826-01-1
Dates of work	February 09, 2010 to March 04, 2010
Guidelines:	OECD 403 (1981) Directive 92/69/EEC Annex V – Method B.2 (1992) US EPA OPPTS 870.1300, Health Effect Guidelines (1998) Japan MAFF, Notification No. 12 NouSan-8147 (2000)
GLP	Yes

Material and Methods:

The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

Three groups (1 control and 2 treated groups) of five male and five female Wistar rats were acclimatized for at least 5 days prior to treatment and housed individually.

Two groups of 10 Wistar rats (5 animals/sex) were exposed to a mean liquid aerosol concentration of 1.956 mg/L and 4.483 mg/L test substance for up to 4 hours using nose only exposure system. The liquid aerosol generated with undiluted test substance was respirable to rats.
The observation period was two weeks. The appearance and behaviour and the body weight of each rat were examined several times on the day of exposure and at least once daily until the end of the study.

Findings:

Table 7.1.3-1: Characteristics of the achieved atmosphere

Target concentration (mg/L)	Actual concentration (mg/L)	Mean mass Aerodynamic Diameter (µm)	Geometric standard deviation (µm)	Respirable fraction (% < 3 µm)
2.500	1.957	1.66	1.69	87.1
5.000	4.483	1.97	1.78	77.2

.

Table 7.1.3-2: Acute inhalation toxicity – 4 h exposure to aerolized test compound

N° group/sex	Actual concentration (mg/L)	Toxicological findings*	Duration of signs (days)	Onset of death after (days)	LC_{50} (mg/L) (14 days)
1/m	0	0/0/5	--	--	LC_{50} male> 4.483 LC_{50} female = 3.496
2/m	1.957	0/5/5	0d -7d	--	
3/m	4.483	2/5/5	0d -6d	1d-2d	
1/f	0	0/0/5	--	--	
2/f	1.957	0/5/5	0d -7d	--	
3/f	4.483	4/5/5	0d -3d	1d-3d	

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

Mortality did not occur at a concentration of 1.957 mg/L (group 2), whilst 60 % mortality at the test atmosphere of 4.483 mg/L (Group 3) was observed.

The rats that died showed findings that were suggestive of nonspecific, systemic toxic effects and emaciation as cause of death.
The rats succumbed on post exposure day and up to day 3. Necropsy findings of the rats which died showed findings which were suggestive to lung edema as cause of death. Average body weights were decreased and reflexes of some group 3 rats were not normal. The rats displayed following reversible clinical signs: Bradypnea, laboured breathing patterns, breathing irregular, piloerection, cyanosis, motility reduced, limp, gait high legged, nasal discharge serous, nose with red encrustations, nose and muzzle with red encrustations, nostrils with red encrustations and hypothermia. On post exposure day 8 all rats were without clinical signs. Overall a higher susceptibility of the female rats is apparent.

Conclusion

In summary, after inhalation the test substance (neat test article) proved to have low to moderate acute toxicity in rats. For the female rats the approximate LC_{50} value is 3.496 mg/L. For the male rats the LC_{50} value is greater than 4.483 mg/L.

According to the Commission Directive 2001/59/EC, the test article should be labelled as follows:
- **Symbol of danger: Xn**
- **Risk phrase: Harmful by inhalation.**

According the GHS criteria, the formulation BYI 02960 SL 200 g/L should be ranked as "Category 4".

IIIA1 7.1.4 Skin irritation

Report:	**KIIIA1 7.1.4/01 ; [redacted] C., 2010**
Title:	BYI 02960 SL 200 g/L - Acute skin irritation/corrosion on rabbits
Report No & Document No	AT 05908 M-370381-01-1
Dates of work	February 23, 2010 to February 26, 2010
Guidelines:	OECD Guidelines N° 404 (2002) EEC Directive 440/2008 EPA OPPTS 870.2500 – 712-C-98-196 (1998)
GLP	Yes

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Material and Methods

The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

One day before the test, the fur was shorn on the right and left side from the dorso-lateral area of the trunk of each of the rabbits. 0.5 ml of the pure liquid test substance was applied first to the skin of 1 female albino rabbit under a gauze patch. The treated skin area was approximately of 6 cm^2. After an exposure period of 4 hours, the dressing and patch were removed and the treated area was carefully washed with water. As no skin reaction was observed the test was completed using two additional animals exposed for four hours.

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

Table 7.1.4-1: Irritant Effects on the skin (Exposure: 4 hours)

Animal		24 hours	48 hours	72 hours	Mean scores	Response	Reversible (days)
1	Erythema (redness) and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na
2	Erythema (redness) and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na
3	Erythema (redness) * and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na

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

Findings

There were no systemic intolerance reactions.

Conclusion

Under our experimental conditions, the formulation BYI 02960 SL 200 g/L is not irritating to the skin.
According to the EC classification criteria (2001/59/EC Directive), the formulation is labeled as follows:
Symbol of danger: None
Risk phrase: None

According the GHS criteria, the formulation AE 1887196 SC 200 g/L should be ranked as "Unclassified".

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IIIA1 7.1.5 Eye Irritation

Report:	**KIIIA1 7.1.5/01; [redacted] C., 2010**
Title:	BYI 02960 SL 200 g/L - Acute eye irritation on rabbits.
Report No & Document No	AT05812 M-364511-01-1
Dates of work	January 26, 2010 to January 29, 2010
Guidelines:	OECD Guidelines N° 405 (2002) EEC Directive 440/2008 EPA (OPPTS 870.2400 - 712C-98-195) (1998).
GLP	Yes

Material and Methods

The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

The test was started with one of three female albino rabbits. 0.1 ml of the pure liquid test substance was placed into the conjunctival sac of one eye after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order to prevent loss of the test compound. The other eye, which remained untreated, served as control. The eye was rinsed approximately 24 hours following instillation. As one hour after treatment no severe irritation was observed two further rabbits were treated as described.

The individual findings of the treated eyes at the various observation times are summarized in Table 7.1.5-1.

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Table 7.1.5-1: Summary of irritant effect

Observations Animal 1	24h	48h	72h	Mean scores (24-48-72h)	Reversible (days)
Degree of cornea opacity	0	0	0	0.0 (-)	na
Iris	0	0	0	0.0 (-)	na
Redness conjunctivae	1	1	0	0.7 (-)	3
Chemosis conjunctivae	0	0	0	0.0 (-)	na

Observations Animal 2	24h	48h	72h	Mean scores (24-48-72h)	Reversible (days)
Degree of cornea opacity	0	0	0	0.0 (-)	na
Iris	0	0	0	0.0 (-)	na
Redness conjunctivae	1	1	0	0.7 (-)	3
Chemosis conjunctivae	0	0	0	0.0 (-)	na

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

Animal 1, 1 h p.a.: test compound adhered to cornea and conjunctiva
na = not applicable
Response: corneal opacity: mean scores <2 = (-), ≥2<3 = (+), ≥3 = (++)
Iritis: mean scores <1 = (-), ≥1<2 = (+), = 2 =(++)
Conjunctival redness: mean scores <2.5 = (-), ≥2.5 = +
Conjunctival oedema: mean scores <2 = (-), ≥2 = +

Findings
There were no relevant systemic intolerance reactions.

Conclusion
Under our experimental conditions, the formulation BYI 02960 SL 200 g/L is not irritating to eyes.

According to the EC classification criteria (2001/59/EC Directive), the formulation is labeled as follows:
Symbol of danger: None
Risk phrase: None

According the GHS criteria, the formulation AE 1887196 SC 200 g/L should be ranked as "Unclassified".

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IIIA1 7.1.6 Skin sensitization

Report:	**KIIIA1 7.1.6/01, [redacted], 2010**
Title:	BYI 02960 SL 200 g/L - Evaluation of potential sensitization in the local lymph node assay in the mouse
Report No. & Document No.	SA 10101 M-368808-01-1
Dates of work	March 23, 2010 to March 31, 2010
Guidelines:	O.E.C.D. Guideline 429 (2002) EPA OPPTS 870.2600 (2003)
GLP	Yes

Material and Methods

The formulation BYI 02960 SL 200 g/L, a brown clear liquid (batch number: 2009-001253) contained the active ingredient BYI 02960 at the nominal concentration of 200 g/L (199.8 g/L certified by analysis).

Twenty-five female CBA/J mice were allocated to 5 groups of five animals each:
- three groups received the test substance at a concentration of 25%, 50% in vehicle or 100%,
- one positive control group received 30% alpha-Hexylcinnamaldehyde (CAS N° 101-86-0, batch N°: MKAA2596) in vehicle,
- one control group received the vehicle, 1% Pluronic Acid L92® in water.

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

Findings

Table 7.1.2-1 Results of the proliferation assay:

Group Number	Test Group Name	Stimulation Index Values (SD)
1	control in 1% aqueous Pluronic Acid L92®	-
2	BYI 02960 SL 200 g/L at 25% in 1% aqueous Pluronic Acid®	1.3 (0.2)
3	BYI 02960 SL 200 g/L at 50% in 1 % aqueous Pluronic Acid L92®	2.3 (0.7)
4	BYI 02960 SL 200 g/L at 100% in 1 % aqueous Pluronic Acid L92®	3.0 (0.8)
5	HCA at 30% in 1% aqueous Pluronic Acid®	6.4 (3.1)

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No cutaneous reactions were observed in the vehicle, reference control or treated groups.

The stimulation index values of the test substance were 1.3 (±0.2), 2.3 (±0.7) and 3.0 (±0.8) at treatment concentrations of 25, 50 and 100%, respectively.
The stimulation index value of the positive control alpha-Hexylcinnamaldehyde was 6.4 (±3.1) at a treatment concentration of 30%.

Positive lymphoproliferative responses (SI>3) were noted for BYI 02960 SL 200 g/L at the concentration of 100%.

Conclusion

The formulation BYI 02960 SL 200 g/L was found to be a slight-sensitizing formulation in the Local Lymph Node Assay.

According to the EC classification criteria (2001/59/EC Directive), the formulation is labeled as follows:
Symbol of danger: Xi, irritant
Risk phrase: R43, may cause sensitization by skin contact

IIIA1 7.1.7 Supplementary studies for combinations of plant protection products

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

IIIA1 7.2 Short-term toxicity studies

Not required by Regulation 1107/2009.

IIIA1 7.3 Operator exposure

'BYI 02960 SL 200' is a water soluble concentrate containing 200 g BYI 02960/L. The proposed use is as an insecticide on hops and lettuce. Applications of 'BYI 02960 SL 200' will be achieved via field crop sprayers, broadcast air assisted sprayers and by hand-held devices in greenhouses. Water will be the diluent/carrier in all cases. Usage information pertinent to operator exposure is summarized in table 7.3-1.

Table 7.3-1: Application parameters for 'BYI 02960 SL 200'

Crop	Application technique	Max no of application	Spray volume (L/ha)	Max dose rate (g BYI 02960 / ha)
Lettuce (field)	FCS	1	500 – 1000	125
Hops	BAA	1	2000 – 3000	150
Lettuce (greenhouse)	HH-GH	2	500 – 1000	125

FCS = Field crop sprayer, BAA = Broadcast air assisted sprayer, HH-GH = Hand-held application in greenhouses

Consideration on AOEL

The proposed AOEL for BYI 02960 is based on the NOAEL from the 90-day dog study (NOAEL: 12 mg/kg bw/day). No adjustment for oral absorption is necessary. Including a safety factor of 100 the AOEL amounts to 0.12 mg/kg bw/day.

Consideration on dermal absorption

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Dermal absorption data are available for BYI 02960 from *in vitro* studies with human/rat skin and from an *in vivo* study with rats (see IIIA1 7.6).
Derived from the results of these studies it is proposed to use 22% and 15% dermal absorption to calculate systemic exposure of BYI 02960 from the concentrate and the spray dilution, respectively.

Consideration on estimation of operator exposure estimates

Operator exposures to 'BYI 02960 SL 200' during the intended tractor mounted ground boom spray application in the field as well as during broadcast air assisted application to hops will be estimated using the EU wide accepted German model[1] as well as the UK-POEM[2].
In addition, the exposure scenario for the greenhouse application is estimated with the 'Greenhouse Model'. Details are presented in IIIA1 7.3.1.

The results of the exposure calculations are summarized in Table 7.3-2.

Table 7.3-2: Predicted systemic exposure as a proportion of the AOEL

Crop	Model	PPE	Total systemic exposure (mg/kg bw/day)	% of AOEL[#]
Lettuce (field)	German model	No PPE[1)]	0.0215	**18**
		With PPE[2)]	0.00102	**<1**
	UK-POEM	No PPE[1)]	0.0776	**65**
		With PPE[2)]	0.00685	**6**
Hop	German model	No PPE[1)]	0.0155	**13**
		With PPE[2)]	0.00475	**4**
	UK-POEM	No PPE[1)]	0.0451	**38**
		With PPE[2)]	0.0175	**15**
Lettuce (greenhouse)	Low crops (standard scenario)	No PPE[1)]	0.00321	**3**
		With PPE[2)]	0.00090	**<1**
	Low crops (intensive scenario)	No PPE[1)]	0.0929	**77**
		With PPE[3)]	0.00316	**3**

[#] BYI 02960: AOEL = 0.12 mg/kg bw/day

1) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear
2) In addition to typical work wear (see 1) protective gloves are worn during mixing and loading as well as when handling contaminated surfaces.
3) Instead of typical work wear spray tight trousers as protective clothing have to be worn. In addition protective gloves are worn during mixing/loading and application.

[1] Landehn, 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

[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 2007

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Assessment

The results of the exposure calculations reveal that the situation regarding operator exposure is favourable with the intended spray uses of 'BYI 02960 SL 200' in all crops.

Field crops (tractor mounted ground boom application)
With the German Model operator exposure to BYI 02960 is estimated to be 18% of the proposed systemic AOEL when assuming that no PPE is worn. Considering PPE model predicted systemic operator exposure amounts to < 1% of the AOEL.
With the UK-POEM the predicted exposure is estimated to be at 65% of the proposed systemic AOEL when no PPE is worn. Considering PPE model predicted systemic operator exposure amounts to 6% of the proposed AOEL.

High crops (tractor mounted air blast application)
Using the German model estimated systemic operator exposure to BYI 02960 accounts for only 13% of the proposed AOEL if no PPE is worn. Considering PPE is worn corresponding exposure estimate accounts for 4% of the proposed AOEL.
With the UK-POEM the corresponding figures amount to 38% and 15% of the proposed AOEL, respectively.

Greenhouse applications
The exposure to BYI 02960 during hand-held application to lettuce in greenhouses was evaluated using data from a number of exposure studies which are summarized in the "Greenhouse Model".

For the "standard" scenario in low crops (with negligible contact with treated foliage) predicted systemic operator exposure for the scenario 'no PPE' amounts to 3% of the proposed systemic AOEL.
Assuming that protective gloves are worn when handling the concentrate and during application, the corresponding exposure estimate accounts for <1% of the proposed systemic AOEL.
For the "intensive" scenario (with direct contact with treated foliage) the use of "no PPE" results in an exposure corresponding to 77% of the proposed AOEL. With appropriate impervious trousers as well as gloves during mixing loading and application the predicted systemic operator exposure amounts to 3% of the proposed systemic AOEL.

Based on these results there is no unacceptable risk anticipated for the operator with the intended uses of 'BYI 02960' if adequate work clothing (i.e. one layer of work clothing (e.g. a coverall)) is worn.
However, according to good occupational hygiene appropriate PPE should also be worn (i.e. protective gloves during mixing and loading as well as when handling contaminated surfaces).
In greenhouses where direct contact with treated foliage during application may occur impervious trousers and gloves are recommended.

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IIIA1 7.3.1 Estimation of operator exposure without personal protective equipment

A. Estimated operator exposure during the intended ground boom spray application of 'BYI 02960' to lettuce in the field

The following assumptions have been made in calculating operator exposure according to the German model and UK-POEM:

Work rate:

German model:	20 ha per day
UK-POEM.	50 ha per day
Maximum application rate:	0.625 L 'BYI 02960 SL 200' (= 125 g BYI 02960/ha)
Minimum water rate:	500 L/ha
Operator clothing :	One layer of typical work wear (e.g. a coverall) as well sturdy foot wear
Dermal absorption:	
- BYI 02960:	22% for the concentrate and 15% for the in-use dilution
Standard operator body weight:	
German model:	70 kg
UK-POEM.	60 kg

The calculation of the estimated operator exposure was made for two alternatives regarding the personal protective equipment (PPE):

- no PPE: disregarding the recommendations on the label, no personal protective equipment is used when handling the undiluted product and during application.
- with PPE: gloves during mixing and loading as well as when handling contaminated surfaces.

It should be noted that this selection of protective measures is not intended to be a recommendation as the required PPE when handling 'BYI 02960 SL 200'. It does not consider specific requirements, which may exist in individual member states. Additional PPE can be used to further reduce the exposure of the operator.

Corresponding exposure estimates are summarised in the following tables.

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Table 7.3.1-1: German model: Predicted systemic exposure to BYI 02960/no PPE and with PPE

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

Product:	BYI 02960 SL 200				
Active substance:	BYI 02960		a.s. concentration:	200	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha]:	0.625			Hands:	Gloves
Work rate [ha/day]:	20		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	22.0	(concentrate)		Body:	Standard protective coverall
	15.0	(dilution)			

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
I_M =	0.0006	2.5	0.000021	1.0	0.000021	I = Inhalation
$D_{M(H)}$ =	2.4	2.5	0.0857	0.01	0.000857	D = Dermal
I_A =	0.001	2.5	0.000036	1.0	0.000036	M = Mix/Loading
$D_{A(C)}$ =	0.06	2.5	0.00214	1.0	0.00214	A = Application
$D_{A(H)}$ =	0.38	2.5	0.0136	0.01	0.000136	H = Hands
$D_{A(B)}$ =	1.6	2.5	0.00286	0.05	0.00286	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	22.0	0.085714	0.018857	0.000857	0.000189
	Application	15.0	0.018571	0.002786	0.005136	0.00077
Inhalation:	Mix/Loading	100	0.000021	0.000021	0.000021	0.000021
	Application	100	0.000036	0.000036	0.000036	0.000036
		Total =		**0.0217**		**0.00102**

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Table 7.3.1-2: UK-POEM: Predicted systemic exposure to tebuconazole/no PPE and with PPE

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**BYI 02960 SL 200**	Active substance	**BYI 02960**
Formulation type	water-based	a.s. concentration	**200** mg/ml
Dermal absorption from product	**22** %	Dermal absorption from spray	**15** %
Container	5 litres 45 or 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**0.625** l/ha	Work rate/day	**50** ha
Application volume	**500** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING					
Container size	5	litres			
Hand contamination/operation	0.01	ml			
Application dose	0.625	litres product/ha			
Work rate	50	ha/day			
Number of operations	7	/day			
Hand contamination	0.07	ml/day			
Protective clothing	None		Gloves		
Transmission to skin	100	%	5	%	
Dermal exposure to formulation	0.070	ml/day	0.0035	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	6	h			6	h	
Total dermal exposure to spray	41.550	ml/day			6.450	ml/day	

ABSORBED DERMAL DOSE							
	Mix/load		Application		Mix/load	Application	
Dermal exposure	0.070		41.550	ml/day	0.004	6.450	ml/day
Concen. of a.s. product or spray	200		0.25	mg/ml	200	0.25	mg/ml
Dermal exposure to a.s.	14.000		10.388	mg/day	0.700	1.613	mg/day
Percent absorbed	22		15	%	22	15	%
Absorbed dose	3.080		1.558	mg/day	0.154	0.242	mg/day

INHALATION EXPOSURE DURING SPRAYING		
Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.25	mg/ml
Inhalation exposure to a.s.	0.015	mg/day
Percent absorbed	100	%
Absorbed dose	0.015	mg/day

PREDICTED EXPOSURE	No PPE		With PPE	
Total absorbed dose	4.6531	mg/day	0.4109	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.0776	mg/kg bw/day	0.00685	mg/kg bw/day

B. Estimated operator exposure during the intended tractor mounted air blast spray application of 'BYI 02960' in hops

The following assumptions have been made in calculating operator exposure according to the German model and UK-POEM:

Work rate:

German model:	8 ha per day
UK-POEM:	15 ha per day
Maximum application rate:	0.75 L 'BYI 02960 SL 200' (= 150 g BYI 02960/ha)
Minimum water rate:	2000 L/ha
Operator clothing:	One layer of typical work wear (e.g. a coverall) as well sturdy foot wear
Dermal absorption:	
- BYI 02960:	22% for the concentrate and 15% for the in-use dilution
Standard operator body weight:	
German model:	70 kg
UK-POEM:	60 kg

The calculation of the estimated operator exposure was made for two alternatives regarding the personal protective equipment (PPE):

- no PPE: disregarding the recommendations on the label, no personal protective equipment is used when handling the undiluted product and during application.
- with PPE: gloves during mixing and loading as well as when handling contaminated surfaces

It should be noted that this selection of protective measures is not intended to be a recommendation as the required PPE when handling 'BYI 02960 SL 200'. It does not consider specific requirements, which may exist in individual member states. Additional PPE can be used to further reduce the exposure of the operator.

Corresponding exposure estimates are summarised in the following tables.

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Table 7.3.1-3: German model: Predicted systemic exposure to BYI 02960/no PPE and with PPE

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

Product:	BYI 02960 SL 20				
Active substance:	BYI 02960		a.s. concentration:	200	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha]:	0.75			Hands:	Gloves
Work rate [ha/day]:	8		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	22.0	(concentrate)		Body:	Standard protective coverall
	15.0	(dilution)			

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
I_M =	0.0006	1.2	0.00001	1.0	0.00001	I = Inhalation
$D_{M(H)}$ =	2.4	1.2	0.0411	0.01	0.000411	D = Dermal
I_A =	0.018	1.2	0.000309	1.0	0.000309	M = Mix/Loading
$D_{A(C)}$ =	1.2	1.2	0.0206	1.0	0.0206	A = Application
$D_{A(H)}$ =	0.7	1.2	0.012	0.01	0.00012	H = Hands
$D_{A(B)}$ =	9.6	1.2	0.00823	0.05	0.00823	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	22.0	0.0411	0.00905	0.000411	0.000091
	Application	15.0	0.0408	0.00612	0.0289	0.00434
Inhalation:	Mix/Loading	100	0.00001	0.00001	0.00001	0.00001
	Application	100	0.000309	0.000309	0.000309	0.000309
		Total =		**0.0155**		**0.00475**

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Table 7.3.1-4: UK-POEM: Predicted systemic exposure to BYI 02960/no PPE and with PPE

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha		
Product	**BYI 02960 SL 200**	Active substance	**BYI 02960**
Formulation type	water-based	a.s. concentration	**200** mg/ml
Dermal absorption from product	**22** %	Dermal absorption from spray	**15** %
Container	5 litres 45 or 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**0.75** l/ha	Work rate/day	**15** ha
Application volume	**2000** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING			
Container size	5 litres		
Hand contamination/operation	0.01 ml		
Application dose	0.75 litres product/ha		
Work rate	15 ha/day		
Number of operations	3 /day		
Hand contamination	0.03 ml/day		
Protective clothing	None		Gloves
Transmission to skin	100 %		5 %
Dermal exposure to formulation	0.030 ml/day		0.0015 ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION						
Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha					
Application volume	2000 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	10	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	0.030	121.200 ml/day	0.002	85.200 ml/day
Concen. of a.s. product or spray	200	0.075 mg/ml	200	0.075 mg/ml
Dermal exposure to a.s.	6.000	9.090 mg/day	0.300	6.390 mg/day
Percent absorbed	22	15 %	22	15 %
Absorbed dose	1.320	1.364 mg/day	0.066	0.959 mg/day

INHALATION EXPOSURE DURING SPRAYING	
Inhalation exposure	0.05 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	0.075 mg/ml
Inhalation exposure to a.s.	0.0225 mg/day
Percent absorbed	100 %
Absorbed dose	0.0225 mg/day

PREDICTED EXPOSURE	No PPE	With PPE
Total absorbed dose	2.7060 mg/day	1.0470 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0.0451 mg/kg bw/day	0.0175 mg/kg bw/day

C. Estimated operator exposure during the spray application of 'BYI 02960 SL 200' in greenhouses

Estimation according to the Greenhouse Model:

To address a data gap for hand-held applications in greenhouses, particularly in Southern Europe, ECPA conducted seven operator exposure studies during the period of 2002 to 2006. Details of the location and the crop are summarized in the following table.

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Table 7.3.1-5: Operator exposure studies in the greenhouse

EOEM Study ID-	Country	Region	Crop	No of Operators	
				Mix/Load	Application
2	Spain	[redacted]	Peppers	10	32
3	Spain	[redacted]	Cucumber	10	10
10	Italy	[redacted]	Pot Plants	10	10
12	Spain	[redacted]	Cucumber	10	10
13	Spain	[redacted]	Tomato	10	10
14	Italy	[redacted]	Melon	10	20
15	Italy	[redacted]	Melon	n.a.	10

n.a.: not applicable

The studies were conducted according to OECD Guidance[3] and were GLP compliant for the field, analytical and report phases, including assessment reports. The studies were monitored by ECPA and conducted using internationally recognized contract research organizations.

Briefly, the exposure was determined using standardized passive dosimetry methodology. This entailed the use of inner and outer dosimeters for body exposure, protective gloves and hand washes for hand exposure, face and neck washes for head exposure. Inhalation exposure was monitored using a suitable collection device located in the breathing zone to collect the inhalable fraction of airborne particles.

Analysis of the work practices and exposure data has identified four exposure scenarios:
High crop (>0.5m):

- Standard scenario – insignificant contact with treated foliage
- Intensive scenario – direct contact with treated foliage

Low crop (<0.5m):

- Standard scenario – insignificant contact with treated foliage
- Intensive scenario – direct contact with treated foliage

In the **'Standard'** scenario, operators wore polyester/cotton standard working coveralls.

In certain cropping scenarios, where contact to treated foliage cannot be avoided rain suit coveralls/trousers are commonly used. Exposure of these operators was determined for an **'Intensive'** scenario.

Algorithms using the 75th percentile of the exposure distributions have been developed based on normalization for the amount of kg a.s. handled or applied. These have been generated for each of the four scenarios' data sets and incorporated into a Microsoft Excel-based model [Greenhouse model v_2.1 (20101223).xls].

[3] OECD (1997) Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 9

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The model has passed through a workshop with European experts from Member States and was further developed during several commenting periods according to the requirements of Member States authorities.

More details about the model and the underlying studies are given in:

Report:	**KIIIA 7.3.1/01, Members of the ECPA Occupational and Bystander Expert Group, Oct 2010 (Revision 9)**
Title:	Southern European Greenhouse Model Overview
Document No	M-400719-01-1
Guidelines:	n.a.
GLP	n.a.

n.a. = not applicable

Calculations are made for the low crop scenario (both 'Standard' as well as 'Intensive').

The following assumptions are made:

Treated area: 1 ha/day
Dose rate: 0.125 kg a.s./ha

Table 7.3.1-6: Calculation of operator exposure during greenhouse application, Low crop - Standard (Greenhouse Model v_2.1, without and with PPE)

Operator exposure estimate, Greenhouse model, Low crop, standard

Product:	BYI 02960 SL 20				
Active substance:	BYI 02960	a.s. concentration:	200	[g/l or kg]	
Formulation:	Liquid	PPE during mix/loading:	Respiration:	None	
Dose [l or kg/ha product] :	0.625		Hands:	Gloves	
Work rate [ha/day]:	1	PPE during application:	Respiration:	None	
Body weight [kg]:	70		Hands:	Gloves	
Inhalation absorption [%]	100		Head:	None	
Dermal absorption [%]	22.0 (concentrate)		Body:	Coverall	
	15.0 (dilution)				

Calculation of route exposure:

Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I_{M} =	0.00049		0.125	0.00000009			I = Inhalation
$D_{M(I)}$ =	2.007001	0.022309	0.125	0.00358393		0.00003984	D = Dermal
I_{A} =	0.443296		0.125	0.00079160			M = Mix/Loading
$D_{A(C)}$ =	0.011494		0.125	0.00002053			A = Application
$D_{A(H)}$ =	5.710485	0.000237	0.125	0.0101973		0.0000004	C = Head
$D_{A(B)}$ =	0.372960		0.125	0.000666			H = Hands
							B = Body

Absorbed dose:

Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	22.0	0.003584	0.0007885	0.000040	0.000009
	Application	15.0	0.010884	0.001633	0.000687	0.0001030
Inhalation:	Mix/Loading	100	0.00000009	0.00000009	0.00000009	0.00000009
	Application	100	0.000792	0.000792	0.000792	0.000792
		Total =		**0.003213**		**0.000903**

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Table 7.3.1-7: Calculation of operator exposure during greenhouse application, Low crop - Intensive (Greenhouse Model v_2.1, without and with PPE)

Operator exposure estimate: Greenhouse model. Low crop, intensive contact with treated crop

Product:	BYI 02960 SL 200				
Active substance:	BYI 02960		a.s. concentration:	200	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha product]:	0.625			Hands:	Gloves
Work rate [ha/day]:	1		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	22.0	(concentrate)		Body:	Impervious clothing
	15.0	(dilution)			

Calculation of route exposure:

Route	Intermediate exposure figures [mg/kg a.s.] used to calculate "Estimated exposure" for		a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day]			
	"Unprotected"	"Protected"		Unprotected	Reduction factor	Protected	
I_M =	0.000049		0.125	0.00000009			I = Inhalation
$D_{M(H)}$ =	2.007001	0.022309	0.125	0.00368393		0.00003984	D = Dermal
I_A =	1.465226		0.125	0.00261647			M = Mix/Loading
$D_{A(C)}$ =	0.363874		0.125	0.00064978			A = Application
$D_{A(H)}$ =	28.618020	0.038972	0.125	0.0511036		0.0000696	C = Head
$D_{A(B)}$ =	305.297355	1.608571966	0.125	0.545174		0.002872	H = Hands
							B = Body

Absorbed dose:

Route		Absorption [%]	Unprotected		Protected	
			Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	22.0	0.003584	0.0007883	0.000040	0.000009
	Application	15.0	0.596027	0.089539	0.003592	0.0005388
Inhalation:	Mix/Loading	100	0.00000009	0.00000009	0.00000009	0.00000009
	Application	100	0.002616	0.002616	0.002616	0.002616
		Total =		**0.0929**		**0.00316**

Narrow or no rows in greenhouse low crops result in additional exposure via direct contact with treated foliage that cannot be avoided. Exposure is substantially different to the 'Standard' crop scenario, thus forms a unique 'Intensive' exposure scenario. Protected operators with intensive contact to treated foliage in the low crop scenario would wear impervious trousers and gloves during mixing/loading and application. A safety phrase must always be incorporated on product labels for this scenario to ensure that exposure due to contact with treated crop is minimised by use of spray tight protective clothing (Cat. III, type 4; low crop trousers), or avoided by use of engineering controls.

IIIA1 7.3.2 Estimation of operator exposure using personal protective equipment

Estimations of operator exposure using PPE are performed using the German model, the UK-POEM, and the Greenhouse Model. Detailed calculations and summaries are presented in IIIA 7.3.1.

IIIA1 7.3.3 Measurement of operator exposure

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

IIIA1 7.4 Bystander exposure

Plant protection products are applied in agriculture in areas that may be accessible to the public. Individuals might therefore be exposed who are not actively involved in the application of these products. The individual may be temporarily located in the vicinity of the application (the so-called 'bystander') or working or living in the vicinity of the application (the so-called 'resident'). Exposure scenarios associated with the product application are evaluated for bystanders and for residents (including children) for both outdoor scenarios. During spraying operations in greenhouses no bystanders will be present in greenhouses. Hence, no assessment is required for this scenario. Calculations are performed according to the German guideline published in 2008 ([redacted] et al. 2008)[4].

Exposure estimates and proportions of the proposed systemic AOEL accounted for by the estimates are summarised in the following table. Detailed information and calculations are presented in chapter IIIA1 7.4.1.

Table 7.4-1: Predicted systemic exposures as a proportion of the proposed AOEL

Scenario	Crop	Person	Total systemic exposure* (mg/kg bw/day)	% of AOEL#
Bystander	Lettuce	Adult	0.00013	**<1**
		Child	0.00011	**<1**
Resident		Adult	0.00004	**<1**
		Child	0.00002	**<1**
Bystander	Hops	Adult	0.00318	**3**
		Child	0.00249	**2**
Resident		Adult	0.00023	**<1**
		Child	0.00044	**<1**

*: Assumes a 60 kg adult and a 16.15 kg child.
BYI 02960: AOEL = 0.12 mg/kg bw/day

Assessment

The results of the calculations reveal that the situation with respect to bystander and resident exposure is favourable with the intended uses of 'BYI 02960 SL 200'.

The estimated systemic bystander exposures to BYI 02960 account for maximum 3% and 2% of the proposed AOEL for the adult and child, respectively, considering the application to hops.

Resident exposure to BYI 02960 is estimated to be <1% of the proposed AOEL for all scenarios.

Based on these exposure estimates there is no unacceptable risk anticipated for a bystander and a resident when being (accidentally) exposed to 'BYI 02960 SL 200'.

[4] S. Martin , D. Westphal , M. Erdtmann-Vourliotis , F. Dechet , C. Schulze-Rosario, F. Stauber, H. Wicke and G. Chester (2008): Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application, J. Verbr. Lebensm. 3, 272 - 281.

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IIIA1 7.4.1 Estimation of bystander exposure without personal protective equipment

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

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

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

Bystander/resident exposure may occur following foliar spray application. Exposure is calculated for adult and child bystanders as well as adult and child residents for the application in field crops (lettuce) as well as in high crops (hops).

Dermal Exposure (Spray Drift):

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

Where: SDE_B = Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)
AR = Application Rate (mg/m²):
BYI 02960: 0.125 kg a.s./ha = 12.5 mg/m² (lettuce)
0.150 kg a.s./ha = 15.0 mg/m² (hops)
D = Drift (%): 0.29 (lettuce), 5.77 (hops)
BSA = Exposed Body Surface Area (m²): 1 m² (adult), 0.21 m² (child)
DA = Dermal Absorption (%):
BYI 02960: 22%
BW = Body Weight (kg/person): 60 kg (adult), 16.15 kg (child)

Inhalation Exposure (Spray Drift):

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

Where: SIE_B = Systemic Exposure of Bystanders via the Inhalation (mg/kg bw/day)
I^*_A = Specific Inhalation Exposure (mg/kg a.s. handled per day):
Adult: 0.001
Child: 0.001/1.74
AR = Application Rate (kg a.s./ha):
BYI 02960: 0.125 kg a.s./ha (lettuce), 0.150 kg a.s./ha (hops)
A = Area Treated (ha/day): 20 (lettuce), 8 (hops)
T = Time [Duration] (min): 5 min. instead of 6 hours for the operator

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IA = Inhalation Absorption (%): 100
BW = Body Weight (kg/person): 60 kg (adult), 16.15 kg (child)

Total Systemic Exposure of Bystanders

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

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

Corresponding exposure calculations are presented in the following tables

Table 7.4.1-1: Detailed calculations of bystander exposure to BYI 02960 , absorbed dose and % of systemic AOEL

Adults	Children
Bystander of Field Crop, tractor mounted/trailed	
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (12.5 x 0.29% x 1 x 22 %) / 60 Absorbed dose: 0.0001329 mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (12.5 x 0.29% x 0.21 x 22 %) / 16.15 Absorbed dose: 0.0001037 mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001 x 0.125 x 20 x 5/360 x 100%) / 60 Absorbed dose: 0.0000005787 mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.001/1.74 x 0.125 x 20 x 5/360 x 100%) / 16.15 Absorbed dose: 0.000001236 mg/kg bw/day
Total systemic exposure: **$SE_B = SDE_B + SIE_B$**	**Total systemic exposure:** **$SE_B = SDE_B + SIE_B$**
Total absorbed dose: 0.000133 mg/kg bw/day	**Total absorbed dose: 0.000105 mg/kg bw/day**
% of AOEL: 0.111	**% of AOEL: 0.0875**

Table 7.4.1-2: Detailed calculations of bystander exposure to BYI 02960 , absorbed dose and % of systemic AOEL

Adults	Children
Bystander of High Crop, tractor mounted/trailed	
Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (15 x 5.77% x 1 x 22 %) / 60 Absorbed dose: 0.003174 mg/kg bw/day	Dermal exposure: $SDE_B = (AR \times D \times BSA \times DA) / BW$ (15 x 5.77% x 0.21 x 22 %) / 16.15 Absorbed dose: 0.002476 mg/kg bw/day
Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.018 x 0.15 x 8 x 5/360 x 100%) / 60 Absorbed dose: 0.000005 mg/kg bw/day	Inhalation exposure: $SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$ (0.018/1.74 x 0.15 x 8 x 5/360 x 100%) / 16.15 Absorbed dose: 0.00001068 mg/kg bw/day
Total systemic exposure: **$SE_B = SDE_B + SIE_B$**	**Total systemic exposure:** **$SE_B = SDE_B + SIE_B$**
Total absorbed dose: 0.00318 mg/kg bw/day	**Total absorbed dose: 0.00249 mg/kg bw/day**
% of AOEL: 2.65	**% of AOEL: 2.08**

b) Resident exposure assessment

Dermal Exposure (via deposits caused by spray drift):

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

Where: SDE_R = Systemic Exposure of Residents via the Dermal Route (mg/kg bw/day)
AR = Application Rate (mg/cm²) x 1 (for no. of applications)
BYI 02960: 0.125 kg a.s./ha x 1 = 0.00125 mg/cm² (lettuce)
0.150 kg a.s./ha x 1 = 0.00150 mg/cm² (hops)
D = Drift (%): 0.29 (lettuce), 5.77 (hops)
TTR = Turf Transferable Residues (%): 5
TC = Transfer Coefficient (cm²/hour): 7300 (adult), 2600 (child)
H = Exposure Duration (hours): 2
DA = Dermal Absorption (%):
BYI 02960: 22%
BW = Body Weight (kg/person): 60 (adult), 16.15 (child)

Inhalation Exposure (Vapour Drift):

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

Where: SIE_R = Systemic Exposure of Residents via Inhalation (mg/kg bw/day)
AC_V = Airborne Concentration of Vapour (mg/m³): vapour pressure of BYI 02960 is very low i.e.: 9.1 x 10^{-7} Pa at 20°C; acc. to guideline this corresponds to a non-volatile substance (vapour pressure <1 x 10^5 Pa at 20°C). Thus, resident inhalation exposure can be estimated as negligible. (i.e. airborne conc. of 0 mg/m³)
IR = Inhalation Rate (m³/day): 16.57 (adult), 8.31 (child)
IA = Inhalation Absorption (%): 100
BW = Body Weight (kg/person): 60 (adult), 16.15 (child)

Child Oral Exposure

Children's hand-to-mouth exposure

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

Where: SOE_H = Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day)
AR = Application Rate (mg/cm²) x 1 (for no. of applications)
BYI 02960: 0.125 kg a.s./ha x 1 = 0.00125 mg/cm² (lettuce)
0.150 kg a.s./ha x 1 = 0.00150 mg/cm² (hops)
D = Drift (%): 0.29 (lettuce), 5.77 (hops)
TTR = Turf Transferable Residues (%): 5
SE = Saliva Extraction Factor (%): 50
SA = Surface Area of Hands (cm²): 20

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Freq = Frequency of Hand-to-Mouth (events/hour): 20
H = Exposure Duration (hours): 2
OA = Oral Absorption (%):
BYI 02960: 100
BW = Body Weight (kg/person): 16.15

Children's object-to-mouth exposure

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

Where: SOE_O = Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day)
AR = Application Rate (mg/cm²) x 1 (for no. of applications)
BYI 02960: 0.125 kg a.s./ha x 1 = 0.00125 mg/cm² (lettuce)
0.150 kg a.s./ha x 1 = 0.00150 mg/cm² (hops)
D = Drift (%): 0.29 (lettuce), 5.77 (hops)
DFR = Dislodgeable Foliar Residues (%): 20
IgR = Ingestion Rate for Mouthing of Grass/Day (cm²):25
OA = Oral Absorption (%):
BYI 02960: 100
BW = Body Weight (kg/person): 16.15

Total Systemic Exposure of Residents

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

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

Corresponding exposure calculations are presented in the following.

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Table 7.4.1-3: Detailed calculations of resident exposure to BYI 02960, absorbed dose and % of systemic AOEL

Adults	**Children**
Resident: Exposure after application with Field Crop, tractor mounted/trailed	
Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.00125 x 0.29% x 5% x 7300 x 2 x 22%) / 60 Absorbed dose: 0.000009703 mg/kg bw/d	Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.00125 x 0.29% x 5% x 2600 x 2 x 22%) / 16.15 Absorbed dose: 0.00001284 mg/kg bw/d
Inhalation exposure: SIE_R = (AC_V x IR x IA) / 1000 x BW (0 x 16.57 x 100%) / 60 Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: SIE_R = (AC_V x IR x IA) / BW (0 x 8.31 x 100%) / 16.15 Absorbed dose: 0.0 mg/kg bw/d
	Oral exposure (hand-to-mouth transfer): SOE_H = (AR x D x TTR x SE x SA x Freq x H x OA) / BW (0.00125 x 0.29% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15 Absorbed dose 0.000004489 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): SOE_O = (AR x D x DFR x IgR x OA) / BW (0.00125 x 0.29% x 20% x 25 x 100%) / 16.15 Absorbed dose 0.000001122 mg/kg bw/d
Total systemic exposure:	**Total systemic exposure:**
$SE_R = SDE_R + SIE_R$	**$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$**
Total absorbed dose: 0.0000097 mg/kg bw/d	**Total absorbed dose: 0.0000185 mg/kg bw/d**
% of AOEL: 0.0081	**% of AOEL: 0.0154**

Table 7.4.1-4: Detailed calculations of resident exposure to BYI 02960, absorbed dose and % of systemic AOEL

Adults	**Children**
Resident: Exposure after application with High Crop, tractor mounted/trailed	
Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.0015 x 5.77% x 5% x 7300 x 2 x 22%) / 60 Absorbed dose: 0.0002317 mg/kg bw/d	Dermal exposure: SDE_R = (AR x D x TTR x TC x H x DA) / BW (0.0015 x 5.77% x 5% x 2600 x 2 x 22%) / 16.15 Absorbed dose: 0.0003065 mg/kg bw/d
Inhalation exposure: SIE_R = (AC_V x IR x IA) / 1000 x BW (0 x 16.57 x 100%) / 60 Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: SIE_R = (AC_V x IR x IA) / BW (0 x 8.31 x 100%) / 16.15 Absorbed dose: 0.0 mg/kg bw/d
	Oral exposure (hand-to-mouth transfer): SOE_H = (AR x D x TTR x SE x SA x Freq x H x OA) / BW (0.0015 x 5.77% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15 Absorbed dose 0.0001072 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): SOE_O = (AR x D x DFR x IgR x OA) / BW (0.0015 x 5.77% x 20% x 25 x 100%) / 16.15 Absorbed dose 0.0000268 mg/kg bw/d
Total systemic exposure:	**Total systemic exposure:**
$SE_R = SDE_R + SIE_R$	**$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$**
Total absorbed dose: 0.000232 mg/kg bw/d	**Total absorbed dose: 0.000441 mg/kg bw/d**
% of AOEL: 0.193	**% of AOEL: 0.368**

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IIIA1 7.4.2 Measurement of bystander exposure

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

IIIA1 7.5 Worker exposure

'BYI 02960 SL 200' is an insecticide that is applied to hops and to lettuce in the field and in greenhouses. These crops require re-entry activities like e.g. harvesting.
Re-entry exposure is therefore evaluated. Corresponding exposure calculations are performed using the re-entry model published by Hoernicke et al. (1998)[5] together with transfer coefficients relating to the appropriate tasks.

Regarding dislodgeable foliar residues measured data – when available – are used in lieu of any default assumptions.

A summary of the exposure calculations and risk assessment is presented in the following table.
Detailed information and calculations are presented in IIIA1 7.5.1.

Table 7.5-1: Predicted systemic exposures as a proportion of the AOEL

Scenario	Crop	Substance	Total systemic exposure (mg/kg bw/day)	% of AOEL#
Worker	Lettuce	BYI 02960	0.0232	**19**
	Hops	BYI 02960	0.0660	**55**

BYI 02960: AOEL = 0.12 mg/kg bw/day

Assessment

The results of the calculations reveal that the situation with respect to worker exposure is favourable for the intended uses of 'BYI 02960 SL 200'.

The estimated systemic worker exposure to BYI 02960 is well below the proposed AOEL in all crops. Calculations reflect standard work clothing worn by adult workers (shoes, socks, long-legged pants, and long sleeved shirt) and no personal protective equipment is considered.

As this scenario – re-entry just after the spray has dried – is considered to represent the worst case of the intended uses there is no unacceptable risk anticipated for the worker when performing re-entry activities in lettuce/hops treated with 'BYI 02960 SL 200'.

[5] 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)

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IIIA1 7.5.1 Estimation of worker exposure without personal protective equipment

Calculations are performed according to the following equation:

$$E = (DFR \times TC \times WR \times AR \times P \times DA)/BW$$

where
- *E* = *Systemic exposure (mg/kg bw/day)*
- *DFR* = *Dislodgeable foliar residues (µg as/cm²) per kg a.i./ha*
- *TC* = *Transfer Coefficient (cm²/person/h)*
- *WR* = *Work rate (hours/day)*
- *AR* = *Application rate (kg as/ha)*
- *P* = *Protection factor for PPE*
- *DA* = *Dermal absorption (%)*
- *BW* = *Body weight (kg/person)*

In case measured dislodgeable foliar residues (DFR_M) are available, which reflect the critical GAP, the equation changes to:

$$E = (DFR_M \times TC \times WR \times P \times DA)/BW$$

Work rates are considered with a maximum of 8 hours for maintenance work and hand harvesting. The maximum dose rate is always applied. A calculation for protective equipment is not made, i.e. P always set to 1.

Considerations on Transfer Coefficients (TC)

In a Tier 1 assessment, the TCs used in this risk assessment are taken from the EUROPOEM II report[6]. The following TC values were used:

Table 7.5-1-4: Transfer coefficients based on EUROPOEM II

Crop	Transfer Coefficients [cm²/h]
Hops	5000*
Vegetables	2500

*: For re-entry activities performed in hops no specific TC is available from EUROPOEM II. Hence, the EUROPOEM II proposed TC for ornamentals is used as a worst case surrogate.

Considerations on DFR:

Dislodgeable foliar residues were experimentally determined under actual use conditions for lettuce. A summary of the respective trials and the results are provided in chapter IIIA1 7.7.1. With a conservative approach the highest DFR_M values observed in the course of the experiments are considered in Table 7.5.1-2.

[6] Post application exposure of workers to pesticides in agriculture (Dec 2002); Re-entry working group EUROPOEM II project – FAIR3 – CT96-1406.

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Table 7.5-1-2: Experimentally derived maximum DFR_M value

Crop	DFR_M [µg/cm²]	Observed in trial	Observed on
Lettuce (field, Northern Europe)	0.291	10-2916-01 M-420640-01-1	Day 0 after 1st application (DAFT 0)
Lettuce (field, Southern Europe)	0.264	10-2917-01 M-420656-01-1	Day 0 after 2nd application (DAFT 10)
Lettuce (Greenhouse)	0.316	10-2918-01 M-420641-01-1	Day 0 after 2nd application (DAFT 10)

DAFT= Days after first treatment

It has to be noted that in all trials the application scheme was identical: two applications at a rate of 0.125 kg a.s./ha, each, with an interval of 10 days. The resulting dislodgeable foliar residues – just after application – were all at the same level being on average around 0.29 µg/cm². Also, regardless whether in Northern or Southern Europe, whether in the field or in greenhouse, the dislodgeable foliar residues always showed an immediate decline resulting in values at or <LOQ already 3 days after application. Hence, no increase or accumulation of residues from a former application was observed. For further details please see IIIA1 7.7.
For a conservative risk assessment for activities in lettuce it is therefore considered sufficient to take just the highest measured DFR value without any further differentiation of zone or indoor/outdoor application.

For hops no measured dislodgeable foliar residues are available. As default figures proposals from EUROPOEM II (3µg a.s./cm² per 1 kg a.s./ha) as well as from the German guidance (1µg a.s./cm² per 1 kg a.s./ha) are available. Data from the dislodgeable foliar residue trials with lettuce have shown that measured values are somewhat in between these two default figures (and corresponding more to the US-EPA default of 2 µg/cm² per kg a.s./ha).
For a conservative assessment the default value from EUROPOEM II is chosen.
In addition, it has to be noted that the estimate covers a worst case as it considers re-entry shortly after application (just when the spray has dried) whereas minimum pre-harvest intervals amount to 3 days (lettuce in greenhouse), 10 days (lettuce in field) or even 21 days (hops).

The following assumptions apply:

Work rate: 8 hours per day
Worker body weight: 60 kg
Application rate:
- hops: 0.15 kg a.s./ha

Dermal absorption:
- worst case: 22%

Clothing: one layer of typical work wear is worn during re-entry
Personal protective equipment: none

Detailed calculations of worker exposure are presented in the following:

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Lettuce

D	=	DFR	x	TC	x	WR	x	P
D	=	0.316	x	2500	x	8	x	1
D	=	6320 µg a.s./person/day						
	=	6.32 mg a.s./person/day						
	=	0.105 mg/kg bw/day (60 kg person)						

and under consideration of 22% dermal absorption:

S	=	0.105 x 0.22
	=	**0.0232 mg/kg bw/day**

Hops

D	=	DFR	x	TC	x	WR	x	AR	x	P
D	=	3.0	x	5000	x	8	x	0.150	x	1
D	=	18000 µg a.s./person/day								
	=	18.0 mg a.s./person/day								
	=	0.300 mg/kg bw/day (60 kg person)								

and under consideration of 22% dermal absorption:

S	=	0.300 x 0.22
	=	**0.0660 mg/kg bw/day**

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 PPE is acceptable. Detailed calculations are presented in IIIA1 7.5.1.

IIIA1 7.5.3 Estimation of worker exposure using data on dislogeable residues

Not considered to be applicable (see IIIA1 7.5).

IIIA1 7.5.4 Measurement of worker exposure

Not considered to be applicable (see IIIA1 7.5).

IIIA1 7.6 Dermal absorption

The extent of dermal absorption of BYI 02960 formulated in the SL 200 formulation was investigated both *in vivo* using the rat and *in vitro* using human and rat skin. A summary of each study is given in the following section. A conclusion and recommendation regarding the dermal absorption of BYI 02960 formulated in the SL 200 formulation is given below.

The *in vivo* study indicated that the mean percentage of [^{14}C]-BYI 02960 considered to be potentially absorbable following an 8 hour exposure for the neat formulation was 22%. The mean percentage of

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[^{14}C]-BYI 02960 considered to be potentially absorbable at the intermediate concentration (0.625 g/L) was 9.7%. The mean percentage of [^{14}C]-BYI 02960 considered to be potentially absorbable at the low concentration (0.1 g/L) was 21%.

The *in vitro* study indicated that the mean percentage of [^{14}C]-BYI 02960 considered to be potentially absorbable over a period of 24 hours for the neat formulation was 0.2% and 0.2% for the human and rat skin, respectively. The mean percentage of [^{14}C]-BYI 02960 considered to be potentially absorbable at the intermediate concentration (0.625 g/L) was 2% and 6% for the human and rat skin respectively. The mean percentage of [^{14}C]-BYI 02960 considered to be potentially absorbable at the low concentration (0.1 g/L) was 5% and 7% for the human and rat skin respectively.

The human *in vitro* dermal absorption values that could be used for exposure assessments are:

- 0.2% for the neat formulation (200 g/L)
- 2% for the intermediate dose (0.625 g/L)
- 5% for the low dose (0.1 g/L).

Alternatively, taking the "triple pack approach" and associating the rat *in vivo* dermal absorption values with the *in vitro* data, the corresponding results are presented in Table 7.6-1.

Table 7.6-1 Derivation of human dermal absorption of BYI 02960 from *in vivo* and *in vitro* dermal absorption data.

Test material	Rat *in vivo* dermal absorption	Human *in vitro* dermal absorption	Rat *in vitro* dermal absorption	Ratio factor between man and rat *in vitro*	Estimated human *in vivo* dermal absorption
Neat formulation	22%	0.2%	0.2%	1	22%
Intermediate formulation	10%	2%	6%	0.3	3%
Spray dilution	21%	5%	7%	0.7	15%

IIIA1 7.6.1 Dermal absorption, in vivo in the rat

Report:	**KIIIA 7.6.1/01; [redacted] (2010)**
Title:	BYI 02960 (SL200) In vivo dermal absorption study in the male rat.
Document No:	M-396841-01-1
Guidelines:	Organization for Economic Cooperation and Development (O.E.C.D.) Guidelines for Testing of Chemicals: Skin Absorption: In Vivo Method for the conduct of skin absorption studies. Guideline 427 (April 2004). Organization for Economic Cooperation and Development (O.E.C.D.) Environmental Health and Safety Publications Series on testing and Assessment N° 28. Guidance Document for the Conduct of Skin Absorption Studies (March 2004). European Commission Guidance Document on Dermal Absorption- Sanco/222/2000 rev 7, (March 2004).
GLP	yes

Material and methods

Rat:

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

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Source: [redacted]

Sex: Male.

Body weights: 260-375 g.

Age: 7 to 9 weeks old.

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

Animal identification: Ear tags.

Environmental conditions:

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

Food: Certified rodent pelleted and irradiated diet A04C-10 (from S.A.F.E Scientific Animal Food and Engineering, Augy, France), ad libitum. Feed was stored in an identified room controlled for temperature and humidify. Diet was used only until the date of expiry.

Water: Filtered and softened tap water from the municipal water supply, ad libitum. Routine analyses of feed and water indicated that there was no contamination which could have compromised the study. Certificates of water analysis were provided by the "Laboratoire de l'Environnement Nice Côte d'Azur" (France) and "Institut Scientifique d'Hygiène et d'Analyse" (Longjumeau, France).

Test Material:

Non-radiolabelled: Batch: NLL 7780-47-7.
Purity = 99.47%.

Radiolabelled: [pyridinylmethyl-14C]-BYI 02960
Batch: KATH 6429.
Specific activity: 4.37 MBq/mg.
Radiopurity of the formulation: 99%.

Formulation: The formulation used in this experiment was the BYI 02960 SL 200 formulation containing BYI 02960 and used at three nominal concentrations: neat, 200 g a.s./L, 0.625 g a.s./L and 0.1 g a.s./L.

Treatment: An area of dorsal skin was shaved approximately 24 hours prior to dosing. Just prior to dosing the animals were lightly anaesthetized and two plastic protective saddles were secured in place using Cyanoacrylate adhesive to define the site for application of the test substance (approximately ≈ 2 x 6 cm2). Approximately 120 µL (2 x 60 µL) of each dose formulation was applied to the shaved area. This amount of formulation corresponded to approximately 425 kBq/rat for the high dose formulation, 331 kBq/rat for the intermediate dose and 53 kBq/rat for the low dose formulation, according the nominal concentrations of radioactivity in the formulations. When dose application was complete, the skin was semi-occluded with a perforated plastic cover (to allow ventilation) held in place over the plastic saddle with surgical tape (approximately 3 x 4 cm). The cover prevented loss of test substance but permitted air circulation over the application site. The cover was not in direct contact with the test material on the skin.
Immediately after dose application the rats were housed individually in metabolism cages.

Treatment Groups There were 4 treatment groups per dose level.
Groups 1 to 4 were treated at the rate of 200 g/L and sacrificed at 8, 24, 72 and 168 hours post application.

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Groups 5 to 8 were treated at the rate of 0.625 g/L and sacrificed at 8, 24, 72 and 168 hours post application.
Groups 9 to 12 were treated at the rate of 0.1 g/L and sacrificed at 8, 24, 72 and 168 hours post application.

Sampling: After the 8-hour exposure time, the filter paper cover was removed. The cover and application site were then swabbed with freshly prepared 2% v/v soap solution using a gauze pad followed by a gauze pad moistened with water and a dry gauze pad. The swabs were retained for analysis. Animals that were required to provide samples beyond 8 hours were then fitted with a clean cover to capture any radioactivity lost by desquamation and replaced in the metabolism cage.

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

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

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

Findings:

There were no treatment related clinical signs observed during the study. After a single topical application of the [14C]-BYI 02960 at 200 g/L, the mean total recoveries of radioactivity were 113%, 102%, 102% and 101% for the 8, 24, 72 and 168 hour groups respectively.

The results are presented in Tables 7.6.1-1. to 7.6.1-3.

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Table 7.6.1-1.: The mean distribution of radioactivity 8, 24, 72 and 168 hours after a single topical application of [14C]-BYI 02960 from a 200 g/L SL 200 formulation

Dose Group: 200 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	8		24		72		168	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8 hr & terminal)	83.36	8.01	74.06	5.56	70.84	7.71	66.75	17.42
Surface dose (tape strips 1 & 2)	0.33	0.08	0.77	0.71	0.29	0.14	0.43	0.28
Fur	0.06	0.08	n.s.	n.a.	1.10	1.05	0.58	0.10
Dressings	7.84	6.20	7.89	2.26	12.47	5.66	14.11	9.13
SKIN COMPARTMENT								
Stratum corneum a	1.05	0.34	4.14	1.84	0.71	0.38	1.34	0.89
Treated skin b	3.31	1.66	5.41	1.70	1.32	0.90	2.00	1.13
Surrounding skin c	15.16	8.86	9.19	4.31	10.57	3.39	7.69	4.12
SYSTEMIC COMPARTMENT								
Urine	0.01	0.01	0.21	0.12	0.78	0.43	2.18	0.54
Faeces	<LOQ	n.a.	0.07	0.03	0.16	0.08	0.94	0.62
Cage wash	0.02	0.02	0.08	0.05	0.22	0.11	2.04	2.25
Cardiac blood	0.01	0.003	0.01	0.004	0.004	0.006	0.013	0.01
Non-treated skin	1.31	1.47	2.68	2.12	2.71	1.53	2.30	2.02
Carcass	0.92	0.37	0.89	0.53	0.52	0.26	0.66	0.32
Total Recovered	113.4	3.89	102.4	4.63	101.7	5.08	101.1	2.40

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

After a single topical application of the [^{14}C]-BYI 02960 at 0.625 g/L, the mean total recoveries of radioactivity were 99.8%, 99.4%, 92.3% and 95.6% for the 8, 24, 72 and 168 hour groups respectively.

Table 7.6.1-2: The mean distribution of radioactivity 8, 24, 72 and 168 hours after a single topical application of [14C]-BYI 02960 from a 0.625 g/L SL 200 formulation.

Dose Group 0.625 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	8		24		72		168	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8 hr & terminal)	89.56	4.68	88.71	6.26	76.93	6.30	85.88	6.50
Surface dose (tape strips 1 & 2)	1.26	0.43	2.15	1.90	4.14	3.06	1.61	0.67
Fur	n.s.	n.s.	n.s.	n.s.	1.17	1.38	1.03	2.07
Dressings	0.07	0.06	0.22	0.10	0.40	0.27	1.53	2.57
SKIN COMPARTMENT								
Stratum corneum a	4.86	4.44	5.06	3.89	6.41	3.31	2.71	2.46
Treated skin b	1.88	0.71	0.67	0.16	0.49	0.33	0.43	0.31
Surrounding skin c	0.31	0.08	0.35	0.06	0.58	0.35	0.15	0.06
SYSTEMIC COMPARTMENT								
Urine	0.26	0.29	0.34	0.17	0.84	0.28	1.10	0.07
Faeces	0.03	0.03	0.09	0.05	0.24	0.10	0.30	0.09
Cage wash	0.15	0.06	0.20	0.17	0.19	0.07	0.29	0.09
Cardiac blood	0.02	0.01	0.03	0.001	0.001	0.003	0.007	0.009
Non-treated skin	0.44	0.33	0.32	0.11	0.47	0.50	0.20	0.07
Carcass	1.33	0.26	0.34	0.13	0.44	0.12	0.353	0.09
Total Recovered	99.84	0.45	99.36	0.46	92.3	1.33	95.59	2.60

[a] = tape strips excluding surface dose strips 1 & 2,

[b] = skin at dose site after tape-stripping procedure,

[c] = skin immediately outside the dose application area,

SD = standard deviation, <LOQ = less than limit of quantification, n.a. = not applicable, n.s. = no sample.

After a single topical application of the [^{14}C]-BYI 02960 at 0.1 g/L, the mean total recoveries of radioactivity were 100%, 95.8%, 103% and 95.6% for the 8, 24, 72 and 168 hour groups respectively.

Table 7.6.1-3: The mean distribution of radioactivity 8, 24, 72 and 168 hours after a single topical application of [^{14}C]-BYI 02960 from the 0.1 g/L dilution of the SL 200 formulation

Dose Group 0.1 g/L (n= 4 rats/group)	% of applied dose							
	Hours post application							
	8		24		72		168	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT								
Skin swabs (8 hr & terminal)	77.99	5.59	82.44	7.12	80.53	3.92	68.67	2.62
Surface dose (tape strips 1 & 2)	3.50	1.56	2.61	1.33	3.66	0.78	3.66	0.84
Fur	1.71	0.83	n.s.	n.a.	n.s.	n.a.	n.s.	n.a.
Dressings	0.64	0.87	0.41	0.28	0.49	0.25	2.65	1.91
SKIN COMPARTMENT								
Stratum corneum a	8.74	4.50	6.26	3.03	11.69	3.14	10.37	2.68
Treated skin b	2.05	0.79	0.87	0.56	0.83	0.53	1.36	1.19
Surrounding skin c	1.53	0.16	0.41	0.03	0.40	0.26	0.73	0.34
SYSTEMIC COMPARTMENT								
Urine	0.08	0.05	0.57	0.28	1.82	0.45	3.00	0.27
Faeces	<LOQ	n.a.	0.11	0.09	0.62	0.20	0.44	0.25
Cage wash	<LOQ	n.a.	0.12	0.15	0.34	0.39	0.70	0.44
Cardiac blood	0.07	0.01	0.06	0.08	0.11	0.09	0.09	0.06
Non-treated skin	1.55	0.38	0.53	0.11	0.76	0.12	0.79	0.05
Carcass	2.63	1.45	1.40	0.18	1.63	0.47	3.09	0.69
Total Recovered	100.5	3.49	95.79	3.27	102.9	1.03	95.56	1.99

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

Total % non-absorbed:
For all treatment levels, the majority of the radioactivity was not absorbed and was recovered from the skin by swabbing. This accounted for 66.8 to 83.4%, 76.9 to 89.3% and 68.7 to 82.4% of the dose applied for the high, intermediate dose and the low dose, respectively. For the high dose groups, high and decreasing percentages of radioactivity were measured in the surrounding swabs, ranging from 19.3% at 8 hours to 1.29% at 168 hours. Percentage recoveries measured in the surface dose (tape-strips 1 and 2) were lower for the high dose formulation compared to the intermediate and low dose formulations. This amount was in the range of 0.29 to 0.77%, from 1.26 to 4.14% and from 2.61 to 3.66% of the dose applied for the high, intermediate and low dose formulations, respectively. Mean percentages of recoveries measured in the fur remained low and could be considered stable over time, despite the individual inter-variability, for the three dose formulations.

Total % at dose site:
Despite the inter-individual variability, the mean fraction of test chemical present in the stratum corneum after washing procedure increased with the treatment level. It was stable over time for the highest treatment level, with values that were relatively low ranging between 0.71% and 4.14% of the dose applied. For the intermediate dose level, the mean amount of radioactivity in the stratum corneum appeared to be stable between 8 hours (4.86%) and 72 hours (6.41%) and decreased thereafter (2.71% at 168 hours).

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For the low dose level, the mean amount of radioactivity seemed to be relatively stable between 8 hours (8.74%) and 24 hours (6.26%) and increased thereafter to 11.7% at 72 hours and 10.4% at 168 hours post-dose. The fraction of test chemical present in the treated skin following removal of both residual dose and stratum corneum appeared to be relatively stable for the three treatment formulations, with percentages of radioactivity slightly higher for the high dose formulation. Skin taken from around the application site (so called "surrounding skin"), to investigate the spreading of the test chemical across or through the skin contained relatively high and stable levels of radioactivity for the high dose formulation. These high levels of radioactivity can be related to those measured in the surrounding swabs.

For the intermediate and low dose formulations the amount of radioactivity in the surrounding skin was much lower than for the high dose group and stable over time. Therefore, the total material remaining at the dose site appeared to be lower for the groups exposed to the intermediate dose formulation. For the high dose, the values decreased from 8 hours post-dose (19.5% of the dose applied) to 168 hours (11.0% of the dose applied). For the intermediate dose, the values obtained at 8h (7.04%), 24h (6.97%) and 72 hours (7.48%) post dose were relatively similar and a decrease occurred thereafter with 3.29% measured at 168 hours.

For the low dose groups, the percentage of radioactivity located at the dose site was stable. The amount was from 12.3% at 8 hours post-dose to 12.5% at 168 hours post dose.

Total % directly absorbed:
The amounts of radioactivity found in the tissues (carcass, cardiac blood, non-treated skin) and eliminated in the excreta (urine, faeces, cage wash) were considered as directly absorbed by the rats. For the neat product a small portion of the radioactivity was absorbed rapidly as 0.92% of the applied dose appeared in the carcass after 8 hours post-application. After that, taking into account the inter-individual variability, the level of radioactivity in the carcass seems to be stable between 8 hours and 24 hours post dose and slightly decreased after 24 until the end of the study. Low and stable levels of radioactivity were detected in the cardiac blood over the duration of the study. Radioactivity detected in the non-treated skin was relatively high, but stable over time. An increase of radioactivity in the excreta (urine, cage washes and faeces) was observed from 0.03% at 8 hours post-application to 5.17% at 168 hours post-application.

At the intermediate dose level, a percentage of 1.33% of the applied dose after 8 hours post application in the carcass showed a rapid absorption of the radioactivity. This level of radioactivity in the carcass decreased between 8 and 24 hours and thereafter was stable until 168 hours. Low and stable levels of radioactivity were detected in the cardiac blood over the duration of the study. Radioactivity levels measured in the non-treated skin were low and stable from 8 hours (0.44%) to 72 hours (0.47%). Thereafter, a small decrease was noted, 0.20% of the dose applied being measured at 168 hours. The total amount of radioactivity excreted increased with time, from 0.43% at 8 hours post dose to 1.69% at 168 hours post-application (urine, cage washes and faeces).

At the low dose level, a higher proportion of the radioactivity - compared to the high and intermediate dose formulations - was absorbed rapidly, as 2.63% of the applied dose was measured in the carcass

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after 8 hours post-application. Thereafter, the level of radioactivity in the carcass seems to be relatively stable with time although an increase of radioactivity in the excreta (urine, faeces and cage wash) was observed (from 0.08% at 8 hours post-application to 4.15% at 168 hours post-application). Low and relatively stable levels of radioactivity were detected in the cardiac blood and non-treated skin over the duration of the study.

Therefore, for the three formulations, the direct dermal absorption seemed to increase over time under the experimental conditions of the study for the high and low dose formulations, ranging from 2.27% at 8 hours post dose to 8.14% at 168 hours post dose for the high dose groups and from 4.32% at 8 hours post dose to 8.12% at 168 hours post dose for the low dose formulation. For the intermediate dose, the direct dermal absorption appeared to be relatively stable over time (from 2.21% at 8 hours to 2.24% at 168 hours post dose). For the three treatment doses, the results indicated that the urine was the major route of elimination following dermal application.

Total % potentially absorbable:
In a conservative approach, the amount of radioactivity recovered in the skin compartment (stratum corneum, treated skin and surrounding skin) was considered to be absorbable. Therefore, following 8-hour exposure, the amount of BYI 02960 potentially absorbable (sum of direct absorption and amount detected in the dose site) ranged from 17 to 22% for the neat product, from 6% to 10% for the intermediate dose and from 10% to 21% for the low dose formulation.

Conclusion:
In conclusion, the amount of applied radiolabelled [^{14}C]-BYI 02960 which can be considered as the maximum percentage that could be considered as potentially absorbable under the experimental conditions of this study was 22%, 10% and 21% for the high, intermediate and low dose formulations respectively.

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

Report: **KIIIA 7.6.2/01, [redacted], (2010).**

Title: BYI 02960 (SL200) Comparative in vitro dermal absorption study using human and rat skin.

Document N°: M-391215-01-1

Guidelines: O.E.C.D. guideline for the testing of chemicals; skin absorption: in vitro Method 428 (April 2004),
O.E.C.D. Environmental health and safety publications series on testing and assessment N°28, Guidance document for the conduct of skin absorption studies (March 2004),
European Commission guidance document on dermal absorption- Sanco/222/2000 rev. 7, (March 2004).

GLP Yes

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Material and methods

Rat skin:

Species, strain:	Rat, Wistar Rj: WI (IOPS HAN).
Source:	[redacted].
Sex:	Male (10).
Anatomical site:	Dorsal.
Rat Skin Preparation:	Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of ca 460 to 540 µm in thickness.
Human skin:	Source: [redacted] Number and sex: 7 donors, female. Anatomical region: Abdomen. Thickness: 437 to 592 µm.
Test Material:	
Non-radiolabelled:	Batch: NLL 7780-47-4. Purity = 99.4% w/w.
Radiolabelled:	[pyridinylmethyl-14C]-BYI 02960 Batch: KATH 6429. Specific activity: 4.37 MBq/mg. Radiopurity of the formulation: 99%.
Formulation:	The formulation used in this experiment was the BYI 02960 SL 200 formulation used at three nominal concentrations: 200 g a.s./L, 0.625 g a.s./L and 0.1 g a.s./L.
Test system:	A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.
Skin integrity:	Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.
Treatment:	The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm2 exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.
Sampling:	The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffer saline) using natural sponge swabs, in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure

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was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay: The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail and were regularly checked by the use of [14C-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:

BYI 02960 was demonstrated to be soluble in the receptor fluid up to the concentration of 800 µg/mL of receptor fluid. The maximal achieved concentration per hour of [^{14}C]-BYI 02960 in the receptor fluid was 0.307 µg/mL. As the achieved concentrations were at least 2606 times lower than the determined solubility concentration, the solubility in the receptor fluid was deemed to be sufficient to have reduced any risk of back diffusion.

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

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 96.4% to 106.1% of the applied dose.

These study results are presented in Table 7.6.2-1.

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Table 7.6.2-1: Mean distribution of radioactivity at 24 hours after dose application of [14C]- BYI 02960 in an SL 200 formulation at the rates of 200 g/L, 0.625 g/L and 0.1 g/L to human and rat skin samples (Results expressed in terms of percentage of applied radioactivity)

	Distribution of radioactivity (% dose)											
Dose Levels	Neat formulation: High dose (SYP13527, 200 g/L)				Dilution: Intermediate dose (SYP13529, 0.625 g/L)				Dilution: Low dose (SYP13530, 0.1 g/L)			
Species	Human (n=6)		Rat (n=6)		Human (n=5)		Rat (n=4)		Human (n=5)		Rat (n=5)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT												
Skin swabs (8h)	105.6	4.37	105.1	1.41	97.28	1.72	85.50	6.25	89.40	3.42	85.48	8.40
Skin swabs (24h)[a]	0.09	0.15	0.02	0.01	0.44	0.31	0.63	0.66	0.97	0.89	5.66	3.19
Surface Dose (tape-strips 1 & 2)	0.13	0.13	0.13	0.21	0.49	0.26	2.14	1.17	0.99	0.52	5.86	3.50
Donor chamber	0.07	0.11	0.10	0.25	0.09	0.08	2.43	2.61	0.10	0.22	n.d.	n.a.
Total % non-absorbed	***105.9***	***4.50***	***105.4***	***1.52***	***98.30***	***1.67***	***90.69***	***3.99***	***91.46***	***3.45***	***96.99***	***4.24***
SKIN COMPARTMENT												
Skin [b]	0.09	0.09	0.02	0.02	0.47	0.32	1.74	1.86	1.11	0.91	1.09	0.86
Stratum corneum [c]	0.10	0.12	0.06	0.08	1.15	0.53	2.83	3.83	3.00	1.83	4.41	2.89
Total % at dose site	***0.19***	***0.21***	***0.07***	***0.09***	***1.62***	***0.82***	***4.59***	***5.65***	***4.11***	***2.72***	***5.50***	***2.63***
RECEPTOR COMPARTMENT												
Receptor fluid (0-24h)	0.01	0.02	0.07	0.07	0.38	0.32	1.03	0.29	0.61	0.43	1.02	0.43
Receptor fluid terminal	0.002	0.005	n.d.	n.a.	0.02	0.02	0.05	0.05	0.04	0.05	0.08	0.06
Receptor chamber	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.	n.d.	n.a.
Total % directly absorbed [d]	***0.02***	***0.03***	***0.07***	***0.07***	***0.39***	***0.34***	***1.08***	***0.33***	***0.65***	***0.48***	***1.11***	***0.44***
Total % Potentially Absorbable	***0.20***	***0.22***	***0.15***	***0.09***	***2.01***	***1.07***	***5.67***	***5.96***	***4.75***	***2.96***	***6.61***	***2.80***
TOTAL % RECOVERY	**106.1**	**4.65**	**105.5**	**1.5**	**100.3**	**1.90**	**96.36**	**5.98**	**96.22**	**4.08**	**103.6**	**2.54**

[a]: sum of radioactivity found in swabs at termination and in surrounding swabs.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a. : not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:

The dermal penetration of [^{14}C]-BYI 02960 through human and rat dermatomed skin from the SL 200 formulation was investigated at three concentrations corresponding to the neat product (200 g /L) and to two representative dilutions (0.625 and 0.1 g/L), respectively.

Overall, the dermal penetration of [^{14}C]-BYI 02960 in the SL 200 formulation was low at all concentrations used. Although there was a tendency for lower mean absorption values for human skin there did not appear to be a significant species difference in the absorption levels at any of the concentrations tested.

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The mean percentage of BYI 02960 in the SL 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.2% and 0.2% for the human and rat skin, respectively.

The mean percentage of BYI 02960 in the SL 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 2% and 6% for the human and rat skin respectively.

The mean percentage of BYI 02960 in the SL 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 5% and 7% for the human and rat skin respectively.

IIIA1 7.7 Dislogeable residues

IIIA1 7.7.1 Dislogeable residues - foliar

Following foliar spray treatment BYI 02960 dislodgeable foliar residues were determined in the field and in greenhouses on lettuce. Summaries of the studies and results are presented in the following.

Report:	**KIIIA 7.7.1/01, [redacted]; [redacted], S; 2011**
Title:	Determination of dislodgeable foliar residues (DFR) of BYI 02960 after spraying of BYI 02960 SL 200 on lettuce in the field in the Netherlands
Report No & Document No	10-2916-01 M-420640-01-1
Dates of work:	July 2010 – November 2011
Guidelines:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a))
GLP	Yes (certified laboratory)

I Material and methods

The purpose of the study was to determine the magnitude of the dislodgeable foliar residues of BYI 02960 on lettuce leaf foliage after each of two spraying applications with BYI 02960 SL 200 (200 g BYI 02960/L). The study was conducted in Northern Europe (The Netherlands) during the 2010 season. The actual application data are presented in the following table.

Table 7.7.1-1: Application parameters

Country	Application				
	Type	No	Interval (days)	Growth stage (BBCH)	Rate (kg a.s./ha)
The Netherlands	Spraying	2	10	45 - 48	0.125

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler ([redacted] Co; El Monte, CA). Each sample consisted of 40 disks cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf

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punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection. The samples were dislodged using a 0.01% Aerosol OT solution (i.e. docusate sodium salt which corresponds to a surfactant).

II Results and discussion

The results are summarised in the following table.

Table 7.7.1-2: Amounts of dislodgeable foliar BYI 02960 residues on lettuce in the Netherlands [µg a.s./cm^2], two sided. Figures in bold indicate day of treatment

Sampling [DA1.T][#]	Dislodgeable foliar residues [µg a.s./cm^2]
-0	<0.01
0	**0.291**
3	<0.01
5	<0.01
7	<0.01
-10	<0.01
10	**<0.01***
11	<0.01
13	<0.01
15	<0.01
17	<0.01
20	<0.01

[#]:DA1.T: day after first treatment; "-" = before respective treatment; * for explanation see text

Already immediately after the treatment there is a clear decline of dislodgeable foliar residues, resulting in values <LOQ. The second application – 10 days after the first one – was performed as no rain was expected. However, 20 minutes after the application there was rainfall for about 20 minutes with one minute of hard rain. Obviously this has washed off any residues from the leaf surfaces.

III Conclusion

The DFR value at day 0 (i.e. shortly after application when the spray has dried) amounts to 0.29 µg/cm^2. This corresponds to 2.3 µg a.s./cm^2 per kg a.s./ha. This value is higher as the one proposed by the German re-entry model but lower than the one proposed by EUROPOEM. Already three days after application the DFR is <LOQ (0.01 µg/cm^2).

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While EUROPOEM does not consider any dissipation after application the German guidance (for bystander/resident exposure) considers default 50% dissipation between applications. With regard to the observed dissipation in the trial this can be regarded as a conservative approach.
Due to the heavy rain shortly after the second application no results are available from this application. However, as the DFR values before the second application were already constantly <LOQ no other figures than the ones from the first application would have been expected for the second application: Three days after application the DFR values are <LOQ.

Report:	**KIIIA 7.7.1/02, [redacted], 2011**
Title:	Determination of dislodgeable foliar residues (DFR) of BYI 02960 after spraying of BYI 02960 SL 200 on lettuce in the field in Portugal
Report No & Document No	10-2917-01 M-420656-01-1
Dates of work:	September 2010 – December 2011
Guidelines:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K Reentry Protection, Series 132-1 (a))
GLP	Yes (certified laboratory)

I Material and methods

The purpose of the study was to determine the magnitude of the dislodgeable foliar residues of BYI 02960 on lettuce leaf foliage after each of two spraying applications with BYI 02960 SL 200 (200 g BYI 02960/L). The study was conducted in Southern Europe (Portugal) during the 2010 season. The actual application data are presented in the following table.

Table 7.7.1-3: Application parameters

Country	Application				
	Type	No	Interval (days)	Growth stage (BBCH)	Rate (kg a.s./ha)
Portugal	Spraying	2	10	43 - 47	0.125

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler ([redacted] Co; El Monte, CA). Each sample consisted of 40 disks cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection. The samples were dislodged using a 0.01% Aerosol OT solution (i.e. docusate sodium salt which corresponds to a surfactant).

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II Results and discussion

The results are summarised in the following table.

Table 7.7.1-4: Amounts of dislodgeable foliar BYI 02960 residues on lettuce in Portugal [µg a.s./cm²], two sided. Figures in bold indicate day of treatment

Sampling [DA1.T][#]	Dislodgeable foliar residues [µg a.s./cm²]
-0	<0.01
0	**0.110**
3	<0.01
5	<0.01
7	<0.01
-10	<0.01
10	**0.264**
11	0.012
13	<0.01
15	<0.01
17	<0.01
20	<0.01

[#]:DA1.T: day after first treatment; " - " = before respective treatment

After the treatment, there is an immediate decline of dislodgeable foliar residues resulting in values <LOQ, already 3 days after application.

III Conclusion

The DFR value at day 0 (i.e. shortly after application when the spray has dried) amounts to 0.11 µg/cm². This could correspond to the default value of the German re-entry model which would be 0.125 µg a.s./cm² (= 1 µg a.s./cm² per kg a.s./ha x 0.125 kg a.s./ha). However, the second application results in a significant higher figure while the samples before the second application were already constantly <LOQ. Hence, there is no indication that residues from a former application could have accumulated. Most likely, there was just a lower target deposition at the first application.
The value of the second application (= 0.26 µg/cm²) corresponds to 2.1 µg a.s./cm² per kg a.s./ha. This value is higher as the one proposed by the German re-entry model but lower than the one proposed by EUROPOEM. Again, within three days after application the DFR values are <LOQ.

Report:	**KIIIA 7.7.1/03, [redacted]; [redacted]; 2011**
Title:	Determination of dislodgeable foliar residues (DFR) of BYI 02960 after spraying of BYI 02960 SL 200 on lettuce in the greenhouse in the Netherlands
Report No & Document No	10-2918-01 M-420641-01-1
Dates of work:	July 2010 – November 2011
Guidelines:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a))
GLP	Yes (certified laboratory)

I Material and methods

The purpose of the study was to determine the magnitude of the dislodgeable foliar residues of BYI 02960 on lettuce leaf foliage after each of two spraying applications with BYI 02960 SL 200 (200 g BYI 02960/L). The study was conducted in Northern Europe (The Netherlands) in the greenhouse during the 2010 season. The actual application data are presented in the following table.

Table 7.7.1-5: Application parameters

Country	**Application**				
	Type	**Number of applications**	**Interval (days)**	**Growth stage (BBCH)**	**Rate (kg a.s./ha)**
The Netherlands	Spraying	2	10	44 - 48	0.125

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler ([redacted] Co, El Monte, CA). Each sample consisted of 40 disks cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection. The samples were dislodged using a 0.01% Aerosol OT solution (i.e. docusate sodium salt which corresponds to a surfactant).

II Results and discussion

The results are summarised in the following table.

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Table 7.7.1-6: Amounts of dislodgeable foliar BYI 02960 residues on lettuce in the Netherlands [µg a.s./cm²], two sided. Figures in bold indicate day of treatment

Sampling [DA1.T][#]	Dislodgeable foliar residues [µg a.s./cm²]
-0	<0.01
0	**0.293**
3	0.010
5	<0.01
7	<0.01
-10	<0.01
10	**0.316**
11	0.235
13	0.010
15	<0.01
17	<0.01
20	<0.01

[#]:DA1.T: day after first treatment;" - " = before respective treatment

After the treatment there is an immediate decline of dislodgeable foliar residues resulting in values at the LOQ already 3 days after application.

III Conclusion

The DFR value at day 0 (i.e. shortly after application when the spray has dried) amounts to 0.29 µg/cm². This corresponds to 2.5 µg a.s./cm² per kg a.s./ha. Then an immediate decline quickly leads to values <LOQ. The DFR value at day 10 – just after the second application when the spray has dried – amounts to 0.32 µg/cm², corresponding to 2.5 µg a.s./cm² per kg a.s./ha. Again, three days after application the DFR values are at the LOQ.
On average, the DFR_0-values amount to 2.4 µg a.s./cm² per kg a.s./ha which is higher as the one proposed by the German re-entry model but lower than the one proposed by EUROPOEM.
With regard to dissipation the assumption in the German guidance (for bystander/resident exposure) can be regarded as a conservative approach considering the observed dissipation in this trial.

IIIA1 7.7.2 Dislogeable residues - soil

Not required by Regulation EC 1107/2009.

IIIA1 7.7.3 Dislogeable residues - indoor surface re-volatization

Not required by Regulation EC 1107/2009.

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IIIA1 7.8 Epidemiology

Not required by Regulation EC 1107/2009.

IIIA1 7.9 Data on formulants

IIIA1 7.9.1 Material safety data sheet for each formulant

Safety data sheet for each formulant is provided in document H

IIIA1 7.9.2 Available toxicological data for each formulant

The available toxicological data for each formulant is provided with the MSDS provided in Document H

IIIA1 7.10 Domestic animal/livestock safety

Not required by Regulation EC 1107/2009.

IIIA1 7.11 Other/special studies

No other/special studies have been conducted.

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