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Fenoxaprop-P-ethyl

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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

The Product PUMA S 69 EW with specification no 102000011507 is an oil in water emulsion which contains 69 g/L fenoxaprop-P-ethyl (substance code AE F046360, old code Hoe 046360) and 75 g/L mefenpyr-diethyl diethyl (substance code AE F107892, old code Hoe 107892).

Old studies that were submitted during the first approval were performed with PUMA S 69 EW. A newly submitted skin sensitisation study in rats was submitted for the renewal of this dossier. All data are summarized in the table below (new submission marked blue).

Summary of acute toxicity data obtained with PUMA S 69 EW

Study [Reference]	Species (sex)	Results	Classification (Regulation (EC) 1272/2008)
Acute oral [redacted] 1993b A51244, CP 7.1.1/01	Rat (male & female)	LD_{50} male > 5000 mg/kg bw female > 4000 mg/kg bw	None
Acute dermal [redacted] 1993 A51088 CP 7.1.2/01	Rat (male & female)	LD_{50} > 4000 mg/kg bw	None
Acute inhalation [redacted] 1993 A51050 CP 7.1.3/01	Rat (male & female)	LC_{50} > 10.74 mg/L Max. attainable conc.	None
Acute skin irritation [redacted] 1993 A51087 CP 7.1.4/01	Rabbit (female)	Slightly irritating	None
Acute eye irritation [redacted] 1993 A50455 CP 7.1.5/01	Rabbit (female)	Slightly irritating Not classified	None
Skin sensitization (Buehler method) [redacted] 1993 A51451 CP 7.1.6/01	Guinea Pig (male)	Not sensitising	None
Skin sensitization (Buehler method) [redacted] 2002 C021468 CP 7.1.6/02	Guinea Pig (male)	Slight reaction (10 %) (no classification)	None
Skin sensitization test, (LLNA) [redacted]; 2006 SA 06100 CP 7.1.6/03	Mouse (female)	Sensitising	**Skin Sens. Cat. 1** **H317 May cause an allergic skin reaction**

According to these information, the classification in accordance with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, is amended as **Skin Sens. Cat. 1 (H317 May cause an allergic skin reaction.)**

B.6.1.1. Oral

The acute oral toxicity of the formulation has been evaluated at EU level in the dossier for Annex I inclusion of fenoxaprop-P ethyl.

Reference:	**Acute oral toxicity in the male and female Wistar rat Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702**
Author(s). year:	[redacted] **1993b**
Report/Doc. number:	A51244 / Hoechst Report No. 93.0496
Guideline(s):	EPA Guideline 81-1 (revised 1984); OECD guideline 401 (adopted 1987); MAFF (1985)
Deviations:	None.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
5 Wistar rats per sex and dose received single doses of 2000, 3150, 4000 or 5000 mg/kg bw of Fenoxaprop-P-ethyl by oral gavage. The test substance was an oil in water emulsion of 69 g Fenoxaprop-P-ethyl per liter The emulsion was emulsified in deionized water and applied in a volume of 10 mL/kg bw to the rats.

Test material: Code AE F046360 24 EW14 A702, batch N°C0133 M020
Content: 7.0% AE F046360 and 7.2% AE F107892 (% w/w) (AZ-No. 05272)

Test animals: Rats, WISKf(SPF71), source: [redacted]
♂ 6 weeks old, mean bw of 191g; ♀ 7 weeks old, mean bw of 171g
Number of animals: 5 rats per sex per dose

During the 15 day observation period the animals were weighed weekly. Lethally intoxicated animals were dissected and examined macroscopically. At the end of the observation period the surviving animals were sacrificed and dissected and also examined for macroscopically visible changes.

Testing Laboratory and Dates: [redacted]
5 April 1993-16 April 1993

Findings:
Clinical signs and mortality: Details are shown in Table 6.1.1-1.
No animal died in the 2000 mg/kg dose group. The mortality rates were 2/5 for males and females at 3150 mg/kg, 0/5 for males and 1/5 for females at 4000 mg/kg, and 0/5 for males and 3/5 for females at 5000 mg/kg. All deaths occurred between 1 and 2 days after treatment. Clinical signs of intoxication were largely the same for males and females. They began to emerge 10 minutes after administration and persisted in some cases up to day 6 of the study. Clinical signs such as irregular respiration, coat bristling, increased salivation, flanks drawn in, stilted gait and decreased spontaneous activity were observed in most animals. The other clinical signs occurred to a lesser extent: respiratory sounds, palpebral fissure narrow, lid margin blood encrusted, pupil dilated, increased lacrimation, diarrhoea, cold to touch, snout blood encrusted, reduced paw reflex to pinching and placing reaction, straddling hind limbs, stupor, mouth wiping movement, ataxic and uncoordinated gait, forward crawling and prone position.
There were no impairments of body weight gains.

Table 6.1.1-1 Summary of results for acute oral toxicity of AE F046360 EW14 A7

Dose [mg/kg bw]	Toxicological result [1/]	Time of death		Total deaths after 15 days	Mortality [%]	Number of animals with symptoms
		day 2	day 3			
Males						

2000	0/5			0/5	0	5/5
3150	2/5			2/5	40	5/5
4000	0/5	2		0/5	0	5/5
5000	0/5			0/5	0	5/5
Females						
2000	0/5			0/5	0	5/5
3150	2/5	1		2/5	40	5/5
4000	1/5	1	1	1/5	20	5/5
5000	3/5	3		3/5	60	5/5
LD_{50} (males and/or females): about 5000 mg/kg bw						

[1/] 1st number = number of dead animals / 2nd number = number of animals used

Pathology: Macroscopic examination of animals found dead during the study revealed the following abnormalities: stomach (full of clear or white yellow fluid or feed mash of full of gas, petechial haemorrhages), light or dark liver discolourations, intestinal tract full of reddish black mass (haemoccult positive), small intestine full of reddish mucous (haemoccult positive) or full of yellowish-white fluid, large intestine full of yellowish-white fluid, caecum full of hardenend feed mash, and general autolysis. The animals sacrificed at the end of the observation period were free of macroscopically visible changes.

Conclusion:
Fenoxaprop-P-ethyl, oil in water emulsion (suspended in distilled water) is of low acute toxicity in Wistar rats after oral administration. The LD_{50} was greater than 5,000 mg/kg for males and greater than 4,000 mg/kg for females. The exact LD_{50} could only be calculated by probit analysis for males and females together and without any confidence limits and showed to be 7,859 mg/kg.
According to Regulation (EC) 1272/2008 no classification is necessary.

B.6.1.2. Dermal

Reference:	**Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L. Testing for acute dermal toxicity in the male and female Wistar rat**
Author(s). year:	[redacted] **1993c**
Report/Doc. number:	A51088 / Hoechst Report No. 93.0410
Guideline(s):	EPA Guideline 81-2 (revised 1984), OECD Guideline 402 (adopted 1987), MAFF (1985)
Deviations:	None.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Groups of 5 Wistar rats/sex received a topical application of 4000 mg/kg bw Fenoxaprop-P-ethyl. The test substance was an oil in water emulsion of 69 g Fenoxaprop-P-ethyl per liter. The emulsion was administered undiluted (original form) on the dorsal region and was covered with a porous gauze and an aluminium foil which was held in place with an elastic plaster bandage. The volume for application was calculated on the basis of the density.

Test material: Code AE F046360 24 EW14 A702, batch N°C0133 M020
Content: 7.0% AE F046360 and 7.2% AE F107892 (% w/w) (AZ-No. 05272)

Test animals: Rats, WISKf(SPF71), source: [redacted]

♂ 6 weeks old, mean bw of 248g; ♀ 10 weeks old, mean bw of 213g
Number of animals: 5 rats per sex per dose

After a dermal exposure of 24 hours, the bandage was removed and the treated skin area washed with warm water. During the 15-day observation period the animals were weighed weekly. At the end of the observation period the animals were sacrificed and examined for macroscopically visible changes.

Testing Laboratory and Dates: [redacted]
5 April 1993-16 April 1993

Findings:
Clinical signs and mortality: No mortality occurred during the 15-day observation period. No clinical signs were observed in the animals with the exception of one female, which showed irregular respiration on day 2 of the study. The animals exhibited strong local signs of skin irritation in the form of moderate to severe erythema, open wounds followed by encrusted, scabbed, dry, rough or chapped skin covered with fine and coarse scales. The skin had completely recovered until day 11 of the study. There were no impairments of body weight gains.
Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
Fenoxaprop-P-ethyl, oil in water emulsion (undiluted) is of low acute toxicity in Wistar rats after dermal application. The LD_{50} for males and females is greater than 4,000 mg/kg bw.
According to Regulation (EC) 1272/2008 no classification is necessary.

B.6.1.3. Inhalation

Reference:	**Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L. Testing for acute aerosol inhalation toxicity in the male and female SPF Wistar rat. 4-hour LC_{50}**
Author(s). year:	[redacted]**, 1993**
Report/Doc. number:	A51050 / Hoechst Report No. 93.0430
Guideline(s):	EPA Guideline 81-3 (revised 1984); OECD guideline 403 (adopted 1981)
Deviations to OECD GD 403 (2009):	Pressure difference in chamber and time required to reach inhalation chamber equilibrium not stated.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
5 male and 5 female Wistar rats were exposed (nose-only) for 4 hours to the technically highest administrable aerosol concentration of 10.74 mg Fenoxaprop-P-ethyl. The test substance was an oil-in-water emulsion of 69 g Fenoxaprop-P-ethyl per litre. As the test substance could not be dispersed in its original state, it was diluted to 75 % in deionized water and distributed homogeneously. Stability in this vehicle was verified for 4 hours. The volume applied was 300 ml/h. Evaluation of the particle size distribution revealed a mass median aerodynamic diameter (MMAD) between 2.0 and 2.5 µm, the geometric standard deviation ranging from 1.8 to 1.9.

Test material: Code AE F046360 24 EW14 A702, batch N°C0133 M020
Content: 6.7% AE F046360 and 7.2% AE F107892 (% w/w) (AZ-No. 05272)

Test animals: Rats, WISKf(SPF71), source: [redacted]
8-10 weeks old, mean bw of ♂ 167g and ♀ 183g
Number of animals: 5 rats per sex

During exposure the behaviour of the animals was recorded. After exposure the animals were kept under observation for further 14 days. At the end of the observation period, the animals were sacrificed and autopsied.

Testing Laboratory and Dates: [redacted]
5 April 1993-16 April 1993

Findings:
Clinical signs and mortality: No mortality occurred under the conditions of the present study. The animals showed irregular respiration, sonorous and sibilant rales, sneezing, stilted gait, uncoordinated gait, decreased spontaneous activity, bristling and ruffled coat, sunken flanks, trembling, blood-coloured encrusted noses, squatting posture, narrowed palpebral fissures and increased salivation. All clinical signs of intoxication were reversible at day 8 of the study. Body weight development was not impaired.
Pathology: The animals killed at termination showed no macroscopically visible changes.

Conclusion:
The acute inhalative LC_{50} of Fenoxaprop-P-ethyl, oil in water emulsion (diluted in distilled water) is higher than 10.74 mg/L in male and female rats after 4 hours of nose-only exposure. 10.74 mg/L air was reported to be the

technically highest administrable dose. Therefore, the oil-in-water emulsion of Fenoxaprop-P-ethyl is of low inhalative toxicity.
According to Regulation (EC) 1272/2008 no classification is necessary.

B.6.1.4. Skin irritation

Reference:	**Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L. Testing for primary dermal irritation in the rabbit**
Author(s). year:	[redacted] **1993a**
Report/Doc. number:	A51087 / Hoechst Report No. 93.0404
Guideline(s):	EPA Guideline 81-5 (revised 1984), OECD Guideline 404 (1981), MAFF (1985)
Deviations to OECD GD 404 (2015):	Individual animal weights at start and conclusion of test not given.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Three female rabbits were treated with Fenoxaprop-P-ethyl. The test substance was an oil-in-water emulsion of 69 g Fenoxaprop-P-ethyl per litre. 0.5 mL of the undiluted test substance was applied on the dorsal region of the animals and covered with a patch and a semi-occlusive bandage. The exposure period was 4 hours. After the exposure period all remnants of the test substance were carefully removed with warm tap water.

Test material: Code AE F046360 24 EW14 A702, batch no C00015/032
Content: 6.7% AE F046360, 7.0% sum of (D+)- and (L-)-enantiomers of AE F046360 and 7.2% AE F107892 (% w/w) (AZ-No. 05272)

Test animals: [redacted]
3-5 months old, bw of 2.5-2.8kg
Number of animals: 3 female rabbits

Examinations of the skin took place 30-60 minutes, and 24, 48 and 72 hours after removal of the patches. If abnormalities were still present on the skin after 72 hours, further examinations were carried out after 7 days. Erythema, eschar formation and oedema were evaluated numerically according to the technique of Draize. In addition, clinical signs of systemic toxicity were recorded.

Testing Laboratory and Dates: [redacted]
5 April 1993-16 April 1993

Findings:
30-60 minutes after removal of the bandage, no skin reaction could be detected. 24 - 72 h later, erythema (grades 1 and 2) was noted in all of the three animals. One animal showed oedema (grade 1) 24 and 48 hours after decontamination. These signs of irritation were reversible within 7 days. In addition, the skin surface was dry and rough and covered with fine and coarse scales in 2 of 3 animals up to study day 7. No clinical signs of toxicity were observed.

Table 6.1.4-1 Draize score, Dermal irritation study in rabbits with AE F046360 EW14 A7

Animal no	30-60 min	24 h	48 h	72 h	7 days	Mean score (24, 48, 72 h)
	Erythema					
1	0	2	2	2	0	**2.0**
2	0	0	1	1	0	**0.7**
3	0	2	2	1	0	**1.7**
	Oedema					
1	0	0	0	0	0	**0.0**
2	0	0	0	0	0	**0.0**
3	0	1	1	0	0	**0.7**

Conclusion:

Slightly irritating effects were observed on the skin of rabbits.
According to Regulation (EC) 1272/2008 no classification is necessary for PUMA S 69 EW , as neither erythema and eschar formation nor oedema formation equivalent to a mean value of ≥ 2.3 calculated for each animal separately had been observed in two or more animals.

B.6.1.5. Eye irritation

Reference:	**Testing for primary eye irritation in the rabbit**
Author(s). year:	[redacted]**, 1993b**
Report/Doc. number:	A50455 / Hoechst Report No. 93.0193
Guideline(s):	EPA Guideline 81-4 (revised 1984); OECD guideline 405 (adopted 1987); MAFF (1985)
Deviations to OECD GD 405 (2012):	Observation period much shorter (3 days) than recommended in the guideline (21 days). However, as the effects recovered on day 3, this is considered a minor deviation. Individual animal weights at conclusion of test not assessed.
GLP:	Yes
Acceptability:	Yes

Material and Methods:
3 female New Zealand albino rabbits were treated with 0.1 mL formulation of Fenoxaprop-P-ethyl. The test substance was an oil-in-water emulsion of 69 g Fenoxaprop-P-ethyl per litre. The test substance was applied to the conjunctival sac of the left eyes of all rabbits. The treated eyes of the animals were left unwashed for 24 hours. Afterwards, the treated eyes were washed out thoroughly with physiological saline at approximately 37°C at all of the designated examination times at which a corneal examination took place.

Test material: Code AE F046360 24 EW14 A701, batch no C00015/031
Content: 7.3% AE F046360 and 7.3% AE F107892 (% w/w) (AZ-No. 05213)

Test animals: New Zealand albino rabbits (source: [redacted]
3-5 months old, bw of 2.1-2.7 kg
Number of animals: 3 female rabbits

The eyes of all animals were examined 1, 24, 48 or 72 hours after application. At 24, 48 and 72 hours the eyes were also examined for corneal lesions under UV light after instillation of one drop of 0.01% fluorescein-sodium solution. All other changes or toxic effects were recorded.

Testing Laboratory and Dates: [redacted]
8 February 1993-5 March 1993

Findings:
The test substance caused transient effects in the eyes of all rabbits in the form of conjunctival reddening, chemosis and discharge ranging in degree from slight to moderate. One animal showed an inflammation of the iris, and another showed corneal opacity. All signs of irritation were completely reversible within 72 hours. No clinical signs of systemic toxicity were observed during the study.

Table 6.1.5-1 Individual eye irritation values in rabbits after application of PUMA S 69 EW

Animal no	1 h	24 h	48 h	72 h	Mean score (24, 48, 72 h)
	Corneal opacity				
1	0	1	1	0	**0.67**
2	0	0	0	0	**0**
3	0	0	0	0	**0**
	Iris lesion				
1	0	0	0	0	**0**
2	0	0	0	0	**0**
3	1	1	0	0	**0.33**
	Redness of conjunctivae				
1	2	2	1	0	**1**
2	1	2	0	0	**0.67**

Animal no	1 h	24 h	48 h	72 h	Mean score (24, 48, 72 h)
3	2	2	0	0	**0.67**
Oedema of conjunctivae					
1	1	1	0	0	**0.33**
2	0	1	0	0	**0.33**
3	1	1	0	0	**0.33**

Conclusion:
Slightly irritating effects were observed on the eyes of rabbits. However, **according to Regulation (EC) 1272/2008, as the individual mean values for redness and oedema of conjunctivae are not ≥ 2, and that for corneal opacity and iris lesion not ≥ 1, no classification is required for PUMA S 69 EW as irritating to the eyes.**

B.6.1.6. Skin sensitization

Reference:	**Fenoxaprop-P-ethyl; oil in water emulsion; 69 g/L. Testing for sensitising properties in the Pirbright-White guinea pig according to the technique of BUEHLER**
Author(s). year:	[redacted]**, 1993c**
Report/Doc. number:	A51451 / Hoechst Report No. 93.0577
Guideline(s):	OECD Guideline 406 (adopted 1987), EPA Guideline 81-6 (revised 1984), MAFF (1985)
Deviations to OECD GD 406 (1992):	None
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Female guinea pigs were administered a formulation of Fenoxaprop-P-ethyl in the Buehler test. The formulation (code: AE F046360 24 EW14 A702) contained 69 g/L Fenoxaprop-P-ethyl and 75 g/L Mefenpyr-diethyl (AE F1027892).

Test material: Code AE F046360 24 EW14 A702, batch N°C0133 M020
Content: 6.7% AE F046360 and 7.2% AE F107892 (% w/w) (AZ-No. 05272)

Test animals: female Pirbright-White guinea pigs, strain DHPK, source: [redacted]
11 weeks old, mean bw of 281 g
Number of animals: 20 + 10 for control group

Induction phase: During study days 1 to 15, the animals received weekly applications of the undiluted test substance. Altogether, three topical applications were performed. 0.5 g of the undiluted test substance was applied over a cellulose patch and fixed to the front of the shaven left flank of the treatment animals. After an exposure period of 6 hours, the occlusive bandage was removed and the flank skin washed. The control animals were treated analogously with 0.5 ml deionised water. Between study days 16 to 28, no further animal treatment was conducted.
Challenge: On study day 29, challenge was performed on the right flank with the undiluted test substance. After removal of the occlusive bandage, any remnants of the test substance were washed off with warm water. 24 hours later, the skin was examined. After 48 hours, the skin of the right flank was reshaved with clippers and examined again.

Testing Laboratory and Dates: [redacted]
1 June 1993-5 March 1993

Findings:
In a preliminary test for skin irritation, 25, 50 and 75 % preparations of the formulation in deionised water and the undiluted formulation were applied under occlusive dressings for an exposure period of 6 hours to four animals. The degree of erythema and oedema was evaluated approximately 24 hours after dressing removal. No irri-

tation was observed at any concentration. Therefore the undiluted formulation was selected for the topical induction stage of the main study.

Skin reactions after topical induction: On the treated skin areas in the treatment and the control groups no signs of irritation were observed.

Skin reactions after topical challenge: After challenge treatment on day 29 with the undiluted test substance, none of the animals of the treatment group exhibited any signs of dermal irritation. In the control group also no dermal reactions after challenge treatment were observed.
No clinical signs of intoxication were observed at any time during the study. No effect on body weight was noted in this study.

Conclusion:
No sensitizing properties of the formulation could be identified in this study. However, no irritation was observed during induction phase, though undiluted test material was applied.

Reference:	**AE F046360 24 EW14 A7: Skin sensitization in the guinea pig (Buehler method)**
Author(s). year:	[redacted]**, 2002**
Report/Doc. number:	C021468 / SPL Project No. 282/623
Guideline(s):	OECD Guideline 406 (adopted 1992), ECC Directive 96/54/EC Method B6
Deviations to OECD GD 406 (1992):	None
GLP:	Yes
Acceptability:	Yes

Material and Methods:
Male albino guinea pigs were administered a formulation of Fenoxaprop-P-ethyl in the Buehler test. The formulation (code: AE F046360 24 EW14 A715) contained 69 g/L Fenoxaprop-P-ethyl and 75 g/L Mefenpyr-diethyl (AE F1027892).

Test material:	Code AE F046360 24 EW14 A7 batch No. AAKH00773
Content:	AE F046360: 6.51% w/w and AE F107892: 6.92% w/w; AZ No.00413
Test animals:	albino Dunkin Harley guinea pigs, source [redacted] 8-12 weeks old, mean bw of 300-450 g
Number of animals:	20 male g.p + 10 for control group

Induction phase: The hair was removed from an area on the left flank of each animal with clippers and treated with a topical application of the undiluted test material. An occlusive dressing was kept in place for six hours. After 6 hours the dressing was carefully removed. This procedure was carried out on days 0, 2, 4, 7, 9, 11, 14, 16 and 18 for a total of nine 6-hour exposures. The treatment sites were decontaminated using distilled water. Approximately 18 hours after each induction application and shortly before the next induction application the degree of erythema and oedema was quantified. Control animals followed the same procedure except that a blank patch was applied.
Challenge: Shortly before treatment on day 28 the right flank of each animals was clipped free of hair. The maximum non-irritant concentration (75 % in distilled water) was applied to the shorn right flank of each animal. To ensure that the maximum non-irritant concentration was used at challenge, the test material at a concentration of 50 % in distilled water was similarly applied to a separate skin site on the right shorn flank. The patches were occlusively fixed and removed after six hours. The treatment sites were decontaminated using distilled water. On day 29 the flanks were clipped free of hair again. Evaluation of skin reactions was performed approximately 24 and 48 hours after dressing removal. Any other reactions were also recorded.

Testing Laboratory and Dates:	[redacted] 21 September 2001-31 October 2001

Findings:
In a preliminary test for skin irritation, 25, 50 and 75 % preparations of the formulation in distilled water and also the undiluted formulation were applied under occlusive dressings for an exposure period of 6 hours to two an-

imals. The degree of erythema and oedema was evaluated approximately 24 and 48 hours after dressing removal. No irritation was observed at any concentration. Therefore the undiluted formulation was selected for the topical induction stage of the main study.

In a preliminary test for the selection of concentration for topical challenge, two animals received dressings without test material on days 2, 4, 7, 9, 11, 14, 16 and 18. On day 21 the guinea pigs were treated with two concentrations of the formulation (50 and 75 % in distilled water). Irritation was evaluated after 24 and 48 hours. Both concentrations did not induce irritation and were used for topical challenge in the main study.

Skin reactions after topical induction: Erythema (grade 1) was noted at the topical induction sites of treated animals after the fourth topical induction (day 8) and lasted up to day 19. On day 12, also grade 2 erythema was observed in about half of the animals. Very slight oedema (grade 1) was noted only on day 12. Other skin reactions were desquamation and crust formation, which appeared between study days 5 and 12. Furthermore, very pale yellow/beige coloured staining was noted in test group animals following topical induction. The staining did not affect evaluation of skin response. No skin reactions were seen at the topical induction sites of control group animals.

Table 6.1.6-1 Skin reactions during induction phase with the undiluted PUMA S 69 EW

Test animals	Effect	Days during induction phase								
		1	2	3	4	5	7	8	9	10
Treated	Erythema	-/20	-/20	-/20	-/20	-/20	-/20	3/20 [1]	4/20 [1]	3/20 [1]
	Oedema	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20
Control	Erythema	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20
	Oedema	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20
		11	**12**	**14**	**15**	**16**	**17**	**18**	**19**	
Treated	Erythema	5/20 [1]	19/20 [1+2]	-/20	-/20	-/20	1/20	1/20	4/20	
	Oedema	-/20	11/20	-/20	-/20	-/20	-/20	-/20	-/20	
Control	Erythema	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20	
	Oedema	-/20	-/20	-/20	-/20	-/20	-/20	-/20	-/20	

[1] grade 1
[1+2] grade 1 and 2

Skin reactions after topical challenge: The same results were observed for the 50 % and the 75 % preparation of the test material: erythema grade 1 was noted at the topical challenge sites of 2 test group animals at the 24 hour observation (2/20 = 10 %). No skin reactions were noted at the challenge sites of the test group animals after 48 hours. No skin reactions were noted at the challenge sites of the controls at 24 and 48 hours.

Table 6.1.6-2 Skin reactions after challenge with 50% and 75% preparations of PUMA S 69 EW

Test group	Skin reactions	50 %		75 %	
		24 h	48 h	24 h	48 h
Treated	Erythema	2/20	-/20	2/20	-/20
	Oedema	-/20	-/20	-/20	-/20
Control	Erythema	-/20	-/20	-/20	-/20
	Oedema	-/20	-/20	-/20	-/20

Conclusion:
2/20 (10 %) of the treated animals showed slight skin reactions (erythema grade 1) at the evaluation 24 hours after challenge but not 48 hours after challenge. It was stated by the study authors that these effects also could be caused by irritation. However, a sensitizing reaction cannot be ruled out. According to the results of this study, no classification is required because only 10 % (and not 15 %) of the test animals showed positive results.

New study

Reference: **Fenoxaprop-P-ethyl + Mefenypr-diethyl EW 69 + 75 g/l - Evaluation of potential der-**

	mal sensitization in the local lymph node assay in the mouse
Author(s). year:	[redacted]**, 2006**
Report/Doc. number:	SA 06100 / M-273147-01-1
Guideline(s):	OECD Guideline 429 (2002)
Deviations to OECD GD 429 (2010):	It is stated that in the screening test an increase in ear thickness of 15% compared to the control animals was observed and considered as irritating, while OECD states that local skin irritation is indicated "…by an increase in ear thickness of at least 25%". However, as responses were clearly positive in the main test, this is considered a minor deviation.
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
The test substance Fenoxaprop-P-ethyl + Mefenpyr-diethyl (PUMA S 69 EW), positive control and the vehicle were applied on external surfaces of each ear (50µl/animal) of female mice for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations (see Table 6.1.6-3). On Day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices and auricular weight.

Test material:	Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69 + 75 g/L, batch No: 2006-001263/EFIM000275 Positive control p-benzoquinone, batch 33410, purity 99.6%
Content:	AE F046360 (FPP) at 6.66% w/w, (AE F046360 - sum of (D+)- and (L-)-enantiomers of AE F046360 at 6.84% w/w) and AE F107892 (MPR) at 6.90% w/w

Test animals:	CBA/J mice, [redacted] At least 8 weeks old, mean bw of 18.2-22.3 g
Number of animals:	4 female animals per group

Table 6.1.6-3 Dosing and experimental design, LLNA assay in the mouse with PUMA S 69 EW

Group	Substance	Concentration (%) Days 0-2	Number of animals
1	Control (Pluronic Acid)	1	4
2	PUMA S 69 EW in 1% aqueous Pluronic Acid	5	4
3		10	4
4		25	4
5		50	4
6	p-Benzoquinone in 25% FPP + MPR EW 69 + 75 g/L (and 75% aqueous Pluronic acid at 1%)	0.25	4

Concentrations of test substance in Pluronic acid as well as the p-Benzoquinone concentration in the formulation were chosen based on results of screening test (detailed results not given in study report), where irritation (measured by ear weight) was observed at the concentration of 100%. Mean ear weight value of 79.7 mg was measured in the group treated at a concentration of 100%. This represent a variation of 15.2% in relation to the value obtained in control animals (69.2 mg) and, as this correspond to an increase of more than 10%, the formulation at the concentration of 100% was considered to be irritant.

Testing Laboratory and Dates:	[redacted] 20 April 2006-12 June 2006

Findings:
No mortality and no clinical signs were observed during the study.
No cutaneous reactions were observed in the vehicle, reference control or treated groups.
The proliferation index values of the test substance were 0.83, 1.55, 2.95 and 8.55 at treatment concentrations of 5 %, 10 %, 25 % and 50%, respectively.
The proliferation index value of the positive control was 8.80 at a treatment concentration of 0.25% of p-Benzoquinone in 25% PUMA S 69 EW and 75% aqueous Pluronic Acid at 1%.
Positive lymphoproliferative responses (SI>3) was noted for PUMA S 69 EW with a dose related effect.

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

Table 6.1.6-4 DPM and Stimulation index values, LLNA assay in the mouse with PUMA S 69 EW

Group Number	Test Group Name	DPM/ nodes	Stimulation Index Values
1	Control (1% aqueous Pluronic Acid)	**390**	1.00
2	PUMA S 69 EW 5%	**322**	**0.83**
3	PUMA S 69 EW 10%	**603**	**1.55**
4	PUMA S 69 EW 25%	**1152**	**2.95**
5	PUMA S 69 EW 50%	**3333**	**8.55**
6	p-Benzoquinone 0.25%	**3428**	**8.80**

Conclusion:
Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69 + 75 g/L was found to be a sensitizing formulation in the Local Lymph Node Assay.
The study result triggers the following classification/labelling according to Regulation (EC) No 1272/2008 (CLP): **Skin Sens. Cat. 1 (H317 May cause an allergic skin reaction**).

B.6.1.7. Supplementary studies on the plant protection product

No supplementary studies with this formulation were conducted.

A percutaneous short-term toxicity study with a formulation containing 75g/L fenoxaprop-P-ethyl and 37.5g/L fenchlorazole was available in the original DAR (2005). However, for the purpose of renewal the study was not re-evaluated.

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

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

B.6.2. DERMAL ABSORPTION

For Annex I inclusion two dermal penetration studies were included in the dossier submitted in 2003 (Dick, I.; 2000 and [redacted]; 2007). As only the *in vivo* dermal absorption study in the rat was conducted with the representative formulation PUMA S 69 EW, a short summary is provided in the first part of this section.
A new dermal absorption study from 2015 ([redacted]; 2015) has been submitted for the renewal of fenoxaprop-P-ethyl. The extent of dermal absorption with the formulation PUMA S 69 EW was investigated *in vitro* using human skin. A summary of the study is given in the in the second part of this section along with the mean values based on the study results and following application of the new EFSA guidance rules.

Reference:	**(14C)-Fenoxaprop-P-ethyl: In vivo dermal absorption in the rat using an oil in water emulsion formulation coded: AE F046360 24 EW14 A7xx**
Author(s). year:	[redacted]**, 2002**
Report/Doc. number:	Doc.No. C025112 / Covance Report No. 1490/021-D1145
Guideline(s):	Draft OECD Guideline (1996): Percutaneous absorption: in vivo method
Deviations to OECD GD 427 (2004):	None.
GLP:	Yes
Acceptability:	Yes

Materials and Methods:
For this in vivo study, 32 male rats were used. The day before dosing an area of the dorso-lumbar skin (100 x 75 mm) was clipped free of hair using veterinary clippers, without abrading the skin. The test substance was prepared as a high dose formulation (68.476 mg Fenoxaprop-P-ethyl/g) and a low dose formulation using a 250-fold dilution of the formulation (0.278 mg Fenoxaprop-P-ethyl/g). This dilution of the formulation was designed to simulate the spray dilution. The nominal dose rate for each formulation was 100 µl per animal. This results in nominal dose levels of 6.9 mg/rat for the high dose animals (16) and 0.0276 mg/rat for the low dose animals (16).

Test material:

Non-radiolabelled:	Fenoxaprop-P-ethyl, batch AALC00028, purity >95%
Radiolabelled:	[^{14}C]-Fenoxaprop-P-ethyl, batch Z31032-0, purity >99%, specific activity 5.133 MBq/mg
Formulation:	AE F046360 24 EW12 A301, batch Op. 220/01 Pfl.Ha.729 AE F046360 24 EW12 A403, batch Op. 221/01 Pfl.Ha.198

Test animals:	Rat, Sprague Dawley (strain: Crl: CD BR; source: [redacted]) 6-10 weeks, bodyweight 188-205g
Number of animals:	16 per test group

Following a single dermal administration of the test substance, the rats were returned to metabolism cages suitable for the separate collection of urine and faeces. Four animals from each dose group were necropsied 8 h following dose administration after application site wash was performed. For all the remaining animals, an interim application site wash was done at 8 h following dose administration. The animals were then returned to metabolism cages. At 24, 72 and 120 h following dose administration, 4 rats from each dose group were taken (2 only at 72 h for the high dose group), the application site was washed again and the animals were sacrificed. Urine and faeces were collected at 8, 24, 48, 72, 96 and 120 h following dose administration. Radioactivity was determined in urine, faeces, application site, adjacent skin, carcass, gastro intestinal tract and its contents, whole blood, plasma, application site washes, dressings (silicone rings, gauze and bandage), cage washings and cage debris.

Findings:
Acute signs of distress were shown by one animal in the high dose group within 24 h of dose application and it therefore was sacrificed. There was no evidence that the problem was related to the test compound, and no signs of any adverse effects on other animals in this dose group.

Results undiluted formulation: Because of the viscous nature of the formulation, there were significant losses and insufficient dose for all sixteen animals. Of the 16 animals dosed, one received less than the target dose and was excluded from the experiment. Another animal was sacrificed 24 h after dosing because of acute distress. The remaining animals were reassigned so that there were 4 rats at each of the 8, 24 and 120 time points, with the 72 h timepoint being reduced to 2 animals only. The mean applied dose was 6.740 mg (14C)-Fenoxaprop-P-ethyl, equivalent to 0.654 mg/cm^2. The mean overall recovery at the four time points was between 89 and 93 % of the applied radioactivity. For the animals sacrificed 8 h following dose administration, a mean of 47 % of the applied radioactivity was recovered from the application site wash and 43 % was contained in the dressings. A further 1.99 % was not removed by the washing procedure and remained on the application site. There was a minimal penetration into the skin adjacent to the application site (0.14%). The amount of radioactivity in urine, faeces, cage wash, gastro intestinal tract and contents, terminal blood sample and carcass was 0.600 %. This value rose from 0.6 % at 8 h post application to 1.3 % at 24 h, to 2.5 % at 72 h, and to a maximum of 2.0 % at 120 h post application. The rate of absorption reached a maximum of 4067 ng Fenoxaprop-P-ethyl/cm^2 skin/h over the period 0-8 h falling to mean rates of 371, 136 and 104 ng/cm^2 skin/h.

Results spray dilution: The mean applied dose was 0.0280 mg (14C)-Fenoxaprop-P-ethyl, equivalent to 0.00272 mg/cm^2. The mean overall recovery at the four time points was between 95 and 97 %. For the animals sacrificed 8 h following dose administration, a mean of 54 % of the applied radioactivity was recovered from the application site wash and 16 % was contained in the dressings. A further 18 % was not removed by the washing procedure and remained on the application site. There was a minimal penetration into the skin adjacent to the application site (<0.3%). The amount of radioactivity in urine, faeces, cage wash, gastro intestinal tract and contents, terminal blood sample and carcass was 6.21 %. This value rose from 6.21 % at 8 h post application to 9.57 % at

24 h, to 15.3 % at 72 h, and to a maximum of 16.3 % at 120 h post application. The rate of absorption reached a maximum of 21.1 ng Fenoxaprop-P-ethyl/cm^2 skin/h over the period 0 – 8 h falling to mean rates of 10.9, 5.76 and 3.70 ng/ cm^2 skin/h.

Table 6.1.8-1 Absorption data for concentrate (69g/L formulation)

Undiluted formulation (% of administered dose)				
	8 h	**24 h***	**72 h***	**120 h***
Absorbed	**0.600**	**1.335**	**2.467**	**2.012**
-urine	0.020	0.228	0.903	0.960
-faeces	<0.001	0.069	0.554	0.393
-cage wash	0.003	0.070	0.264	0.319
-final cage wash	0.002	0.012	0.019	0.017
-cage debris	<0.001	0.004	0.007	0.007
-GI tract	0.051	0.061	0.029	0.011
-contents of GI tract	0.034	0.152	0.167	0.030
-blood	0.018	0.025	0.025	0.007
-carcass	0.472	0.714	0.498	0.269
Application site	**1.986**	**0.697**	**0.394**	**0.251**
Adjacent skin	**0.137**	**0.567**	**0.249**	**0.092**
Maximal dermal penetration rate (absorbed+application site+adjacent skin)	**2.7**	**2.6**	**3.1**	**2.4**
8 h application wash	47.05	57.45	60.11	61.81
8 h dressing (1st extraction)	41.76	23.53	23.26	20.84
8 h dressing (2nd extraction)	1.161	0.695	0.405	0.561
Final application site wash	Not applicable	1.131	0.872	0.152
Final dressings	Not applicable	5.913	2.413	3.271
Total recovery	**92.69**	**91.31**	**90.17**	**89.00**

* 8 hours exposure period

Table 6.1.8-2 Absorption data for spray dilution (0.276 g/L formulation)

Spray dilution (% of administered dose)				
	8 h	**24 h***	**72 h***	**120 h***
Absorbed	**6.212**	**9.571**	**15.28**	**16.31**
-urine	0.208	2.030	6.328	7.998
-faeces	0.011	0.795	3.853	4.455
-cage wash	0.263	0.695	1.576	1.438
-final cage wash	0.031	0.027	0.180	<0.001
-cage debris	<0.001	0.020	<0.001	<0.001
-GI tract	0.695	1.136	0.199	0.256
-contents of GI tract	0.163	0.430	0.443	0.147
-blood	0.199	0.229	0.121	0.116
-carcass	4.640	4.208	2.524	1.897
Application site	**18.30**	**6.130**	**4.116**	**4.400**
Adjacent skin	**0.290**	**0.306**	**0.304**	**2.168**
Maximal dermal penetration rate (absorbed+application site+adjacent skin)	**24.8**	**16.0**	**19.7**	**22.9**
8 h application wash	53.98	58.27	60.63	57.05
8 h dressing	16.32	10.70	8.555	8.243
Final application site wash	Not applicable	7.638	3.218	4.282
Final dressings	Not applicable	3.906	4.174	4.897
Total recovery	**95.10**	**96.52**	**96.27**	**97.35**

* 8 hours exposure period

Conclusion:

Fenoxaprop-P-ethyl was administered once as a single topical application of the undiluted formulation (69 g/L) and the spray dilution (1:250, 0.276 g/L) to rats for 8 hours. Investigations on absorbed radioactivity were performed 8, 24, 72 and 120 h after application and showed systemically absorbed amounts of 0.6, 1.3, 2.5 and 2.0 %, resp., for the undiluted formulation and 6.2, 9.6, 15.3 and 16.3 % for the spray formulation. The maximum dermal penetration rate was calculated from systemic absorption plus the remnants on the application site and the adjacent skin which is a worst case scenario. However, there is no information on which layer of the skin the ma-

terial was located. Material first bound in the skin might be lost from the skin by exfoliation but also further absorption from this depot into the systemic circulation over time can be assumed as radioactivity detected in the systemic compartments increased over time while radioactivity located on the application site decreased. Maximum dermal penetration rates of 2.7 % for the undiluted formulation and 24.8 % for the spray dilution after a treatment period of 8 hours were used for risk assessment.

New Study

Reference:	**In-vitro human skin penetration of 14C-fenoxaprop-P-ethyl in the fenoxaprop-P-ethyl and mefenpyr-diethyl EW 69+75 formulation**
Author(s). year:	**Bernal J., 2015**
Report/Doc. number:	SA14-02497 / M-533620-01-1
Guideline(s):	OECD Guideline 428 (2004), OECD Guideline 28 (2004); EFSA Guidance on Dermal Absorption (2012)
Deviations to OECD GD 428 (2004):	None.
GLP:	Yes
Acceptability:	Yes

Materials and Methods:

Test system: A flow-through diffusion cell system was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid used in this study was PBS 0.01M pH 7.4 + 5% bovine serum albumin (BSA). The skin surface temperature was maintained at 32°C ± 1°C, with a fixed water bath integrated in the dynamic system (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1 mL/h.

Test material:

Non-radiolabelled:	Fenoxaprop-P-ethyl, batch RDL 180-2-1, purity 99.4%
Radiolabelled:	[phenyl-UL-14C]-fenoxaprop-P-ethyl, batch KML 9749, specific activity: 112 µCi/mg, radiopurity >98%
Formulation:	Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69+75 formulation (specification no 102000011507) containing fenoxaprop-P-ethyl at a concentration of 69 g/L, used at two
Concentrations used:	69 g/L and 0.22 g/L (nominal)

Test system:	Human abdominal skin, Polyclinique Grand Sud or Banque de Tissu de Lyon, FR Thickness of 338-394 µm
Number:	4 donors (1 male and 3 female)

Skin integrity: The skin integrity was evaluated before use by measuring the trans-epidermal water loss (TEWL) and the absence of water on the skin was controlled. The measurement was carried out away from any heating source and air stream after at least 1 hour stabilisation. The human skin was included in the study if the TEWL was ≤ 4 $g/m^2/h$.

Treatment: The dose preparation was applied to the split-thickness skin sample with a positive displacement pipette at the rate of approximately 10 $\mu L/cm^2$ exposed skin. The specific activity of 6 aliquots of fenoxaprop-P-ethyl and the homogeneity of the test items were checked on the day of preparation, before and during application. The homogeneity of the test items before the application was acceptable if the obtained CV was < 5%. The specific activity of the test items obtained during the application was used to calculate the recovery. The coefficient of variation between this series of samples was stated as a measure of variability of the application system.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector, one vial per time point and per cell at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 10h, 12h, 15h, 18h, 21h and 24h after application. At 8 hours post-application, the skin was swabbed twice using cotton buds. Skin surface was washed with washing solution, which was collected for analysis. Then, skin surface was carefully dried with three cotton-buds in order to remove and retain the non-absorbed dose.
At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. The strips were performed using adhesive scotch tape Magic 3M. In order to standardise stripping, a weight of 150

g/cm² was placed top of the tape for 10 s before taking off. A maximum of 15 strips were performed until the slightly shiny layer below the stratum corneum was visible, corresponding to the viable epidermis (presumed to be the region around the stratum spinosum). All strips were analysed separately. The first two strips are considered in the calculation as material likely to be lost to the external environment due to desquamation of the superficial external layers of the skin surface.

Radioassay: Samples were analysed for radiolabel content by scintillation counter and the related software. Calculations were performed directly from the raw data obtained with the scintillation counter. Conversion of the counts per minute (cpm) to disintegrations per minute (dpm) was performed directly by the instrument.

Findings:
Fenoxaprop-P-ethyl was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.
Measurements of the homogeneity of the two concentrations of formulation applied indicated that it was acceptable.
The study results are presented in Table 6.1.8-3.

Table 6.1.8-3 Absorption data for neat (69 g/L) and diluted formulation (0.22 g/L) of PUMA S 69 EW

	Distribution of radioactivity (% dose)			
Dose Levels	**Neat formulation: High dose (69 g/L)**		**Dilution: Low dose (0.22 g/L)**	
Species	Human (n=6)		Human (n=5)	
	Mean	*SD*	Mean	*SD*
SURFACE COMPARTMENT				
Skin Excess (24h)[a]	100.17	*0.97*	47.91	*12.60*
Surface Dose (1st two tape-strips)	0.40	*0.16*	21.73	*6.04*
SKIN COMPARTMENT				
Skin [b]	***0.21***	***0.08***	***11.84***	***6.59***
Stratum corneum [c]	***0.21***	***0.09***	14.98	*4.39*
RECEPTOR COMPARTMENT				
Total % directly absorbed [d]	***0.11***	***0.9***	***7.91***	***3.60***
STUDY: Total % Potentially Absorbable [e]	**0.53**	***0.15***	**19.75**	***8.26***
TOTAL % RECOVERY	101.1	*0.88*	99.38	*2.11*
Evaluation according to EFSA Guidance				
absorption >75% within half of study duration	No		Yes	
standard deviation >25%	Yes 0.53 + 0.15 = 0.68		Yes 19.75 + 8.26 = 28.01	
recovery <95%	No		No	
adjusted: Total % Potentially Absorbable [f]	**0.7**		**28**	

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

Conclusion:
The extent of dermal absorption of fenoxaprop-P-ethyl formulated as an EW 144 (Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69+75) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following section along with the mean values based on the study results and following application of the new EFSA[1] guidance rules. A conclusion and recommendation regarding the dermal absorption of fenoxaprop-P-ethyl formulated as an EW 144 is given below.

The mean percentage of fenoxaprop-P-ethyl in the EW 144 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.5% for the human skin. Applying the new EFSA guidance this value adjusts to 0.7%.

The mean percentage of fenoxaprop-P-ethyl in the EW 144 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 20% for human skin. Applying the new EFSA guidance this value adjusts to 27%.

According to the new EFSA guidance there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were met by the low dose group in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-fenoxaprop-P-ethyl in the Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69+75 formulation:

0.7% for the neat formulation (69 g/L)
27% for the low dose (0.22 g/L).

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

CONFIDENTIAL information - data provided separately (Document J).

B.6.4. EXPOSURE DATA

PUMA S 69 EW is an oil emulsion in water (EW) formulation containing the active ingredient fenoxaprop-P-ethyl (69 g/L) (company-internal substance) and the safener mefenpyr-diethyl (75 g/L). Evaluation of the safener mefenpyr-diethyl is not presented in the dossier. This formulation is applied with a tractor boom on cereal fields on grassy weed species.
The product is to be packaged in 0.5, 1, 5 or 15 L containers. Water will be the diluent/carrier in all situations. Usage information pertinent to operator exposure is summarized in the table below.

Summary of representative uses

Crop	Application type	Dose (L/ha)	Active substance applied (a.i kg/ha)	Volume applied (L/ha)	Max No of trmt.
Cereal	Tractor boom	1.2	0.083 (fenoxaprop-P-ethyl) 0.090 (mefenpyr-diethyl)	100 to 400	1

Consideration on critical GAPs selection

[1] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.

Selected critical GAPs cover relevant aspects of risk envelop approach to operators. The **maximum total amount of active ingredient handled per day (as a product of the application rate and the assumed area treated per day)** as a worst case representative for the application technique has been applied.

Exposure assessment
No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission[2]. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by

- the European Food Safety Authority[3], and

the European Commission Standing Committee[4].
Therefore, this waiver is presented in line with the Guidance of the European Commission.

Relevant toxicological reference values:

Dermal absorption
The dermal penetration through human dermatomed skin of [^{14}C]- fenoxaprop-P-ethyl formulated as an EW 144 (Fenoxaprop-P-ethyl + Mefenpyr-diethyl EW 69+75) formulation was investigated *in vitro* conditions using human skin at two concentrations corresponding to the neat product (69 g /L) and to the spray dilution (0.22 g/L), respectively (details are given in point CP 7.3).
Based on the study results obtained with human skin the following dermal absorption values are proposed for the risk assessment:

- 0.7% for the neat formulation (69 g/L)
- 27% for the low dose (0.22 g/L).

AOEL
The AOEL of fenoxaprop-P-ethyl was set in the Review Report (SANCO/3777/08 – rev. 1) and EFSA Scientific Report (EFSA Scientific Report (2007) 121, 1-76 at 0.014 mg/kg bw/day. It is derived from a multigeneration study in rat study applying a safety factor of 100.

B.6.4.1. Operator exposure

Operator exposure estimation to PUMA S 69 EW was calculated on the basis of the "*EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products*"[5] for application scenario: "*outdoor vehicle-mounted upward*", without and with PPE. Exposure predictions were obtained out of the available version of the currently exposure calculation spreadsheet[6]. Details of calculations are given in CP 7.2.1.1. The results of exposure calculations are summarized in Table 6.4.1-1.

Table 6.4.1-1 Estimation of operator exposure

Application technique	PPE	Total systemic exposure (mg FPP#/kg bw/day)***	% of AOEL****
Outdoor vehicle-mounted downward	Without PPE*	0.0047	34
	With PPE**	0.0031	22

* work wear – arms, body and legs covered, bare hands; ** work wear – arms, body and legs covered, gloves mixing/loading; *** 60 kg body weight; dermal absorption 0.7% concentrate and 27% dilution; inhalation absorption 100%; **** 0.014 mg/kg bw/day.
#FPP = fenoxaprop-P-ethyl

Assessment
The results of the calculations reveal that the situation is favourable for operator for the intended outdoor uses of PUMA S 69 EW in cereals.

[2] Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013
[3] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874)
[4] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015
[5] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of 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
[6] EFSA (European Food Safety Authority), 2014. Exposure calculation spreadsheet. Available at http://www.efsa.europa.eu/fr/efsajournal/doc/3874ax1.zip. Version of 30.03.2015.

The exposure predictions of systemic operator exposure to fenoxaprop-P-ethyl account for 34% and 22% of the AOEL (0.014 mg/kg bw/day), while operating vehicle-mounted downward application equipment, without and with PPE, respectively.

Conclusion
Based on the above presented results there is no unacceptable risk anticipated for operator with the intended uses of PUMA S 69 EW in cereals considering fenoxaprop-P-ethyl.

B.6.4.1.1.1. Estimation of operator exposure

Data used for the calculation
The following assumptions have been made in calculating operator exposure:

- the area treated in one day is 50 ha
- the application rate is 1.2 L/ha of PUMA S 69 EW resulting in 0.083 kg of fenoxaprop-P-ethyl.

Operator exposure estimations to PUMA S 69 EW were calculated on the basis of EFSA[2,3]. Summaries of assumptions and the calculation details are presented in Table 6.4.1-3.

Critical GAPs
Critical GAPs for operator exposure are presented in Table 6.4.1-2.

Table 6.4.1-2 Critical GAP for operator exposure assessment

Crop	Application technique	Dose (L/ha)	Active substance applied (a.i kg/ha)	Volume applied (L/ha)**	Max No of trmt.
Cereals	Tractor boom	1.2	0.083 (fenoxaprop-P-ethyl) 0.090 (mefenpyr-diethyl)	100	1

Table 6.4.1-3 Predicted systemic exposure to fenoxaprop-P-ethyl according to EFSA. (Downward spraying. Vehicle-mounted. Without and with PPE)

Substance	fenoxaprop-P-ethyl	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate- 0.083 kg a.s. /ha	Spray dilution = 0.83 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 0.7	Dermal for in use dilution = 27	Oral = 100	Inhalation = 100	
RVNAS	0.014 mg/kg bw/day				

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0074	% of RVNAS	52.66%
Without PPE					
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	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	0.0047	% of RVNAS	33.89%
With PPE				
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application	Gloves = No	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	0.0031	% of RVNAS	21.86%

RVNAS = Reference value non acutely toxic active substance (equivalent to AOEL)

B.6.4.2. Bystander and resident exposure

As explained in paragraph B.6.4 no acute non-dietary risk assessment is included in this submission. The following risk assessment therefore considers the longer term exposure which will be compared with the AOEL. In this context only resident exposure is calculated using the EFSA model and is considered as covering the bystander exposure.

The intended outdoor use is on cereal crops. Treatment is achieved via downward vehicle-mounted spray application. The application parameters of the critical GAP (cGAP) is summarized in Table 6.4.2-1.

Table 6.4.2-1 Critical GAP parameters

Crop	Application technique	Dose (L/ha)	Active substance applied (a.i kg/ha)	Volume applied (L/ha)**	Max No of treatment
Cereal	Tractor boom	1.2	0.083 (fenoxaprop-P-ethyl) 0.090 (mefenpyr-diethyl)	100 to 400	1

Consideration on estimation of resident exposure

Resident exposure estimation to PUMA S 69 EW is estimated using the EFSA model[7] with the relevant scenario "Tractor-mounted/trailed boom sprayer: hydraulic nozzles". Details of calculations are given in CP 7.2.2.1. The results of exposure calculations are summarized in Table 6.4.2-2. Exact calculations are given in Table 6.4.2-4.

Table 6.4.2-2 Estimation of resident exposure (EFSA model)

Application Scenario	Exposure Scenario		Total systemic exposure (mg FPP#/kg bw/day)*	% of AOEL**
Field Crop	Resident	Adult	0.0027	19.3
		Children	0.0077	55

* 60 and 10 kg body weight for adult and children respectively; dermal absorption 27% diluted spray; inhalation absorption 100%; ** 0.014 mg/kg bw/day.

\# FPP = fenoxaprop-P-ethyl

Consideration on estimation of bystander exposure

Since there is no accepted relevant endpoint (e.g. Acute AOEL), calculation of bystander exposure according to EFSA Guidance assessment is not addressed. Bystander exposure estimation to PUMA S 69 EW is assessed using the model after Martin *et al.* (2008) and summarized in Table 6.4.2-3. Exact calculations are given in Table 6.4.2-5 and Table 6.4.2-6.

[7] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Pesticides Exposure Assessment of Operators, Worker, Residents and Bystanders, EFSA Journal 2014;12(10):3874.

Table 6.4.2-3 Estimation of bystander and resident exposure after Martin *et al.*

	Fenoxaprop-P-ethyl	
	Adult	**Child**
Bystander		
Dermal exposure (mg/kg bw/day)	1.03×10^{-2}	0.81×10^{-3}
Inhalation exposure (mg/kg bw/day)	0.04×10^{-5}	0.08×10^{-5}
Total systemic exposure (mg/kg bw/day)	1.04×10^{-3}	0.81×10^{-3}
% of AOEL	7.39	5.77
Resident		
Dermal exposure (mg/kg bw/day)	7.55×10^{-5}	9.99×10^{-5}
Inhalation exposure (mg/kg bw/day) (mg/kg bw/day)	-	-
Oral exposure (hand-to-mouth transfer) (mg/kg bw/day)	-	2.85×10^{-5}
Oral exposure (object-to-mouth transfer) (mg/kg bw/day)	-	7.12×10^{-6}
Total systemic exposure (mg/kg bw/day)	7.55×10^{-5}	1.36×10^{-4}
% of AOEL	0.54	0.97

Assessment

The results of the calculations reveal that the situation is favourable for bystanders and residents for the intended outdoor uses of PUMA S 69 EW for cereal crops.

Conclusion

Based on above presented results there is no unacceptable risk anticipated for bystanders and residents, both adults and children, exposed to fenoxaprop-P-ethyl with the intended uses of PUMA S 69 EW.

B.6.4.2.1. Estimation of bystander and resident exposure

The following definitions and assumptions for bystanders/residents may be applied.
Bystanders and residents are not involved in application or handling plant protection products or the professional handling of treated crops.

Bystander/resident exposure may occur following foliar spray application outdoors. Bystander/resident exposure is calculated regarding the application scenario leading to the highest drift value. Application scenarios causing lower spray drift will be covered by this calculation and separate evaluations are not made. Exposure is calculated for adult and child residents.

Data used for the calculation

The following assumptions have been made in calculating resident exposure:

- the application rate is 1.2 L/ha of PUMA S 69 EW resulting in 0.083 kg of fenoxaprop-P-ethyl.

Table 6.4.2-4 Calculation of Resident exposure (EFSA model)

Substance	fenoxaprop-P-ethyl	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.083 kg a.s. /ha	Spray dilution = 0.83 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 0.7	Dermal for in use dilution = 27	Oral = 100	Inhalation = 100	
RVNAS	0.014 mg/kg bw/day				

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0060	% of RVNAS	43.05%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	7.64%
	Surface deposits (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	2.81%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0038	% of RVNAS	27.01%
	All pathways (mean) mg/kg bw/day	0.0077	% of RVNAS	54.97%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0014	% of RVNAS	10.29%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.64%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.09%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0021	% of RVNAS	15.01%
	All pathways (mean) mg/kg bw/day	0.0027	% of RVNAS	19.30%

RVNAS = Reference value non acutely toxic active substance (equivalent to AOEL)

Table 6.4.2-5 Calculation of Bystander exposure (Martin *et al.*)

Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of bystander exposure:

Intended use(s):	cereals		**Drift (D):**	2,77	% (FCTM, 1 m)
Application rate (AR):	0,083	kg a.s./ha	**Exposed Body Surface Area (BSA):**	1	m² (adults)
				0,21	m² (children)
Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I^*_A):**	0,001	mg/kg a.s. (6 hours, adults)
	16,15	kg/person (children)		0,00057	mg/kg a.s. (6 hours, children)
Dermal absorption (DA):	27,00	% ('worst case')	**Area Treated (A):**	20	ha/d (based on Field Crops, Tractor Mounted (FCTM))
Inhalation absorption (IA):	100	%	**Exposure duration (T):**	5	min
AOEL:	0,014	mg/kg bw/d			

Bystander exposure towards Fenoxaprop-P-ethyl					
Adults			**Children**		
Bystander: Dermal exposure after application in cereals (via spray drift)					
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(8,3 x 2,77% x 1 x 27%) / 60			(8,3 x 2,77% x 0,21 x 27%) / 16,15		
External exposure	0,22991	mg/person	External exposure	0,0482811	mg/person
External exposure	0,00383183	mg/kg bw/d	External exposure	0,00298954	mg/kg bw/d
Absorbed dose:	**0,0010346**	**mg/kg bw/d**	**Absorbed dose:**	**0,0008072**	**mg/kg bw/d**
Bystander: Inhalation exposure after application in cereals					
SIE_B = (I^*_A x AR x A x T x IA) / BW			SIE_B = (I^*_A x AR x A x T x IA) / BW		
(0,001 / 360 x 0,083 x 20 x 5 x 100%) / 60			(0,001 / 360 x 0,083 x 20 x 5 x 100%) / 16,15		
External exposure	2,3056E-05	mg/person	External exposure	1,325E-05	mg/person
External exposure	3,8426E-07	mg/kg bw/d	External exposure	8,2045E-07	mg/kg bw/d
Absorbed dose:	**0,0000004**	**mg/kg bw/d**	**Absorbed dose:**	**0,0000008**	**mg/kg bw/d**
Total systemic exposure: $SE_B = SDE_B + SIE_B$			Total systemic exposure: $SE_B = SDE_B + SIE_B$		
Total systemic exposure (absorbed dose)	0,06209876	mg/person	Total systemic exposure (absorbed dose)	0,01304915	mg/person

Total systemic exposure (absorbed dose)	**0,0010350**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0,0008080**	**mg/kg bw/d**
% of AOEL:	**7,39**	**%**	**% of AOEL:**	**5,77**	**%**

Table 6.4.2-6 Calculation of Resident exposure (Martin *et al.*)

Estimation of resident exposure after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):	cereals		**Drift (D):**	2,77	% (FCTM, 1 m)
Application rate (AR):	0,083	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16,15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	none	
Dermal absorption (DA):	27,00	% ('worst case')	**Inhalation Rate (IR):**	16,57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8,31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%
AOEL	0,014	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards Fenoxaprop-P-ethyl					
Adults			**Children**		
Residents: Dermal exposure after application in cereals (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0,00083 x 1 x 2,77% x 5% x 7300 x 2 x 27%) / 60			(0,00083 x 1 x 2,77% x 5% x 2600 x 2 x 27%) / 16,15		
External exposure	0,01678343	mg/person	External exposure	0,00597766	mg/person
External exposure	0,00027972	mg/kg bw/d	External exposure	0,00037013	mg/kg bw/d
Absorbed dose:	**0,0000755**	**mg/kg bw/d**	**Absorbed dose:**	**0,0000999**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0 x 16,57 x 100%) / 60			(0 x 8,31 x 100%) / 16,15		
External exposure		mg/person	External exposure		mg/person
External exposure		mg/kg bw/d	External exposure		mg/kg bw/d
Absorbed dose:		**none**	**Absorbed dose:**		**none**

			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) / BW		
			(0,00083 x 1 x 2,77% x 5% x 50% x 20 x 20 x 2 x 100%) / 16,15		
			External exposure	0,00045982	mg/person
			External exposure	2,8472E-05	mg/kg bw/d
			Absorbed dose	**0,0000285**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0,00083 x 1 x 2,77% x 20% x 25 x 100%) / 16,15		
			External exposure	0,00011496	mg/person
			External exposure	7,118E-06	mg/kg bw/d
			Absorbed dose	**0,0000071**	**mg/kg bw/d**
Total systemic exposure: $SE_R = SDE_R + SIE_R$			Total systemic exposure: $SE_R = SDE_R + SIE_R + SOE_H + SOE_O$		
Total systemic exposure (absorbed dose)	0,00453153	mg/person	Total systemic exposure (absorbed dose)	0,00218874	mg/person
Total systemic exposure (absorbed dose)	**0,0000755**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0,0001355**	**mg/kg bw/d**
% of AOEL:	**0,54**	**%**	**% of AOEL:**	**0,97**	**%**

B.6.4.2.2. Measurement of bystander and resident exposure

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

B.6.4.3. Worker exposure

Worker exposure estimation to PUMA S 69 EW was calculated without PPE on the basis of the "EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products" after application in cereals for inspection. Exposure predictions were obtained out of the available version of the currently exposure calculation spreadsheet . Details of calculations are given in CP 7.2.3.1. The results of exposure calculations are summarized in Table 6.4.3-1.

Table 6.4.3-1 Predicted systemic worker exposure (mg FPP/kg bw/day) as a proportion of the AOEL

Crop	PPE	Total systemic exposure (mg FPP[#]/kg bw/day)[**]	% of AOEL[****]
Re-entry in cereals	Without PPE[*]	0.0031	22.41

[*] work wear – arms, body and legs covered, bare hands; [**] 60 kg body weight; dermal absorption 0.7% concentrate and 27% dilution; inhalation absorption 100%; [****] 0.014 mg/kg bw/day.
[#] FPP = fenoxaprop-P-ethyl

Assessment

The results of the calculations reveal that the situation is favourable for worker after re-entry in cereals treated with PUMA S 69 EW.

The exposure predictions of systemic worker exposure account for 22.41% of the AOEL (0.014 mg/kg bw/day) without PPE.

Conclusion
Based on above presented results there is no unacceptable risk anticipated for worker with the intended uses of PUMA S 69 EW in cereals considering fenoxaprop-P-ethyl.

B.6.4.3.1. Estimation of worker exposure

Worker exposure estimations to PUMA S 69 EW were calculated on the basis of EFSA[2,3]. The calculation details are presented in Table 6.4.3-3.

Critical GAP
Critical GAP for operator exposure are presented in Table 6.4.3-2

Table 6.4.3-2 Critical GAP for worker assessment

Crop	Application technique	Dose (L/ha)	Active substance applied (a.i kg/ha)	Volume applied (L/ha)**	Max No of treatment
Cereal	Tractor boom	1.2	0.083 (fenoxaprop-P-ethyl) 0.090 (mefenpyr-diethyl)	100 to 400	1

Table 6.4.3-3 Predicted systemic exposure to fenoxaprop-P-ethyl according to EFSA. (Downward spraying. Vehicle-mounted. Re-entry in cereals, without and with PPE)

Substance	fenoxaprop-P-ethyl	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate- 0.083 kg a.s. /ha	Spray dilution = 0.83 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 0.7	Dermal for in use dilution = 27	Oral = 100	Inhalation = 100	
RVNAS	0.014 mg/kg bw/day				
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0280	% of RVNAS	200.09%
	Working clothing mg/kg bw/day	0.0031	% of RVNAS	22.41%

RVNAS = Reference value non acutely toxic active substance (equivalent to AOEL)

B.6.4.3.1.1. Measurement of worker exposure

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

B.6.5. EXPOSURE AND RISK ASSESSMENT

Detailed exposure with result tables are provided in the relevant exposure sections under B.6.4 Exposure data.

B.6.6. REFERENCES RELIED ON

A literature search was performed according to the EFSA guidance document "Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009" (EFSA Journal 2011; 9(2): 2092). No specific search was included for any product names. For further details please refer to Volume 3 CA_B-6.

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCP 7.1.1 /01	[redacted]	1993	Acute oral toxicity in the male and female Wistar rat Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702 [redacted] Bayer CropScience, Report No.: A51244, Edition Number: M-132214-01-1 Date: 1993-08-25 GLP/GEP: yes, unpublished	Y	N		Bayer Crop-Science	Yes, in DAR (2005)
KCP 7.1.2 /01	[redacted]	1993	Acute dermal toxicity in the female and male Wistar rat Fenoxa-prop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702 [redacted] Bayer CropScience, Report No.: A51088, Edition Number: M-132066-01-1 Date: 1993-07-12 GLP/GEP: yes, unpublished	Y	N		Bayer Crop-Science	Yes, in DAR (2005)
KCP 7.1.3 /01	[redacted]	1993	Acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC50 Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702 [redacted] Bayer CropScience, Report No.: A51050, Edition Number: M-132032-01-1 Date: 1993-07-14 GLP/GEP: yes, unpublished	Y	N		Bayer Crop-Science	Yes, in DAR (2005)
KCP 7.1.4 /01	[redacted]	1993	Primary dermal irritation in the rabbit Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702 [redacted] Bayer CropScience, Report No.: A51087, Edition Number: M-132065-01-1 Date: 1993-07-14 GLP/GEP: yes, unpublished	Y	N		Bayer Crop-Science	Yes, in DAR (2005)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCP 7.1.5 /01	[redacted]	1993	Primary eye irritation in the rabbit Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A701 [redacted] Bayer CropScience, Report No.: A50455, Edition Number: M-131472-01-1 Date: 1993-04-20 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2005)
KCP 7.1.6 /01	[redacted]	1993	Sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Fenoxaprop-P-ethyl oil in water emulsion 69 g/L Code: Hoe 046360 24 EW14 A702 [redacted] Bayer CropScience, Report No.: A51451, Edition Number: M-132385-01-1 Date: 1993-09-24 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2005)
KCP 7.1.6 /02	[redacted]	2002	Skin sensitization in the guinea pig (Buehler method) AE F046360 24 EW14 A7 [redacted] Bayer CropScience, Report No.: C021468, Edition Number: M-211263-01-1 Date: 2002-01-25 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2005)
KCP 7.1.6 /03	[redacted]	2006	Fenoxaprop-P-ethyl + Mefenypr-diethyl EW 69 + 75 g/l - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse [redacted] Bayer CropScience, Report No.: SA 06100, Edition Number: M-273147-01-1 Date: 2006-06-12 GLP/GEP: yes, unpublished	Y	Y	Study was done to evaluate the senitising potential of the representative product according to the latest available testing standard	Bayer CropScience	Submitted for the purpose of renewal

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCP 7.1.7 /01	[redacted]	1990	Repeated-dose dermal toxicity study (21 applications within 29 days) in rats with a 14-day withdrawal period [redacted] Bayer CropScience, Report No.: A42695, Edition Number: M-125685-01-1 Date: 1990-01-03 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	Yes, in DAR (2005)
KCP 7.2.1.1 /01	Salahud, D.; Hamey, P. Y.	1993	Instructions for use of POEM (EXCEL spreadsheet) Predictive operator exposure model (POEM): a users guide Bayer CropScience, Report No.: C019013, Edition Number: M-207102-01-1 Date: 1993-05-27 GLP/GEP: n.a., unpublished	N	N		Bayer CropScience	Yes, in DAR (2005)
KCP 7.2.1.1 /02	Krieger, R. I.; Ross, J. H.; Tian, T.	1992	Assessing human exposures to pesticides Journal:Reviews of Environmental Contamination and Toxicology, Volume:128, Pages:1;15, Year:1992, Report No.: C019011, Edition Number: M-207099-01-1 GLP/GEP: n.a., published	N	N		Public data	Yes, in DAR (2005)
KCP 7.2.2.1 /01	Ganzelmeier, H.; Rautmann, D.; Spangenberg, R.; Streloke, M.; Herrmann, M.; Wenzelburger, H. J.; Walter, H. F.	1995	Studies on the spray drift of plant protection products Results of a test program carried out throughout the Federal Republic of Germany Journal:Mitteilungen aus der Biologischen Bundesanstalt fuer Land- und Forstwirtschaft Berlin-Dahlem, Issue:305, Pages:1;111, Year:1995, Report No.: A56850, Edition Number: M-140628-01-1 GLP/GEP: n.a., published	N	N		Public data	Yes, in DAR (2005)

Annex point / reference number	Author(s)	Year	Title Source *(where different from company)* Company name, Report No., Date, GLP status *(where relevant)*, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
KCP 7.2.2.1 /02	Lloyd, G. A.; Bell, G. J.	1983	Hydraulic nozzles: Comparative spray drift study Year:1983, Report No.: C020610, Edition Number: M-209884-01-1 GLP/GEP: n.a., published	N	N		Public data	Yes, in DAR (2005)
KCP 7.3 /01	Dick, I.	2000	Comparative in vitro dermal penetration study in human and rat skin applied as an oil in water suspension (14C)-fenoxaprop-P-ethyl Code: AE F046360 24 EW07 A5 Huntingdon Life Sciences Ltd., Huntingdon, United Kingdom Bayer CropScience, Report No.: C007848, Report includes Trial Nos.: TOX98095 Edition Number: M-196782-01-1 Date: 2000-03-28 GLP/GEP: yes, unpublished	N	N		Bayer Crop-Science	Yes, in DAR (2005)
KCP 7.3 /02	[redacted]	2002	(14C)-fenoxaprop-P-ethyl: In vivo dermal absorption in the rat using an oil in water emulsion formulation coded: AE F046360 24 EW14 A7xx [redacted] Bayer CropScience, Report No.: 1490/021, Report includes Trial Nos.: 1490/021-D1145 NG31555 Edition Number: M-208696-01-2 EPA MRID No.: 47113321 Date: 2002-07-03 GLP/GEP: yes, unpublished	Y	N		Bayer Crop-Science	Yes, in DAR (2005)

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KCP 7.3 /03	Bernal, J.	2015	In-vitro human skin penetration of 14C-fenoxaprop-P-ethyl in the fenoxaprop-P-ethyl and mefenpyr-diethyl EW 69+75 formulation Eurofins Agroscience Services, Chem SAS, Vergèze, France Bayer CropScience, Report No.: S14-02497, Edition Number: M-533620-01-1 Date: 2015-06-25 GLP/GEP: yes, unpublished	N	Y	required for refinement of non-dietary risk assessments	Bayer CropScience	Submitted for the purpose of renewal