

# REGISTRATION REPORT

## Part B

### Section 6

#### Mammalian Toxicology

Detailed summary of the risk assessment

Product code: SAP50SCF

Product name(s): FOLPEC

Chemical active substance:

Folpet, 500 g/L

Central Zone

Zonal Rapporteur Member State: Poland

#### CORE ASSESSMENT

(authorization)

Applicant: Selectis Produtos para a Agricultura, S.A.

Submission date: December 2023, update April 2024

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August 2024 (final Core Assessment)

### Version history

When	What
December 2023	V0 - Initial version submitted by the Selectis Produtos para a Agricultura, S.A. for submission to Poland in the frame of new PPP registration (According Art. 33 of Regulation EC No 1107/2009).
April 2024	V1 – Revised version from Selectis Produtos para a Agricultura, S.A. according to the data gaps identified by Poland.
May 2024	<p>Initial assessment by the zRMS</p> <p>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and <b>highlighted in grey</b>. Not agreed or not relevant information are <del>struck through</del> and <b>shaded</b> for transparency.</p> <p>Note: Following the evaluation and before sending the document for commenting, all coloured high-lighting was removed, from the parts updated by the Applicant, for better legibility.</p>
August 2024	<p>Final report (Core Assessment updated following the commenting period)</p> <p>No additional information or assessments after the commenting period.</p>

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#### Reviewer general comment:

This part of dossier (B6) summarizes data related to the toxicological profile and NDE assessment for the plant protection product FOLPEC (product code SAP50SCF) containing the active substance folpet (500g/L), formulated as Suspension Concentrate. Information has been submitted to support registration according art. 33 of 1107/2009 in Poland also for zonal registration for which PL was designated zRMS.

Intended use of PPP is fungicide in the protection of wheat and barley. The zRMS's per-review all of the elements that are crucial for risk assessment and decision-making. Regarding evaluation of the toxicity potential of the product SAP50SCF/FOLPEC, data submitted by the Applicant has been based on *in vivo* testing. There is no duplication of vertebrate studies and extrapolation to data of similar formulations is not possible. The testing strategy considered by the Applicant takes into account methods compliant with the 3R concept for refinement, reduction and replacement of animal testing where applicable and acceptable.

NDE assessment for operator, workers and B&R has been calculated using the EFSA calculator, on-line version 1.01 considering the worst-case exposure scenario to cover all the intended uses (highest application rate per application as well as the highest application rate per year with the shorter interval between each application). All NDE calculations provided for operator, workers and B&R resulting from use of PPP, considering all tasks according to the critical use(s), identify safe use of the product SAP50SCF/FOLPEC.

## 6 Mammalian Toxicology (KCP 7)

### 6.1 Summary

**Table 6.1-1: Information on SAP50SCF / Folpet 500 SC\***

Product name and code	SAP50SCF / Folpet 500 SC
Formulation type	SC
Active substance(s) (incl. content)	Folpet; 500 g/L
Function	Fungicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

\* Information on the detailed composition of SAP50SCF / Folpet 500 SC can be found in the confidential dRR Part C.

#### Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

**Table 6.1-2: Justified proposals for classification and labelling for SAP50SCF / Folpet 500 SC according to Regulation (EC) No 1272/2008**

Hazard class(es), categories	Eye Irrit. 2, Skin Sens. 1 and Carc.2
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS07 and GHS08
Signal word	Warning
Hazard statement(s)	H319: Causes serious eye irritation. H317: May cause an allergic skin reaction H351: Suspected of causing cancer.
Precautionary statement(s)	P102: Keep out of reach of children P201: Obtain special instructions before use P261: Do not breathe dust/fume/gas/mist/vapours/spray. P302 + P352: IF ON SKIN: Wash with plenty of water/... P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P308 + P313: IF exposed or concerned: Get medical advice/attention. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P337 + P313: If eye irritation persists: Get medical advice/attention. P362 + P364: Take off contaminated clothing and wash it before reuse. P280: Wear protective gloves/protective clothing/eye protection/face protection. P405: Store locked up. P501: Dispose of the contents/containers in accordance with the current legislation on waste treatment
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
Other phrases:	Operator must wear adequate <del>work clothing and protective gloves</del> protective gloves/protective clothing during mixing/loading and application. In addition, the use of eye protection is required during mixing/loading. Treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried. In case a worker enters the treated area, long trousers and long-sleeved shirt should be worn. The use of gloves is recommended.

**Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for SAP50SCF / Folpet 500 SC**

	Result	PPE / Risk mitigation measures
Operators	Acceptable	None <b>Note:</b> considering classification of the formulation as H317 and H351, the use of protective gloves/protective clothing is required during mixing/loading and application. In addition, considering classification as considering classification of the formulation as H319, the use of eye protection is required during mixing/loading.
Workers	Acceptable	None
Residents	Acceptable	None
Bystanders	Acceptable	None

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. No specific PPE is necessary.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table.

**Table 6.1-4 Critical uses and overall conclusion of exposure assessment**

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks:  (e.g. safener/synergist (L/ha))  critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind  (incl. application technique ***	Max. number (min. interval between applications)  a) per use b) per crop/ season	Max. application rate kg as/ha  a) per app. b) Total rate per crop /season	Water L/ha  min / max			Operator	Worker	Residents	Bystander
1	Wheat (BBCH 30-59)	F	Spraying, LCTM	a) 2 (14) b) 2 (14)	a) 0.45 – 0.6 b) 0.9 – 1.2	150 - 400	42	Guidance document on the assessment of exposure; EFSA	A	A	A	A
2	Barley (BBCH 30-59)	F	Spraying, LCTM	a) 2 (14) b) 2 (14)	a) 0.45 – 0.6 b) 0.9 – 1.2	150 - 400	42	Journal 2022;20(1):7032 EFSA on-line model OPEX 1.01	A	A	A	A

\* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1

\*\* F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

\*\*\* e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 “Acceptability of exposure assessment”

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

## Data gaps

Noticed data gaps are: **None**.

## 6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

**Table 6.2-1: Information on active substance(s)**

Folpet	
Common Name	Folpet
CAS-No.	133-07-3
<b>Classification and proposed labelling</b>	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: Code(s) for hazard pictogram(s): GHS07, GHS08 Signal word: Warning Hazard statement(s): H317 – May cause an allergic skin reaction H319 – Causes serious eye irritation H332 – Harmful if inhaled H351 – Suspected of causing cancer. Precautionary statement(s): P261 – Avoid breathing dust; P273 – Avoid release to the environment; P280 – Wear protective gloves/ protective clothing; P305+P351+P338 - IF IN EYES – Rinse cautiously with water for several

	Folpet
	minutes. Remove contact lenses, if present and easy to do. Continue rinsing; P308+P313 - IF exposed or concerned - Get medical advice/attention; P501 - Dispose of contents/container in accordance with local/ regional/ national regulation. Supplemental information: EUH401: To avoid risks to human health and the environment, comply with the instructions for use
Additional C&L proposal	-
<b>Agreed EU endpoints</b>	
AOEL systemic	0.1 mg/kg bw/d
Reference	EFSA Scientific Report (2009) 297, 1-80
<b>Conditions to take into account/critical areas of concern with regard to toxicology</b>	
EFSA Conclusion for Folpet	None

### 6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for SAP50SCF / Folpet 500 SC is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

**Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for SAP50SCF / FOLPEC**

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD <sub>50</sub> oral, rat (OECD 423)	5000 mg/kg bw	Yes	None	■■■■ (2011a)
LD <sub>50</sub> dermal, rat (OECD 402)	(>) 2000 mg/kg bw	Yes	None	■■■■ (2011b)
LC <sub>50</sub> inhalation	> 3.850 mg/L air (max. attainable)	Yes	None	■■■■ (2013)
Skin irritation (OECD 404)	Non-irritant	Yes	None	■■■■ (2011c)
Eye irritation (OECD 405)	Irritant	Yes	H319	■■■■ (2011d)
Skin sensitisation, mice (OECD 429, LLNA)	Sensitising	Yes	H317	■■■■ (2011e)
Supplementary studies for combinations of plant protection products	No data – not required	--	--	--

**Table 6.3-2: Additional toxicological information relevant for classification/labelling of SAP50SCF / FOLPEC**

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Folpet (40% (w/w))	Acute Tox. 4: H332; Aquatic Acute 1: H400; Carc. 2: H351; Eye Irrit. 2: H319; Skin Sens. 1: H317 - Warning	Reg. 1272/2008 (ATP ATP01)	H400; H351; H319; H317

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of non-active substance(s) (relevant for classification of product)	-	-	-	-
Further toxicological information	No data – not required			

\* Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS.

\*\* Material safety data sheet by the applicant

## 6.4 Toxicological Evaluation of Groundwater Metabolites

All metabolite concentrations are predicted to stay below 0.1 µg/L – no groundwater assessment is required.

## 6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in SAP50SCF / Folpet 500 SC are presented in the following table.

**Table 6.5-1: Dermal absorption rates for active substances in SAP50SCF / Folpet 500 SC**

	Folpet	
	Value	Reference
Concentrate	0.5%	New study reported in Appendix 2
Dilution	5.2% * <del>3.9%</del>	New study reported in Appendix 2

\* Dilution: 5.2 % (1.125 g/L, based on pro rata approach. Please see section A 2.10.1 for detailed calculations)

### 6.5.1 Justification for proposed values - Folpet

Proposed dermal absorption rates for Folpet are based on dermal absorption study on a formulation SAP50SCF / Folpet 500 SC. The study results are summarised in the following table. Full summary of study on the dermal absorption of Folpet 500 SC that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

**Table 6.5-2: Summary of the results of submitted dermal absorption studies for Folpet**

Test	Concentrate (500 g/L)	Spray dilution (1/333 v/v = 1.5 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
<i>In vitro</i> (human)	0.5%	5.2% * <del>3.9%</del>	Folpet 50 SC	Yes	Yes (see Appendix A 2.10)	Justification accepted. Endpoint can be used for current product	Ian R Johnson, 2015

\* Dilution: 5.2 % (1.125 g/L, based on pro rata approach. Please see section A 2.10.1 for detailed calculations)

## 6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

**Table 6.6-1: Product information and toxicological reference values used for exposure assessment**

Product name and code	SAP50SCF / FOLPEC
Formulation type	SC



Category	Fungicide
Active substance(s) (incl. content)	<b>Folpet</b> 500 g/L (520.8 g/L <i>technical material</i> )
AOEL systemic	0.1 mg/kg bw/d
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	Concentrate: 0.5% Dilution: 5.2 % (1.125 g/L, based on <i>pro rata</i> approach. Please see section A 2.10.1 for detailed calculations) (Based on product (Folpet 50 SC))

**Note:** The evaluation was carried out with the concentration of technical active substance, since AOEL has been established based on the technical substance and will be a worst-case scenario.

### 6.6.1 Selection of critical use(s) and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4. A list of all intended uses within the EU is given in Part B, Section 0.

*The calculations were done considering the maximum and minimum application rate.*

#### Justification

None.

## 6.6.2 Operator exposure (KCP 7.2.1)

<b>Comments of zRMS:</b>	NDE calculation (EFSA on-line model OPEX ver. 1.01) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. The risk for operators is acceptable under conditions of intended uses and considering below mentioned risk mitigation measures such as Work wear (arms, body and legs covered) during M, L and A.
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### 6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of SAP50SCF / FOLPEC according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in Appendix 3.

**Table 6.6-2: Exposure models for intended uses**

Critical use(s)	Cereals (Wheat and Barley) (min. 0.9 - max. 1.2 L product/ha)
Model(s)	EFSA (European Food Safety Authority), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. <a href="https://doi.org/10.2903/j.efsa.2022.7032">https://doi.org/10.2903/j.efsa.2022.7032</a>

### Estimated operator exposure (acute exposure)

An AAOEL was not allocated for Folpet. Therefore, estimates of the acute exposure to operators has not been conducted.

**Table 6.6-3: Estimated operator exposure (longer term exposure)**

Folpet					
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to low crops					
Dermal absorption: <b>0.5%</b> (Concentrate) and <b>5.2%</b> (In-use dilution)					
Number of applications: 2					
Interval between application: 14 days					
Application rate		0.469 kg a.s./ha		0.625 kg a.s./ha	
<b>Spray application</b> (AOEM; 75 <sup>th</sup> percentile) Body weight: 60 kg	Potential exposure	0.0134	<b>13.4</b>	0.0168	<b>16.8</b>
	Work wear (arms, body and legs covered) M/L and A	0.0086	<b>8.6</b>	0.0108	<b>10.8</b>

## CONCLUSION

An acceptable risk is anticipated for the operator, even without PPE.

However, considering classification of the formulation as H317 and H351, the use of gloves is required during mixing/loading and application. In addition, considering classification as considering classification of the formulation as H319, the use of eye protection is required during mixing/loading.

Overall, the following phrases should be included in the product label:

*“Operator must wear adequate work clothing and protective gloves during mixing/loading and application. In addition, the use of eye protection is required during mixing/loading”.*

## 6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and consideration of the above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

## 6.6.3 Worker exposure (KCP 7.2.3)

<b>Comments of zRMS:</b>	NDE calculation (EFSA on-line model OPEX ver. 1.01) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. Exposure for workers (entry into a previously treated area or handling a crop according to the critical uses) is acceptable under conditions of intended uses considering below mentioned risk mitigation measures such as Work wear, (arms, body and legs covered) but no PPE is used.
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### 6.6.3.1 Estimation

Table 6.6-4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with SAP50SCF / FOLPEC according to the critical use(s). Outcome of the estimation is presented in

Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3.

**Table 6.6-4: Exposure models for intended uses**

Critical use(s)	Cereals (Wheat and Barley) (min. 0.9 - max. 1.2 L product/ha)
Model	EFSA (European Food Safety Authority), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. <a href="https://doi.org/10.2903/j.efsa.2022.7032">https://doi.org/10.2903/j.efsa.2022.7032</a>

**Table 6.6-5: Estimated worker exposure (long-term exposure)**

Folpet					
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Inspection, irrigation Outdoor Work rate: 2 hours/day DT <sub>50</sub> : 30 days DFR: 3 µg/cm <sup>2</sup> /kg a.s./ha					
Application rate		0.469 kg a.s./ha		0.625 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm <sup>2</sup> /person/h	0.0524	<b>52.4</b>	0.0699	<b>69.9</b>
	Work wear (arms, body and legs covered) TC: 1400 cm <sup>2</sup> /person/h	0.0059	<b>5.9</b>	0.0078	<b>7.8</b>
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm <sup>2</sup> /person/h	0.0052	<b>5.2</b>	0.007	<b>7</b>

## CONCLUSION

An acceptable risk has been identified for a worker re-entering the treated field, even without gloves, assuming only adequate work clothing.

However, considering classification of the formulation as H317 and H351, the use of gloves is recommended.

In terms of good agriculture practice, the following phrases should be included in the product label:

*“Treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried. In case a worker enters the treated area, long trousers and long-sleeved shirt should be worn. The use of gloves is recommended”.*

### 6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required.

### 6.6.3.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mention PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

### 6.6.4 Resident and bystander exposure (KCP 7.2.2)

<b>Comments of zRMS:</b>	Justification of waiving acute risk assessment discussed by the applicant is reliable thus, zRMS agrees to the conclusions. Also no AAOEL has been set for folpet, therefore in line with <i>EFSA, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA, Journal 2022;20(1):7032, 134 pp.</i> exposure assessment for residents also covers bystander exposure refer point 2.3.1 Step 1; Table 2. Risk for bystanders and residents is acceptable under conditions of intended uses.
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#### 6.6.4.1 Estimation of resident and bystander exposure

The acute exposure assessment for bystanders covers the exposure that a resident could reasonably be expected to incur in a single day. Therefore, there is no need for a separate acute risk assessment for residents.

No bystander risk assessment is required for PPPs that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

Table 6.6-6 shows the exposure model(s) used for estimation of resident and bystander exposure to Folpet. The outcome of the estimation is presented in Table 6.6-7 **Błąd! Nie można odnaleźć źródła odwołania.**(longer term resident exposure). Detailed calculations are in Appendix 3.

**Table 6.6-6: Exposure models for intended uses**

Critical use(s)	Cereals (Wheat and Barley) (min. 0.9 - max. 1.2 L product/ha)
Model	EFSA (European Food Safety Authority), Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. <a href="https://doi.org/10.2903/j.efsa.2022.7032">https://doi.org/10.2903/j.efsa.2022.7032</a>

**Table 6.6-7: Estimated resident exposure (longer term exposure)**

Folpet					
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3 (m) Drift reduction technology: No DT <sub>50</sub> : 30 days DFR: 3 µg/cm <sup>2</sup> /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.469 kg a.s./ha		2 x 0.625 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 <sup>th</sup> perc.)	0.0044	4.4	0.0059	5.9
	Vapour (75 <sup>th</sup> perc.)	0.0008	0.8	0.0008	0.8
	Deposits (75 <sup>th</sup> perc.)	0.0013	1.3	0.0017	1.7
	Re-entry (75 <sup>th</sup> perc.)	0.0071	7.1	0.0094	9.4
	<b>Sum (mean)</b>	0.0098	<b>9.8</b>	0.0128	<b>12.8</b>
Resident adult Body weight: 60 kg	Drift (75 <sup>th</sup> perc.)	0.001	1	0.0014	1.4
	Vapour (75 <sup>th</sup> perc.)	0.0003	0.3	0.0003	0.3
	Deposits (75 <sup>th</sup> perc.)	0.0003	0.3	0.0004	0.4
	Re-entry (75 <sup>th</sup> perc.)	0.0039	3.9	0.0052	5.2
	<b>Sum (mean)</b>	0.0041	<b>4.1</b>	0.0054	<b>5.4</b>

## CONCLUSION

there is no undue risk anticipated for bystanders and residents (adults and children) on the condition that the product is applied as intended. No specific mitigation measures are required.

### 6.6.4.2 Measurement of resident and/or bystander exposure

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for Folpet will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

### 6.6.5 Combined exposure

Not relevant. The product contains only one active substance.

## Appendix 1 Lists of data considered in support of the evaluation

### List of data submitted by the applicant and 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	Owner
-	-	-	-	-	-

### List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

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	Owner
KCP 7.1.1	████	2011a	Acute oral toxicity study of Folpet Sapec 50 SC in Rats ████ Study No. 401-1-01-2050 Date 2011-08-03 GLP: yes Not published	Y	ASCENZA AGRO S.A.
KCP 7.1.2	████	2011b	Acute dermal toxicity study of Folpet Sapec 50 SC in Rats ████ Study No. 403-1-01-2051 Date 2011-08-03 GLP: yes Not published	Y	ASCENZA AGRO S.A.
KCP 7.1.3	████	2013	Acute inhalation toxicity study of Folpet Sapec 50 SC in rats ████ Study No. 405-1-01-5390 Date 2013-01-22 GLP: yes Not published	Y	ASCENZA AGRO S.A.
KCP 7.1.4	████	2011c	Acute dermal irritation study of Folpet Sapec 50 SC in rabbits ████ Study No. 406-1-01-2052 Date 2011-08-03 GLP: yes	Y	ASCENZA AGRO S.A.

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	Owner
			Not published		
KCP 7.1.5	████	2011d	Acute eye irritation study of Folpet Sapec 50 SC in rabbits ████ Study No. 407-1-01-2053 Date 2011-08-03 GLP: yes Not published	Y	ASCENZA AGRO S.A.
KCP 7.1.6	████	2011e	Skin sensitization study of Folpet Sapec 50 SC by local lymph node assay in mice ████ Study No. 409-1-01-2054 Date 2011-08-02 GLP: yes Not published	Y	ASCENZA AGRO S.A.
KCP 7.3	Johnson, I.	2015	Folpet 50 SC - In Vitro Absorption of Folpet through Human Dermatomed Skin using [14C]-Radiolabelled Folpet Dermal Technology Laboratory Ltd. Document No JV2317-REG GLP	N	ASCENZA AGRO S.A.

**List of data submitted by the applicant and not 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	Owner
-	-	-	-	-	-

**List of data relied on not submitted by the applicant but necessary for evaluation**

<b>Data point</b>	<b>Author(s)</b>	<b>Year</b>	<b>Title</b> <b>Company Report No.</b> <b>Source (where different from company)</b> <b>GLP or GEP status</b> <b>Published or not</b>	<b>Vertebrate study Y/N</b>	<b>Owner</b>
-	-	-	-	-	-



## Appendix 2 Detailed evaluation of the studies relied upon

### A 2.1 Statement on bridging possibilities

Not required.

Comments of zRMS:	Agree, the toxicological profile was tested on the same product as the one requested for registration. No further comments regarding this point
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### A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Study (■■■■■. (2011a) has been reviewed for compliance with the current guidelines resulting from scientific progress (OECD 423). Study (■■■■■ (2011a) implements 3R rules minimizing the number of animals required to estimate the acute oral toxicity of a chemical. No deviation has been noted. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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**Reference Number:** KCP 7.1.1

**Report:** ■■■■■ (2011a), "Acute oral toxicity study of Folpet Sapec 50 SC in rats";  
■■■■■; Study number 401-1-01-2050

**Guidelines:** The Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals, N° 423, "Acute Oral Toxicity - Acute Toxic Class Method", adopted by the Council on December 17, 2001.

**Deviations:** None.

**GLP:** Yes; Laboratory certified by AAALAC International

#### Executive Summary

Female Wistar rats fasted overnight were dosed with Folpet SAPEC 50 SC in distilled water as single oral gavage dose using an intubation cannula. The feed was withheld until three hours post dosing. The first set (set I) of three female rats was given a single dose of 2000 mg Folpet SAPEC 50 SC/kg body weight. As no mortality was observed at this dose level so second set (set II) of three female rats was administered at the same dose level of 2000 mg Folpet SAPEC 50 SC/kg body weight. No mortality was observed at second set, so the endpoint was achieved and further testing was not required.

No signs of toxicity were observed in all surviving rats treated at the dose level of 2000 mg Folpet SAPEC 50 SC /kg body weight. Normal gain in body weight was observed in all surviving rats treated at the dose level of 2000 mg Folpet SAPEC 50 SC/kg body weight at the end of the experiment. All the surviving rats at termination were subjected to gross pathological examination. External and visceral examination of terminally sacrificed rats did not reveal any abnormality of pathological significance. In absence of any pathological lesion in terminally sacrificed rats, it was concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

The acute oral median lethal dose (LD<sub>50</sub> cut-off value) of Folpet SAPEC 50 SC in Wistar rats was found to be 5000 mg/kg body weight.

## I. MATERIALS AND METHODS:

### A. MATERIALS

**1. Test Material:** Folpet Sapec 50 SC

**Description:** Liquid/off white  
**Lot/Batch #:** C-MRA  
**Purity (ai content):** 500 g/L  
**Stability of test compound:** Expiry date: December, 2012

**2. Vehicle:** Purified water by reverse osmosis

### 3. Test animals

**Species:** Female rat  
**Strain:** Wistar  
**Age:** 8 to 10 weeks at the time of dosing  
**Weight before dosing:** Minimum: 152, Maximum: 179  
**Source:** Animal Breeding Facility, [REDACTED]  
**Acclimation period:** 6 days for set I (rat N° 1, 2 and 3), 8 days for set II (rat N° 4, 5 and 6) prior to dosing  
**Diet:** Teklad certified Global High Fiber Rat/Mice Feed manufactured by Harlan, Nederland.  
**Water:** Drinking water filtered through an Aquaguard water Filtration system/reverse osmosis water filtration system, provided *ad libitum*  
**Housing:** In groups of three; in polypropylene cages, covered with stainless steel grid top were used. Bedding consisted of autoclaved clean rice husk.  
**Environmental conditions -**  
**Temperature:** 22 ± 2°C  
**Humidity:** 64 to 66%  
**Air changes:** Minimum 15 air changes/h  
**Photoperiod:** 12 h light / 12 h dark

## B. STUDY DESIGN AND METHODS

### 1. Animal assignment and treatment

The first set (set I) of three female rats was given a single dose of 2000 mg Folpet SAPEC 50 SC/kg body weight. As no mortality was observed at this dose level so second set (set II) of three female rats was administered at the same dose level of 2000 mg Folpet SAPEC 50 SC/kg body weight. No mortality was observed at second set, so the endpoint was achieved and further testing was not required.

The rats were observed for signs of toxicity and mortality at 30 minutes, 1, 2, 3, 4 and 6 h on the day of dosing. Subsequently, the rats were observed twice a day for morbidity and mortality for a period of 14 days following oral dosing (Table 1). The clinical signs were recorded once a day. Individual body weight was recorded prior to dosing on day 0 and on days 7, 14 and at death following oral dosing.

At the end of the observation period surviving animals were sacrificed and subjected to a gross necropsy.

## II. RESULTS AND DISCUSSION

### Mortality

No deaths were observed during the study.

### Clinical Observations

No signs of toxicity were observed in all surviving rats treated at the dose level of 2000 mg Folpet SAPEC 50 SC/kg body weight.

### Body weight

Normal gain in body weight was observed in surviving rats from set I and set II treated at dose level of 2000 mg Folpet SAPEC 50 SC/kg body weight at the end of the experiment.

#### **Necropsy**

No specific findings were noted.

### **III. CONCLUSIONS**

The acute oral median lethal dose (LD<sub>50</sub> cut-off value) of Folpet SAPEC 50 SC in Wistar rats was found to be 5000 mg/kg body weight.

Based on the results folpet SAPEC 50 SC is classified under Category 5 or Unclassified according to Globally Harmonized System of Classification and labelling of Chemicals (GHS, 2009) and OECD Harmonised System for Classification of Chemicals (OCED 2001).

#### **A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)**

Comments of zRMS:	Study [REDACTED] (2011b), has been reviewed for compliance with the current guidelines, resulting from scientific progress. OECD 402 procedure is still valid and acceptable. No deviation has been noted from the study protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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##### **A 2.3.1 Study 1**

**Reference Number:** KCP 7.1.2

**Report:** [REDACTED] (2011b), “Acute dermal toxicity study of Folpet SAPEC 50 SC in rats”;  
[REDACTED]; Study number 403-1-01-2051

**Guidelines:** OECD guideline No. 402, 24th February 1987; Council Regulation (EC) (No. 440/2008, Part B.3, 30 May 2008); Classification: Council Directive 67/548/EEC (and subsequent adaptations).

**Deviations:** None.

**GLP:** Yes; Laboratory certified by AAALAC International

#### **Executive Summary**

This study was performed as a limit study to assess the acute dermal toxicity of Folpet SAPEC 50 SC in Wistar rats. Two groups of rats, each comprising 5 males and 5 females were randomly selected for the study. Approximately, 10 percent of the body surface area was clipped 24 h prior to the dermal application of the test item. One group (group I) served as the control and was treated with 0.39 L distilled water. The other group (group II) was treated with a limit dose of 2000 mg Folpet SAPEC 50 SC/kg body weight which was applied over the clipped area (approximately 10 % of body surface) by single dermal application and observed for a period of 14 days. No sign of toxicity and no mortality were observed in rats treated with 2000 mg Folpet SAPEC 50 SC mg/kg body weight (group II) as well as in rats treated with 0.39 mL distilled water (group I). In absence of any pathological lesion in terminally sacrificed rats, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

### **I. MATERIALS AND METHODS:**

#### **A. MATERIALS**

**1. Test Material:** Folpet SAPEC 50 SC

**Description:** Liquid/off white  
**Lot/Batch #:** C-MRA  
**Purity (ai content):** 500 g/L  
**Stability of test compound:** Expiry date: December 2012

**2. Vehicle:** Purified water by reverse osmosis

**3. Test animals -**

**Species:** Male and female rat  
**Strain:** Wistar  
**Age:** 9 to 10-weeks old

**Weight at dosing:** Male: Minimum: 210g, Maximum: 245g  
Female: Minimum: 203g, Maximum: 212g

**Source:** Animal Breeding Facility, JRF

**Acclimation period:** 6 days prior to dosing

**Diet:** Teklad certified Global High fiber rats/mice feed manufactured by Harlan Nederland

**Water:** Drinking water filtered through an Aquaguard water Filtration system/reverse osmosis water filtration system, provided *ad libitum*

**Housing:** In groups of three; in polypropylene cages, covered with stainless steel grid top were used. Bedding consisted of autoclaved clean rice husk.

**Environmental conditions -**

**Temperature:** 20 to 22° C

**Humidity:** 64 to 67%

**Air changes:** Minimum 15 air changes/h

**Photoperiod:** 12 h light / 12 h dark

## B. STUDY DESIGN AND METHODS

### 1. Animal assignment and treatment

Two groups of rats comprising 5 males and 5 females per group were randomly selected and one group (group II) was given a limit dose of 2000 mg Folpet SAPEC 50 SC/kg body weight by single dermal application. A calculated dose quantity (0.33 to 0.39 ml) of Folpet SAPEC 50 SC was applied over the clipped area (approximately, 10% of the body surface) of the treatment group rats.

The test item was held in contact with the skin using porous gauze dressing (not more than 8 ply) and a non-irritating tape (Medi tape 330 hypo-allergenic surgical tape) throughout the 24 h of exposure period to prevent any loss of the test item, and also to ensure that the animals did not lick or ingest it. The other group (group I) of ten rats (5 males and 5 females) served as the control were simultaneously treated with 0.39mL of distilled water and were maintained under the same experimental conditions. At the end of the observation period surviving animals were sacrificed and subjected to a gross necropsy.

## II. RESULTS AND DISCUSSION

- Clinical signs and mortality: no deaths occurred during the study.

- Body weight: The mean body weight of rats belonging to the treatment group was comparable to that of the control group

- Pathology: macroscopic examination of the main organs of the animals revealed no apparent abnormalities.

### III. CONCLUSIONS

No mortality and no signs of toxicity were observed at the dose level of 2000 mg/kg body weight, hence the acute dermal median lethal dose (LD<sub>50</sub>) of Folpet SAPEC 50 SC in Wistar rats was found to be greater than 2000 mg/kg body weight. Since the LD<sub>50</sub> value was found to be greater than 2000 mg/kg body weight, Folpet SAPEC 50 SC is classified under **Category 5 or Unclassified** according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS 2009) and OECD Harmonised System for Classification of Chemicals (OCED 2001).

#### A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Study [REDACTED] (2013), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 403 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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##### A 2.4.1 Study 1

**Reference Number:** KCP 7.1.3

**Report:** [REDACTED] (2013), “Acute inhalation toxicity study of Folpet 500 SC in rats”  
[REDACTED]; Study number 405-1-01-5390

**Guidelines:** OECD (No. 403, September, 2009)

**Deviations:** None.

**GLP:** Yes

##### Executive Summary

This study was performed to assess the acute inhalation toxicity (LC<sub>50</sub>) of Folpet 500 SC (supplied by Sapec Agro S.A., Setubal) in Wistar rats. The method followed was as per the guidelines of the OECD N° 403 (September, 2009).

This study was conducted as a limit study. One group of rats, comprising three males and three females were used for the study. The rats from group I were exposed to the maximum achievable breathing zone concentration of Folpet 500 SC in distilled water (3.850 mg/L air). The rats were exposed for 4 h followed by observation period of 14 days. No mortality and no sign of toxicity were observed in group I rats exposed to maximum achievable breathing zone concentration of Folpet 500 SC in distilled water (3.850 mg/L air).

Normal gain in body weight was observed in rats exposed to maximum achievable breathing zone concentration of 3.850 mg/L air of Folpet 500 SC in distilled water.

All the treated rats at termination were subjected to gross pathological examination. In absence of any pathological lesion in terminally sacrificed rats, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

No mortality was observed in the treatment group rats (group I) at maximum achievable breathing zone concentration (3.850 mg/L air) of Folpet 500 SC in distilled water. The acute median lethal concentration (LC<sub>50</sub>) of Folpet 500 SC in distilled water was found to be greater than 3.850 mg/L air.

### I. MATERIALS AND METHODS:

#### A. MATERIALS

**1. Test Material:** Folpet 500 SC

**Description:** Liquid/off white  
**Lot/Batch #:** C-MRA  
**Purity (ai content):** 500 g/L  
**Stability of test compound:** Expiry date: December 2012

**2. Vehicle:** None

**3. Test animals -**

**Species:** Rat (*Rattus norvegicus*)  
**Strain:** Wistar rats  
**Age:** 8-11 weeks  
**Weight at dosing:** males 345 - 388 g, females 175 - 193 g  
**Source:** Animal Breeding Facility, [REDACTED]  
**Acclimation period:** 6 days  
**Diet:** Teklad certified Global High Fiber Feed for rat manufactured by Harlan, USA  
**Water:** UV sterilized water filtered through reverse osmosis water filtration system was provided *ad libitum*  
**Housing:** In groups of three; in polypropylene cages, covered with stainless steel grid top were used. Bedding consisted of autoclaved clean rice husk.

**Environmental conditions -**

**Temperature:** 19 to 22°C  
**Humidity:** 64 to 65%  
**Air changes:** Minimum 15 air changes/h  
**Photoperiod:** 12 h light / 12 h dark

## II. RESULTS AND DISCUSSION

### A. MORTALITY

No mortality was observed in the rats exposed to maximum achievable breathing zone concentration of 3.850 mg Folpet 500 SC/L air in distilled water.

### B. CLINICAL OBSERVATION

No sign of toxicity was observed in rats exposed to maximum achievable breathing zone concentration of 3.850 mg Folpet 500 SC/L air in distilled water.

### C. BODY WEIGHT

Normal gain in body weight was observed in rats exposed to maximum achievable breathing zone concentration of 3.850 mg/L air of Folpet 500 SC in distilled water.

### D. NECROPSY

#### External

External examination of terminally sacrificed rats did not reveal any abnormality of pathological significance.

#### Internal

Visceral examination of the terminally sacrificed rats did not reveal any lesion of pathological significance. In absence of any pathological lesion in terminally sacrificed rats, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

#### **E. DEFICIENCIES**

None.

#### **III. CONCLUSIONS**

No mortality was observed in the treatment group rats (group I) at maximum achievable breathing zone concentration (3.850 mg/L air) of Folpet 500 SC in distilled water. The acute median lethal concentration (LC<sub>50</sub>) of Folpet 500 SC in distilled water was found to be greater than 3.850 mg/L air.

Under the conditions of the study, performed as a limit test, the maximum attainable concentration of folpet was 3.580 mg/L, and the mass median aerodynamic diameter (MMAD) of particles was 3.8 µm with a geometric standard deviation (GSD) of 1.79.

The LC<sub>50</sub> was found to be >3.850 mg/L (max. attainable) and thus, classification is not warranted according to the Regulation (EC) No. 1272/2008.

## A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Study [REDACTED] (2011c), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 404 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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### A 2.5.1 Study 1

**Reference Number:** KCP 7.1.4

**Report:** [REDACTED] (2011c), “Acute dermal irritation study of Folpet SAPEC 50 SC in rabbits”; [REDACTED] Study number 406-1-01-2052

**Guidelines:** OECD (No. 404, 24th April 2002); Council Regulation (EC) (No. 440/2008, B.4, 30 May 2008). Classification: Council Directive 67/548/EEC (and subsequent adaptations).

**Deviations:** None.

**GLP:** Yes; Laboratory certified by AAALAC International.

### Executive Summary

This study was performed to assess the acute dermal irritation potential of Folpet Sapec 50 SC (supplied by Sapec Agro S.A.) in New Zealand White rabbits. The method followed was as per the guidelines of OECD N° 404 (April 2002).

Three healthy, adult female albino rabbits of New Zealand White strain were selected for the study. Initially one rabbit was tested with a single patch for a period of 4 h. Based on the observation at 24 h post patch removal, the irritant response was confirmed by testing two additional rabbits simultaneously. A quantity of 0.5 mL Folpet Sapec 50 SC (undiluted) was applied evenly to the clipped intact skin of rabbits. The treated and the control sites were covered with gauze patches and secured at the margins by non-irritating tape for a period of 4 h. At the end of the exposure period, the residual test item was removed with cotton soaked in distilled water. The skin reactions were observed and scored at 1, 24, 48 and 72 h post patch removal. Distilled water was applied to the control skin site of the rabbits and the skin was normal throughout the experimental period.

The mean dermal irritation scores of erythema (0.67 to 1.00) and oedema (0.00) were observed at 24, 48 and 72 h observation period.

According to the observed mean dermal irritation scores, Folpet Sapec 50 SC is not classified as a skin irritant.

## I. MATERIALS AND METHODS:

### A. MATERIALS

<b>1. Test Material:</b>	Folpet SAPEC 50 SC
<b>Description:</b>	Liquid/off white
<b>Lot/Batch #:</b>	C-MRA
<b>Purity (ai content):</b>	500 g/L
<b>Stability of test compound:</b>	Expiry date: December 2012



**2. Vehicle:** Purified water by reverse osmosis

**3. Test animals -**

**Species:** Rabbit (*Oryctolagus cuniculus*)  
**Strain:** New Zealand white  
**Age:** 2-5 months  
**Weight at dosing:** 1.702-1.876 Kg  
**Source:** Mahaveera Enterprise, Hyderabad, India  
**Acclimation period:** 5 days prior to dosing  
**Diet:** Teklad certified Global High fiber rats/mice feed manufactured by Harlan Nederland  
**Water:** Drinking water filtered through an Aquaguard water Filtration system/reverse osmosis water filtration system, provided *ad libitum*  
**Housing:** In groups of three; in polypropylene cages, covered with stainless steel grid top were used. Bedding consisted of autoclaved clean rice husk.

**Environmental conditions -**  
**Temperature:** 19 to 23°C  
**Humidity:** 64 to 66%  
**Air changes:** Minimum 15 air changes/h  
**Photoperiod:** 12 h light / 12 h dark

## B. STUDY DESIGN AND METHODS

### 1. Animal assignment and treatment

A quantity of 0.5 ml Folpet Sapec 50 SC (undiluted) was applied evenly to one of the clipped sites of each rabbit and on the other clipped site 0.5 mL of distilled water was applied. The latter served as the control site. The treated and the control sites were covered with gauze patches of approximately 6 cm<sup>2</sup> (gauze rolled) which was not more than 8-ply and that was secured at the margins by non-irritating tape (Medi tape 330, hypo-allergenic surgical tape) to prevent access by the rabbit to the patch and resultant ingestion /inhalation of the test item. At the end of a 4 h exposure period (day 0) the residual test item was removed with cotton soaked in distilled water.

Dermal irritation and corrosiveness were evaluated according to the scoring scale as proposed by the guideline.

## II. RESULTS AND DISCUSSION

### Skin reactions

Observed skin reaction are summarised in the following tables:

Individual scores of the skin reactions		
Score at time point	Erythema (Animal No. 1/2/3)	Oedema (Animal No. 1/2/3)
1 h	1/1/1	0/0/0
24 h	2/1/1	0/0/0
48 h	1/1/1	0/0/0
72 h	0/0/0	0/0/0
Average 24-72 h	1/0.67/0.67	0/0/0

Rabbit N°	Mean of Scores at 24, 48 and 72 Hours	
	Erythema	Oedema
1	1.00	0.00
2	0.67	0.00
3	0.67	0.00

Following the 4 h exposure period (day 0), the skin of each rabbit was observed at 1, 24, 48 and 72 h post patch removal.

At 1 h post patch removal the treated skin site of all the three rabbits revealed very slight erythema.

At 24 h post patch removal the treated skin site of rabbit N° 2 and 3 revealed very slight erythema and rabbit N° 1 revealed well-defined erythema.

At 48 h post patch removal the treated skin site of all the three rabbits revealed very slight erythema.

At 72 h post patch removal the treated skin site of all the three rabbits recovered completely and appeared normal.

The control skin site of all the three rabbits was normal throughout the experimental period.

#### **Clinical Observations**

No mortalities or clinical signs of toxicity were noted in any animal throughout the study period.

#### **Body weight**

There were no effects on body weight development noted.

### **III. CONCLUSIONS**

Since the mean scores of erythema (0.67 to 1.00) and oedema (0.00) following 24, 48 and 72 h observations were non-significant in any of the treated rabbits (Table 2), Folpet Sapec 50 SC is being classified as “**Not classified as a skin irritant**” as per the Globally Harmonized System of Classification and Labelling of Chemicals (GHS 2009) and OECD Harmonized System for Classification of Chemicals (August 2001).

## A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Study [REDACTED] (2011d), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 405 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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### A 2.6.1 Study 1

**Reference Number:** KCP 7.1.5

**Report:** [REDACTED] (2011d), “Acute eye irritation study of Folpet SAPEC 50 SC in rabbits”; [REDACTED]; Study number 407-1-01-2053

**Guidelines:** The Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals, N° 405, “Acute Eye Irritation/Corrosion”, adopted by the Council on April 24, 2002.

**Deviations:** None.

**GLP:** Yes; Laboratory certified by AAALAC International.

#### Executive Summary

This study was performed to assess the acute eye irritation potential of Folpet Sapec 50 SC (supplied by Sapec Agro S.A., Portugal) in New Zealand White rabbits. The method followed was as per guidelines of the OECD N° 405 (April 2002).

Three healthy, adult, female albino rabbits of New Zealand White strain were selected for the study. Initially one rabbit was tested. Based on the results obtained at 24 h post instillation observation, the irritation response was confirmed by testing two additional rabbits simultaneously. A quantity of 0.1 mL Folpet Sapec 50 SC was instilled into one eye of each rabbit. The contralateral eye served as the control and was instilled with 0.1 mL of 0.9% normal saline. Observations were made following the method described in the guidelines at 1 h (on day 0), 24, 48, 72 h and on day 7 post instillation.

The mean eye irritation scores (following grading at 24, 48 and 72 h post instillation) of the corneal opacity (0.00), iritis (0.00), conjunctival redness (1.67 to 2.00) and chemosis (1.33) were observed in all the three treated rabbits.

Folpet Sapec 50 SC is being classified as **Mildly Irritating to Eyes (Category 2B)**.

## I. MATERIALS AND METHODS:

### A. MATERIALS

**1. Test Material:** Folpet SAPEC 50 SC

**Description:** Liquid/off white

**Lot/Batch #:** C-MRA

**Purity (ai content):** 500 g/L

**Stability of test compound:** Expiry date: December 2012

**2. Vehicle:** Purified water by reverse osmosis

### 3. Test animals -

<b>Species:</b>	Rabbit ( <i>Oryctolagus cuniculus</i> )
<b>Strain:</b>	New Zealand white rabbits
<b>Age:</b>	2-5 months
<b>Weight at dosing:</b>	1.864- 2.034 kg
<b>Source:</b>	Mahaveera Enterprises, Hyderabad, India
<b>Acclimation period:</b>	9 days for rabbit N° 1 and 11 days for rabbit N° 2 and 3 prior to test item instillation
<b>Diet:</b>	Teklad certified Global High fiber rats/mice feed manufactured by Harlan Nederland
<b>Water:</b>	Drinking water filtered through an Aquaguard water Filtration system/reverse osmosis water filtration system, provided <i>ad libitum</i>
<b>Housing:</b>	Stainless steel wire meshed cages were used.

### Environmental conditions -

<b>Temperature:</b>	19 to 23°C
<b>Humidity:</b>	64 to 66%
<b>Air changes:</b>	Minimum 15 air changes/h
<b>Photoperiod:</b>	12 h light / 12 h dark

## B. STUDY DESIGN AND METHODS

### 1. Animal assignment and treatment

Initially one rabbit was tested. Based on the results obtained at 24 h post instillation observation, the irritation response was confirmed by testing two additional rabbits simultaneously. A quantity of 0.1 mL Folpet Sapec 50 SC was instilled into the conjunctival sac in the anterior surface of one eye of each rabbit after gently pulling the lower eyelid away from the eyeball. The eyelids were then gently held together for about one second in order to prevent loss of the test item. The contralateral eye of each rabbit served as a control and was instilled with 0.1 mL of 0.9% normal saline. At 24 h post instillation of the test item, both the eyes (control and treated) of the three rabbits were gently washed with 0.9% normal saline.

The treated and the control eyes were gently washed with 0.9% normal saline after 24 h post treatment period. The eyes of each rabbit were then examined using fluorescein dye staining (Swinyard, 1990). One drop of normal saline was placed on a sterile ophthalmic fluorescein strip and one drop was instilled into the eye.

The fluorescein strip was then placed in the eye. The eyelids were closed for few seconds. The fluorescein strip was then removed and the eye was examined with the aid of HEINE Ophthalmoscope XHL bulb through a cobalt blue filter (corneal damage showing as green fluorescein staining). Any loss or damage in corneal epithelium was recorded (Appendix 4).

## II. RESULTS AND DISCUSSION

The individual and mean ocular irritation scores are presented in the table below:

Score at time point / Reversibility	Corneal opacity (Animal No. 1/2/3)	Iritis (Animal No. 1/2/3)	Conjunctival redness (Animal No. 1/2/3)	Conjunctival chemosis (Animal No. 1/2/3)
1 h	0/0/0	0/0/0	1/1/1	1/1/1
24 h	0/0/0	0/0/0	2/2/2	2/2/2
48 h	0/0/0	0/0/0	2/2/2	1/1/1
72 h	0/0/0	0/0/0	1/2/2	1/1/1
Average 24h, 48h, 72h	0/0/0	0/0/0	1.67/2.00/2.00	1.33/1.33/1.33
/Reversibility*	-	-	c	c

Average time (days) for reversion	-	-	7	7
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\* Reversibility: c. = completely reversible

### **Description of Eye Irritation**

#### **Treated Eye**

At 1 h post instillation, eye examination revealed conjunctival redness [some blood vessels hyperaemic (injected)] and chemosis [some swelling above normal (includes nictitating membranes)] in all the three rabbits.

At 24 h post instillation, eye examination revealed conjunctival redness [diffuse, crimson colour, individual vessels not easily discernible] and chemosis [obvious swelling with partial eversion of lids] in all the three rabbits (Appendix 3). Examination at 24 h with fluorescein dye and cobalt blue filter (corneal damage showing as green fluorescein) revealed no corneal epithelium damage in treated eyes of all three rabbits.

At 48 h post instillation eye, examination revealed conjunctival redness [diffuse, crimson colour, individual vessels not easily discernible] and chemosis [some swelling above normal (includes nictitating membranes)] in all the three rabbits.

At 72 h post instillation, eye examination revealed conjunctival redness [some blood vessels hyperaemic (injected) in rabbit N° 1 to diffuse, crimson colour, individual vessels not easily discernible in rabbit N° 2 and 3] and chemosis [some swelling above normal (includes nictitating membranes) in all the three rabbits].

On day 7 post instillation eye examination, treated eye of all the three rabbits recovered completely and appeared to be normal.

Iritis and corneal opacity were not observed in any of the treated eye of all the rabbits throughout the experimental period.

#### **Control Eye**

No abnormalities were detected in the control eye of all the rabbits during the course of this study (Appendix 3). No damage to corneal epithelium was observed during the examination with fluorescein dye and cobalt blue filter. (Appendix 4).

### **III. CONCLUSIONS**

The mean eye irritation scores (following grading at 24, 48 and 72 h post instillation) of the corneal opacity (0.00), iritis (0.00), conjunctival redness (1.67 to 2.00) and chemosis (1.33) were found to be significant in two out of three treated rabbits.

The classification criteria for eye irritation (Category 2) under the Regulation (EC) No. 1272/2008 are defined as follows:

If, when applied to the eye of an animal, a substance produces:  
at least in 2 of 3 tested animals, a positive response of:

- corneal opacity  $\geq 1$  and/or
- iritis  $\geq 1$ , and/or
- conjunctival redness  $\geq 2$  and/or
- conjunctival oedema (chemosis)  $\geq 2$

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

Based on the above, classification of the formulation as **Eye Irrit. 2 – H319** is required, according to the CLP Regulation.

## A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Study [REDACTED] (2011e), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 429 procedure is valid and acceptable. Study is in line with the suggestions of point 5 of Regulation 284/2013 and Annex VII to REACH REG (EC) No 1907/2006. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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### A 2.7.1 Study 1

**Reference Number:** KCP 7.1.6

**Report:** [REDACTED] (2011e), “Skin sensitization study of Folpet SAPEC 50 SC by local lymph node assay in mice”; [REDACTED]; Study number 409-1-01-2054

**Guidelines:** The Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals, N° 429, “Skin Sensitization: Local Lymph Node Assay”, adopted by the Council on July 22, 2010

**Deviations:** None

**GLP:** Yes; Laboratory certified by AAALAC International

#### Executive Summary

Total seven groups of female mice of CBA/J strain (age 10 to 12 weeks) comprising 4 females per group were selected for the experiment. Five groups were topically applied with Folpet SAPEC 50 SC in 1% aqueous L92 at the dose concentrations of 1% (G3), 5% (G4), 10% (G5), 25% (G6) and 50% (G7) (v/v) for three consecutive days (on days 0, 1 and 2) on the dorsum of both ears (25 µL per ear). The group 1 (G1) served as vehicle control and was treated with 1% aqueous L92 and a concurrent positive control group (G2) was treated with  $\alpha$ -hexylcinnamaldehyde (HCA) at the dose concentration of 25% (v/v) in 1% aqueous L92 in same manner to confirm the sensitivity and reliability of the test method.

On day 5 of treatment, the proliferation of lymph node cells in the lymph node draining the application site was measured by incorporation of <sup>3</sup>H-methyl thymidine. The obtained values were used to calculate stimulation index (SI).

Stimulation Index (SI Value) calculated for Folpet SAPEC 50 SC treatment groups was found to be 19.97, 25.24, 28.20, 31.22 and 36.19 for the dose concentrations of 1%, 5%, 10%, 25% and 50% (v/v), respectively. Stimulation Index (SI Value) calculated for positive control group treated with 25% v/v HCA was found to be 3.83%.

Since Stimulation Index obtained for 1%, 5%, 10%, 25% and 50% (v/v) tested dose concentrations of Folpet SAPEC 50 SC showed more than three-fold increase over the vehicle control, so the EC<sub>3</sub> value calculation was not possible. Hence, it was concluded that under these experimental conditions, Folpet SAPEC 50 SC induced contact sensitization to CBA/J strain mice in the Local Lymph Node Assay.

## I. MATERIALS AND METHODS:

### A. MATERIALS

**1. Test Material:** Folpet SAPEC 50 SC

**Description:** Liquid/off white  
**Lot/Batch #:** C-MRA

**Purity (ai content):** 500 g/L  
**Stability of test compound:** Expiry date: December 2012

**2. Vehicle:** Purified water by reverse osmosis

**3. Test animals -**

**Species:** Mice  
**Strain:** *Mus musculus* (CBA/J)  
**Age:** 10-12 weeks  
**Weight at dosing:** 19.7-25.1 g  
**Source:** Animal Breeding facility, JRF, India  
**Acclimation period:** 6 days prior to dosing  
**Diet:** Teklad certified Global High fiber rats/mice feed manufactured by Harlan Nederland  
**Water:** Drinking water filtered through an Aquaguard water Filtration system/reverse osmosis water filtration system, provided *ad libitum*  
**Housing:** In groups of three; in polypropylene cages, covered with stainless steel grid top were used. Bedding consisted of autoclaved clean rice husk.

**Environmental conditions -**

**Temperature:** 19 to 22°C  
**Humidity:** 64 to 66%  
**Photoperiod:** 12 h light / 12 h dark

## B. STUDY DESIGN AND METHODS

### 1. Animal assignment and treatment

To assess the irritant potential of the test substance (through ear thickness measurement), a preliminary assay was carried out. Four groups of mice comprising 2 females per group were applied with folpet SAPEC 50 SC (25 µL) at 10%, 25%, 50% and 75% (v/v) in 1% aqueous L92 for three consecutive days (day 0, 1 and 2). Clinical observation was recorded daily during the experiment. Ear thickness was measured on days 0, 2 and on day 5 (at 72 hours post last application). Based on the result of the preliminary assay, the following dose concentrations were selected for the main study: 1%, 5%, 10%, 25% and 50% (v/v). Five groups (G3 to G7) were topically applied with folpet SAPEC 50 SC at the dose concentrations of 1%, 5%, 10%, 25% and 50% (v/v) in 1% aqueous L92 for three consecutive days during induction (on day 0, 1 and 2) at the dorsum surface of both ear (25 mL/ear) using micropipette.

Animals from control groups were handled in similar manner and applied with 25 mL of 1% aqueous L92 (G1). Positive control group (G2) was treated with a-hexylcinnamaldehyde at the dose concentration of 25% (v/v) in 1% aqueous L92 in the same manner.

On day 5 of treatment, all mice from the vehicle control and positive control as well as the treatment groups were injected 250 µL of sterile phosphate buffered saline (PBS) containing approximately 20 µCi (7.4e+5 Bq) of <sup>3</sup>H-methyl thymidine *via* the tail vein.

Five hours after administration of <sup>3</sup>H-TdR, all the animals from the controls as well as the treatment groups were euthanized by CO<sub>2</sub> asphyxiation. The draining auricular lymph nodes from both the ears were excised and pooled in phosphate buffered saline for each mouse.

## II. RESULTS AND DISCUSSION

### Clinical Observations

No mortalities or clinical signs of toxicity were noted in any animal throughout the study period.

### Body weight

There were no effects on body weight development noted.

### Stimulation Index (SI Value) and EC<sub>3</sub> Value

No treatment related systemic clinical signs were observed in animals from the controls as well as Folpet SAPEC 50 SC treated groups *i.e.* G3, G4, G5, G6 and G7 treated at the dose concentrations of 1%, 5%, 10%, 25% and 50% (v/v), respectively. Animals from positive control group treated with  $\alpha$ -hexylcinnamaldehyde (HCA) at the dose concentration of 25% (v/v) in 1% aqueous L92 exhibited erythematic response [very slight erythema (barely perceptible)] on days 1 to 4.

Stimulation Index (SI Value) calculated for Folpet SAPEC 50 SC treatment groups was found to be 19.97, 25.24, 28.20, 31.22 and 36.19 for the dose concentrations of 1%, 5%, 10%, 25% and 50% (v/v), respectively. Stimulation Index (SI Value) calculated for positive control group treated with 25% v/v HCA was found to be 3.83%.

## III. CONCLUSIONS

Since Stimulation Index obtained for 1%, 5%, 10%, 25% and 50% (v/v) tested dose concentrations of Folpet SAPEC 50 SC showed three-fold increase over the vehicle control, so the EC<sub>3</sub> value calculation was not possible. Under the conditions of this study (LLNA), the formulation was found to be skin sensitizing and therefore, classification as Skin Sens. 1 – H317 is required, according to the Regulation (EC) No. 1272/2008.

### A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

Not required.

### A 2.9 Data on co-formulants (KCP 7.4)

#### A 2.9.1 Material safety data sheet for each co-formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

#### A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

### A 2.10 Studies on dermal absorption (KCP 7.3)

#### A 2.10.1 Study 1 – Folpet in SAP50SCF / Folpet 500 SC

#### Comparative dermal absorption, in vitro using rat and human skin

Comments of zRMS:	Study Johnson, I., 2015 is considered to be acceptable, however due to fact that for spray dilution the concentration tested (1.5 g/L) is higher than the lowest concentration presented on GAP (450 g / 400 L = 1.125 g/L) Pro rata approach has been used and therefor dermal absorption for a.s. folpet is covered by this study. DA values obtained from the study are reliable and can be used for risk assessment.
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Reference KCP 7.3/01

Report Folpet 50 SC - In Vitro Absorption of Folpet through Human Dermatomed Skin using [14C]-Radiolabelled Folpet, Johnson, I., 2015, Document No JV2317-REG



Guideline(s)	OECD Test Guideline 428 (2004); OECD Guidance Document No. 28 (2004); OECD Guidance Notes on Dermal Absorption No. 156 (2011); EFSA (2012)
Deviations	No
GLP	Yes
Acceptability	Yes

## Executive Summary

The absorption and distribution of Folpet from a SC formulation concentrate (Folpet 50 SC) was measured *in vitro* through human dermatomed skin conforming to the Regulatory Guidelines given in Section 2.2. The doses were applied as the formulation concentrate (500 g Folpet/L) and as a 1/333 v/v (1.5 g Folpet/L) aqueous spray strength dilution of the formulation. The doses were applied to the skin surface at 10 µL/cm<sup>2</sup> and left unoccluded for an exposure period of 6 hours. The formulation concentrate was included to assess exposure to mixer/loaders. The spray strength dilution used (1/333 v/v) represented a typical in-use concentration. These applications were designed to simulate potential human dermal exposure to the formulation during normal use.

[<sup>14</sup>C]-radiolabelled Folpet was added to the formulations prior to skin application. The applications were washed off the skin surface after the 6 hour contact period, with the absorption of Folpet through the skin being assessed over an observation period of 24 hours, by sampling the fluid (60% v/v ethanol/water) in the receptor chamber 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after application. At the end of the experiment, the distribution of Folpet in the test system was assessed, which included a tape stripping technique to determine its adsorption to the *stratum corneum*. All samples were analysed by LSC.

## STUDY DESIGN:

<b>Skin type:</b>	Human dermatomed skin
<b>Cells per application:</b>	N = 8
<b>Diffusion cell type:</b>	Static; 2.54 cm <sup>2</sup> exposure area
<b>Dose preparation:</b>	Doses contained [ <sup>14</sup> C]-Folpet, incorporated into the formulation concentrate and an aqueous dilution
<b>Applications:</b>	<ul style="list-style-type: none"> <li>• Formulation concentrate - 6 hour exposure &amp; 24 hour run time</li> <li>• 1/333 v/v aqueous dilution - 6 hour exposure &amp; 24 hour run time</li> </ul>
<b>Application amount:</b>	10 µL/cm <sup>2</sup>
<b>Occlusion:</b>	No
<b>Carbon filters:</b>	No
<b>Receptor fluid:</b>	60% v/v ethanol/water
<b>Receptor sample volume:</b>	500 µL
<b>Experiment temperature:</b>	32°C ± 1°C
<b>Sampling times:</b>	Pre-treatment plus x hours post application x = 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24
<b>Interim decontamination:</b>	Yes, 6 hours
<b>Wash details:</b>	Sponge wash
<b>Total run time:</b>	24 hours
<b>Final decontamination</b>	Yes
<b>Wash details:</b>	Sponge wash
<b>Mass balance:</b>	Yes
<b>Tape stripping:</b>	Yes, 5 strips
<b>Analysis:</b>	<u>Liquid Scintillation Counting (LSC)</u>

Radioactivity content of radiolabel, dose preparations, time course and mass balance samples.

High Performance Liquid Chromatography/Flow Scintillation Analysis (HPLC/FSA)

Radiochemical purity of radiolabel and dose preparations.

## RESULTS:

### Absorption

Application	Actual dose (µg/cm <sup>2</sup> )	% Recovery	24 h Absorption rate (µg/cm <sup>2</sup> /h)	Amount absorbed <sup>#</sup> (µg/cm <sup>2</sup> )	% absorbed <sup>#</sup>
Formulation concentrate	4012	107	0.498	15.5	0.386
1/333 v/v aqueous dilution	14.5	98.5	0.017	0.486	3.35

<sup>#</sup> Receptor fluid + remaining skin, excluding all tape strips (>75% of the total absorbed in the first 12 hours – EFSA, 2012).

### Distribution

Test compartment	Mean % of applied dose			
	Formulation concentrate		1/333 v/v dilution	
	N = 7		N = 7	
	Mean	SD	Mean	SD
Donor chamber	0.061	0.030	0.045	0.018
Skin wash at 6 hours	105	4.02	93.6	3.83
Skin wash at 24 hours	1.10	1.45	0.686	0.653
<i>Stratum corneum</i> Tape strip 1	0.002	0.002	0.008	0.008
<i>Stratum corneum</i> Tape strip 2	0.002	0.0008	0.004	0.006
<i>Stratum corneum</i> Tape strip 3	0.0009	0.0005	0.004	0.004
<i>Stratum corneum</i> Tape strip 4	0.003	0.006	0.006	0.010
<i>Stratum corneum</i> Tape strip 5	0.0004	0.0002	0.003	0.003
Remaining skin	<b>0.113</b>	0.079	<b>0.639</b>	0.510
Receptor fluid at 12 h	0.248	0.053	2.21	0.700
Receptor fluid at 24 h	<b>0.273</b>	0.057	<b>2.71</b>	0.673
Total absorbable <sup>#</sup>	<b>0.386</b>	0.122	<b>3.35</b>	0.558
Total recovered	107	2.77	97.7	3.53

Values contributing to the total % of Folpet absorbable are shown in bold face type.

## CONCLUSIONS

The results obtained in this study demonstrate that the absorption of Folpet through human dermatomed skin is extremely slow and the majority of the applied dose is washed off the skin at 6 hours.

The total Folpet potentially absorbed from the formulation concentrate (receptor fluid + remaining skin) was 0.386% of the dose applied and the total absorbable from the 1/333 v/v dilution (receptor fluid + remaining skin) was 3.35% of the dose applied.

These data predict that the dermal absorption of Folpet from potential exposure to this SC formulation would be minimal.

According to the criteria laid down in the EFSA Guidance document on dermal absorption (2017), following dermal absorption values were derived for Folpet:

#### Total absorbable

(500 g/L) Concentrate: 0.386 % ± 0.122 (n = 7)

(1.5 g/L) Spray Dilution: 3.35% ± 0.558 (n = 7)

According to Dermal Absorption Guidance 2017, to address variability between replicates/animals, dermal absorption should be calculated as follows: Absorption (mean value) + ks, where s is the sample standard deviation.

<b>Concentrate</b>	Dermal Absorption = 0.386 + (0.92 * 0.122) = 0.498% ~ <b>0.5%</b>
<b>Spray Dilution</b>	Dermal Absorption = 3.35 + (0.92 * 0.558) = 3.86% ~ <b>3.9%</b>

GD 2017, page 14: “*The concentration(s) tested should cover the extremes of those recommended on the product label. If the lowest concentration tested is greater than the lowest concentration of the same formulation recommended on the label, consideration should be given to increasing the dermal absorption pro rata to account for any limitation of absorption due to the amount of material applied to the test site.*”

Since for spray dilution the concentration tested (1.5 g/L) is higher than the lowest concentration presented on GAP (450 g / 400 L = 1.125 g/L) Pro rata approach was considered.

#### Pro Rata Approach

**Final Dermal absorption = Study dermal absorption value x (Concentration tested / GAP concentration)**

**= 3.9% x (1.5 / 1.125) = 5.2 %**

- Formulation concentrate: **0.5%**

- 1/333 v/v in-use dilution: **5.2%.**

**NOTE:** Should be highlighted that the *pro rata* approach calculated above takes into account a worst-case scenario since the lowest concentration recommended on label used is based on the pure material instead of technical material. If the technical material is considered, an in-use dilution value of 4.99%\* is obtained (GAP concentration = 0.469/400 = 1718 g/L)

**\*Dermal Absorption (in-use dilution) = 3.9% x (1.5 / 1.1718) = 4.99 %**

For the dose of 1.5 L pf/ha no *pro rata* is deemed necessary since the lowest concentration tested is equal to the lowest concentration recommended on the label. However, the in-use dilution value of **5.2%** was also considered on the risk assessment for the higher dose (1.5 L pf/ha).

#### A 2.11 Other/Special Studies

Not required.

## Appendix 3 Exposure calculations

Please find below the word report generate by the EFSA calculator as well as the zip for the online tool.

### ***WORD REPORT***



DGA - Folpet 500 SC  
(09.2023).v0\_202311:

### ***ZIP***



DGA - Folpet 500 SC (09.2023).v0\_20231120\_16h00\_opex1.0.1.zip

## Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Not required.