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METCONAZOLE

Volume 3 – B.6 (PPP) – 'BAS 555 01 F'

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Version History

When	*What*
2003	Initial DAR Draft Assessment Report (DAR) – prepared by RMS BE in the context of the application for first inclusion of the a.s. in Annex I to Council Directive 91/414/EEC
2017-11-30	Renewal Assessment Report (RAR) – prepared by RMS BE in the context of the application for renewal of approval of the a.s. according to Reg (EU) No 844/2012. Data requirements for the plant protection products are addressed according to Commission Regulation (EU) No 284/2013. For the renewal of the a.s., one new formulation is proposed as representative formulation.

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B.6. TOXICOLOGY AND METABOLISM DATA AND ASSESSMENT OF RISKS FOR HUMANS

B.6.1. ACUTE TOXICITY OF PLANT PROTECTION PRODUCT

Summary of acute toxicity

The product BAS 555 01 F was not the representative formulation during the last Annex I process. The acute toxicity of BAS 555 01 F is assessed using the studies listed below in Table 7.1-1.

The following tests for BAS 555 01 F were performed: acute LD_{50} oral (rat), acute LD_{50} dermal (rat), acute LC_{50} inhalation (rat), skin irritation (rabbit), eye irritation (rabbit) and sensitisation of the skin [Buehler Test (guinea pig) and LLNA test (mouse)].

Detailed study summaries are presented below under the respective chapters CP 7.1.1- 7.1.6

Table 7.1-1: Summary of acute toxicity studies conducted with BAS 555 01 F

Type of study	Result Classification	Reference (BASF DocID)
Oral route - rat	LD_{50} > 2000 mg/kg bw (both sexes) LD_{50} = 3536 mg/kg bw (males) LD_{50} = 2102 mg/kg bw (females) No classification	[redacted] 1997a (MK-460-016)
Dermal route - rat	LD_{50} > 4000 mg/kg bw No classification	[redacted] 1997b (MK-460-017)
Inhalation route - rat	LC_{50} > 4.8 mg/L (both sexes) No classification	[redacted] 2014a (2014/1035856)
Skin irritation - rabbit	Non-irritating to rabbit skin, No classification	[redacted] 1997a (MK-460-018)
Eye irritation - rabbit	**Irritating to rabbit eye** **Eye Irrit 2 (H 319)**	[redacted]., 1997b (MK-460-019)
Skin sensitization - Buehler-Assay	Non-sensitising No classification	[redacted] 1998a (MK-460-026)
Skin sensitization Local Lymph node assay	Non-sensitising No classification	[redacted] 2014a (2014/1035857)

BAS 555 01 F has a low acute toxicity by the oral, dermal and inhalation route of exposure. It is not irritating to the skin but causes serious eye irritation. BAS 555 01 F is not a skin sensitizer in the Buehler Assay and LLNA.

Based on the available acute toxicity studies BAS 555 01 F meets the criteria for classification as **Eye Irrit 2 (H319)** according to the CLP (Regulation (EC) No. 1272/2008).

B.6.1.1. Oral

- **Oral LD_{50} study in albino rats with BAS 555 01 F ([redacted] 1997a)**

Guidelines: in compliance with Method B.1 of directive 92/69/CEE, equivalent to OECD 401.
GLP: yes.

Materials and methods:
After overnight fasting, 5 rats/sex/dose (Albino Crl:CD®(SD)BR) received BAS 555 01 F (metconazole 92.5 g/l, 8.57% w/w, batch n° R1811-106) by gavage at dose levels of 5000, 2500 and 1250 mg/kg b.w. The test material was administered as received, without dilution. The animals were observed for mortality and clinical signs of toxicity daily during the 14-day test period. Body weights were recorded on the day of dosing (day 0), at death, day 7 and at termination (day 14). Necropsies were performed on all decedents and survivors at the end of the 14-day observation period.

The study is accepted.

Findings:

Mortality: generally occurred within 24 hours of treatment.

Table 7.1.1-1 - Oral LD_{50} study in albino rats with BAS 555 01 F ([redacted] 1997a): mortality and clinical signs in albino rats administered BAS 555 01 F

Dose (mg/kg bw)	Mortality (N° died/ N° dosed)			Predominant clinical signs of toxicity observed
	Males	Females	Combined sexes	
5000	4/5	5/5	9/10	Salivation, prostration
2500	1/5	3/5	4/10	Salivation, decreased activity, prostration
1250	0/5	1/5	1/10	Salivation

Clinical signs of toxicity: they were first observed in both decedents and surviving animals within two hours following dosing. Surviving animals in the 2500 and 1250 mg/kg b.w. dose groups recovered by three days post-dosing. The one surviving male at the 5000 mg/kg b.w. dose level recovered six days post-dosing.

Body weight: all surviving animals gained weight during the 14-day study period.

Necropsy: gross pathological changes in decedents consisted of hemorrhagic intestinal tracts. There were no gross pathological findings observed in animals which were sacrificed at the termination of the study.

Conclusion:
Under the conditions of this study the rat oral LD_{50} value for BAS 555 01 F was found to be greater than 2000 mg/kg b.w. with an oral LD_{50}, in male rats of 3536 mg/kg b.w. and an oral LD_{50} in female rats of 2102 mg/kg b.w.).

BAS 555 01 F need not to be classified for acute oral toxicity, neither on the basis of Dir. 67/548/EEC, nor on the basis of the CLP regulation Reg. (EC) no 1272/2008.

B.6.1.2. Dermal

- **Dermal LD_{50} study in albino rats with BAS 555 01 F [redacted] 1997b)**

Guidelines: protocol in compliance with test method B.3 of directive 92/69/EEC, equivalent to OECD 402.
GLP: yes

Materials and methods:
Five rats/sex/dose (Albino Crl:CD®(SD)BR) received a single dermal application of 4000 mg/kg b.w. BAS 555 01 F (metconazole 92.5 g/l; 8.57% w/w, batch n° R1811-106). The corresponding dose per unit of area of treated skin ranged from 22.5 to 40.8 mg/cm^2 (representing approximately 10% of the body surface area). The test substance, as received, was placed on a 10 cm x 10 cm, 2-ply porous gauze covering and evenly distributed over a 6 cm x 6 cm. area on the gauze. The gauze was immediately placed on the dorsal area of the trunk and covered with an occlusive wrapping. Following approximately 24-h of exposure, the wrappings were removed and any remaining test material was removed by irrigating the test site with tap water. The animals were observed for mortality and clinical signs of toxicity daily during the 14-day test period. Body weights were reported on the day of dosing (day 0), day 7 and at termination (day 14). Necropsies were performed on all survivors at the end of the 14-day observation period.

The study is accepted.

Findings:

Mortality: all animals survived the 14-day observation period.

Clinical signs: chromodacryorrhea was observed in two female animals from one day post-dosing to three days post-dosing. The remaining three females as well as all the male animals dosed were normal throughout the study period.

Bodyweight: with one exception, all animals gained weight at day 7 and 14. One female exhibited a slight weight loss at day 14, which could not compensate the weight gain in the first 7 days. In conclusion, all animals gained weight during the 14-day study period.

Necropsy: there were no gross pathological findings observed in animals which were sacrificed at the termination of the study.

Conclusion:
Based on the mortality data, the dermal LD_{50} values with 95% confidence limits for BAS 555 01 F were as follows:
Males : >4.000 mg/kg b.w. (highest dose tested)
Female : >4.000 mg/kg b.w. (highest dose tested)

BAS 555 01 F need not to be classified for acute dermal toxicity, neither on the basis of Dir. 67/548/EEC, nor on the basis of the CLP regulation Reg. (EC) no 1272/2008.

B.6.1.3. Inhalation

- **BAS 555 01 F 4-hour acute inhalation toxicity study in the rat ([redacted] 2014a)**

Guidelines: protocol in compliance with test method B.2 of Regulation (EC) N°440/2008, equivalent to OECD 403 (2009)
GLP: yes

Materials and methods:
5 rats/sex albino rats (RccHan™: WIST(SPF)) were exposed by nose-only, flow-past inhalation for four hours to BAS 555 01 F (metconazole 87.5 g/L, batch n° FRE-000986) at a chemically determined mean concentration of 4.8 mg/L air (maximum technically feasible concentration). All animals were observed for clinical signs and mortality during the inhalation exposure and the subsequent 14-day observation period. Body weights were recorded at acclimatization start, prior to exposure on test day 1 and during the observation period on test days 2, 4, 8, 10, 13 and 15 before necropsy. On test day 15 all surviving animals were sacrificed and necropsied.

The study is accepted.

Findings:

Mortality: one male was found dead two days after exposure. All remaining animals survived the scheduled observation period.
Based on the observed mortality the following LC_{50} values were determined:

- LC_{50} (both sexes): > 4.8 mg/L

Clinical signs: Principal signs of toxicity observed after exposure consisted of decreased activity, ruffled fur, bradypnea, and breathing noses. This was observed for all animals. From test day 5 onwards, all animals were free of clinical signs. The maximum incidence and duration of the observations are indicated in **Table 6.1.3-1**.

Table 6.1.3-1 BAS 555 01 F 4-hour acute inhalation toxicity study in the rat ([redacted] 2014a): clinical signs observed throughout the experiment and observation period.

Concentration [mg/L air]	4.8
Males	
- Decreased activity	5/5 (day 3)
- Ruffled fur	5/5 (day 2)
- Breathing noises	5/5 (day 4)
Females	
- Decreased activity	5/5 (day 3)
- Ruffled fur	5/5 (day 2)
- Breathing noises	5/5 (day 4)

Bodyweight: between test days 1 and 4, body weight loss was noted in all surviving females. Slight body weight loss or stagnation of body weight gain continued into the second week after exposure in all females. The male which was found dead on test day 3 had lost body weight on test day 2 (**Table 6.1.3-2**).

Table 6.1.3-2 BAS 555 01 F 4-hour acute inhalation toxicity study in the rat ([redacted] 2014a): body weights

Sex		Time						
		Day 1	**Day 2**	**Day 4**	**Day 8**	**Day 10**	**Day 13**	**Day 15**
Males		260.8 ± 6.6	225.0 ± 4.4	201.1 ± 7.8	189.2 ± 21.1	232.8 ± 14.4	258.4 ± 11.1	272.4 ± 9.8
Females		167.9 ±5.6	155.3 ± 3.3	144.3 ± 2.6	160.1 ± 4.4	181.4 ± 5.7	188.6 ± 7.1	192.6 ± 5.0

Necropsy: no macroscopic findings were present.

Conclusion:

Based on the findings of this study, the LC_{50} for 4-hour exposure of BAS 555 01 F was greater than 4.8 mg/L (chemically determined mean aerosol concentration, maximum technically feasible concentration). There was no indication of relevant sex-related differences in toxicity of the test item. The extent of mortality as well as the clinical signs observed at 4.8 mg/L strongly indicates that the LC_{50} is above 5 mg/L.

BAS 555 01 F need not to be classified for acute inhalation toxicity, neither on the basis of Dir. 67/548/EEC, nor on the basis of the CLP regulation Reg. (EC) no 1272/2008.

B.6.1.4. Skin irritation

- **Primary dermal irritation study with BAS 555 01 F ([redacted] 1997a)**

Guidelines: protocol in compliance with test method B.4 of directive 92/69/EEC, equivalent to the OECD 404
GLP: yes

Materials and methods:
The hair of three New Zealand White male rabbits was closely clipped to expose the dorsal area. Each rabbit was dosed with 0.5 mL of BAS 555 01 F (metconazole 92.5 g/l, batch n° 1811-106). The test substance, as received, was placed on a 4-ply 6 cm^2 gauze patch, and applied directly to one intact test site per animal. The patches were secured with hypoallergenic tape, and the trunk was wrapped with a semi-occlusive wrap consisting of a non-allergenic adhesive tape and a filter cloth. The test site was semi-occluded during the 4-hour exposure period. After a 4-hour exposure, the wraps were removed and the test sites were irrigated with tap water to remove any residual test substance.
The test sites were examined for dermal irritation at approximately 60 minutes, and at 24, 48 and 72 hours following removal of the patches.
The study is accepted.

Findings:
No signs of systemic toxicity or mortality were observed during the study period.
At the one-hour observation, all three test animals exhibited very slight erythema. By 24 hours after application, the very slight erythema had resolved in one of three animals. The very slight erythema was resolved in the remaining two animals by the remaining 72-hour. No signs of oedema were noted for any animals at any observation period (**Table B.6.1.4-1 and B.6.1.4-2**).

Table B.6.1.4-1 Rabbit, dermal irritation/corrosion, BAS 555 01 F acute toxicity study ([redacted] 1997): erythema and oedema scores.

Effect	Time (h) 1	24	48	72	Mean 24-72
Erythema (n = 3)	1,1,1 (mean: 1.0)	1,0,1 (mean: 0.7)	1,0,0 (mean: 0.3)	0,0,0 (mean: 0.0)	**3/9 = 0.3**
Oedema (n =)	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	**0/9 = 0.0**

Table B.6.1.4-2 Rabbit, dermal irritation/corrosion, BAS 555 01 F acute toxicity study ([redacted] 1997): skin irritation scores expressed per animal.

	Scoring Erythema / Oedema				
	Skin effect - Reading [h] after patch removal				
Sex (Animal #)	1 h	24 h	48 h	72 h	Mean*
Male (296)	1/0	1/0	1/0	0/0	0.7/0.0
Male (295)	1/0	0/0	0/0	0/0	0.0/0.0
Male (314)	1/0	1/0	0/0	0/0	0.3/0.0

*Mean of the test animals for the period 24 to 72 h

Conclusion:

The evaluation of the skin irritation data on 3 rabbits, according to the EU methodology:

<Score erythema>$_{24+48+72h}$ = 0.67 / 0.0 / 0.33
<score oedema >$_{24+48+72h}$ = 0.0 / 0.0 / 0.0

(i) which compares to the criteria for CLP-classification (bold indication if trigger attained in 2/3 animals): erythema / oedema ≥2.3, ≤4.0

(ii) Which compares to the criteria for DPD-classification (bold indication if trigger attained in 2/3 animals): erythema / oedema ≥2

Based on the mean scores for erythema and oedema for each animal for the 24-, 48- and 72-hour observations, it was concluded that BAS 555 01 F was non-irritating to the rabbit skin.

BAS 555 01 F need not to be classified for skin corrosion/irritation, neither on the basis of Dir. 67/548/EEC, nor on the basis of the CLP regulation Reg. (EC) no 1272/2008.

B.6.1.5. Eye irritation

- **Primary eye irritation study with BAS 555 01 F ([redacted] 1997)**

Guidelines: Protocol in compliance with test method B.5 of directive 92/69/EEC, equivalent to OECD 405
GLP: yes

Materials and methods:
Three male albino rabbits (New Zealand White strain) were used for the study. Each rabbit was dosed with a 0.1 mL volume of the test substance BAS 555 01 F (metconazole 95.5 g/l, batch n° R 1811-106), as received, which was instilled into the conjunctival sac of the left eye. The right eye served as the untreated control. At the end of the 24-hour exposure period, the treated eyes were rinsed with tap water to remove any residual test substance. The eyes were examined at the following intervals: pretreatment (the day prior to test substance administration), 1 hour, 24 hours, 48 hours, 72 hours, day 7 and day 14.
The study is accepted.

Findings:

No signs of systematic toxicity or mortality were observed during the study period.
Diffuse corneal opacities were present in all test animals from 24-hours to the 72-hour observation period. By day 7, translucent areas of corneal opacity were present in two of three animals accompanied by a slight corneal vascularisation in all three animals. By day 14, all signs of corneal opacity and vascularisation had resolved in all test animals.
Iris effects were observed at 24 hours in one test animal, and in all three test animals at 48 hours and persisted in most of the animals until day 7.
Conjunctival irritation was present in all test animals beginning at the 1-hour observation period and persisted in all animals through study day 7. Conjunctival irritation resolved in all animals by day 14. Conjunctival irritation ranged from slight to moderate conjunctival redness, slight to moderate chemosis and slight to copious ocular discharge.

Table B.6.1.5-1 Rabbit, eye irritation, BAS 555 01 F acute toxicity study ([redacted] 1997): irritation scores per animal (N=3) and mean values.

	Pre-treatment	1h	24h	48h	72h	7 days	14 days	Mean 24-72h
Corneal opacity	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	1,1,1 (mean: **1.0**)	1,1,1 (mean: **1.0**)	1,1,1 (mean: **1.0**)	2,2,1 (mean: 1.7)	0,0,0 (mean: 0.0)	9/9 = **1.0**
Iris	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	1,0,0 (mean: **0.3**)	1,1,1 (mean: **1.0**)	1,1,0 (mean: **0.7**)	0,1,0 (mean: 0.3)	0,0,0 (mean: 0.0)	6/9 = **0.7**
Conjunctiva:								
Redness	0,0,0 (mean: 0.0)	2,2,2 (mean: 2.0)	2,2,2 (mean: **2.0**)	2,2,1 (mean: **1.7**)	2,2,1 (mean: **1.7**)	1,1,1 (mean: 1.0)	0,0,0 (mean: 0.0)	16/9 = **1.8**
Chemosis	0,0,0 (mean: 0.0)	2,2,1 (mean: 1.7)	1,1,1 (mean: **1.0**)	1,1,0 (mean: **0.7**)	1,1,0 (mean: **0.7**)	0,0,0 (mean: 0.0)	0,0,0 (mean: 0.0)	7/9 = **0.8**
Discharge	0,0,0 (mean: 0.0)	3,3,2 (mean: 2.7)	2,2,1 (mean: **1.7**)	1,2,0 (mean: **1.0**)	2,2,0 (mean: **1.3**)	1,0,0 (mean: 0.3)	0,0,0 (mean: 0.0)	12/9 = **1.3**
Other						**V1, V1, V1**		

V1: slight vascularisation of the cornea.

Table 6.1.5-2 Rabbit, eye irritation, BAS 555 01 F acute toxicity study ([redacted] 1997): mean and individual eye irritation scores and other findings observed after ocular administration of BAS 555 01 F

Readings	Sex (Animal#)	Cornea	Iris	Conjunctiva			Other
		Opacity		Redness	Chemosis	Discharge	
1 h	Male (291)	0	0	2	2	3	-
	Male (306)	0	0	2	2	3	-
	Male (292)	0	0	2	1	2	-
24 h	**Male (291)**	**1**	**1**	**2**	**1**	**2**	-
	Male (306)	**1**	**0**	**2**	**1**	**2**	-
	Male (292)	**1**	**0**	**2**	**1**	**1**	-
48 h	**Male (291)**	**1**	**1**	**2**	**1**	**1**	-
	Male (306)	**1**	**1**	**2**	**1**	**2**	-
	Male (292)	**1**	**1**	**1**	**0**	**0**	-
72 h	**Male (291)**	**1**	**1**	**2**	**1**	**2**	-
	Male (306)	**1**	**1**	**2**	**1**	**2**	-
	Male (292)	**1**	**0**	**1**	**0**	**0**	-
7 days	Male (291)	2	0	1	0	1	V1
	Male (306)	2	1	1	0	0	V1
	Male (292)	1	0	1	0	0	V1
14 days	Male (291)	0	0	0	0	0	-
	Male (306)	0	0	0	0	0	-
	Male (292)	0	0	0	0	0	-
Mean*	Male (291)	**1.0**	**1.0**	**2.0**	**1.0**		
	Male (306)	**1.0**	**0.7**	**2.0**	**1.0**		
	Male (292)	**1.0**	**0.3**	**1.3**	**0.3**		

V1= slight vascularisation of the cornea
* = the average scores for 24, 48 and 72 hour observation period

RMS-BE: According to the CLP regulation Reg. (EC) no 1272/2008, classification criteria are as follows:

Irreversible effects on the eye (EYE DAMAGE, category 1):
If, when applied to the eye of an animal, a substance produces:

– at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days;

and/or

– at least in 2 of 3 tested animals, a positive response of:
– corneal opacity ≥ 3 and/or
– iritis > 1,5
calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

Irritating to eyes (EYE IRRITATION, category 2):
if, when applied to the eye of an animal, a substance produces:

– at least in 2 of 3 tested animals, a positive response of: – ***corneal opacity ≥ 1*** and/or – iritis ≥ 1, and/or – conjunctival redness ≥ 2 and/or – conjunctival oedema (chemosis) ≥ 2
– calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days

The evaluation of the eye irritation data on 3 rabbits, according to the EU methodology:
<Score cornea opacity>$_{24+48+72h}$ = 1.0 / 1.0 / 1.0
<Score iris>$_{24+48+72h}$ = 1.0 / 0.7 / 0.3
<Score erythema>$_{24+48+72h}$ = 2.0 / 2.0 / 1.3
<Score chemosis>$_{24+48+72h}$ = 1.0 / 1.0 / 0.3
On d14, the animals showed no observable lesions.

(iii) Which compares to the criteria for CLP-classification (bold indication if trigger attained in 2/3 animals): corneal opacity ≥**1.0**; iris: ≥1.0; erythema **≥2**; chemosis ≥2

(iv) Which compares to the criteria for DPD-classification (bold indication if trigger attained in 2/3 animals): corneal opacity ≥2,<3; iris: ≥1.0,<2; erythema **≥**2.5; chemosis ≥2

All these changes were fully reversed after 14 days.
According to the CLP regulation Reg. (EC) no 1272/2008, this triggers a classification of the product as EYE IRRITATION (category 2), but it does not trigger the classification according to the old DPD-directive (Dir 1999/45/EC).

Conclusion:

It was concluded, based on the above results, that BAS 555 01 F was irritating to the rabbit eye.

- It is not classified on the basis of Dir. 1999/45/EC
- It is classified for **EYE IRRITATION** (category 2), **H319** ("*Causes serious eye irritation*") on the basis of the CLP regulation Reg. (EC) no 1272/2008.

B.6.1.6. Skin sensitisation

B.6.1.6.1

- **Dermal sensitisation study with BAS 555 01 F in guinea pig – Buehler method (nine inductions) ([redacted] 1998)**

Guidelines: protocol in compliance with method B.6 of directive 92/69/EEC, equivalent to OECD TG406
GLP: Yes

Materials and methods:
BAS 555 01 F (metconazole 89.2 g/L, batch n° R1811-123) was administered topically, to the clipped skin of 20 (10/sex) Dunkin Hartley guinea pigs. Based on results from a preliminary irritation screen, the test material was administered undiluted during the induction phase.
Induction: the undiluted material (0.3 ml) was applied to an adhesive pad (Hilltop Chamber®, 25-mm diameter). The pas was then applied to the dorsal, anterior right quadrant, covered by dental dam, and secured by an elastic adhesive bandage (Elastoplast®). After six hours, the chamber was removed. The skin was irrigated with warm tap water and patted dry with a disposable paper towel. This induction procedure was performed three times per week, for three consecutive weeks, for a total of nine exposures ("Induction One" to "Induction Nine"). Due to pronounced irritation, the test site was moved to a position slightly posterior to the original test site after Induction Three. The test site was also moved after Inductions Seven and Eight. All induction test sites were on the right side of the midline.
Challenge: fourteen days after the last induction exposure ("Induction Nine"), the challenge dose was administered. Based on the results from the irritation screen, undiluted test material was used; it was administered at a naïve site, along the dorsal anterior left quadrant, in the same manner as in the induction. After six hours of exposure, the chambers were removed and the skin was irrigated with warm tap water and patted dry with a paper towel.
In order to differentiate dermal reactions produced by irritation from those produced by sensitization, ten previously untreated animals (5/sex) were subjected to the same challenge procedures as the animals which received the induction exposures. The challenge application was administered along the dorsal anterior left quadrant.

Preliminary irritation screening: prior to study initiation, an irritation screening was performed to select a minimally irritating concentration for topical induction and the highest non-irritating concentration for the challenge application.
During the irritation screen, four animals were treated topically with undiluted test material and with concentrations of 75%, 50%, 25% v/v of the test material in sterile water (4 chambers per animal). The administration procedure was the same as described above.

Based on results of the irritation screen, the following concentrations were selected for study:
Induction (minimally-irritating concentration): undiluted
Challenge (maximum non-irritating concentration): undiluted

Findings:
Mortality: all animals survived to study termination.
Body weights: all animals gained weight during the study.
Clinical signs: no clinical signs of toxicity were noted in the study.
Dermal responses:

1. Induction (Table B.6.1.6.1-1): repeated administration at the same dose site resulted in cumulative irritation as demonstrated by an increase in the incidence and severity of dermal irritation. After the first induction, very faint (score of 0.5*) erythema was observed in 3 of the 20 animals. By the third induction, 15 of 20 animals exhibited very faint to faint (score of 1*) erythema. In addition, oedema was noted for 10 of the 20 animals. Due to the level of irritation, the fourth induction dose was administered at a site posterior to the first three inductions. After this induction, only 2 of the animals exhibited very faint erythema. However, repeated administrations at the new location ("second site") also resulted in an increase in the incidence and severity of the irritation. By the seventh induction dose, 16 of the 20 animals exhibited oedema. Although the test site was moved following the seventh and eight induction doses, it was re-located to the previously used site ("first site") and subsequent reduction in irritation was not observed.

Table B.6.1.6.1-1 Dermal sensitization –Buehler ([redacted] 1998): skin irritation scores at Induction with undiluted BAS 555 01 F.

	Inductions with undiluted BAS 555 01 F									
Grade*	**1nd**		**2nd**		**3rd**		**4th**		**5th**	
	24 hours	42 hours	24 hours	42 hours	24 hours	42 hours	24 hours	42 hours	24 hours	42 hours
0	17/20	-	14/20	18/20	6/20	7/20	18/20	-	11/20	17/20
0.5	3/20	-	5/20	2(2)/20	7(1)/20	9(4)/20	2/20	-	9/20	3/20
1	-	-	1(1)/20	-	7(6)/20	3(3)/20	-	-	-	-
2	-	-	-	-	-	1(1)/20	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-
Grade*	**6th**		**7th**		**8th**		**9th**			
	24 hours	42 hours	24 hours	42 hours	24 hours	42 hours	24 hours	48 hours		
0	10/20	14/20	6/20	4/20	3/20	7/20	7/20	4/20		
0.5	9/20	5/20	10(3)/20	8(3)/20	9/20	8/20	8(4)/20	9(1)/20		
1	1(1)/20	1(1)/20	4(4)/20	8(7)/20	8(5)/20	5(5)/20	5(5)/20	7(7)/20		
2	-	-	-	-	-	-	-	-		
3	-	-	-	-	-	-	-	-		
Mean										

x(y)/z = number of erythema (number of edema)/ number of animals tested;
- = no erythema/edema of this grade in all tested animals;
* Grade 0: No visible change; Grade 0.5: Very faint erythema, usually nonconfluent; Grade 1: Faint erythema, usually confluent (accompanied with edema); Grade 2: Moderate erythema (accompanied with edema); Grade 3: Strong erythema, (accompanied with edema).

2. Challenge (Tables B.6.1.6.1-2 and Table B.6.1.6.1-3): none of the 20 test animals challenged with the undiluted test material, BAS 555 01 F, exhibited a sensitisation response (score of 1.0*). Two of the 20 test animals and two of the 10 irritation control animals exhibited very faint erythema (score of 0.5). The remaining animals did not exhibit any signs of dermal irritation. The Incidence Index of Sensitisation to BAS 555 01 F at Challenge was 0%. The Mean Severity Indices at 24 hours for the test material and irritation control group were 0.05 and 0.1, respectively. The Mean Severity Index at 48 hours was 0.0 for both the test material and irritation control group

Table B.6.1.6.1-2 Dermal sensitisation –Buehler ([redacted] 1998): individual dermal scores at challenge[a]

		Animals treated during induction					
Animal N°	Sex	24 hours	48 hours	Animal N°	Sex	24 hours	48 hours
4804	M	0	0	**4848**	F	0	0
4805	M	0	0	**4849**	F	0	0
4806	M	0	0	**4850**	F	0	0
4807	M	0	0	**4851**	F	0.5	0
4808	M	0	0	**4852**	F	0	0
4809	M	0	0	**4853**	F	0	0
4810	M	0	0	**4854**	F	0	0
4811	M	0	0	**4855**	F	0	0
4812	M	0.5	0	**4856**	F	0	0
4813	M	0	0	**4857**	F	0	0
					Sum of scores	**1.0**	**0.0**
					Mean[b]	**0.05**	**0.0**
					IIS[c]	**0%**	

a: scored using the following scoring system: Grade 0: No visible change; Grade 0.5: Very faint erythema, usually nonconfluent; Grade 1: Faint erythema, usually confluent (accompanied with edema); Grade 2: Moderate erythema (accompanied with edema); Grade 3: Strong erythema, (accompanied with edema).
b: mean = severity index at 24 and 48 hours.
c: IIS = Incidence Index of Sensitization = [number of sensitization reactions (scores of 1 or greater) divided by total number of animals in that group] x 100. Animals that showed sensitization reactions at both intervals are counted only once.

Table B.6.1.6.1-3 Dermal sensitisation –Buehler ([redacted] 1998): individual dermal scores at challenge[a] (controls, treated at challenge only).

Animal N°	Sex	24 hours	48 hours
4814	M	0	0
4815	M	0	0
4816	M	0	0
4817	M	0.5	0
4818	M	0	0
4858	F	0	0
4859	F	0	0
4860	F	0.5	0
4861	F	0	0
4862	F	0	0
	Sum of scores	**1.0**	**0.0**
	Mean[b]	**0.1**	**0.0**

a: scored using the following scoring system: Grade 0: No visible change; Grade 0.5: Very faint erythema, usually nonconfluent; Grade 1: Faint erythema, usually confluent (accompanied with edema); Grade 2: Moderate erythema (accompanied with edema); Grade 3: Strong erythema, (accompanied with edema).
b: mean = severity index at 24 and 48 hours.

Conclusions:
None of the animals exhibited a dermal response indicative of sensitisation and the severity indices were similar between the test and control groups. Therefore, BAS 555 01 F was not a dermal sensitizer in guinea pigs under conditions of this study.

B.6.1.6.2

- BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014)

Guidelines: protocol in compliance with method B.42 of regulation (EC) N°440/2008, equivalent to OECD TG429.

Deviations: the relative humidity in the animal room was between approximately 27.1 – 65%, instead of 45-65% for several hours on four single days.

GLP: yes

Materials and methods:

The ears of twenty nulliparous and non-pregnant females mice (CBA/CaOlaHsd strain) were exposed by topical application to BAS 555 01 F (metconazole 87.5 g/L, batch n° FRE-000986) at concentrations of 2, 5 and 10 % (w/w), or to the vehicle (acetone/olive oil -4+1 v/v-). The highest concentration tested was the highest concentration that could be achieved whilst avoiding systemic toxicity and excessive local skin irritation, as determined by two pre-experiments (pre-test)..

Pre-test:

(first pre-test) Two mice were treated by (epidermal) topical application to the dorsal surface of each ear with test item concentrations of 50 and 100% once daily each on three consecutive days. Prior to the first application of the test item and before sacrifice the body weight was determined. Clinical signs were recorded at least once daily. Any signs of local irritation were documented and a score was used to grade a possible erythema of the ear skin.

Furthermore, prior to the first application of the test item (day 1), on day 3 and before sacrifice (day 6) the ear thickness was determined. Additionally, for both animals, the ears were punched after sacrifice (day 6) at the apical area and were immediately pooled per animal and weighed. Ear irritation was considered to be excessive if an erythema of the ear skin of a score value ≥3 was observed at any observation time and/or if an increase in ear weight of ≥25% was recorded on day 3 or on day 6.

(second pre-test) Since the first pre-test was positive, a second pre-test was performed using test item concentrations of 10 and 25%.

Main test:

The test item was applied once daily for three consecutive days to the dorsum of each ear. Five days after the first topical application, mice were injected intravenously into a tail vein with radio-labelled thymidine (^{3}H-methyl thymidine, aqueous solution, specific activity:74 GBq/mmol (2 Ci/mmol), concentration: 37 mBq/mL (1 mCi/mL)). Approximately five hours after this injection, the mice were sacrificed, the draining auricular lymph nodes excised, pooled per animal and immediately weighed. Furthermore, after excision of the lymph nodes, both ears of the mice were punched at the apical area using a biopsy punch and were immediately weighed pooled per animal using an analytical balance. Afterwards, single cell suspensions of lymph node cells were prepared from pooled lymph nodes per animal. An aliquot of each cell suspension was used for determination of lymph node cell count. Subsequently, the suspensions were washed and incubated with trichloroacetic acid overnight. The proliferative capacity of pooled lymph node cells was determined by the incorporation of ^{3}H-methyl thymidine measure in a β-scintillation counter.

Findings:

First pre-test:

Both animals treated with 50 and 100% test item concentration showed an erythema of the ear skin (score 1) between day 2 and 6. Furthermore, both animals showed an increase in ear weight of 32.0 and 48.0 %, respectively, compared to historical control (vehicle) values (mean: 24.9 mg/animal). Thus, a second pre-test was performed using test item concentrations of 10 and 25%.

Second pre-test:

Both animals showed an erythema of the ear skin (score 1) between day 2 and 5. In addition, the animal treated with 25% test item concentration showed an increase in ear weight of 26.7% compared to historical vehicle values (mean: 24.9 mg/animal).

Thus, the test item in the main study was assayed at 2, 5 and 10%.

Main test:

Bodyweights: there were no effects on body weight development. The increase of body weights during the study was within the expected range.
Clinical signs: the animals did not show any signs of systemic toxicity during the course of the study and no case of mortality were observed. Animals treated with a test item concentration of 10% showed an erythema of the ear skin (score 1) from day 3 to day 6. On day 3 and 4, the animals treated with a test item concentration of 5% showed an erythema of the ear skin as well (score 1). Animals treated with 2% test item concentration did not show any signs of local irritation.
Ear weight: a statistically significant increase in ear weights was observed in all dose groups in comparison to the vehicle control group ($p<0.05$, **Table B.6.1.6.2-1**). For BALB/c mice, a cut-off value of 1.1 for the ear index was reported for a positive response regarding ear skin irritation (Ulrich P. *et al*., 2001). The dose groups treated with a test item concentration of 2% and 10% marginally exceeded or reached this cut-off value (index of 1.12 and 1.10, respectively) while the index for the 5% dose group was in a comparable range and nearly reached the cut-off value (index of 1.09). However, this was considered to be not biologically relevant, as the observed increase did not exceed the threshold value of 25% for excessive local skin irritation mentioned in OECD TG429. Nevertheless, the observed increase in all dose groups indicated a slight irritant property of the test item.

Table B.6.1.6.2-1 BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014): ear weights after sacrifice.

Test item concentration % (w/w)	Animal number	Ear weight (mg/animal)	Mean Ear weight (mg)	SD	Index (Value Test Group vs. Value Control)
Vehicle Control (acetone/olive oil (4+1, v/v))	1	23.86	23.1	1.1	1.00
	2	21.32			
	3	22.94			
	4	23.75			
	5	23.74			
2%	6	24.63	25.9	1.9	1.12*
	7	25.40			
	8	29.11			
	9	24.46			
	10	25.94			
5%	11	24.00	25.2	1.4	1.09*
	12	23.42			
	13	26.05			
	14	26.90			
	15	25.50			
10%	16	25.11	25.4	1.5	1.10*
	17	24.62			
	18	24.04			
	19	25.52			
	20	27.89			

*: statistically significant when compared to vehicle controls ($p<0.05$)

A test item is regarded as a sensitiser in the LLNA if exposure to one or more test item concentration(s) results in a 3-fold or greater increase in incorporation of 3HTdR compared with concurrent controls, as indicated by the Stimulation Index (S.I.). The estimated test item concentration required to produce a S.I. of 3 is referred to as the EC3 value.

In this study, as shown in Table B.6.1.6.2-2, S.I. of 0.90, 0.69 and 0.79 were determined with the test item at concentrations of 2, 5 and 10% in acetone/olive oil (4+1, v/v), respectively. A dose response was not observed. The EC3 value could not be calculated, since none of the tested concentrations induced a S.I. greater than the threshold value of 3.

Table B.6.1.6.2-2 BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014): stimulation indices (S.I.) per dose group.

Test item concentration	Group calculation		
	Mean DPM per animal (2 lymph nodes)[a]	SD	S.I.
Vehicle Control (acetone/olive oil (4+1, v/v))	1234.3	323.1	1.00
2%	1106.3	301.9	0.90
5%	855.1	145.3	0.69
10%	970.3	362.2	0.79

a: Mean DPM/animal was determined by dividing the sum of the measured values from lymph noded of all animal within a group by the number of animals in that group (5 animals)

A statistically significant or biologically relevant increase in DPM values, lymph node weights (Table B.6.1.6.2-3) and lymph node cell counts (Table B.6.1.6.2-4) was not observed in any treated group in comparison to the vehicle control group.

Table B.6.1.6.2-3 BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014): lymph node weights after sacrifice.

Test item concentration % (w/w)	Animal number	Lymph Node weight (mg/animal)	Mean Lymph Node weight (mg)	SD	Index (Value Test Group vs. Value Control)
Vehicle Control (acetone/olive oil (4+1, v/v))	1	7.67	6.5	0.8	1.00
	2	5.64			
	3	6.49			
	4	6.78			
	5	6.07			
2%	6	6.65	5.9	0.7	0.91
	7	5.05			
	8	6.51			
	9	5.73			
	10	5.78			
5%	11	5.36	4.9	0.6	0.75
	12	4.89			
	13	4.43			
	14	5.71			
	15	4.21			
10%	16	4.70	5.4	0.7	0.83
	17	4.55			
	18	5.63			
	19	5.90			
	20	6.16			

Table B.6.1.6.2-4 BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014): lymphocyte cell counts after sacrifice.

Test item concentration % (w/w)	Animal number	Lymph Node Cell Count x 10^6 per animal	Mean Lymph Node Cell Count x 10^6 per animal	SD	Index (Value Test Group vs. Value Control)
Vehicle Control (acetone/olive oil (4+1, v/v))	1	15.35	11.9	2.6	1.00
	2	13.50			
	3	11.54			
	4	10.47			
	5	8.64			
2%	6	10.55	11.2	2.4	0.94
	7	7.31			
	8	13.21			
	9	11.65			
	10	13.21			
5%	11	8.49	8.4	1.0	0.71
	12	7.60			
	13	7.81			
	14	9.82			
	15	8.46			
10%	16	6.40	9.1	2.2	0.77
	17	7.00			
	18	9.92			
	19	11.62			
	20	11.36			

Ulrich P, Streich J, Suter W. Intralaboratory validation of alternative endpoints in the murine local lymph node assay for the identification of contact allergic potential: primary ear skin irritation and ear-draining lymph node hyperplasia induced by topical chemicals. Arch Toxicol. 2001 Feb;74(12):733-44.

Positive control:
The sensitivity of mice (CBA) and the reliability of experimental techniques are assessed regularly using a known sensitizer. Positive results were consistently obtained over the years using several variations of the methods and different vehicles. The results of 6 control studies are presented in Table 6.1.6.2-5.

Table 6.1.6.2-5 BAS 555 01 F skin sensitisation: local lymph node assay ([redacted] 2014): Positive control LLNA studies performed

Date of performance	Apr 2014	Oct 2013	Apr 2013	Oct 2012	Apr 2012	Feb 2012
Name of test substance	alpha-hexylcinnam aldehyde	alpha-hexylcinnam-aldehyde	alpha-hexylcinnam-aldehyde	alpha-hexylcinnam-aldehyde	alpha-hexylcinnam-aldehyde	alpha-exylcinnam-aldehyde
Concentrations tested	25%	25%	25%	25%	25%	25%
Vehicle	acetone/olive oil (4:1, v/v)	acetone/olive oil (4:1, v/v)	acetone/olive oil (4:1, v/v)	acetone/olive oil (4:1, v/v)	acetone/olive oil (4:1, v/v)	acetone/olive oil (4:1, v/v)
Stimulation index ^{3}H-thymidine incorporation[b]	6.8	5.8	5.9	5.7	3.7	4.7
Evaluation of study results	Positive	Positive	Positive	Positive	Positive	Positive

[b] = Ratio of test group values to control group values (Stimulation index) greater than 3.0 indicates a positive result

Conclusion:
Based on the results of this study it is concluded that BAS 555 01 F has no sensitising properties under the test conditions chosen.

B.6.1.7 Summary of acute toxicity including irritancy and skin sensitisation of the preparation BAS 555 01 F.

Table 6.1.7-1: Summary of acute toxicity studies conducted with BAS 555 01 F

Type of study	Result Classification	Reference (BASF DocID)
Oral route - rat	LD_{50} > 2000 mg/kg bw (both sexes) LD_{50} = 3536 mg/kg bw (males) LD_{50} = 2102 mg/kg bw (females) No classification	[redacted] 1997a (MK-460-016)
Dermal route - rat	LD_{50} > 4000 mg/kg bw No classification	[redacted] 1997b (MK-460-017)
Inhalation route - rat	LC_{50} > 4.8 mg/L (both sexes) No classification	[redacted] 2014a (2014/1035856)
Skin irritation - rabbit	Non-irritating to rabbit skin, No classification	[redacted] 1997a (MK-460-018)
Eye irritation - rabbit	**Irritating to rabbit eye** **Eye Irrit 2 (H 319)**	[redacted] 1997b (MK-460-019)
Skin sensitisation - Buehler-Assay	Non-sensitizing No classification	[redacted]., 1998a (MK-460-026)
Skin sensitisation Local Lymph node assay	Non-sensitizing No classification	[redacted] 2014a (2014/1035857)

B.6.1.7. Supplementary studies on the plant protection product

No data, not necessary.

B.6.1.8. Supplementary studies for combinations of plant protection products

No data, not necessary.

B.6.1.9. Summary of acute toxicity studies

BAS 555 01 F has a low acute toxicity by the oral, dermal and inhalation route of exposure. It is not irritating to the skin but causes serious eye irritation. BAS 555 01 F is not a skin sensitizer in the Buehler Assay and LLNA. Based on the available acute toxicity studies BAS 555 01 F meets the criteria for classification as **Eye Irrit 2 (H319)** according to the CLP (Regulation (EC) No. 1272/2008.

Table B.6.1.9-1: Summary of acute toxicity studies conducted with BAS 555 01 F

Study	Species (strain)	a.s; Purity; Batch n°	Result Classification	Reference
Oral	Rat (Albino Crl:CD®(SD)BR)	Metconazole 92.5 g/l; 8.57% w/w; Batch n° R1811-106	LD_{50} > 2000 mg/kg bw (both sexes) LD_{50} = 3536 mg/kg bw (males) LD_{50} = 2102 mg/kg bw (females) No classification	[redacted] 1997a
Dermal	Rat (Albino Crl:CD®(SD)BR)	Metconazole 92.5 g/l; 8.57% w/w; Batch n° R1811-106	LD50 > 4000 mg/kg bw No classification	[redacted] 1997b
Inhalation	Rat (Albino RccHanTM: WIST(SPF))	Metconazole 87.5 g/L; Batch n° FRE-000986	LC50 > 4.8 mg/L (both sexes) No classification	[redacted] 2014a
Skin irritation	Rabbit (New Zealand White)	Metconazole 92.5 g/l ; Batch n° 1811-106	Non-irritating to rabbit skin No classification	[redacted] ,, 1997a
Eye irritation	Rabbit (New Zealand White)	Metconazole 95.5 g/l ; Batch n° R 1811-106	**Irritating to rabbit eye** **Eye Irrit 2 (H 319)**	[redacted] 1997b
Skin sensitisation - Buehler-Assay	Guinea pigs (Dunkin Hartley)	Metconazole 89.2 g/L ; Batch n° R1811-123	Non-sensitising No classification	[redacted] ,, 1998a
Skin sensitisation Local Lymph node assay	♀ Mouse (CBA/CaOlaHsd strain)	Metconazole 87.5 g/L ; Batch n° FRE-000986	Non-sensitising No classification	[redacted]

B.6.2. DERMAL ABSORPTION

This section reviews the dermal absorption studies considered applicable for the product BAS 555 01 F in the context of the Annex I renewal evaluation of the active ingredient metconazole.

In vitro dermal absorption studies through human skin were performed with metconazole formulated in BAS 555 01 F for the undiluted preparation and the diluted preparations. The study results are presented below. No in vivo dermal penetration studies are available.

The dermal penetration estimate to be used for risk assessment are based on the criteria laid down in the EFSA guidance on dermal absorption [EFSA Journal 2012;10(4):2665].

The conclusion for relevant endpoints adopted to the new list of endpoint format for the current re-registration is adopted as follows:

Dermal absorption (Regulation (EU) N° 284/2013, Annex Part A, point 7.3)

BAS 555 01 F 90.2 g/L metconazole	Concentrate (90.2 g/L): 4% Spray dilution (0.46 g/L): 13% Spray dilution (0.22 g/L): 28%

6.2.1
-14C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro*
(Fabian E., Landsiedel R., 2011a)

Guidelines: OECD 428, OECD Environmental health and safety publications series on testing and assessment No. 28. Draft guidance document for the conduct of skin absorption studies (2002)
GLP: yes

Materials and methods:
In an *in-vitro* experiment, the dermal penetration of metconazole (BAS 555 F) formulated as BAS 555 01 F (metconazole 90.2 g/l, batch number FRE-000698) through human skin was determined.
The formulation concentrate was applied to human dermatomed (split thickness) skin membranes (from 2 donors, thickness: 250 - 350 µm, prepared and supplied frozen by BIOPTA Ltd) at a volume of 10 µL/cm² and nominal doses of 97.35 mg/mL. The skin was mounted into a modified Franz-type diffusion cells operated in static mode. The study was carried out using 5 skin preparations per step.

Before the penetration experiment, the integrity of the skin preparations was determined by measuring electrical resistance. For intact skin preparations using physiological saline electrical resistances in the range of > 1 kΩ were expected. In addition, the skin preparations integrity was checked by visual inspection. In case of low resistance skin preparations were used unless the visual check revealed any damage.

The following findings were reasons for not using a skin preparation in the study or rejecting results from calculation of the mean penetration parameters:

- A skin preparation showed low resistance and physical damage or leakage of receptor medium to the surface.
- A skin preparation displayed clearly aberrant test substance recovery rates (according to the guidelines of OECD a total recovery per membrane of 100 ± 10% is considered to be acceptable).
- A membrane displayed clearly aberrant penetration kinetics.

The exposure of the skin to the test material lasted 8 hours; thereafter the skin was thoroughly washed. Samples of the receptor fluid were taken 1, 2, 4, 6, 8, 10 and 24 hours after the start of the exposure in order to determine kinetic parameters (lag phase, absorption rate and permeability constant).

Findings:

Absorption kinetics:
The mean values of the kinetic parameters determined from the linear region of the cumulative absorbed dose curve are presented in Table 6.2.1-1. An absorption rate of 0.1 µg/cm²·h and a permeability coefficient (Kp) of $0.1 \cdot 10^{-5}$ cm/h was obtained for the formulation concentrate of BAS 555 01 F. A lag time of 5.62 hours was determined for the formulation concentrate.

Table 6.2.1-1. ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2011a) : penetration kinetics

Dose group	High dose* (Formulation concentrate)	
Target concentration [mg/mL]	90	
Target dose [µg/cm²]	900	
Mean actual applied dose [µg/cm²]	930.6 ± 38.0	
Number of cells used/Valid cells	5/4	
	Mean cumulative absorption	
	[µg/cm²]	[%]
Sample time [h]		
1	0.00	0.00
2	0.00	0.00
4	0.00	0.00
6	0.05	0.00
8	0.25	0.03
10	18.01	1.94
24	14.67	1.58
Kp[*10^{-5} cm/h]	0.10	-
Absorption rate [µg/cm²·h]	0.10	-
Lag time [h]	5.62	-
% absorbed within 10 hours	123%	

Applied dose and recovery of dose:

The applied doses and the number of usable skin samples per dose group are given in Table 6.2.1-2.

Table 6.2.1-2. ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2011a) : actual nominal doses compared to the target dose

Dose group	Target dose [µg/cm²]	Actual nominal dose [µg/cm²]	
1 (concentrate)	900	930.6 ± 38.0	(n=4/5) [a]

[a] number of valid cells/total number of cells); cell no 1 was excluded from calculation due to an invalid first skin wash

The mean recovery was 99.9 ± 4.22% for the formulation concentrate (see Table 6.2.1-3). All individual cell recoveries were within the OECD acceptance criteria (100 ± 10%). The individual values ranged between 93.47 and 102.68% for the formulation concentrate. Furthermore, the group mean total recovery was > 95%, therefore no adjustment to the dermal penetration values was necessary.

Nearly the entire dose, i.e. 97.5 ± 4.83% was recovered from the skin washing after 8 h. The amount associated with the skin preparations was 0.23 ± 0.27% for the formulation concentrate. The absorbed dose, i.e. the sum of

receptor samples, the receptor fluid recovered at the end of the experiment as well as the receptor chamber, amounted to 2.17 ± 1.41%. The absorption estimate, which corresponds to the amount recovered from skin and the absorbed dose, thus, sum up to 2.4%. As absorption was essentially complete after 12 h tape strip samples were not taken into account for calculation of the absorption estimate.

Table 6.2.1-3. ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2011a) : recovery data.

Dose group	**High dose*** (Formulation concentrate)	
Target concentration [mg/mL]	90	
Target dose [µg/cm²]	900	
Mean actual applied dose [µg/cm²]	930.6 ± 38.0	
Number of cells used/Valid cells	5/4	
	Recovery [%]	
	Mean	S.D.
Unabsorbed dose		
Skin washing after 8 hours	97.39	4.88
Skin washing after 24 hours	0.10	0.16
Donor chamber	0.01	0.02
Dose associated to skin[a]		
Tape strip (1st pool, strips 1 -2)	0.0	0.0
Tape strips (2nd pool; strips 3 - 6)	0.0	0.0
Skin preparation	0.23	0.27
Absorbed dose		
Sum receptor samples incl. wash out	0.95	0.64
Receptor fluid	0.94	0.64
Receptor chamber wash	0.27	0.15
Total recovery[#]	**99.90**	**4.22**
Absorption essentially complete at end of study (>75% absorption within half the study duration)	**Yes**	
Absorption estimate when absorption not essentially completed (= absorbed dose + dose associated to skin - tape strips 1 and 2)	**n.a.**	**n.a.**
Absorption estimate when absorption essentially completed (= absorbed dose + dose associated to skin - all tapes)	**2.40**	**1.67**
Absorption estimate normalized[b]	**n.a.**	**n.a.**
Absorption estimate used for risk assessment[c]	**4%**	

* Results of one cell not used for calculation due to failed 1st skin wash

[#] values may not calculate exactly due to rounding of figures

[a] Grouping is different than in the report: In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) the radioactivity in the second tape-strip pool (3rd to 6th tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. Finally, the skin preparation is also considered potentially absorbable.

[b] Cells with insufficient recovery (<95%) were corrected by normalization of absorption estimate to 100% recovery.

[c] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) one standard deviation was added to the mean % dermal penetration in cases where the standard deviation was ≥ 25% of the mean value. This value was then rounded to the required number of significant figures.

n.a.: not applicable

The total amount of metconazole recovered in the receptor media and receptor chamber after 24 hours was 20 µg for the formulation concentrate. The solubility of metconazole in the receptor medium was 280 µg/mL. When compared to the maximum solubilisation capacity in the total receptor medium volume of 8.2 mL of 2296 µg, the solubility in the receptor media was ~115-fold higher than actually needed for the formulation concentrate. Even if the receptor volume of 4 mL is considered only, the solubility was at least 56-fold higher than actually needed. These results show that the maximum concentration of the test substance in the receptor chamber does not exceed 10% of the saturation concentration as recommended by EFSA.

Conclusion:

The absorption estimate (sum of the absorbed dose and the remaining dose associated to the skin membrane) for metconazole is 2.40 ± 1.67% for the formulation concentrate. The absorption estimate used for risk assessment is **4%**, based on in-vitro dermal absorption of 14C-metconazole formulated as BAS 555 01 F through human skin.

B.6.2.2

- ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E., Landsiedel R., 2015a)

Guidelines: OECD 428, OECD Guidance Document No. 28 for the conduct of skin absorption studies (March 2004)
GLP: yes

Materials and methods:
In an *in-vitro* experiment, the dermal penetration of metconazole (BAS 555 F) formulated as BAS 555 01 F (metconazole 90.2 g/l, batch number ???) through human skin was determined.
Two spray dilutions (1:200 and 1:400) doses were applied to human dermatomed (split thickness) skin membranes (from 8 donors, thickness: 270 - 401 µm, prepared and supplied frozen by BIOPREDIC International) at a volume of 10 µL/cm² and nominal doses of 0.46 and 0.22 mg/mL. The skin was mounted into a modified Franz-type diffusion cells operated in static mode. The study was carried out using 8 skin preparations per step.

Before the penetration experiment, the integrity of the skin preparations was determined by measuring electrical resistance. For intact skin preparations using physiological saline electrical resistances in the range of > 1 kΩ were expected. In addition, the skin preparations integrity was checked by visual inspection. In case of low resistance skin preparations were used unless the visual check revealed any damage.

The following findings were reasons for not using a skin preparation in the study or rejecting results from calculation of the mean penetration parameters:

- A skin preparation showed low resistance and physical damage or leakage of receptor medium to the surface.
- A skin preparation displayed clearly aberrant test substance recovery rates (according to the guidelines of OECD a total recovery per membrane of 100 ± 10% is considered to be acceptable).
- A membrane displayed clearly aberrant penetration kinetics.

The exposure of the skin to the test material lasted 8 hours; thereafter the skin was thoroughly washed. Samples of the receptor fluid were taken 1, 2, 4, 6, 8, 12 and 24 hours after the start of the exposure in order to determine kinetic parameters (lag phase, absorption rate and permeability constant).

Preparation of the dosing solutions:
Spray dilution 1 (1:200):
To obtain the desired specific activity, a respective aliquot of the radiolabeled formulation concentrate ^{14}C-BAS 555 01 F (nominal specific activity: 206.14 MBq/g) was taken and added to the required amount of tap water (1:200 / v:v; BAS 555 01 F : spray dilution 1) yielding a radiolabeled spray dilution 1 with a nominal concentration of BAS 555 F of 0.46 mg/g (= 0.46 mg/mL) and a nominal specific activity of 1.08 MBq/g (= 1.08 MBq/mL).

Spray dilution 1 (1:400):
Due to the low concentration of active ingredient in the 1:400 / v:v aqueous spray dilution, an applied radioactivity of about 21.0 kBq/cm² was selected as a result of a pure radiolabeled test substance, prepared in the aqueous dilution of blank formulation without BAS 555 F. To obtain the desired specific activity, a respective aliquot of the radiolabeled test substance ^{14}C-BAS 555 F (specific activity: 9.32 MBq/mg) was taken the solvent was evaporated to dryness. The appropriate aqueous dilution of the blank formulation was added to the radiolabeled test substance yielding a radiolabeled spray dilution 2 with a nominal concentration of BAS 555 F of 0.22 mg/g (= 0.22 mg/mL) and a nominal specific activity of 2.10 MBq/g (= 2.10 MBq/mL).

The preparations were stirred and sonicated in order to ensure homogeneity.

Analyses:
Liquid scintillation counting and/or HPLC verified the homogeneity and accuracy of the test substance preparations. Taking and analyzing samples before and after the application period confirmed the stability of the test-substance in the preparation.

Findings:

Applied dose and recovery of dose: the applied doses are given in Table 6.2.2-1.

Table 6.2.2-1. ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2015a): actual nominal doses compared to the target dose

Dose group	Target dose [µg/cm²]	Actual nominal dose [µg/cm²]
spray dilution 1	4.50	4.52 ± 0.06
spray dilution 2	2.25	2.11

The mean recovery was 95.57% and 101.1% for spray dilution 1 and 2, respectively (see Table 6.2.2-2). All individual cell recoveries were within the OECD acceptance criteria (100 ± 10%). The individual values ranged between 90.60 and 98.40% for spray dilution 1 and between 99% and 102% for spray dilution 2. Furthermore, the group mean total recovery was > 95%, therefore no adjustment to the dermal penetration values was necessary.

Majority of the dose, about 82% and 72% was recovered from the skin washing after 8 h and 24 and from the donor chamber washing for spray dilution 1 and 2, respectively. The amount associated with the skin preparations and the 3rd to 6th skin strip was about 6% and 7% for spray dilution 1 and 2, respectively.

The absorbed dose, i.e. the sum of receptor samples, the receptor fluid recovered at the end of the experiment as well as the receptor chamber, amounted to about 7% and 21% for spray dilution 1 and 2, respectively. The absorption estimate used for risk assessment, which corresponds to the amount recovered from skin and the absorbed dose, thus, sum up to 13% and 28 %. As absorption was essentially complete after 12 h tape strip samples were not taken into account for calculation of the absorption estimate for spray dilution 1. In contrast, for spray dilution 2 tape strip samples (second pool) were added to the absorption estimate, as absorption was not essentially complete after 12 h.

Table 6.2.2-2. ^{14}C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2015a): recovery data.

Dose group	Spray dilution 1 1:200		Spray dilution 2 1:400	
Target concentration [mg/mL]	0.45		0.23	
Target dose [µg/cm²]	4.50		2.25	
Mean actual applied dose [µg/cm²]	4.52		2.11	
Number of cells used/Valid cells	8/8		8/7*	
	Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.
Unabsorbed dose				
Skin washing after 8 hours	69.76	8.55	69.50	7.11
Skin washing after 24 hours	4.25	2.25	2.15	1.38
Donor chamber	7.59	7.57	0.31	0.27
Dose associated to skin[a]				
Tape strip (1st pool, strips 1 -2)	0.29	0.22	0.65	0.44
Tape strips (2nd pool; strips 3 - 6)	0.28	0.21	1.21	1.00
Skin preparation	5.79	2.66	6.17	3.72
Absorbed dose				
Sum receptor samples incl. wash out	1.07	0.25	1.36	0.41
Receptor fluid	1.64	0.59	3.24	0.61
Receptor chamber wash	4.91	1.61	16.51	2.82
Total recovery[#]	**95.57**	**2.59**	**101.1**	**1.10**
Absorption essentially complete at end of study (>75% absorption within half the study duration)	**Yes**		**No**	
Absorption estimate when absorption not essentially completed (= absorbed dose + dose associated to skin - tape strips 1 and 2)	**n.a.**	**n.a.**	**28.49**	**6.66**
Absorption estimate when absorption essentially completed (= absorbed dose + dose associated to skin - all tapes)	**13.41**	**2.72**	**n.a.**	**n.a.**
Absorption estimate normalized[b]	**n.a.**	**n.a.**	**n.a.**	**n.a.**
Relevant absorption estimate[c]	**13.41**		**28.49**	
Absorption estimate used for risk assessment[c]	**13**		**28**	

* Results of one cell not used for calculation due to defect skin preparation after first skin wash

\# values may not calculate exactly due to rounding of figures

[a] Grouping is different than in the report: In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) the radioactivity in the second tape-strip pool (3rd to 6th tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. Finally, the skin preparation is also considered potentially absorbable.

[b] Cells with insufficient recovery (<95%) were corrected by normalization of absorption estimate to 100% recovery.

[c] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) one standard deviation was added to the mean % dermal penetration in cases where the standard deviation was ≥ 25% of the mean value. This value was then rounded to the required number of significant figures.
n.a.: not applicable

The total amount of metconazole recovered as absorbed dose after 24 hours was about 0.35 and 0.45 µg for spray dilution 1 and 2, respectively. The solubility of metconazole is 30.4 mg/L in the receptor medium. When compared to the maximum solubilisation capacity in the total receptor medium volume of 8.2 mL of 249 µg, the solubility in the receptor media was at least 550-fold higher than actually needed for the spray dilutions. Even if the receptor volume of 4 mL is considered only, the solubility was at least 270-fold higher than actually needed. These results show that the maximum concentration of the test substance in the receptor chamber does not exceed 10% of the saturation concentration as recommended by EFSA.

Absorption kinetics: The mean values of the kinetic parameters determined from the linear region of the cumulative absorbed dose curve are presented in Table 6.2.2-3. An absorption rate of 0.0157 and 0.0023 µg/cm²·h was obtained for the formulation concentrate of BAS 555 01 F.

Table 6.2.2-3. ^{14}C-BAS 555 F in BAS 555 01 F - study of penetration through human skin *in vitro* (Fabian E.,Landsiedel R., 2015a): penetration kinetics.

Dose group	**Spray dilution 1 (1:200)**		**Spray dilution 2 (1:400)**	
Target concentration [mg/mL]	0.45		0.23	
Target dose [µg/cm²]	4.50		2.25	
Mean actual applied dose [µg/cm²]	4.52		2.11	
Number of cells used/Valid cells	8/8		8/7	
	Mean cumulative absorption		Mean cumulative absorption	
	[µg/cm²]	[%]	[µg/cm²]	[%]
Sample time [h]				
8	0.06	1.40	0.01	0.66
12	0.08	1.81	0.02	0.79
24	0.10	2.16	0.02	1.11
Absorption rate [µg/cm^2·h]	0.0157		0.0023	
% absorbed within 12 hours	84		71	

Conclusion:

The absorption estimate of ^{14}C-BAS 555 F formulated as BAS 555 01 F is 13.41 ± 2.72% and 28.49 ± 6.66% for spray dilution 1 and 2, respectively. The absorption estimates used for risk assessment are 13% and 28% for spray dilution 1 and 2, respectively.

B.6.3. AVAILABLE TOXICOLOGICAL DATA RELATING TO CO-FORMULANTS

Data provided separately in the confidential part.

B.6.4. EXPOSURE DATA

B.6.4.1. Operator exposure

B.6.4.1.1 Assessment according to the models in place at time of submission ("German Model" and "UK POE Model")

Estimation of operator exposure without personal protective equipment

Regarding the intended use of BAS 555 01 F on wheat, cereals and oilseed rape the exposure situation that has to be considered, is:

– Outdoor tractor mounted boom sprayer application to low crops

Estimations of potential operator exposure have been undertaken for BAS 555 01 F using the intended uses shown above and the following predictive models:

- Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection); Mitteilungen aus der Biologischen Bundesanstalt, Heft 277, Berlin 1992, 1992. ("German model").
- Revised UK POE Model, as available on http://www.pesticides.gov.uk/ uploadedfiles/Web_Assets/PSD/UK_POEM1.xls [UK Predictive Operator Exposure Model (POEM): Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 7 of 2008, (UK MAFF), 1992. ("UK Model").

The following parameters were applied for the model estimates

German model

Table B.6.4.1.1-1: Input parameters for tractor mounted boom sprayer application in wheat, cereals and oilseed rape in the BBA model

Application method:	Tractor-mounted boom sprayers with hydraulic nozzles, field crop	
Treated area:	20 ha/day	
Max. dose rate:		1 L BAS 555 01 F/ha
	corresponding to:	0.09 kg metconazole/ha
Operator body weight:	70 kg	

UK-POEM

Table B.6.4.1.1-2: Input parameters for tractor mounted boom sprayer application in wheat, cereals and oilseed rape in the UK-POEM

Application method:	Tractor-mounted/trailed boom sprayer: hydraulic nozzles	
Treated area:	50 ha/day	
Max. dose rate:	1	L BAS 555 01 F/ha
	corresponding to: 0.09	kg metconazole/ha
Spray volume:	110 L/ha	
Duration:	6 h	
Container:	10 litres 63 mm closure	
Operator body weight:	60 kg	

The operator exposure estimates assuming that no protective clothing was worn are summarized in Table 6.4.1.1-3 below; details are presented in the referenced appendices.

Table B.6.4.1.1-3: BAS 555 01 F: Exposure prediction and risk assessment without PPE

Application method Crop	**Model**	**Active ingredient**	**Total systemic exposure[1] (mg/kg bw/day)[2]**	**AOEL covered[3)]**	**Reference Appendix**
tractor mounted boom sprayer application wheat, cereals and oilseed rape	BBA	metconazole	0.02	200%	**7.2-1**
	UK POEM	metconazole	0.17	1745%	**7.2-2**

[1]) Systemic exposure based on dermal absorption of 4% for mixing/loading and 28% for application for metconazole.

[2]) Body weight 70 kg/person in German model and 60 kg/person in UK POEM and in AOEM

[3)] Total systemic exposure x 100 / systemic AOEL systemic AOEL for metconazole = 0.01 mg/kg bw/day

BBA- and UK-POE model estimates suggest that under the conditions of use of BAS 555 01 F in wheat, cereals, oilseed rape the predicted systemic exposure is about 200% in the BBA-model and about 1745% of the systemic AOEL for metconazole in the UK-POEM. Neither in the BBA-model nor in the UK POEM a safe use could be demonstrated.

Conclusion

Considering the results of the estimations, a safe use of the product BAS 555 01 F could not be demonstrated for all representative use exposure scenarios. Therefore, further calculations taking personal protective equipment into account have to be performed.

Estimation of operator exposure when applying personal protective equipment

BBA-model and/or UK-POEM estimates suggest that under the conditions of use of BAS 555 01 F in wheat, cereals and oilseed rape no safe use could be demonstrated. Thus, a refined risk assessment is presented below. The standard risk assessment when applying PPE during mixing/loading and application is summarized here, details are given in the referenced appendices.

The German model estimates were conducted applying:
- gloves during mixing/loading and gloves, coverall and sturdy footwear during application for low crop field application

The UK POEM estimates were conducted applying:
- gloves during mixing/loading
- gloves during application

Table B.6.4.1.1-4: BAS 555 01 F: Exposure prediction and risk assessment when using PPE during mixing/loading and application

Application method Crop	Model	PPE	Active ingredient	Total systemic exposure[1] (mg/kg bw/day)[2]	AOEL covered[3)]	Reference Appendix
tractor mounted boom sprayer application wheat, cereals and oilseed rape	BBA	gloves during M/L and gloves and coverall and sturdy footwear during Appl.	metconazole	0.0011	11%	**7.2-3**
	UK POEM	gloves during M/L and gloves during Appl.	metconazole	0.0262	262%	**7.2-4**

[1]) Systemic exposure based on dermal absorption of 4% for mixing/loading and 28% for application for metconazole.

[2]) Body weight 70 kg/person in German model and 60 kg/person in UK POEM and in AOEM

[3)] Total systemic exposure x 100 / systemic AOEL systemic AOEL for metconazole = 0.01 mg/kg bw/day

According to BBA-model assumptions for tractor mounted boom sprayer application when wearing gloves during mixing/loading and gloves and coverall and sturdy footwear during application 11% of the AOEL when applying metconazole are used for BAS 555 01 F. According to UK POEM assumptions for tractor mounted boom sprayer application when wearing gloves during mixing/loading and gloves during application 262% of the AOEL for metconazole are used. Thus, while in the BBA-model a safe use could be demonstrated without PPE, no safe use could be shown in the UK-POEM.

In conclusion operators when exposed to metconazole under the use conditions of BAS 555 01 F are not considered to be at risk.

B.6.4.1.2 Assessment according to the EFSA guidance model

Estimations of potential operator exposure have been undertaken for BAS 555 01 F using the intended uses shown above and the following predictive models:

1. EFSA guidance operator model (AOEM) [European Food Safety Authority (2014); Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment for Plant Protection Products; http://www.efsa.europa.eu/en/efsajournal/pub/3874 htm] that was developed in a joint co-operation of
   - Federal Institute for Risk Assessment (BfR)
   - Health and Safety Executive (HSE)
   - French Agency for Food, Environmental and Occupational Health and Safety ANSES)
   - Federal Research Centre for Cultivated Plants, Julius Kühn Institut (JKI)
   - Federal Office of Consumer Protection and Food Safety (BVL)
   - German Crop Protection Pest Control and Fertilizer Association (Industrieverband Agrar, IVA)
   - European Crop Protection Association (ECPA)
   - observed by EFSA and TNO

As compared to the previous standard models the AOEM has the following advantages.

1. The previously used German and UK-model developed over 20 years ago, do not reflect the current application techniques and practices
2. The database used for the model development does contain much more data points than the previously used models.
3. The exposure studies evaluated for the AOEM ensure a very high quality of data e.g. GLP-conformity, compliance with OECD guidance.
4. Statistical measures were implied to derive exposure factors.
5. The whole project report is publically available.
6. The criteria for the selection of studies are transparent and allow reproducibility of the outcome.

Accordingly the EFSA working group decided to replace the relevant scenario (outdoor treatment of low crops by vehicle mounted/trailed or self propelled sprayers) with the new AOEM data. The 75th percentile data were taken into account for long-term exposure assessment.

Estimation of operator exposure without personal protective equipment

Estimations according to the AOEM without PPE are provided in the Table 6.4.1.2-1.

Table B.6.4.1.2-1: BAS 555 01 F: Exposure prediction and risk assessment without PPE

Application method Crop	Model	Active ingredient	Total systemic exposure[1] (mg/kg bw/day)[2]	AOEL covered[3)]	Reference Appendix
tractor mounted boom sprayer application wheat, cereals, oilseed rape	AOEM	metconazole	0.0224	224%	**7.2-5**

[1]) Systemic exposure based on dermal absorption of 4% for mixing/loading and 28% for application for metconazole.
[2]) Body weight 70 kg/person in German model and 60 kg/person in UK POEM and in AOEM
[3)] Total systemic exposure x 100 / systemic AOEL systemic AOEL for metconazole = 0.01 mg/kg bw/day

Estimates according to the new European operator exposure model for tractor mounted boom sprayer application suggest that under the conditions of use of BAS 555 01 F in wheat, cereals, oilseed rape the predicted systemic exposure is about 224% of the systemic AOEL for metconazole. No safe use could be demonstrated based on estimates conducted without PPE.

Conclusion

Considering the results of the estimations, a safe use of the product BAS 555 01 F could not be demonstrated. Therefore, further calculations taking personal protective equipment into account have to be performed.

Estimation of operator exposure when applying personal protective equipment

The estimates based on the AOEM were conducted applying:
- protective gloves, workwear + sturdy footwear during mixing/loading
- protective gloves, workwear + sturdy footwear during application

Table B.6.4.1.2-2: BAS 555 01 F: Exposure prediction and risk assessment when using PPE during mixing/loading and application

Application method Crop	Model	PPE	Active ingredient	Total systemic exposure[1] (mg/kg bw/day)[2]	AOEL covered[3)]	Reference Appendix
tractor mounted boom sprayer application wheat, cereals, oilseed rape	AOEM	protective gloves, workwear + sturdy footwear, during mixing loading and protective gloves, workwear + sturdy footwear, during application	metconazole	0.001	9.9%	**7.2-5**

[1]) Systemic exposure based on dermal absorption of 4% for mixing/loading and 28% for application for metconazole.
[2]) Body weight 70 kg/person in German model and 60 kg/person in UK POEM and in AOEM
[3)] Total systemic exposure x 100 / systemic AOEL systemic AOEL for metconazole = 0.01 mg/kg bw/day

A safe use could be demonstrated when applying PPE (protective gloves, workwear + sturdy footwear, during mixing loading and protective gloves, workwear + sturdy footwear, during application) by estimates conducted with the recently developed European operator exposure model.

Conclusion
In conclusion operators when exposed to metconazole under the use conditions of BAS 555 01 F are not considered to be at risk.

B.6.4.1.3 Measurement of operator exposure

Since the risk assessments performed indicate that the health-based limit value (AOEL) for metconazole will not be exceeded under practical conditions of use, studies to provide field data on operator exposure to BAS 555 01 F were not considered to be necessary and were, therefore, not carried out.

B.6.4.2. Bystander and resident exposure

Measurement of bystander and resident exposure.

The EU-commission has released a guidance note on May 29, 2015 [SANTE-10832-2015, see KCP 7.2.2.1/1 2015/1174492] acknowledging that: "*for the acute risk assessment for bystanders and residents, the derivation of the corresponding toxicological reference value (AAOEL) is still outstanding. Similarly, no higher tier risk assessment schemes are available for residents and bystanders scenarios. Both aspects are essential to be able to fully apply the guidance document for the approval of active substances under Regulation (EC) No 1107/2009."* In consequence, it was concluded that: "*For the approval of active substances under Regulation (EC) No 1107/2009, the risk assessment on residents and bystanders cannot be fully considered until a procedure for the derivation of the AAOEL and higher risk assessment schemes, identified as missing by the Standing Committee, are available."* Thus, the applicant provided for metconazole bystander and resident estimates according to the models in place at time of submission only.

In order to evaluate bystander and resident exposure to BAS 555 01 F as part of the EU review of metconazole all relevant data and risk assessments are provided here and are considered adequate. Table 7.2.1-1 summarizes the GAPs evaluated for bystander and resident risk assessment.

Risk assessment for bystander and resident

B.6.4.2.1 Assessment according to the models in place at time of submission

As the objective of this dossier is to apply for approval of BAS 555 01 F in Europe the bystander and resident risk assessment presented has been based according to the EU requirements on the following model:

- Martin S. et al. (2008) Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application. J. Verbr. Lebensm. for the bystander and resident.

A summary of the bystander risk assessment is provided in **Table B.6.4.2.1-1**.

Table B.6.4.2.1-1: Estimated bystander exposure to metconazole and % of the AOEL

	Active Substance	
	metconazole	
	AOEL = 0.01 mg/kg bw/day	
	Adults	**Children**
Estimations according to German bystander model		
Systemic exposure via dermal route (mg/kg bw/day)	0.0001	0.0001
Systemic exposure via inhalation (mg/kg bw/day)	0.000001	0.000002
Total systemic exposure (mg/kg bw/day)	**0.0001**	**0.0001**
% of AOEL	**1.2%**	**1.0%**

A summary of the risk assessment for residents is provided in Table B.6.4.2.1-2.

Table B.6.4.2.1-2: Estimated resident exposure to metconazole and % of the AOEL

	Active Substance	
	metconazole	
	AOEL = 0.01 mg/kg bw/day	
	Adults	**Children**
Estimations according to German model for bystander and resident exposure assessment.		
Systemic exposure via dermal route (mg/kg bw/day)	0.00001	0.00002
Systemic exposure via inhalation (mg/kg bw/day)	0	0
Systemic exposure via oral route (mg/kg bw/day)		0.00001
Total systemic exposure (mg/kg bw/day)	**0.00001**	**0.00003**
% of AOEL	**0.15%**	**0.3%**

Conclusion

It is concluded that there is no undue risk to any bystander or residents after accidental exposure to BAS 555 01 F. This has no labelling implications.

B.6.4.2.2 Assessment according to the EFSA guidance model

As discussed above the EFSA model for bystander and residents is currently not in the status to be fully applied thus, no calculations according to this approach were provided.

B.6.4.2.3 Estimation of bystander and resident exposure

Bystanders and residents are not involved in application or handling of plant protection products or the professional handling of treated crops. Therefore, exposure scenarios differs significantly from operator exposure.

1. Assessment according to the models in place at time of submission

The exposure assessment presented in the following is based on:

– the German guidance paper for evaluation of bystander and resident exposure (Martin S. et al. (2008)) for bystander and residents.

A. Bystander exposure

The presence of bystanders is incidental within or directly adjacent to an area where plant protection products are applied. A situation in which bystander exposure could occur would be a person walking alongside an area being treated at the same time. Under these conditions the bystander would never walk directly next to the outer spraying nozzle. A distance of some meters from the spraying device can always be expected. It can further be assumed that any bystander, as soon as becoming aware of an exposure will leave the spraying area. Therefore, bystander exposure is of short duration, typically a matter of minutes. Thus, an exposure duration of 5 minutes is assumed.

Bystander exposure results from spray drift that deposits on the body surface or passes the breathing zone. Assuming that bystanders wear only light clothing (i.e., short-sleeved shirt and shorts), the exposed, uncovered body surface of an adult (head, face, neck front and back, forearms, half upper arms, hands, lower half of thighs, lower legs and feet) amounting to about 1 m². For children the exposed body surface with the same level of clothing amounts to 0.21 m²

For the professional use scenario it is assumed that the bystander is located at a distance of 10 m, downwind from the spraying source. The extent of spray drift and the consequent deposition depends on the plant protection product application rate, the particular crop being treated and the method of application. Measurements of spray drift following different crop/equipment combinations are available from Rautmann D. et al. (2001) New basic drift values in the authorisation procedure for plant protection products. In: Forster, B. and Streloke, M. (eds.) Workshop on Risk Assessment and Risk Mitigation Measures (WORMM). 27–29 September 1999, Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, booklet 383, 2001; actual version of 27th March 2006: Rautmann, D. (2006); http://www.jki.bund.de/no_cache/de/startseite/institute/anwendungstechnik/abdrift-eckwerte.html.

Thus, for the corresponding application scenario in strawberries, lettuce in field, the proposed drift value at 10 m distance of 0.29% (90th percentile value) is used for estimations of dermal exposure. However, the drift deposition data by Rautmann D. et al. (2001) cannot easily be transposed into airborne concentrations and consequent inhalation exposure values.

Therefore, to ensure a conservative evaluation, measured inhalation exposure data for the unprotected operator during spray applications (Lundehn J.R. et al. (1992), German BBA model) are used for the bystander inhalation exposure estimation.

The parameters used for bystander exposure calculations are summarized in Table 7.2.2.1-1.

Table B.6.4.2.3.1-1: Parameters used for bystander exposure calculations

	Parameter	metconazole	
AR	Maximum application rate (kg a.i./ha)	0.09	
ar	Maximum application rate (mg a.i./m²)	9.0	
DA	Dermal absorption	28%	
IA	Inhalation absorption	100%	
		Default values	
D	Drift at 10 meter distance for field crop (% of application rate)	0.29	
TB	Exposure duration bystander (minutes)	5	
TO	Exposure duration operator (hours)	6	
TF	Exposure duration factor (TB / TO) 1	0.0139	
A	Area treated (ha/day)	50	
		Adult	Child
BSA	Exposed body surface (m²)	1	0.21
IA	Specific inhalation exposure (mg a.i./kg a.i. handled) [2]	0.001	0.00057
BW	Bystander body weight (kg)	60	16.15

[1] Since the German model values based on an application period of 6 hours/day, adjustment to 5 minutes is required for exposure calculations.

[2] Based on geometric mean values proposed by the German BBA Model (Lundehn at al, 1992) and inhalation rates of 1.74 m³/h and 1.0 m³/h for adults and children.

Bystander exposure for adults and children is estimated according the following equations:

Systemic dermal exposure

$$SDE_B = \frac{ar \times D \times BSA \times DA}{BW}$$

Systemic inhalation exposure

$$SIE_B = \frac{I_A \times AR \times A \times TF \times IA}{BW}$$

Total systemic exposure

$$SE_B = SDE_B + SI_B$$

Assessment

For the exposure of a bystander passing by the field treated with BAS 555 01 F the systemic exposure to metconazole was assessed based on 5 minutes exposure applying generic spray drift deposits of 0.29% of the application rate at 10 meter distance and air borne spray concentrations of 0.001 mg/kg a.i./person for adults and 0.00057 mg/kg a.i. / person for children.
The result of the bystander exposure estimation is presented in the following Table 7.2.2.1-2. Details of the estimations are presented in the referenced appendices.

Table B.6.4.2.3.1-2: Summary of bystander exposure during application of BAS 555 01 F in field crop

	Active ingredient	Estimated bystander exposure1 (mg/kg bw/day)	% of AOEL[2]	Reference Appendix
adult	metconazole	0.00012	1.2%	7.2-6
child	metconazole	0.00010	1.0%	7.2-6

[1] According to the German model for bystander and resident exposure assessment; Martin S. et al. (2008)

[2] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole.

This estimates result for adults in 1.2% usage of the AOEL for metconazole. For children the estimates are 1.0% usage of the AOEL for metconazole. Thus, the exposure of adult bystanders passing by a field treated with BAS 555 01 F is considered to be safe.

In conclusion, bystanders are not considered to be at risk if exposed to spray drift of metconazole under the conditions of use for which the authorization of BAS 555 01 F is requested.

B. Resident exposure

Residents are persons who live, work or attend any institution adjacent to an area that has been treated with a plant protection product. Possible situations are persons who are standing, working, or sitting in a garden in the vicinity of the application. They may be exposed to the 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 substances. For infants and toddlers oral exposure via hand-to-mouth transfer or object-to-mouth transfer has to be considered, too.

As for the bystander it can be assumed that residents are unlikely to take actions to avoid or control exposure, and they wear only light clothing and no protective equipment. In addition, as conservative approach it is assumed that residents are located directly downwind of the centre of the treatment area from the point of spray emission for professional uses. The field crop application is here considered to represent the worst case scenario for which a distance of 10 m from the spraying device is taken into consideration. Considering that residents are dermally exposed to residue deposits it can be assumed that residues from more than one application are present. Thus as proposed by the German model for bystander and resident exposure assessment; Martin S. et al. (2008) the 82nd percentile drift value is used for a product that is applied twice per season. The corresponding drift value for wheat, cereals, oilseed rape is 0.24% at a distance of 10 meter. Furthermore taking into account a 50% decline from one application to the next the double application rate is applied as a worst case. It can be assumed that the exposure duration of residents being in a garden is longer than the exposure duration of bystanders. Therefore, a default exposure duration of 2 hours is adopted for risk evaluations. Inhalation exposure has only to be considered for semi-volatile (vapour pressures (VP) of 1 x 10-5 – 5 x 10^{-3} Pa) and volatile (> 5 x 10^{-3} Pa) active substances (see German model for bystander and resident exposure assessment). As metconazole has a vapour pressure of 2.1 x 10^{-08} see [EFSA Scientific Report (2006) 64, 1-71] it is considered non-volatile. Thus, no inhalative exposure is taken into account. For assessment of the oral exposure of children and toddlers in a first-tier approach the default values proposed by German model for bystander and resident exposure assessment; Martin S. et al. (2008) as derived from a US-EPA policy paper are used. Table 7.2.2.1-3 summarizes the parameters used for resident exposure of adults and children.

Table B.6.4.2.3.1-3: Parameters used for resident exposure estimations

	Parameter	metconazole	
	vapour Pressure (Pa)	2.10E-08	
	Volatility	non-volatile	
	Maximum application rate (kg a.i./ha)[1]	0.09	
	Maximum number of applications	2	
AR	Application rate relevant for resident (kg a.i./ha)	0.18	
Ar	Maximum application rate (mg a.i./cm²)	0.0018	
DA	Dermal absorption (%)	28%	
IA	Inhalation absorption (%)	100%	
OA	Oral absorption (%)	100%	
ACV	Airborne concentration of vapour (mg/m³) [2]	0	
		Default values	
D	Drift (%) at 10 m distance - 82nd percentile values[3] for field crop	0.24%	
H	Duration (hours)	2	
		Adult	Child
TTR	Turf transferable residues hand (%)	5%	5%
TC	Transfer coefficient (cm²/hour)	7300	2600
IR	Inhalation rate (m³/day)	16.57	8.31
SE	Salivation extraction factor (%)		50%
SA	Surface area of hands (cm²)		20
Freq	Frequency of hand-to-mouth events (events/hour)		20
DFR	Dislodgeable foliar residue object to mouth (%)		20%
IgR	Ingestion rate for mouthing of grass (cm²)		25
BW	Resident body weight (kg)	60	16.15

[1] As BAS 555 01 F will be applied twice per season at maximum, the double application rate is considered relevant for residential exposure according to German model for bystander and resident exposure assessment.

[2] Since metconazole is non-volatile i.e. a vapour pressure is below 1 x 10-5 the ACv value is 0 mg/m³.

[3] 90th percentile of drift recommended for one application, 82nd percentile of drift for double application rate recommended for more than one application according to Martin S. et al. (2008).

Resident exposure for adults and children is estimated according the following equations:

Systemic dermal exposure $$SDE_R = \frac{AR \times D \times TTR \times TC \times H \times DA}{BW}$$

respectively

Systemic inhalation exposure $$SIE_R = \frac{AC \times IR \times IA}{BW}$$

$$SIE_R = \frac{CAC \times IR \times IA}{BW}$$

Systemic exposure due to hand-to-mouth transfe only) $$SOE_H = \frac{AR \times D \times TTR \times SE \times SA \times F \times H \times OA}{BW}$$

Systemic exposure due to mouthing (children onl $$SOE_O = \frac{AR \times D \times DFR \times IgR \times OA}{BW}$$

Total systemic exposure (adults) $$SE_R = SDE_R + SIE_R$$

Total systemic exposure (children) $$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$$

The resulting predicted exposures are summarized below.

Assessment

For the exposure of a resident located next to a field treated with BAS 555 01 F the systemic exposure to metconazole was assessed based on 2 hour exposure to spray drifts via dermal and oral route. The results of the resident exposure calculations are summarized in Table 7.2.2.1-4 below. Details of the estimations are presented in the referenced appendix.

Table B.6.4.2.3.1-4: Summary of residential exposure during application of BAS 555 01 F in field crop

	Active ingredient	Route of exposure	Estimated residential exposure[1] (mg/kg bw/day)	AOEL covered[2]	Reference Appendix
German model[2]					
adult	metconazole	Vapour and surface deposits	0.000015	0.15%	**7.2-7**
child	metconazole		0.000026	0.3%	**7.2-7**

[1] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole.
[2] Based on German model for bystander and resident exposure assessment; Martin S. et al. (2008).

This estimates result for adults in 0.15% usage of the AOEL for metconazole. For children the estimates are 0.3% usage of the AOEL for metconazole. Thus, the exposure of adult and child residents living next to a field treated with BAS 555 01 F is considered to be safe.
In conclusion, residents are not at risk if exposed to spray drift of metconazole under the conditions of use for which the authorization of BAS 555 01 F is requested.

2. Assessment according to the EFSA guidance model

Note: The EU-commission has released a guidance note on May 29, 2015 [SANTE-10832-2015, see KCP 7.2.2.1/1 2015/1174492] acknowledging that: "*for the acute risk assessment for bystanders and residents, the derivation of the corresponding toxicological reference value (AAOEL) is still outstanding. Similarly, no higher tier risk assessment schemes are available for residents and bystanders scenarios. Both aspects are essential to be able to fully apply the guidance document for the approval of active substances under Regulation (EC) No 1107/2009."* In consequence the concluded that: *"For the approval of active substances under Regulation (EC) No 1107/2009, the risk assessment on residents and bystanders cannot be fully considered until a procedure for the derivation of the AAOEL and higher risk assessment schemes, identified as missing by the Standing Committee, are available."* Thus, no assessment according to the EFSA approach was provided.

B.6.4.2.4 Measurement of bystander and resident exposure

Since the risk assessment performed indicates that the health-based limit values (AOEL) will not be exceeded under practical conditions of use, studies to provide field data on bystander or residential exposure to BAS 555 01 F were not considered to be necessary and were thus not performed.

B.6.4.3. Worker exposure.

In order to evaluate re-entry worker exposure to BAS 555 01 F as part of the EU review of metconazole all relevant data and risk assessments are provided here and are considered adequate. Table 7.2.1-1 summarizes the GAPs evaluated for re-entry worker exposure assessment. Due to the in between time of submission with regard to exposure models to be considered the applicant decided to provide a full data package including both the models in place at time of submission as well as the recently published models of the EFSA Guidance on the Assessment of Exposure for Operators, Workers, Residents and Bystanders in Risk Assessment for Plant Protection Products [EFSA Journal 2014;12(10):3874 [55 pp.]. doi:10.2903/j.efsa.2014.3874; http://www.efsa.europa.eu/en/efsajournal/pub/3874.htm].

Risk assessment for worker

B.6.4.3.1 Assessment according to the models in place at time of submission

Estimations of potential worker exposure have been undertaken for BAS 555 01 F applying the intended use shown in chapter 7.2.1 and the following guidance for exposure prediction:

- Europoem - Re-entry exposure model final draft adopted by more specific US EPA agricultural transfer coefficients.

A summary of the worker risk assessment is provided in Table 6.4.3-1.

Table 6.4.3-1: Estimated worker exposure to metconazole in BAS 555 01 F

		Exposure parameter	
Active substance	**AOEL (mg/kg bw/day)**	**Absorbed dose (mg/kg bw/day)**	**% of AOEL**
Europoem draft model adopted with more specific transfer coefficient published by the US EPA			
		unprotected worker[1]	
metconazole	0.01	0.00554	55.4%

[1)] Worker wearing shoes, socks, long-sleeved shirt and long trousers

Conclusion

It is concluded that there is no unacceptable risk anticipated for the unprotected worker wearing adequate work clothing (but no PPE) when re-entering wheat, cereals, oilseed rape treated with BAS 555 01 F. As a standard rule, it should be mentioned on the label that treated fields should not be re-entered before spray deposits on leaf surfaces have completely dried.

B.6.4.3.2 Assessment according to the EFSA guidance model

Furthermore, in order to comply with the upcoming recommendations a risk assessment for re-entry worker according to the model of the EFSA guidance document [EFSA, 2014] is provided. The estimations are summarized in Table 6.4.3-2.

Table 6.4.3-2: Estimated worker exposure to metconazole in BAS 555 01 F

		Exposure parameter	
Active substance	**AOEL (mg/kg bw/day)**	**Absorbed dose (mg/kg bw/day)**	**% of AOEL**
EFSA Guidance Model			
		unprotected worker[1]	
metconazole	0.01	0.0061	60.8%

[1)] Worker wearing shoes, socks, long-sleeved shirt and long trousers

Conclusion

It is concluded that there is no unacceptable risk anticipated for the unprotected worker wearing adequate work clothing (but no PPE) when re-entering wheat, cereals, oilseed rape treated with BAS 555 01 F. As a standard rule, it should be mentioned on the label that treated fields should not be re-entered before spray deposits on leaf surfaces have completely dried.

1. Assessment according to the models in place at time of submission

BAS 555 01 F will be used as a fungicide during BBCH code stages wheat, cereals (30-69), oilseed rape (autumn 10-20, spring 21-71). Hand operations in these crops, which may result in re-entry exposure do not belong to standard growing procedures after the application of the product. Exposure scenarios one may think of as a worst case may be scouting and irrigation. These operations are considered to be of limited duration and of limited direct contact to the treated plants. For these operations a working period of 2 hours per day is considered a reasonable approach. BAS 555 01 F will be applied at maximum twice per season. Thus, the considered reasonable worst case of maximum applied amount of metconazole is 0.18 kg/ha taking into account a respective decline from one application to the next.

Exposure Estimation Models used

The exposure estimation of the re-entry worker presented below is based on the:

- Europoem - Re-entry exposure model final draft adopted by more specific US EPA agricultural transfer coefficients.

The default exposure assessment is based on the following assumptions:

- Re-entry exposure is predominantly via the dermal route (contact with the foliage)
- Residues on the foliage depend on:
  - application rate
  - the crop habitat [total size of foliage compared to surface area, Leaf Area Index (LAI)].
- Transfer of residues from the foliage to clothes or skin of workers is more or less independent of the product applied, but depend mainly on the intensity of contact with foliage (work activity).
- Activities with a similar pattern can be grouped and generic Transfer Coefficients (TC) can be used for one group.
- Based on the EUROPOEM proposal an Dislodgeable Foliar Residue (DFR) default value of 3 µg a.i./cm² is taken into account.

Farmers will only do consecutive treatments if the efficacy of the previous treatment is no longer sufficient. Low efficacy is mainly caused by a decline of residues. Therefore, accumulations of residues on plant surfaces after repeated applications will only occur to a small extend depending on the degree of decline. Where no DFR or residue data are available it may be assumed that residues will decline by 50% from the total deposit of the previous application. Consequently, the double application rate is taken into account as a worst case default for exposure considerations directly after the 2nd application. It is reasonably presumed that workers re-enter the treated crop after the spray has dried.

Taking into account up to 2 consecutive applications the worst case maximum application rate for metconazole is 0.18 kg/ha based on default DFR values.

Within the EU, there are no commonly accepted specific transfer coefficients (TC) available to assess scouting and irrigation activities in wheat, cereals, oilseed rape, . Following the US EPA agricultural transfer coefficients a TC of 1100 cm²/hour based on ARTF data cluster SSs from ARF009 in sweet corn and ARF021 in dry beans/peas is recommended which will therefore be used.

In the following Table 6.4.3-3 the parameters used in the re-entry worker risk assessment are presented.

Table 6.4.3-3: Parameters used for the worker risk assessment

	Parameter	**metconazole**	
MR	Application rate considered for default worker exposure	0.18	kg a.i./ha
DF	Dermal absorption:[1]	28%	
DFR	Default dislodgeable foliar residue:	3	µg/cm² x kg a.i. applied
		Default values	
BW	Re-entry worker body weight	60	kg
TC	Transfer coefficient[2]:	1,100	cm²/h x person
A	Working period:	2	h/day
TR	Transmission to skin for unprotected worker:	1.00	(factor, equal to 100%)

[1] The given values for dermal absorption of metconazole represent the estimates for spray dilutes. Exposure during re-entry occurs to dry residues for which it is adequate to expect a very low dermal absorption. Therefore, it is considered to be a conservative approach to use the dermal absorption values determined for the liquid spray dilutes.
[2] A TC of 1100 cm²/h x person was used [according to US EPA agricultural transfer coefficients] for activities like scouting and irrigation in wheat, cereals, oilseed rape based on recommendations for ARTF data cluster SSs from ARF009 in sweet corn and ARF021 in dry beans/peas.

Based on the assumptions and consideration made above, worker exposure is calculated as follows:

External dermal exposure ED_W

$$ED_W = MR \times A \times DFR \times TC \times TR$$

Total systemic exposure SE_W

$$SE_W = \frac{ED_W}{BW} \times DF$$

Estimation of worker exposure without personal protective equipment

The results of the re-entry worker risk assessment without PPE is presented in Table 6.4.3-4 below, details are given in the referenced appendices.

Table 6.4.3-4: Summary of re-entry workers exposure following application of BAS 555 01 F without protective equipment (standard assessment)

	Active ingredient	Estimated worker exposure (mg/kg bw/day)	AOEL covered[1]	Reference Appendix
Europoem draft model adopted with more specific transfer coefficient published by the US EPA				
2 hour/day scouting and irrigation in wheat, cereals, oilseed rape,	metconazole	0.00554	55.4%	**7.2-8**

[1] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole.

Based on the proposed exposure estimation, the maximum coverage of the metconazole AOEL was 47.1%. Thus, even under the worst-case assumption that workers are performing post-treatment activities (cereals, corn: scouting and irrigation) without gloves or protective clothing for 2 hours, the estimated worker exposure levels for metconazole is within the acceptable range.

It can be concluded that there is no unacceptable risk anticipated for the unprotected re-entry worker within the intended use of BAS 555 01 F.

2. Assessment according to the EFSA guidance model

The EFSA approach considers principally exposure via the dermal as well as via the inhalative route.

- Dermal exposure results from contact to the crop canopy and is considered as the most important route of exposure in line with the above Europoem approach
- Inhalation exposure is considered to result from vapour and/or airborne aerosols (including dusts). This route of exposure is considered relevant for indoor application but not for the in here evaluated outdoor application
- The estimation approach is similar to the Europoem approach
- For repeated application a multiple application factor is included
- The task specific TC considered applicable is derived for a worker entering the treated field wearing long-legged trouser and long-sleeved shirt but conducting the inspection tasks with bare hands.

For the standard assessment the following parameters are taken into account:

Table 6.4.3-5: Parameters used for the worker risk assessment according to EFSA guidance model (wheat, cereals, oilseed rape)

	Parameter	metconazole		
d_BwAdult	Re-entry worker body weight		60	kg
d_WorkHr	Working period:		2	h/day
Outdoor, field crop, inspection and irrigation				
i_AppRate	Application rate for active substance		0.09	kg a.i./ha
i_AbsorpInuse	Dermal absorption of the in-use dilution:		28%	
i_DFR	Initial dislodgeable foliar residue:	standard	3	µg/cm² x kg a.i. applied
d_DFR	Default dislodgeable foliar residue:	standard	0.27	µg a.i. /cm²
i_AppNo	Number of applications		2	
i_AppInt	Interval between multiple applications		14	days
d_HalflifeAS	Default: Half-life of active substance	standard	30	days
d_MAF	Multiple application factor	standard	1.7	
d_DermTcCV1	Dermal transfer coefficient - arms, body and legs covered		1400	cm²/h x person
d_DermTcCV2	Dermal transfer coefficient - hands, arms, body and legs covered		Not available	cm²/h x person

[1] The given values for dermal absorption of metconazole represent the estimates for spray dilutes. According to the EFSA approach the higher of the 2 values for undiluted product and in use dilution has to be chosen for the estimation of dermal absorption from dry residues which is considered to be a conservative approach.

Exposure is estimated according to the following formula

EFSA guidance re-entry worker model

ED_W: External exposure dermal workwear - Arms, body and legs covered	*d_DermTcCV1 * d_WorkHr * d_DFR * d_MAF / 1000*
SE: Total systemic exposure	*ED *MAX(i_AbsorpProduct;i_AbsorpInuse) / d_BwAdult*

Estimations

The results of the re-entry worker risk assessment without PPE and standard parameters is presented in Table 6.4.3-7 below, details are given in the referenced appendices.

Table 6.4.3-7: Summary of re-entry workers exposure following application of BAS 555 01 F without protective equipment according to EFSA guidance model (standard model)

	Active ingredient	Estimated worker exposure[1] (mg/kg bw/day)	AOEL covered[2]	Reference Appendix
Outdoor, field crop (wheat, cereals, oilseed rape,), scouting and irrigation				
2 hour/day scouting and irrigation	metconazole	0.00681	60.81%	**7.2-5**

[1] For a worker wearing long-sleeved and long-armed working clothing but no PPE

[2] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole.

Based on the proposed exposure estimation, the maximum coverage of the metconazole AOEL was 60.81% for the outdoor application of BAS 555 01 F in wheat, cereals, oilseed rape.

It can be concluded that there is no unacceptable risk anticipated for the unprotected re-entry worker within the intended use of BAS 555 01 F.

Estimation of worker exposure applying personal protective equipment

Exposure estimations assuming that only adequate work clothing and no PPE is worn showed that the exposure of workers is well below acceptable levels. Thus, exposure estimations with PPE taken into account are considered not necessary and were therefore not performed.

B.6.4.3.3 Measurement of worker exposure

Since the risk assessment performed indicates that the health-based limit value (AOEL) will not be exceeded under practical conditions of use, studies to provide field data on worker exposure to BAS 555 01 F were not considered to be necessary and were thus not performed.

B.6.5. SUMMARY OF EXPOSURE ASSESSMENT

Summary - Operator exposure

Application method Crop	Model	PPE	Active ingredient	Total systemic exposure[1] (mg/kg bw/day)[2]	AOEL covered[3]
Tractor mounted boom sprayer application wheat, cereals, oilseed rape	BBA	gloves during M/L and gloves and coverall and sturdy footwear during Appl.	metconazole	0.0011	**11%**
	UK POEM	gloves during M/L and gloves during Appl.	metconazole	0.0262	262%
	AOEM	NO PPE	metconazole	0.0224	224%
	AOEM	protective gloves, workwear + sturdy footwear, during mixing loading and protective gloves, workwear + sturdy footwear, during application	metconazole	0.001	**9.9%**

[1] Systemic exposure based on dermal absorption of 4% for mixing/loading and 28% for application for metconazole.
[2] Body weight 70 kg/person in German model and 60 kg/person in UK POEM and in AOEM
[3] Total systemic exposure x 100 / systemic AOEL systemic AOEL for metconazole = 0.01 mg/kg bw/day

Summary - Bystander and resident exposure

Model		Active ingredient	Route of exposure	Estimated bystander exposure[1] (mg/kg bw/day)	AOEL covered[2]
German model	Bystander (adults)	Metconazole		0.00012	**1.2%**
	Bystander (children)	Metconazole		0.00010	**1.0%**
German model	Resident (adults)	Metconazole	Vapour and surface deposits	0.000015	**0.15%**
	Resident (children)	Metconazole		0.000026	**0.3%**

[1] According to the German model for bystander and resident exposure assessment; Martin S. et al. (2008)
[2] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole

Summary – Worker exposure

Model			Exposure parameter	
	Active substance	**AOEL (mg/kg bw/day)**	**Absorbed dose (mg/kg bw/day)**	**AOEL covered[2]**
Europoem draft model adopted with more specific transfer coefficient published by the US EPA			Unprotected worker[1]	
	metconazole	0.01	0.00554	**55.4%**
EFSA Guidance Model			Unprotected worker[1]	
	metconazole	0.01	0.0061	**60.8%**

[1] Worker wearing shoes, socks, long-sleeved shirt and long trousers
[2] Based on a systemic AOEL of 0.01 mg/kg bw/day for metconazole

Appendices to section B.6.4

Appendix 7.2-1: Metconazole: BBA model estimations for tractor mounted boom sprayer application without PPE

Product:	BAS 555 01 F		**Formulation type:**	EC			
Active ingredient:	Metconazole		**Concentration:**	90.0	g/L		
AOELsys:	0.01	mg/kg bw/day	**Assessment factor:**	400			
Maximum Rate:	0.090	kg a.i. per ha	**Area treated per day:**	20	ha		
Amount of a.i. handled / day:	1.80	kg a.i. per day	**Dermal absorption (M/L):**	4%			
Application technique	tractor-mounted boom sprayers with hydraulic nozzles, field crop		**Dermal absorption (Spray):**	28%			
Personal protective equipment:	None						

$D_{M(H)}$ =	2.4	mg / person x kg a.i.	x	1.8	x	100%	=	4.3200	mg / person / day
$D_{A(H)}$ =	0.38	mg / person x kg a.i.	x	1.8	x	100%	=	0.6840	mg / person / day
$D_{A(B)}$ =	1.6	mg / person x kg a.i.	x	1.8	x	100%	=	2.8800	mg / person / day
$D_{A(C)}$ =	0.06	mg / person x kg a.i.	x	1.8	x	100%	=	0.1080	mg / person / day
I_M =	0.0006	mg / person x kg a.i.	x	1.8	x	100%	=	0.00108	mg / person / day
I_A =	0.001	mg / person x kg a.i.	x	1.8	x	100%	=	0.0018	mg / person / day

				External exposure		Abs. factor		Systemic exposure	
Inhalation	mix/load	I_M	=	0.0011	x	100%	=	0.00108	mg / person / day
	spray	I_A	=	0.0018	x	100%	=	0.0018	mg / person / day
Dermal	mix/load	D_M	=	4 3200	x	4%	=	0.1728	mg / person / day
	spray	D_A	=	3.6720	x	28%	=	1.0282	mg / person / day

Total exposure (assuming person weighing 70 kg):	=	**1.20**	**mg / person / day**
Total exposure (mg/kg bw/day):	=	**0.02**	**mg/kg bw/day**
Total exposure (% AOEL):	=	**200%**	

Appendix 7.2-2: Metconazole: UK POEM model estimations for tractor mounted boom sprayer application without PPE

Appendix 7.2-2: Metconazole: UK POEM estimations for tractor mounted boom sprayer application without PPE

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**BAS 555 01 F**	Active ingredient	**Metconazole**
Formulation type	water-based	a.i. concentration	**90.0** mg/ml
Dermal absorption from product	**4** %	Dermal absorption from spray	**28.0** %
Container	10 litres 63 mm closure		
PPE during mix/loading	None	PPE during application	None
Dose	**1** l/ha	Work rate/day	**50** ha
Application volume	**110** litres spray/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1	litres product/ha
Work rate	50	ha/day
Number of operations	5	per day
Hand contamination	0.25	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.25	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	110	litres spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mixing/loading		Spray application	
Dermal exposure	0.25	ml/day	41.55	ml/day
Concen. of a.i. in product or spray	90	mg/ml	0.818181818	mg/ml
Dermal exposure to a.i.	22.5	mg/day	33.99545455	mg/day
Percent absorbed	4	%	28	%
Absorbed dose	**0.9000**	**mg/day**	**9.519**	**mg/day**

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.i. in spray	0.818181818	mg/ml
Inhalation exposure to a.i.	0.049090909	mg/day
Percent absorbed	100	%
Absorbed dose	**0.049090909**	**mg/day**

PREDICTED EXPOSURE

Total absorbed dose	10.47	mg/day
Operator body weight	60	kg
Operator exposure	0.175	mg/kg bw/day
Total exposure (% AOEL)	**1745%**	

Appendix 7.2-3: Metconazole: BBA model estimations for tractor mounted boom sprayer application with PPE during mixing/loading and application

Product:	BAS 555 01 F		**Formulation type:**	EC	
Active ingredient:	Metconazole		**Concentration:**	90.0	g/L
AOELsys:	0.01	mg/kg bw/day	**Assessment factor:**	400	
Maximum Rate:	0.090	kg a.i. per ha	**Area treated per day:**	20	ha
Amount of a.i. handled / day:	1.80	kg a.i. per day	**Dermal absorption (M/L):**	4%	
Application technique	tractor-mounted boom sprayers with hydraulic nozzles, field crop		**Dermal absorption (Spray):**	28%	
Personal protective equipment:	gloves during mixing/loading and gloves and coverall and sturdy footwear during application				

$D_{M(H)}$ =	2.4	mg / person x kg a.i.	x	1.8	x	1%	=	0.0432 mg / person / day
$D_{A(H)}$ =	0.38	mg / person x kg a.i.	x	1.8	x	1%	=	0.00684 mg / person / day
$D_{A(B)}$ =	1.6	mg / person x kg a.i.	x	1.8	x	5%	=	0.144 mg / person / day
$D_{A(C)}$ =	0.06	mg / person x kg a.i.	x	1.8	x	100%	=	0.108 mg / person / day
I_M =	0.0006	mg / person x kg a.i.	x	1.8	x	100%	=	0.00108 mg / person / day
I_A =	0.001	mg / person x kg a.i.	x	1.8	x	100%	=	0.0018 mg / person / day

				External exposure		Abs. factor		Systemic exposure	
Inhalation	mix/load	I_M	=	0.0011	x	100%	=	0.00108	mg / person / day
	spray	I_A	=	0.0018	x	100%	=	0.0018	mg / person / day
Dermal	mix/load	D_M	=	0.0432	x	4%	=	0.001728	mg / person / day
	spray	D_A	=	0.2588	x	28%	=	0.0724752	mg / person / day

Total exposure (assuming person weighing 70 kg):	=	**0.077**	**mg / person / day**
Total exposure (mg/kg bw/day):	=	**0.001**	**mg/kg bw/day**
Total exposure (% AOEL):	=	**11.0%**	

Appendix 7.2-4: Metconazole: UK POEM estimations for tractor mounted boom sprayer application with PPE during mixing/loading and application

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**BAS 555 01 F**	Active ingredient	**Metconazole**
Formulation type	water-based	a.i. concentration	**90.0** mg/ml
Dermal absorption from product	**4** %	Dermal absorption from spray	**28.0** %
Container	10 litres 63 mm closure		
PPE during mix/loading	gloves	PPE during application	gloves
Dose	**1** l/ha	Work rate/day	**50** ha
Application volume	**110** litres spray/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1	litres product/ha
Work rate	50	ha/day
Number of operations	5	per day
Hand contamination	0.25	ml/day
Protective clothing	gloves	
Transmission to skin	5	%
Dermal exposure to formulation	0.0125	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	110	litres spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	gloves	Permeable	Permeable	
Penetration	10%	5%	15%	
Dermal exposure	0.65	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	6.45	ml/day		

ABSORBED DERMAL DOSE

	Mixing/loading		Spray application	
Dermal exposure	0.0125	ml/day	6.45	ml/day
Concen. of a.i. in product or spray	90	mg/ml	0.818181818	mg/ml
Dermal exposure to a.i.	1.125	mg/day	5.277272727	mg/day
Percent absorbed	4	%	28	%
Absorbed dose	**0.045**	**mg/day**	**1.477636364**	**mg/day**

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.i. in spray	0.818181818	mg/ml
Inhalation exposure to a.i.	0.049090909	mg/day
Percent absorbed	100	%
Absorbed dose	**0.0491**	**mg/day**

PREDICTED EXPOSURE

Total absorbed dose	1.57	mg/day
Operator body weight	60	kg
Operator exposure	0.0262	mg/kg bw/day
Total exposure (% AOEL)	**262.0%**	

Appendix 7.2-5: Metconazole: EFSA Guidance model estimations for tractor mounted boom sprayer application during mixing/loading and application

Substance name	Metconazole	
Product name	BAS 555 01 F	
Reference value non acutely toxic active substance (RVNAS)	0.01	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)	0.01	mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	110	L/ha
Maximum application rate of active substance	0.09	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	4.00%	
Dermal absorption of in-use dilution	28.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	2	
Interval between multiple applications	14	days
Season (upward spraying orchards only)	not relevant	

Substance	Metconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.09 kg a s. /ha	Spray dilution = 0.6 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 4	Dermal for in use diluation = 28	Oral = 100	Inhalation = 100	
RVNAS	0 01 mg/kg bw/day		RVAAS	0 01 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0224	% of RVNAS	223.80%
	Acute systemic exposure mg/kg bw/day		0.1697	% of RVAAS	1696 89%
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0010	% of RVNAS	9 88%
	Acute systemic exposure mg/kg bw/day		0.0356	% of RVAAS	356.17%

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0543	% of RVNAS	542.94%
	Working clothing mg/kg bw/day	0.0061	% of RVNAS	60.81%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Appendix 7.2-6: Estimated exposure and risk assessment for bystanders exposed to metconazole during the product application of BAS 555 01 F

Product:	BAS 555 01 F		**Active ingredient:**	metconazole	
Crop:	field crop		**AOELsys:**	0.01	mg/kg bw/day
Max. application rate (AR):	0.090 kg/ha		**Dermal absorption spray (DA):**	28%	
Max. application rate (ar):	9.0 mg a.i./m²				
			Inhalation absorption (IA):	100%	
Area treated (A):	50 ha				
Drift deposition at 10-m distance (D):	0.29	% of application rate			
Exposure duration operator during spraying (TO):	6 h				
Exposure duration bystander (TB):	5 min				
Exposure duration factor (TF = TB / TO):	0.014				

		Adults	**Children**
Exposed body surface area (BSA):		1 m²	0.21 m²
Specific inhalation exposure operator (IA*):		0.001 mg/kg a.i.	0.00057 mg/kg a.i
Breathing rate (BR):		1.74 m³/h	1 m³/h
Body weight:		60 kg	16.15 kg
		mg / person / day	mg / person / day
External exposure of bystanders via the dermal route			
ar x D x BSA	=	0.03	0.01
External exposure of bystanders via the inhalative route			
IA* x AR x A x TF	=	0.00006	0.00004
		mg / kg bw / day	mg / kg bw / day
Systemic exposure via the dermal route (SDE_B)			
(ar x D x BSA x DA) / BW	=	0.0001	0.0001
Systemic exposure via the inhalation route (SIE_B)			
(IA* x AR x A x TF x IA) / BW	=	0.000001	0.000002
Total systemic exposure (SE_R)		**Adults**	**Children**
		mg / kg bw / day	mg / kg bw / day
$= SDE_B + SIE_B$	=	0.000	0.000
% AOEL	=	**1.2%**	**1.0%**

According to the German model for bystander and resident exposure assessment; Martin S. et al. (2008)

Appendix 7.2-7: Estimated exposure and risk assessment for adult residents exposed to metconazole during the product application of BAS 555 01 F

Product:	BAS 555 01 F	**Active ingredient:**	metconazole
Crop:	field crop	**AOELsys:**	0.01 mg/kg bw/day
Applications per season:	2		
Max. application rate (x2):	0.18 kg a.i./ha	**Oral absorption (OA):**	100%
Max. application rate (Ar):	0.0018 mg a.i./cm²	**Dermal absorption spray (DA):**	28%
Drift deposition at 10-m distance (D):		**Inhalation absorption (IA):**	100%
0.24%	(82nd percentile)	**Vapour pressure:**	2.10E-08 Pa
Dislodgeable foliar residue (DFR):	20%	**Volatility of metconazole:**	non-volatile
Turf Transferable Residues (TTR):	5%	**Airborne vapour conc. (ACv):**	0 mg/m³

		Adults	Children
Duration of exposure			
- dermal (H):		2 h	2 h
- inhalation:		0 h	0 h
- mouthing (H):		----	2 h
Transfer Coefficient (TC):		7300 cm²/h	2600 cm²/h
Body weight (BW):		60 kg bw	16 kg bw
Inhalation rate (IR):		16.6 m³/day	8.3 m³/day
Saliva extraction factor (SE):		----	50%
Hand surface area (SA):		----	20 cm²
Hand-to-mouth frequency (Freq):		----	20 events/h
Ingestion rate for mouthing of grass/day (IgR):		----	25 cm²
		mg / person / day	mg / person / day
External exposure of residents via the dermal route			
Ar x D x TTR x TC x H	=	0.003	0.001
External exposure of residents via the inhalative route			
ACv x IR (a.i. is considered non-volatile)	=		
Exposure via hand to mouth route			
Ar x D x TTR x SE x SA x Freq x H	=	----	0.0001
Exposure via object to mouth route			
Ar x D x DFR x IgR	=	----	0.0000
		mg / kg bw / day	mg / kg bw / day
Systemic exposure via the dermal route (SDE_R)			
(Ar x D x TTR x TC x H x DA) / BW	=	0.00001	0.00002
Systemic exposure via the inhalation route (SIER)			
(ACv x IR x IA) / BW	=		
Systemic exposure via hand-to-mouth (SOE_H)			
(Ar x D x TTR x SE x SA x Freq x H x OA) / BW	=	----	0.000005
Systemic exposure via object-to-mouth (SOE_O)			
(Ar x D x DFR x IgR x OA) / BW	=	----	0.000001
Total systemic exposure (SE_R)		**Adults** mg / kg bw / day	**Children** mg / kg bw / day
= SDER + SIER	=	0.000015	----
= SDER + SIER + SOEH + SOEO	=	----	0.000026
% AOEL	=	0.15%	0.26%

According to the German model for bystander and resident exposure assessment; Martin S. et al. (2008).

Appendix 7.2-8: Estimated exposure and risk assessment for an unprotected worker exposed to metconazole from the product BAS 555 01 F (standard assessment)

Product:	BAS 555 01 F	**Active ingredient:**		metconazole	
Maximum application rate (MR):	0 180 kg a i per ha	**AOELsys:**		0 01	mg/kg bw/day
Crop:	wheat, cereals, oilseed rape	**Assessment factor:**		400	
Growth stage BBCH:	wheat, cereals (30-69), oilseed rape (autumn 10-20, spring 21-71)	**Dermal absorption (DF):**		28%	
Activity:	cereals, corn: scouting and irrigation	**Working duration (A):**		2	hours/day
		Worker bodyweight:		60	kg
Dislodgeable Foliar Residue (DFR):	0 003 mg/cm²	**Transfer coefficient (TC):**		1,100	cm²/hour
Protective clothing:	None	**Transmission to skin (TR):**		100%	
Dermal exposure (mg/person/d):		MR x A x DFR x TC x TR	=	1 188	mg/person/day
Systemic exposure (mg/person/d):		MR x A x DFR x TC x TR x DF	=	0 333	mg/person/day
Total systemic exposure (assuming person of 60 kg):				**0.00554 4**	**mg/kg bw/day**
Total exposure (% AOEL):				**55.4%**	

Based on the Europoem - Re-entry exposure model final draft adopted by more specific US EPA agricultural transfer coefficients.

B.6.6. REFERENCES RELIED ON:

Section 7: Toxicological studies on the plant protection product

Author(s)	Data Point	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
[redacted]	KCP 7.1.6/1	1998	Dermal sensitization study with AC 900768 90 g/L SL (RLF 12307) in guinea pigs - BUEHLER method (nine inductions) MK-460-026 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.4/1	1997	Primary dermal irritation study with AC 900768 90 g/L SL formulation (RLF 12307) MK-460-018 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.5/1	1997	Primary eye irritation study with AC 900768 90 g/L SL formulation (RLF 12307) MK-460-019 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.1/1	1997	Oral LD50 study in albino rats with AC 900768 90 g/L SL (RLF 12307) MK-460-016 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.2/1	1997	Dermal LD50 study in albino rats with AC 900768 90 g/L SL (RLF 12307) MK-460-017 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.6/2		BAS 555 01 F - Skin sensitisation: Local lymph node assay 2014/1035857 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No
Fabian E. Landsiedel R	KCP 7.3/1	2011	14C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin in vitro 2011/1140832 BASF SE,	No	Yes	New data for AIR3 renewal	BASF	No

Author(s)	Data Point	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
			Ludwigshafen/Rhein, Germany Fed.Rep. yes Unpublished					
Fabian E., Landsiedel R	KCP 7.3/2	2015	14C-BAS 555 F in BAS 555 01 F - Study of penetration through human skin in vitro 2014/1035858 BASF SE, Ludwigshafen/Rhein, Germany Fed.Rep. yes Unpublished	No	Yes	New data for AIR3 renewal	BASF	No
[redacted]	KCP 7.1.3/1	2014	BAS 555 01 F: 4 hour acute inhalation toxicity study in the rat 2014/1035856 [redacted] yes Unpublished	Yes	Yes	New data for AIR3 renewal	BASF	No