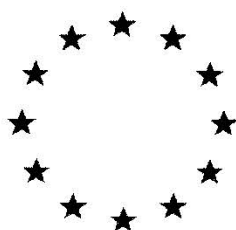


# ***European Commission***



**Draft Renewal Assessment Report prepared according to the Commission  
Regulation (EU) N° 1107/2009**

## **ETHOFUMESATE**

### **Volume 3 – B.6 (PPP) – Ethofumesate SC 500**

Rapporteur Member State: Austria  
Co-Rapporteur Member State: Denmark

**Version History**

<b>When</b>	<b>What</b>
1998	Initial DAR, RMS SE (no addenda to DAR containing additional information on toxicology and metabolism could be identified on CIRCABC or were provided by the original RMS SE)
2015/01	DRAR

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

Search in the scientific peer reviewed open literature was conducted, covering a period from 2003 to 2013. The notifier stated that the literature search was conducted according to EFSA Guidance “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. [49 pp.]).

The TaskForce conducted the search using only the name of active substance, known metabolites and its trade names without considering any toxicological keywords. Regarding the inclusion of the trade names in the search it is considered that this should be done case by case (if it is known that the formulation has a higher toxicity than the active substance) since trade names might tremendously increase the “background noise” (amount of information not related to the topic) in the search.

After the rapid and the full-text assessment the TaskForce concluded that none of the articles retrieved was relevant regarding the properties of the formulations containing ethofumesate. After detailed assessment of the chosen approach for the literature search, the RMS concluded that the TaskForce appropriately addressed the scientific peer reviewed open literature for the representative formulation.

### **B.6.1. ACUTE TOXICITY OF PLANT PROTECTION PRODUCT**

One representative formulation, Ethofumesate SC 500 (Specification No. 102000002286-03) was submitted by the TaskForce (BayerCrop Science and Adama, former Feinchemie Schwebda). The studies on acute oral toxicity, acute dermal toxicity, skin irritation, eye irritation and Buehler method for skin sensitization were already evaluated in the original DAR (1998). All these studies were conducted with very similar formulation Nortron 50 SC (AE B04991300SC45 A1) (for comparison of formulations please see Volume 4).

No acute inhalation toxicity study was submitted/evaluated in the original DAR (1998). Based on the new data requirements (Commission regulation (EU) No 284/2013) where it is stated that an acute inhalation toxicity study is required if *(i) PPP is to be applied by spraying*, the TaskForce was asked to provide arguments why no acute inhalation study with Ethofumesate SC 500 is necessary. Upon this request the TaskForce submitted an acute inhalation toxicity study with comparable formulation Nortron SC (Specification No. 102000013443-01) (for comparison of formulations please see Volume 4).

Regarding the skin sensitization the notifier submitted, additionally to Buehler 3 induction test originally evaluated in the DAR (1998) and having only limited acceptability according to new OECD guideline, also an LLNA test conducted with comparable formulation AE B04991300SC45 A2 (for comparison of formulations please see Volume 4).

#### **B.6.1.1. Oral**

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<b>Reference:</b>	NORTON 50 SC (CR 18654/7): RAT ACUTE ORAL TOXICITY STUDY
Author(s), year:	██████████ 1989
Report/Doc. number::	A83199 / M-155471-01-1
Guideline(s):	OECD 401 (1987)
GLP:	Yes
Deviations:	No

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Acceptability:	Yes
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### Materials and Methods

Nortron 50 SC was administered by gavage to five male and five female Sprague-Dawley rats which were 6-7 weeks old. The test material (2 ml/kg bw) was administered undiluted at the dose level of 2100 mg/kg bw. The observation period was 14 days. Gross pathological examination (external examination and necropsy) was performed in all animals that died during study procedure or were sacrificed at study termination.

### Results

No mortalities and no clinical signs were observed during the study. The oral LD<sub>50</sub> for male and female rats is concluded to be > 2100 mg/kg. All animals gained weight during the study. No treatment related macroscopic pathological changes were noted at necropsy.

### Conclusions

Under the conditions of the study and based on the information given in the study report, the oral LD<sub>50</sub> of Nortron 50 SC is greater than 2100 mg/kg bw in rats. Thus, no classification is required for the comparable formulation Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

#### B.6.1.2. Dermal

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<b>Reference:</b>	NORTRON 50 SC (CR 18654/7): RAT ACUTE DERMAL TOXICITY STUDY
Author(s), year:	1989
Report/Doc. number::	A83200 / M-155472-01-1
Guideline(s):	OECD 402 (1981)
GLP:	Yes
Deviations:	No
Acceptability:	Yes

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### Material and Methods

Approximately 24 hours prior to the application of the test item Nortron 50 SC, five Sprague-Dawley rats of each sex were shaven closely with electric clippers. Nortron 50 SC was applied topically undiluted at the dose level of 4100 mg/kg. A piece of aluminium foil was placed over the treatment area. The test item remained in contact with the skin of each animal for 24 hours. After the treatment time the plaster and foil were removed and the treated skin washed with soap and water to remove residual test item. Gross pathological examination (external examination and necropsy) was performed in all animals that died during study procedure or were sacrificed at study termination.

### Results

There were no mortalities and no treatment related clinical signs during the study. The dermal LD<sub>50</sub> for male and female rats is concluded to be > 4100 mg/kg. All animals gained weight during the study. No treatment related macroscopic pathological changes were noted at necropsy.

## Conclusion

Under the conditions of the study and based on the information given in the study report, dermal LD<sub>50</sub> in male and female rats was above 4100 mg/kg bw. Thus, no classification is required for the comparable formulation Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

### B.6.1.3. Inhalation

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<b>Reference:</b>	Acute inhalation toxicity study in rats (Nortron SC)
Author(s), year:	██████████ 2008
Doc. number::	M-327134-01-1
Guideline(s):	OECD 403 (1981)
GLP:	Yes
Deviations from OECD 403 (2009):	No
Acceptability:	Yes

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## Materials and Methods

5 male and 5 female albino Sprague-Dawley rats, 10 to 11 weeks old, received a 4-hour nose-only exposure to Nortron SC. The highest attainable concentration was 2.6 mg/L. MMAD was 2.4 µm. Gross pathological examination was performed in all animals. Tissues and organs of the thoracic and abdominal cavities were examined.

## Results

No mortalities were observed. The inhalative LC<sub>50</sub> for male and female rats is concluded to be > 2.6 mg/L, the highest attainable concentration. No clinical signs were observed during 14-days observation period. All animals gained weight during the study. No treatment related macroscopic pathological changes were noted at necropsy.

## Conclusions

Under the conditions of the study and based on the information given in the study report, inhalative LC<sub>50</sub> in male and female rats was above 2.6 mg/L when exposed nose-only to Nortron SC for four hours. Thus, no classification is required for the comparable formulation Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

### B.6.1.4. Skin irritation

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<b>Reference:</b>	NORTRON 50 SC CR 18654/7: RABBIT SKIN IRRITANCY STUDY
Author(s), year:	██████████ 1989
Report/Doc. number::	A83201 / M-155473-01-1
Guideline(s):	OECD 404 (1981)
GLP:	Yes
Deviations from OECD (2002):	No
Acceptability:	Yes

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### Materials and Methods

One day prior to the application of Nortron 50 SC, three female New Zealand White rabbits were clipped free of fur from the dorso-lumbar region. 0.5 ml of the test item was applied under a gauze patch. The patch was secured in position with Elastoplast. The test substance remained in contact with the skin of each animal for 4 hours. Afterwards the patches were removed and any residual test material removed by washing with water and soap. Approximately one hour following the removal of the patches and 24, 48 and 72 hours later, the test sites were examined for evidence of primary irritation and scored.

### Results

The overall mean erythema and oedema scores from the 24-, 48- and 72-hour observations were both 0.00. Nortron 50 SC is considered as non-irritant to skin.

### Conclusions

Under the conditions of the study and based on the information given in the study report, rabbits exposed dermally to Nortron 50 SC for four hours did not develop any sign of skin irritation. Thus, no classification is required for the comparable formulation Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

#### B.6.1.5. Eye irritation

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<b>Reference:</b>	NORTRON 50 SC, CR 18654/7: RABBIT EYE IRRITANCY STUDY
Author(s), year:	████████████████████ 1989
Report/Doc. number::	A83202 / M-155474-01-1
Guideline(s):	OECD 405 (1987)
GLP:	Yes
Deviations from OECD (2012):	- It is not reported in the study if the eyes were rinsed with saline or distilled water
Acceptability:	Yes

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### Materials and Methods

On the day of dosing, 0.1 ml of Nortron 50 SC was applied into the conjunctival sac of one eye of three female New Zealand White rabbits. The eyelids were then gently held together for about one second and released to allow the animal to blink freely. The other eye of each rabbit was not treated and served as a control. It is not reported in the study if the eyes were rinsed with saline or distilled water after 24 hours. The cornea, iris, and conjunctiva of the treated and control eyes were examined with a standard ophthalmoscope prior to the test and at 1, 24, 48, and 72 hours after treatment.

### Results

Very slight chemosis of the conjunctivae of one rabbit was seen 24 hours after instillation and had reversed by 48 hours. No other irritation signs were observed. Nortron 50 SC is considered to be non-irritant to eyes.

### Conclusions

Under the conditions of the study and based on the information given in the study report, rabbit eyes exposed to Nortron 50 SC developed only slight signs of irritation. Thus, no classification is required for the comparable formulation Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

#### B.6.1.6. Skin sensitization

##### *B.6.1.6.1. Buehler test*

<b>Reference:</b>	Nortron 50, SC CR 18654/7: Delayed contact hypersensitivity study in the Guinea-pig (Buehler test)
Author(s), year:	██████████ 1989
Report/Doc. number::	A83204 / M-155476-01-1
Guideline(s):	OECD 406 (1981)
GLP:	Yes
Deviations from OECD (1992):	- Only 10 animals per treatment group
Acceptability:	Limited information; the number of animals used in the treatment group (10) too low for the Buehler test, however positive control (formalin) with also 10 animals gave appropriate results

#### Materials and Methods

Nortron 50 SC was tested according to Buehler test (3 inductions) on female guinea pigs of the Dunkin-Hartley strain. Undiluted Norton 50 SC was chosen for the main study for induction and challenge phase, since no irritation was observed in the preliminary investigations.

Patch of the surgical gauze was saturated with approximately 0.5 ml of Nortron 50 SC and placed on the skin of ten guinea pigs clipped free of hair on the left shoulder region. Contact with the skin was maintained for approximately 6 hours for each induction exposure. The challenge sites were evaluated 24, 48 and 72 hours after removal of the patches. The control animals were treated similarly to the test animals with the exception that the test compound was omitted. The test and control animals were challenged topically on the right flank two weeks after the third induction application using 0.5 ml undiluted Nortron 50 SC. The sensitivity of the strain was checked in the laboratory periodically with formalin, showing positive results.

#### Results

No dermal reactions were seen in any of the test or control animals either after induction or after challenge phase.

#### Conclusion

Under the conditions of the study and based on the information given in the study report, none of the treated guinea pigs showed dermal sensitising reaction, however, number of animals used for the treated group was too low and additionally, only 3 inductions were applied.

**B.6.1.6.2. Local lymph node assay (LLNA)**

<b>Reference:</b>	Ethofumesate SC 500 (AE B049913 00 SC45 A2) (Project: Ethofumesate) - Local lymph node assay in mice (LLNA/IMDS)
Author(s), year:	██████████ 2005
Report/Doc. number::	AT02190 / M-257228-01-1
Guideline(s):	OECD 429 (2002)
GLP:	Yes
Deviations from OECD 429 (2010):	- study finalised on Day 4 and not Day 6 - no historical control data overview included in the study report, only statement on validation - no information on clinical observations in the study report
Acceptability:	Limited information based on shorter duration and absence of real positive control for sensitisation

**Materials and Methods**

Ethofumesate SC 500 was tested according to modified LLNA assay (cell counting) on female NMRI mice. Although not the species of choice according to OECD 429 (2010), NMRI strain was validated for modified (cell counting) LLNA in series of intra- and inter-laboratory validation testings. 6 animals per group were used. The groups were vehicle (Pleuronic PE 9200 / 0.9% NaCl solution 1%), 2% test item, 10% test item and 50% test item containing positive control (50% test item and 2% p-benzoquinone). RMS notes that p-benzoquinone is not a positive control for skin sensitisation (and not recommended by OECD 429) but a skin irritating substance. Therefore, it is considered that there was no concurrent positive control. However, it is stated in the study report that the NMRI strain is validated in the laboratory using Alpha Hexyl Cinnamic Aldehyde formulated in different vehicles at 3%, 10% and 30%. However, no detailed information on positive historical control data was included in the study report.

The test item and the positive control in the test item were applied epicutaneously onto the dorsal part of both ears of the animals. The treatment was repeated on 3 consecutive days. On day 4 the animals were sacrificed. The weight and cell count determinations were carried out by appropriate laboratory procedures. Before the first treatment and before sacrifice the thickness of both auricles of the animals was measured. The body weights were recorded at the start and at the end of the study.

The "positive levels" mentioned in the study are exclusively defined for the NMRI outbred mice. Such positive limits have to be calculated for each strain of mice individually.

**Results**

The NMRI mice did not show an increase in the stimulation indices for cell counts (validated threshold of 1.4 for cell counting LLNA in NMRI mice) or for weights of the draining lymph nodes after application of the test item. The positive level of ear swelling (about 10% increase) has not been reached in any dose group. In the positive 2% p-benzoquinone group the weights and cell counts of the draining lymph nodes as well as ear swelling and ear weight were statistically significantly increased and cell count index of 1.4 for NMRI mice exceeded. The body weights were not affected by the treatment.

**Table B.6.1.6.2-1. Tabular summary of LLNA results**

Group	Weight index	Cell count index (+/- SD of mean in %)	Ear swelling (mean +/- SD in %)		Ear swelling index Day 4	Ear weight (mean +/- SD in %) Day 4	Ear weight index Day 4
			Day 1	Day 4			
Vehicle Control	1.00	1.00 +/- 36.42	17.33 +/- 4.49	17.25 +/- 4.37	1.00	11.42 +/- 4.88	1.00
2%	1.12	1.01 +/- 14.54	17.92 +/- 3.73	17.83 +/- 4.02	1.03	11.67 +/- 7.47	1.02
10%	1.18	0.87 +/- 37.64	17.17 +/- 3.36	17.42 +/- 2.96	1.01	10.81 +/- 5.56	0.95
50%	1.00	0.66 +/- 13.45	17.00 +/- 3.55	17.33 +/- 3.76	1.00	11.15 +/- 3.85	0.98
positive control (50% test item and 2% p-benzoquinone)	1.86*	1.79* +/- 16.42	16.75 +/- 3.71	18.25* +/- 3.41	1.06	14.02* +/- 11.08	1.23

\* Statistically significant increase ( $p \leq 0.05$ ), Mann-Whitney or Wilcoxon significance test

### Conclusion

Under the conditions of the study and based on the information given in the study report, Ethofumesate SC 500 does not have skin sensitising or skin irritating properties, however, the application regime was shorter (4 days) and no real positive control was included. Nonetheless, based on the overall picture, no classification is proposed for Nortron 50 SC (and comparable representative formulation) Ethofumesate SC 500 according to the classification criteria of Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

#### B.6.1.7. Supplementary studies on the plant protection product

No supplementary studies on the representative formulations were submitted and not considered necessary.

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

Ethofumesate SC 500 is not used in association with other plant protection products. No supplementary study is required.

### B.6.2. DERMAL ABSORPTION

In the original DAR (1998) no studies on dermal absorption were submitted. For the purpose of renewal the TaskForce submitted an *in vitro* dermal absorption study through human and rat skin conducted with the comparable formulation Nortron SC 500 (for comparison of formulations please see Volume 4).

<b>Reference:</b>	Nortron SC 500 formulation: [14C]-ethofumesate comparative in vitro dermal absorption study using human and rat skin
Author(s), year:	██████████ 2011
Report/Doc. number::	SA 11099 / M-415675-01-1
Guideline(s):	OECD 428 (2004)
GLP:	Yes
Deviations from OECD:	No
Acceptability:	Yes

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**Materials and methods****Rat skin:**

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

Source: R. Janvier (France).

Sex: Male (16).

Anatomical site: Dorsal.

Rat skin Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of ca 440 to 550 µm in thickness.

Human skin: Source: Biopredic, Rennes, France.

Number and sex: 9 donors, female.

Anatomical region: Abdomen.

Thickness: 456 to 586 µm.

**Test Material:**

Non- Batch: R000047.

radiolabelled: Purity = 99.9% w/w.

Radiolabelled: [<sup>14</sup>C]-ethofumesate

Batch: KML 3563-1.

Specific activity: 3.78 MBq/mg.

Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the Nortron SC 500 formulation used at three nominal concentrations: 500 g a.s./L, 10 g a.s./L and 0.5 g a.s./L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm<sup>2</sup> skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300®, System, Courage & Khazaba) was placed securely on the top of the donor chamber

and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm<sup>2</sup> were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study

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

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

**Radioassay:** The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail and were regularly checked by the use of [<sup>14</sup>C]-n-hexadecane standards. The scintillation counter was recalibrated when a deviation of greater than 2% was observed when counting quality control standards. The limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails.

## Results

[<sup>14</sup>C]-ethofumesate was demonstrated to be soluble in the receptor fluid up to the concentration of 0.51 mg/mL of receptor fluid. The maximal hourly achieved concentration of [<sup>14</sup>C]- ethofumesate in the receptor fluid was 1.31 µg/mL. As the achieved concentrations were at least 389 times lower than the determined solubility



concentration, the solubility in the receptor fluid was deemed to be sufficient to have reduced any risk of back diffusion.

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

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 96.5% to 103.4% of the applied dose.

The study results are presented in the following table.

**Table 6.2-1: Mean distribution of radioactivity at 24 hours after dose application of [<sup>14</sup>C]- ethofumesate in an SC 500 formulation at the rates of 500 g/L, 10 g/L and 0.5 g/L to human and rat skin samples.**

Results expressed in terms of percentage of applied radioactivity.

Dose Levels	Distribution of radioactivity (% dose)											
	Neat formulation: High dose (SYP13653, 500 g/L)				Dilution: Intermediate dose (SYP13656, 10 g/L )				Dilution: Low dose (SYP13658, 0.5 g/L )			
	Human (n=6)		Rat (n=6)		Human (n=6)		Rat (n=4)		Human (n=5)		Rat (n=4)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<b>SURFACE COMPARTMENT</b>												
Skin swabs (8h)	101.7	5.69	94.61	5.40	96.67	2.31	95.98	2.43	92.14	3.79	69.76	2.36
Skin swabs (24h) <sup>a</sup>	0.14	0.12	1.27	0.75	0.61	0.63	0.09	0.07	1.14	0.91	5.30	6.65
Surface Dose (tape-strips 1&2)	0.16	0.17	3.71	1.99	0.64	0.72	0.14	0.11	0.22	0.13	0.44	0.26
Donor chamber	0.03	0.04	0.12	0.09	0.02	0.01	0.02	0.02	0.10	0.06	0.59	0.40
<b>Total % non-absorbed</b>	<b>102.0</b>	<b>5.56</b>	<b>99.71</b>	<b>4.39</b>	<b>97.93</b>	<b>1.44</b>	<b>96.23</b>	<b>2.54</b>	<b>93.60</b>	<b>3.64</b>	<b>76.09</b>	<b>6.37</b>
<b>SKIN COMPARTMENT</b>												
Skin <sup>b</sup>	0.04	0.02	0.27	0.41	0.18	0.20	0.03	0.02	0.16	0.08	0.31	0.24
Stratum corneum <sup>c</sup>	0.06	0.03	2.98	2.98	0.51	0.46	0.11	0.17	0.27	0.17	0.47	0.40
<b>Total % at dose site</b>	<b>0.10</b>	<b>0.05</b>	<b>3.25</b>	<b>3.26</b>	<b>0.69</b>	<b>0.65</b>	<b>0.14</b>	<b>0.18</b>	<b>0.43</b>	<b>0.24</b>	<b>0.78</b>	<b>0.64</b>
<b>RECEPTOR COMPARTMENT</b>												
Receptor fluid (0-24h)	0.03	0.02	0.22	0.12	0.37	0.21	0.67	0.23	5.14	1.67	18.73	4.91
Receptor fluid terminal	n.d.	n.a.	0.03	0.00	0.01	0.01	0.01	0.01	0.03	0.03	0.18	0.04
Receptor chamber	0.07	0.18	0.15	0.37	n.d.	n.a.	0.24	0.49	0.57	0.05	0.74	0.22
<b>Total % directly absorbed<sup>d</sup></b>	<b>0.11</b>	<b>0.19</b>	<b>0.40</b>	<b>0.46</b>	<b>0.38</b>	<b>0.21</b>	<b>0.92</b>	<b>0.33</b>	<b>5.73</b>	<b>1.69</b>	<b>19.65</b>	<b>4.88</b>
<b>Total % Potentially Absorbable</b>	<b>0.20</b>	<b>0.20</b>	<b>3.65</b>	<b>3.10</b>	<b>1.07</b>	<b>0.83</b>	<b>1.06</b>	<b>0.41</b>	<b>6.16</b>	<b>1.71</b>	<b>20.43</b>	<b>4.40</b>
<b>TOTAL % RECOVERY</b>	<b>102.2</b>	<b>5.54</b>	<b>103.4</b>	<b>1.86</b>	<b>99.00</b>	<b>1.51</b>	<b>97.29</b>	<b>2.91</b>	<b>99.76</b>	<b>4.24</b>	<b>96.53</b>	<b>3.14</b>

<sup>a</sup>: sum of radioactivity found in swabs at termination and in surrounding swabs.

<sup>b</sup>: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.

<sup>c</sup>: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

<sup>d</sup>: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.

<sup>e</sup>: total % directly absorbed + total % at dose site

SD: standard deviation

n.d.: not detected (below the limit of detection)

n.a. : not applicable

n: number of skin cells used for calculation

In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

## Conclusion

The dermal penetration of [<sup>14</sup>C]-ethofumesate through human and rat dermatomed skin from the Nortron SC 500 formulation was investigated at three concentrations corresponding to the neat product (500 g/L) and to two representative dilutions (10 and 0.5 g/L), respectively.

Overall, the dermal penetration of [<sup>14</sup>C]-ethofumesate in the SC 500 formulation was low at all concentrations used.

The mean percentage of [<sup>14</sup>C]-ethofumesate in the SC 500 formulation that was considered to be potentially absorbable (*directly absorbed plus total remaining at dose site*) over a period of 24 hours for the neat formulation was 0.2% and 3.7% for the human and rat skin, respectively.

The mean percentage of [<sup>14</sup>C]-ethofumesate in the SC 500 formulation that was considered to be potentially absorbable (*directly absorbed plus total remaining at dose site*) over a period of 24 hours for the intermediate dose rate was 1.1% for both the human and rat skin.

The mean percentage of [<sup>14</sup>C]-ethofumesate in the SC 500 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 6.2% and 20.4% for the human and rat skin, respectively.

According to the new EFSA guidance<sup>1</sup> 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 84<sup>th</sup> percentile value of the results. Thus, the application of the guidance results in the following values for [<sup>14</sup>C]-ethofumesate in the Nortron SC 500 formulation (ETO SC 500):

- 0.4% for the neat formulation (500 g/L)
- 2% for the intermediate dose (10 g/L)
- 8% for the low dose (0.5 g/L).

According to the GAP for representative uses, the highest dilution is 0.5 g/L (0.2 kg/ha ethofumesate in 400 L) and the lowest 10 g/l (1 kg/ha ethofumesate in 100 L). Both dilutions are covered by the calculated dermal absorption.

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

Available toxicological data for each co-formulant can be found in the confidential part of the dossier and in Volume 4.

### **B.6.4. EXPOSURE DATA**

Ethofumesate SC 500 is a suspension concentrate formulation containing 500 g a.s./L ethofumesate. The product is used as an herbicide in sugar beet, fodder beet and red beet. Non-dietary exposure is estimated and subsequent risk assessments are made for operators, bystanders/residents and workers. Exposure estimates are based on the respective critical GAP (cGAP) for the relevant scenario providing the highest exposure estimate.

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<sup>1</sup> 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.

Non-dietary risk assessment is made assuming exposure to total ethofumesate as a mixture of both enantiomers and comparison with the ethofumesate AOEL (2.5 mg/kg bw/d). The AOEL is established from toxicological studies using the racemic mixture (50:50).

Operators, workers, bystanders and residents are expected to be always exposed to the racemate. The enantiomer ratio was shown to be stable in the environment (both the water/sediment study as well as the lysimeter study in soil) demonstrating that there is no enantio-selective microbial degradation or photolysis. Therefore, a change of the ratio is neither expected in the spray volume (relevant for the operator and the bystander) nor in leaf surface deposits (relevant for workers and residents).

As the enantiomeric ratio of ethofumesate isomers is stable in the environment additional safety factors for the AOEL are not necessary and the non-dietary risk assessment is considered to cover the worst case exposure scenario.

#### B.6.4.1. Operator exposure

Exposure of operators is estimated using the UK-POEM and the German Model. A summary of the critical GAP used for operator risk assessment is presented in Table 6.4.1-1.

**Table 6.4.1-1 Summary of critical GAP for operator exposure evaluations**

Crop (grouping)	F/ G	Application method	UK-POEM		German Model
			Dose rate(kg a.s./ha)	Water volume (L/ha)	Dose rate (kg a.s./ha)
Sugar beet, fodder beet, red beet	F	Field crop sprayer	1.0	100	1.0

#### Justification:

The product will be applied with tractor-mounted/-trailed field crop (boom) sprayers. The cGAP will result in the maximum exposure. Differences in the application rate are accounted for by using the maximum application rate (1.0 kg a.s./ha) when using the German Model. The critical GAP when using the UK-POEM results from a combination of highest dose rate with lowest water volume.

The representative use scenario includes different spray concentrations for which different dermal absorption data are available. In order to determine the cGAP when using the UK-POEM possible dose rate/water volume combinations with the relevant dermal absorption and the resulting exposures (unprotected operator) were calculated. For UK-POEM, where the worst case is estimated to be a concentration of 10 g/L, dermal absorption of 2% is considered appropriate. In German Model, dermal absorption of 8% for lowest dilution (0.5 g/L) is taken into account.

The product is sold in 1 L and 5 L containers. The 5 L narrow closure container is considered in the calculations as the worst case for UK-POEM.

Table 6.4.1-2: Predicted operator exposure

Crops	F/ G	Application method	PPE	Systemic exposure * (mg/kg bw/day)		% of AOEL (2.5 mg/kg bw/day)	
				UK-POEM*	German Model**	UK- POEM*	German Model**
Sugar beet, fodder beet, red beet	F	Field crop sprayer	No <sup>1</sup>	0.28183	0.0498	11	2
			With <sup>2</sup>	0.03817	0.0037	2	< 1

<sup>1</sup> No PPE: German Model: Operator wearing T-shirts and shorts; UK POEM: Operator wearing long sleeved shirt, long trousers (“permeable”) but no gloves

<sup>2</sup> With PPE: German Model: Coverall/sturdy footwear during application and gloves during mixing/loading and application; UK POEM: gloves during mixing/loading and application

\* Dermal absorption of 0.4% (concentrate) and 2% (spray), 100% absorption *via* inhalation route

\*\* Dermal absorption of 0.4% (concentrate) and 8% (spray), 100% absorption *via* inhalation route

## Conclusion

Exposure of unprotected operators is estimated to be 11% of the AOEL in the UK-POEM and 2% of the AOEL in German Model if no PPE is worn. Thus, it is concluded that the use of Ethofumesate SC 500 does not result in an unacceptable risk for operators.

## B.6.4.2. Bystander and resident exposure

A harmonized European guidance for the estimation of bystander and resident exposure is not available. The German guidance (Martin, S. et al., 2008)<sup>2</sup> is chosen in the following evaluation.

The cGAP for bystanders and residents is presented in the following table. Bystanders and residents will be exposed during and after spray applications in the field by off-target drift.

Table 6.4.2-1: Summary of critical GAPs for bystanders and residents

Crop (grouping)	Application technique	Max. dose rate (kg a.s./ha)	No. of applications	% Drift (1 appl., 90 <sup>th</sup> perc., 1 m)
Beet crops	Field crop sprayer	1.0	1	2.77

Justification of the selection of the critical GAP:

The exposure scenario for field crop spray application with off-target drift is in this case to be considered with a maximum dose rate. The worst case for the resident is also the single exposure to 1 kg ethofumesate per hectare. A minimum distance of 1 m in arable crops is considered.

Table 6.4.2-2: Predicted systemic exposures as a proportion of the AOEL

Target group	Scenario	Total systemic exposure (mg/kg bw/d)*	AOEL (mg/kg bw/d)	% of AOEL
Bystander	Adult	0.0037	2.5	0.15
	Child	0.0029		0.12

<sup>2</sup> Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G.: Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application, J. Verbr. Lebensm. 3, 272-28, 2008

Resident	Adult	0.0044	2.5	0.18
	Child	0.0085		0.34

\* Assumes a 60 kg bodyweight for an adult and 16.15 kg for a child

Absorption: 8% (spray) via the dermal route, 100 % via the inhalation route

### Conclusion

Exposure is calculated for a distance of 1 m to the application equipment. Estimates of adult and child bystander exposure are 0.15% and 0.12% of the AOEL, respectively. Estimates of adult and child resident exposure are 0.18% and 0.34% of the AOEL, respectively. Thus, it is concluded that the use of Ethofumesate SC 500 does not result in an unacceptable risk for bystanders and residents.

### B.6.4.3. Worker exposure

The evaluation of worker exposure provided in the EUROPOEM II report<sup>3</sup> is recommended for four different manual harvesting scenarios with bare hands:

Crop group	Transfer Coefficient (cm <sup>2</sup> /h)
Fruits (from trees):	4500
Vegetables:	2500
Ornamentals:	5000
Strawberries:	3000

Ethofumesate SC 500 will only be used in beet crops for which a re-entry scenario is not defined. A possible scouting scenario is considered for risk assessment assuming duration of 2 hours/day. Potential re-entry is early post-emergence when only few leaves are unfolded and leaves cover less than 10% of the ground (up to BBCH 16-18). Since a transfer coefficient (TC) is not recommended for this scenario a conservative TC of 2500 cm<sup>2</sup>/h (from hand harvesting of vegetables) is used in the following risk assessment.

A summary of proposed uses and selection of the cGAP used for worker risk assessment is presented in Table 6.4.3-1.

**Table 6.4.3-1: Critical GAPs for worker exposure**

Crop grouping	Re-entry task	Duration (h)	Max. dose rate		No of applications
			(L/ha product)	(kg a.s./ha)	
Beet crops	Scouting	2	2	1.0	1

<sup>3</sup> EUROPOEM II project FAIR3-CT96-1406; Post Application Exposure of Workers to Pesticides in Agriculture, Report of the Re-entry Working Group; December 2002

Predicted exposures are calculated from a cumulative foliar deposit based on the maximum number of applications, the maximum dose rate and 2 hours/day contact with the foliage. Exposure is compared with the AOEL. Exposure estimates and proportions of the AOEL accounted for by the estimates are summarised in the following table.

**Table 6.4.3-2: Predicted worker exposure**

<b>Crop grouping</b>	<b>Re-entry task</b>	<b>Systemic exposure* (mg/kg bw/d)</b>	<b>% of AOEL (2.5 mg/kg bw/d)</b>
Beet crops	Scouting	0.02	1

\* 8% dermal absorption, 60 kg worker

### Conclusions

Exposure of workers re-entering treated beet crops for scouting activities is at maximum 1% of the AOEL. Calculations reflect standard work clothing worn by adult workers (shoes, socks, long-legged pants, and long sleeves) working with bare hands. Thus, an unacceptable risk is therefore not anticipated.

**B.6.5. EXPOSURE AND RISK ASSESSMENT****THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)**

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	<b>Ethofumesate SC 500</b>	Active substance	<b>Ethofumesate</b>
Formulation type	water-based	a.s. concentration	<b>500</b> mg/ml
Dermal absorption from product	<b>0,4</b> %	Dermal absorption from spray	<b>2,00</b> %
Container	5 litres narrow closure		
PPE during mix/loading	None	PPE during application	None
Dose	<b>2</b> l/ha	Work rate/day	<b>50</b> ha
Application volume	<b>100</b> l/ha	Duration of spraying	<b>6</b> h

**EXPOSURE DURING MIXING AND LOADING**

Container size	5 litres
Hand contamination/operation	0,2 ml
Application dose	2 litres product/ha
Work rate	50 ha/day
Number of operations	20 /day
Hand contamination	4 ml/day
Protective clothing	None
Transmission to skin	100 %
Dermal exposure to formulation	4 ml/day

**DERMAL EXPOSURE DURING SPRAY APPLICATION**

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Application volume	100 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**

	Mix/load	Application	
Dermal exposure	4 ml/day	41,55 ml/day	
Concen. of a.s. product or spray	500 mg/ml	10 mg/ml	
Dermal exposure to a.s.	2000 mg/day	415,5 mg/day	
Percent absorbed	0,4 %	2 %	
Absorbed dose	8 mg/day	8,31 mg/day	

**INHALATION EXPOSURE DURING SPRAYING**

Inhalation exposure	0,01 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	10 mg/ml
Inhalation exposure to a.s.	0,6 mg/day
Percent absorbed	100 %
Absorbed dose	0,6 mg/day

**PREDICTED EXPOSURE**

Total absorbed dose	16,91 mg/day
Operator body weight	60 kg
Operator exposure	0,281833333 mg/kg bw/day
AOEL	2,5 mg/kg bw/day
% AOEL	11,27333333



## THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	Ethofumesate SC 500		Active substance
Formulation type	water-based		a.s. concentration
Dermal absorption from product	0,4 %		Dermal absorption from spray
Container	5 litres narrow closure		
PPE during mix/loading	Gloves		PPE during application
Dose	2 l/ha		Work rate/day
Application volume	100 l/ha		Duration of spraying
			Gloves
			50 ha
			6 h

## EXPOSURE DURING MIXING AND LOADING

Container size	5 litres
Hand contamination/operation	0,2 ml
Application dose	2 litres product/ha
Work rate	50 ha/day
Number of operations	20 /day
Hand contamination	4 ml/day
Protective clothing	Gloves
Transmission to skin	5 %
Dermal exposure to formulation	0,2 ml/day

## DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Application volume	100 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

	Mix/load	Application
Dermal exposure	0,2 ml/day	6,45 ml/day
Concen. of a.s. product or spray	500 mg/ml	10 mg/ml
Dermal exposure to a.s.	100 mg/day	64,5 mg/day
Percent absorbed	0,4 %	2 %
Absorbed dose	0,4 mg/day	1,29 mg/day

## INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0,01 ml/h
Duration of exposure	6 h
Concentration of a.s. in spray	10 mg/ml
Inhalation exposure to a.s.	0,6 mg/day
Percent absorbed	100 %
Absorbed dose	0,6 mg/day

## PREDICTED EXPOSURE

Total absorbed dose	2,29 mg/day
Operator body weight	60 kg
Operator exposure	0,038166667 mg/kg bw/day
AOEL	2,5 mg/kg bw/day
% AOEL	1,526666667

## THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	Ethofumesate 500 SC	Active substance	Ethofumesate
Formulation type	Liquid	a.s. concentration	500 g/l
Dermal absorption from product	0,4 %	Dermal absorption from spray	8 %
RPE during mix/loading	None	RPE during application	None
PPE during mix/loading	None		
PPE during application: Head	None	Hands	None
		Body	None
Dose	2 l product/ha	Work rate/day	20 ha

## DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2,4 mg/kg a.s.
Hand contamination/day	48 mg/day
Protective clothing	none
Transmission to skin	100 %
Dermal exposure to a.s.	48 mg/day

## INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0006 mg/kg a.s.
Inhalation exposure/day	0,012 mg/day
RPE	none
Transmission through RPE	100 %
Inhalation exposure to a.s.	0,012 mg/day

## DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
	Head	Hands	Rest of body
Dermal contamination/kg a.s.	0,06	0,38	1,6
Dermal contamination/day	1,2	7,6	32
Protective clothing	none	none	none
Transmission to skin	100	100	100 %
Total dermal exposure to a.s.	40,8 mg/day		

## INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,001 mg/kg a.s.
Inhalation exposure/day	0,02 mg/day
RPE	none
Transmission through RPE	100 %
Inhalation exposure to a.s.	0,02 mg/day

## ABSORBED DOSE

	Mix/load	Application
Dermal exposure to a.s.	48 mg/day	40,8 mg/day
Percent absorbed	0,4 %	8 %
Absorbed dose (dermal route)	0,192 mg/day	3,264 mg/day
Inhalation exposure to a.s.	0,012 mg/day	0,02 mg/day
Total systemic exposure	0,204 mg/day	3,284 mg/day

## PREDICTED EXPOSURE

Total systemic exposure	3,488 mg/day
Operator body weight	70 kg
Operator exposure	0,049828571 mg/kg bw/day

## THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	Ethofumesate 500 SC	Active substance	Ethofumesate
Formulation type	Liquid	a.s. concentration	500 g/l
Dermal absorption from product	0,4 %	Dermal absorption from spray	8 %
RPE during mix/loading	None	RPE during application	None
PPE during mix/loading	Gloves		
PPE during application: Head	None	Hands	Gloves
		Body	Coverall and sturdy footwear
Dose	2 l product/ha	Work rate/day	20 ha

## DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2,4 mg/kg a.s.
Hand contamination/day	48 mg/day
Protective clothing	gloves
Transmission to skin	1 %
Dermal exposure to a.s.	0,48 mg/day

## INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0,0006 mg/kg a.s.
Inhalation exposure/day	0,012 mg/day
RPE	none
Transmission through RPE	100 %
Inhalation exposure to a.s.	0,012 mg/day

## DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
	Head	Hands	Rest of body
Dermal contamination/kg a.s.	0,06	0,38	1,6
Dermal contamination/day	1,2	7,6	32
Protective clothing	none	gloves	coverall and sturdy footwear
Transmission to skin	100	1	5 %
Total dermal exposure to a.s.	2,876 mg/day		

## INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0,001 mg/kg a.s.
Inhalation exposure/day	0,02 mg/day
RPE	none
Transmission through RPE	100 %
Inhalation exposure to a.s.	0,02 mg/day

## ABSORBED DOSE

	Mix/load	Application	
Dermal exposure to a.s.	0,48 mg/day	2,876 mg/day	
Percent absorbed	0,4 %	8 %	
Absorbed dose (dermal route)	0,00192 mg/day	0,23008 mg/day	
Inhalation exposure to a.s.	0,012 mg/day	0,02 mg/day	
Total systemic exposure	0,01392 mg/day	0,25008 mg/day	

## PREDICTED EXPOSURE

Total systemic exposure	0,264 mg/day
Operator body weight	70 kg
Operator exposure	0,003771429 mg/kg bw/day

Estimation of bystander and resident exposure (adults and children)			
Active substance (a.s.)		Ethofumesate	
Product		Ethofumesate 500 SC	
Intended uses		Field Crops, Tractor Mounted (FCTM) ▼	
Treated area per day (A)	20	ha/d	
Application rate (AR)	1	kg a.s./ha	
Number of applications (NA)	1	1)	
1) Consideration of more than two applications are not necessary if degradation of the active substance on foliage of at least 50 % can be assumed between two applications (otherwise use multiple application factor).			
Dermal absorption (DA)	8	% (worst case, e.g. during application)	
Inhalation absorption (IA)	100	%	
Oral absorption (OA)	100	%	
Systemic AOEL	2,5	mg/kg bw/d	
Body weight (BW)	60	kg/person (adults)	
	16,15	kg/person (children)	
Distance between application and bystander or resident:			
FCTM:	1	m	
High crops not selected		▼	
	0	m	
Home & garden not selected		▼	
		m	
Drift deposit (D) for 1 appl. based on appl. technique and distance:		2,77 % (FCTM, 1 m)	
Airborne vapour concentration (ACv)		0,015	mg/m <sup>3</sup> 2)
2) 1 µg/m <sup>3</sup> for semivolatile substances, i.e. vapour pressure (20 °C): ≥ 1x10 <sup>-5</sup> - < 5x10 <sup>-3</sup> Pa; 15 µg/m <sup>3</sup> for volatile substances, i.e. vapour pressure (20 °C): ≥ 5x10 <sup>-3</sup> Pa			

#### Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted

Input parameters considered for the estimation of bystander exposure:

Intended use(s):		Drift (D):	2,77 % (FCTM, 1 m)
Application rate (AR):	1 kg a.s./ha	Exposed Body Surface Area (BSA):	1 m <sup>2</sup> (adults)
			0,21 m <sup>2</sup> (children)
Body weight (BW):	60 kg/person (adults)	Specific Inhalation Exposure (I <sup>*</sup> <sub>A</sub> ):	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):	8,00 % ('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:	2,5 mg/kg bw/d		

Bystander exposure towards Ethofumesate					
Adults			Children		
Bystander: Dermal exposure after application in (via spray drift)					
SDE <sub>B</sub> = (AR x D x BSA x DA) / BW			SDE <sub>B</sub> = (AR x D x BSA x DA) / BW		
(100 x 2,77% x 1 x 8%) / 60			(100 x 2,77% x 0,21 x 8%) / 16,15		
External exposure	2,77	mg/person	External exposure	0,5817	mg/person
External exposure	0,0461667	mg/kg bw/d	External exposure	0,0360186	mg/kg bw/d
Absorbed dose:	0,0036933	mg/kg bw/d	Absorbed dose:	0,0028815	mg/kg bw/d
Bystander: Inhalation exposure after application in					
SIE <sub>B</sub> = (I* <sub>A</sub> x AR x A x T x IA) / BW			SIE <sub>B</sub> = (I* <sub>A</sub> x AR x A x T x IA) / BW		
(0,001 / 360 x 1 x 20 x 5 x 100%) / 60			(0,001 / 360 x 1 x 20 x 5 x 100%) / 16,15		
External exposure	0,0002778	mg/person	External exposure	0,0001596	mg/person
External exposure	4,63E-06	mg/kg bw/d	External exposure	9,885E-06	mg/kg bw/d
Absorbed dose:	0,0000046	mg/kg bw/d	Absorbed dose:	0,0000099	mg/kg bw/d
Total systemic exposure: SE <sub>B</sub> = SDE <sub>B</sub> + SIE <sub>B</sub>			Total systemic exposure: SE <sub>B</sub> = SDE <sub>B</sub> + SIE <sub>B</sub>		
Total systemic exposure (absorbed dose)	0,2218778	mg/person	Total systemic exposure (absorbed dose)	0,0466956	mg/person
Total systemic exposure (absorbed dose)	0,0036980	mg/kg bw/d	Total systemic exposure (absorbed dose)	0,0028914	mg/kg bw/d
% of AOEL:	0,15	%	% of AOEL:	0,12	%

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

Input parameters considered for the estimation of resident exposure:

Intended use(s):		Drift (D):	2,77 % (FCTM, 1 m)
Application rate (AR):	1 kg a.s./ha	Transfer coefficient (TC):	7300 cm <sup>2</sup> /h (adults)
Number of applications (NA):	1		2600 cm <sup>2</sup> /h (children)
Body weight (BW):	60 kg/person (adults)	Turf Transferable Residues (TTR):	5 %
	16,15 kg/person (children)	Exposure Duration (H):	2 h
Dermal absorption (DA):	8,00 % ('worst case')	Air borne Concentration of Vapour (ACV):	0,015 mg/m <sup>3</sup>
Inhalation absorption (IA):	100 %	Inhalation Rate (IR):	16,57 m <sup>3</sup> /d (adults),
Oral absorption (OA)	100 %		8,31 m <sup>3</sup> /d (children)
AOEL	2,5 mg/kg bw/d	Saliva Extraction Factor (SE):	50 %
		Surface Area of Hands (SA):	20 cm <sup>2</sup>
		Frequency of Hand to Mouth (Freq):	20 events/h
		Dislodgeable foliar residues (DFR):	20 %
		Ingestion Rate for Mouthing of Grass/Day (IgR):	25 cm <sup>2</sup> /d

Resident exposure towards Ethofumesate					
Adults		Children			
Residents: Dermal exposure after application in (via deposits caused by spray drift)					
$SDE_R = (AR \times NA \times D \times TTR \times TC \times H \times DA) / BW$		$SDE_R = (AR \times NA \times D \times TTR \times TC \times H \times DA) / BW$			
$(0,01 \times 1 \times 2,77\% \times 5\% \times 7300 \times 2 \times 8\%) / 60$		$(0,01 \times 1 \times 2,77\% \times 5\% \times 2600 \times 2 \times 8\%) / 16,15$			
External exposure	0,20221	mg/person	External exposure	0,07202	mg/person
External exposure	0,0033702	mg/kg bw/d	External exposure	0,0044594	mg/kg bw/d
Absorbed dose:	0,0002696	mg/kg bw/d	Absorbed dose:	0,0003568	mg/kg bw/d
Residents: Inhalation exposure to vapour					
$SIE_R = (AC_V \times IR \times IA) / BW$		$SIE_R = (AC_V \times IR \times IA) / BW$			
$(0,015 \times 16,57 \times 100\%) / 60$		$(0,015 \times 8,31 \times 100\%) / 16,15$			
External exposure	0,24855	mg/person	External exposure	0,12465	mg/person
External exposure	0,0041425	mg/kg bw/d	External exposure	0,0077183	mg/kg bw/d
Absorbed dose:	0,0041425	mg/kg bw/d	Absorbed dose:	0,0077183	mg/kg bw/d
		Residents: Oral exposure (hand-to-mouth transfer)			
		$SOE_H = (AR \times NA \times D \times TTR \times SE \times SA \times Freq \times H \times OA) /$			
		$(0,01 \times 1 \times 2,77\% \times 5\% \times 50\% \times 20 \times 20 \times 2 \times 100\%) /$			
		External exposure	0,00554	mg/person	
		External exposure	0,000343	mg/kg bw/d	
		Absorbed dose	0,0003430	mg/kg bw/d	
		Residents: Oral exposure (object-to-mouth transfer)			
		$SOE_O = (AR \times NA \times D \times DFR \times IgR \times OA) / BW$			
		$(0,01 \times 1 \times 2,77\% \times 20\% \times 25 \times 100\%) / 16,15$			
		External exposure	0,001385	mg/person	
		External exposure	8,576E-05	mg/kg bw/d	
		Absorbed dose	0,0000858	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)	0,2647268	mg/person	Total systemic exposure (absorbed dose)	0,1373366	mg/person
Total systemic exposure (absorbed dose)	0,0044121	mg/kg bw/d	Total systemic exposure (absorbed dose)	0,0085038	mg/kg bw/d
% of AOEL:	0,18	%	% of AOEL:	0,34	%



WORKER EXPOSURE		EUROPOEM II MODEL	
form		Re-entry in the field	
a.s.			
Parameter	Value	Unit	References, comments
<b>Re-entry activities in the field</b>			
AR Application rate	1	kg a.s./ha	summary of intended uses
<b>Worker</b>			
Duration			
T	2	hours / day	default: 6 h (Europoem II)
<b>Inhalation Exposure</b>			without PPE
no model available	-		
<b>Dermal Exposure</b>			
DFR Dislodgeable foliar residue	30	mg a.s./m <sup>2</sup> /kg a.s./ha	default (Europoem II)
TC Transfer coefficient	0,25	m <sup>2</sup> / hour	vegetable (field): 0.25; ornamentals: 0.5; small fruit: 0.3; large fruit: 0.45 (Europoem II)
Dermal Exposure	15	mg a.s./ day	DE = DFR x AR x TC x T
<b>Internal exposure</b>			
DA Dermal Absorption	8	%	
PPE-factor dermal	5		gloves*
AOEL	150	mg a.s./ day	based on 60 kg bw
	<b>Without PPE</b>	<b>With PPE</b>	
<b>Internal exposure</b>	<b>[mg a.s./ day ]</b>	<b>[mg a.s./ day]</b>	
Inhalation	-	-	no model available
Dermal	1,200	0,240	DE(int) = DE x (DA/100)
<b>Total</b>	<b>1,200</b>	<b>0,240</b>	<b>sum</b>
<b>% AOEL</b>			
Inhalation	-	-	no model available
Dermal	1	0	%AOEL = 100 x DE(int) / AOEL
<b>Total</b>	<b>1</b>	<b>0</b>	<b>sum</b>


\* It is assumed in the used TC values, that body exposure is already reduced by (protective) clothing. The use of gloves will result in an extra reduction factor of 5.

**B.6.6. REFERENCES RELIED ON**

Data Point	Author(s)	Year	Title Company 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
KCP 7.1.1	[REDACTED]	1989	NORTRON 50 SC (CR 18654/7): RAT ACUTE ORAL TOXICITY STUDY [REDACTED] Bayer CropScience, Report No.: A83199, Report includes Trial Nos.: TOX 89231 Edition Number: M-155471-01-1 EPA MRID No.: 414301-01 Date: 1989-05-26 GLP/GEP: yes, unpublished	Y	N	-	Bayer CropScience	In DAR (1998)
KCP 7.1.2	[REDACTED]	1989	NORTRON 50 SC (CR 18654/7): RAT ACUTE DERMAL TOXICITY STUDY [REDACTED] Bayer CropScience, Report No.: A83200, Report includes Trial Nos.: TOX 89232 Edition Number: M-155472-01-1 Date: 1989-05-26 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	In DAR (1998)
KCP 7.1.3	[REDACTED]	2008	Acute inhalation toxicity study in rats (Nortron SC) [REDACTED] Laboratory Study number 25983, M-327134-01-1 GLP/GEP: yes, unpublished	Y	Y	Required according to new data requirements	Bayer CropScience	Submitted for the purpose of renewal (2014)
KCP 7.1.4	[REDACTED]	1989	NORTRON 50 SC CR 18654/7: RABBIT SKIN IRRITANCY STUDY [REDACTED] Bayer CropScience, Report No.: A83201, Report includes Trial Nos.: TOX 89233 Edition Number: M-	Y	N		Bayer CropScience	In DAR (1998)

Data Point	Author(s)	Year	Title Company 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
			<u>155473-01-1</u> Date: 1989-06-13 GLP/GEP: yes, unpublished					
KCP 7.1.5		1989	NORTON 50 SC, CR 18654/7: RABBIT EYE IRRITANCY STUDY Bayer CropScience, Report No.: A83202, Report includes Trial Nos.: TOX 89234 Edition Number: <u>M-155474-01-1</u> Date: 1989-06-13 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	In DAR (1998)
KCP 7.1.6		1989	Norton 50, SC CR 18654/7: Delayed contact hypersensitivity study in the Guinea-pig (Buehler test) Bayer CropScience, Report No.: A83204, Report includes Trial Nos.: 891017D/ SMS 189/SS TOX 89313 Edition Number: <u>M-155476-01-1</u> Date: 1989-10-30 GLP/GEP: yes, unpublished	Y	N		Bayer CropScience	In DAR (1998)
KCP 7.1.6		2005	Ethofumesate SC 500 (AE B049913 00 SC45 A2) (Project: Ethofumesate) - Local lymph node assay in mice (LLNA/IMDS) Bayer CropScience, Report No.: AT02190, Edition Number: <u>M-257228-01-1</u> Date: 2005-06-30 GLP/GEP: yes, unpublished	Y	Y	Old Buehler test from DAR only with limited acceptability	Bayer CropScience	Submitted for the purpose of renewal (2014)
KCP 7.3		2011	Norton SC 500 formulation: [14C]-	Y	Y	Default value used at 1st	Task Force	Submitted for the purpose of



Data Point	Author(s)	Year	Title Company 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
			ethofumesate comparative in vitro dermal absorption study using human and rat skin  Bayer CropScience, Report No.: SA 11099, Edition Number: M-415675-01-1 Date: 2011-10-12 GLP/GEP: yes, unpublished			inclusion, required for representative formulation	Ethofumesate	renewal (2014)