REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: ADM.03502.F.1.A
(alternative codes: MCW-2091)

Product name: see part A

Chemical active substances:

Prothioconazole, 175 g/L
Fenpropidin, 250 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorisation)

Applicant: Country organisation / representative
as specified in Part A

Submission date: September 2021

MS Finalisation date: December 2022 (initial Core Assessment)

April 2023 (final Core Assessment)

Version history

When	What
2021/09	Version 1 Applicant
December 2022	Initial zRMS assessment 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 highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.
April 2023	Final report (Core Assessment updated following the commenting period) Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~.

DATA PROTECTION CLAIM

In order to present a dossier fully compliant with today's requirements (Reg. 284/2013), studies have been performed on ADM.03502.F.1.A. Under Article 59, Regulation 1107/2009/EC. On behalf of the Sponsor Company the applicant claims data protection for the studies conducted with ADM.03502.F.1.A. The data protection status and corresponding justification as valid for the respective country will be confirmed in the respective PART A.

STATEMENT FOR OWNERSHIP

The summaries and evaluations contained in this document may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it. Other registration authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this document unless they have received the data on which the summaries and evaluation are based, either –

- from the owner of the data, or
- from a second party that has obtained permission from the owner of the data for this purpose or,
- following expiry of any period of exclusive use, by offering – in certain jurisdictions – mandatory compensation, unless the period of protection of the proprietary data concerned has expired.

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Reviewer comments:

This dossier has been prepared to support registration of ADM.03502.F.1.A/ FORAPRO 425 EC in Poland and zonal registration for which PL was designated zRMS.
Current application has been submitted for the approval under Art.33 of EU Regulation 1107/2009 of the product with commercial name FORAPRO 425 EC (developmental code ADM.03502.F.1.A), an emulsifiable concentration (EC) formulation containing prothioconazole 175g/L and fenpropidin 250g/L ADM.03502.F.1.A is a fungicide (details see GAP dRR B0).
Product was not a representative formulation reviewed during the Annex I inclusion/active substance renewal and has not previously been evaluated in any EU countries according to the Uniform Principles, thus it is not possible to refer to the DRAR conclusion on PTZ and Fenpropidin with regard to the formulation studies. Therefore, relevant data on the plant protection product ADM.03502.F.1.A had to be generated for authorization purposes.
NOTE: Applicant clarified that both *in vivo* studies were not performed with intention for use within the EU. It was however performed to satisfy the regulatory requirements of countries outside of the EU.

Annex point	Study reference	Justification for provision of new vertebrate data (Article 33.3c)
KCP 7.1.3/01	… (2021) Acute inhalation toxicity study in Wistar rats - OECD 403 Report no.: G19710; sponsor no.: 000104833 Eurofins Advinus Ltd., Bangaluru, India GLP; Unpublished	Data relevant to ADM.03502.F.1.A and required for classification and labelling since results of the study deviates from predicted classification based on the properties of the individual components in ADM.03502.F.1.A. Regulatory authorities outside of the EU, also request the data for classification purposes.
KCP 7.1.5/02	… (2021) Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A Report no.: 2000201; sponsor no.: 000104834 BSL Bioservice Scientific Laboratories Munich GmbH, Planegg, Germany; GLP; Unpublished	Data relevant to ADM.03502.F.1.A and required for classification and labelling since results of an in-vitro study was not conclusive. Regulatory authorities outside of the EU, also request the data for classification purposes.

Regarding studies on acute toxicity including irritancy for eye and skin– based on alternative (*in vitro*) studies zRMS decided as follow:

- KCP 7.1.4/01 Groß, C., 2021 (*In vitro* skin irritation: Human Skin Model Test (EpiDerm™) with ADM.3502.F.1.A (OECD 439)) considering information available in GD OECD 439 revision 14 June 2021 INITIAL CONSIDERATIONS AND LIMITATIONS Subsection 8: p.2 (..) data indicates a lack of applicability of the RhE based *in vitro* skin irritation test for agrochemical formulations (47). (..). See also: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). Regulatory accepted but out of domain: *In vitro* skin irritation tests for agrochemical formulations. Regul. Toxicol. Pharmacol 89, 125-130.
  Thus, taking into account mentioned above information zRMS decided to conclude assessment in this hazard category for the ADM.03500.F.2.B taking into account outcome of the *in vivo* study …. (2021) *Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A.* and classify product ADM.03502.F.1.A with hazard category H315 "Causes skin irritation" as a precautionary approach.

- KCP 7.1.5/01 Regarding *in vitro* study Julienne, S., 2020 (Eye irritation, BCOP assay, isolated corneas of bovine eyes (OECD 437)), zRMS reviewer draws attention to the following information available in the paper: Kolle S.N., van Cott A., van Ravenzwaay B. and Landsiedel R. (2017): Lacking applicability of in vitro eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS. Regulatory Toxicology and Pharmacology 85 (2017) 33-47. Thus, taking into account mentioned above information zRMS decided to conclude assessment in this hazard category for the ADM.03500.F.2.B based on *in vivo* study … (2021) *Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A.*

Regarding study on acute inhalation toxicity ZRMS decided as follow:

- KCP 7.1.3/01 …. (2021) Acute inhalation toxicity study in Wistar rats - OECD 403 and assessment based ATEmix/additivity formula and components content gave the different outcome. Based on the alternative approach by using the calculation method, ADM.03502.F.1.A has a calculated LC_{50} of 3.94 mg/L and classified as acutely toxic via the inhalation route would be required. However, based on the results of the acute inhalation toxicity study, the acute LC_{50} is > 5.0 mg/L. Thus, classification of ADM.03502.F.1.A is not required according to Regulation (EC) No. 1272/2008 and subsequent regulations. Thus, the relying on the results of an acute inhalation toxicity study is considered justified for adequate classification of the product

NDE assessment for operator, workers and B&R exposure to the fenpropidin, PTZ and PTZ-desthio considering all critical use(s) and all tasks, identify safe use of the product ADM.03502.F.1.A/ FORAPRO 425 EC.

Based on the results of the acute toxicity and non-dietary risk assessments conducted for ADM.03502.F.1.A/ FORAPRO 425 EC, the following personal protective equipment (PPE)/risk management measures (RMM) are recommended:
Operator: Operators must wear adequate workwear covering arms, body and legs during M/L and A also protective gloves during M/L.
Note: precautionary measures based on classification & labelling:
Due to the classification of the product with H315, H317 and H318 protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.

Worker: Worker should use adequate workwear covering arms, body and legs when entering in a treated area.

Note: All changes regarding NDS assessment which reflects comments made by cMS countries has been included in this revised RR. Additional calculations for each exposed group are placed in separate boxes highlighted in yellow and turquoise (Appendix 3) colour. In case of exposure to PTZ-desthio it has been considered into the assessment 50% conversion factor. Buffer zones accepted for NDE calculations are 2-3m and 5m.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on ADM.03502.F.1.A*

Product name and code	ADM.03502.F.1.A
Formulation type	Emulsifiable Concentrate [Code: EC]
Active substance(s) (incl. content)	Prothioconazole; 175 g/L; Fenpropidin, 250 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 ADM.03502.F.1.A 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 ADM.03502.F.1.A according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Skin Irrit. 2 Skin Sens. 1B Eye Dam. 1 STOT SE 3 STOT RE 2
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS05, GSH07, GSH08
Signal word:	Danger
Hazard statement(s):	H315 “Causes skin irritation” H317 “May cause an allergic skin reaction” H318 “Causes serious eye damage” H335 “May cause respiratory irritation” H373 “May cause damage to organs through prolonged or repeated exposure” (nervous system, eyes, lungs)
Precautionary statement(s):	P102 Keep out of reach of children P260 Do not breathe dust/fume/gas/mist/vapors/spray P280 Wear protective gloves, protective clothing and eye/face protection P302 + P352 - IF ON SKIN: Wash with plenty of soap and 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 P501 - Dispose of contents/container to an approved waste disposal plant
Additional labelling phrases:	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
	Do not contaminate water with the product or its container (Do not clean application equipment near surface water/Avoid contamination via drains from farmyards and roads). [SP1]

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for ADM.03502.F.1.A

	Result	PPE / Risk mitigation measures
Operators	Acceptable	**Results of risk assessment:** Operator wearing workwear covering arms, body and legs during mixing/loading and application and gloves during mixing/loading. **Precautionary measures based on classification & labelling:** Due to the classification of the product with H315, H317 and H318 protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.
Workers	Acceptable	No PPE - Work wear covering arms, body and legs
Bystanders	Acceptable	~~None~~ Risk mitigation measures as buffer strip of 5 m or drift reduction nozzles
Residents	Acceptable	~~None~~ Risk mitigation measures as buffer strip of 5 m or drift reduction nozzles

No unacceptable risk for operators, workers, bystanders and residents was identified when the product is used as intended and provided that the PPE/risk mitigation measures stated in

Table 6.1-3 are applied. Due to the classification of the product with H315, H317 and H318, protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and bystanders/residents 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.(1)	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I(2)**	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, bystander or resident exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind (incl. application technique)(3)	**Max. number (min. interval between applications) a) per use b) per crop/ season**	**Max. application rate kg as/ha(4) a) a.s. 1 b) a.s. 2**	**Water L/ha min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
1-29, 106-110	**Cereals** (Oats, spring + winter barley, spring + winter wheat, rye and triticale)	F	Foliar spraying, overall, LCTM	a) 1 b) 1	a) 0.175 b) 0.250	100 - 400	30	Operators, workers, bystanders and residents (EFSA Guidance)	*			

(1) Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
(2) 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
(3) e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held
(4) Active substances: a.s. 1 = prothioconazole, a.s. 2 = fenpropidin

* **Reviewer remind:** Based on NDE assessment operator wearing workwear covering arms, body and legs during mixing/loading and application plus protective gloves during M/L
Precautionary measures based on classification & labelling:
Due to the classification of the product with H315, H317 and H318 protective gloves, protective clothing and eye protection/face protection should be worn for all tasks (when handling the product).

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 substances

	Prothioconazole	**Prothioconazole-desthio** (Toxicological relevant metabolite of active substance prothioconazole*)	**Fenpropidin**
Common Name	Prothioconazole	Prothioconazole-desthio	Fenpropidin
CAS-No.	178928-70-6	120983-64-4	67306-00-7
Classification and proposed labelling			

	Prothioconazole	**Prothioconazole-desthio** (Toxicological relevant metabolite of active substance prothioconazole*)	**Fenpropidin**
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	None	None	~~Hazard classes (s), categories:~~ ~~Acute Tox. 4~~ ~~Skin Sens. 1B~~ ~~Eye Dam. 1~~ ~~STOT SE 3~~ ~~STOT RE 2~~ ~~Code(s) for hazard pictogram(s):~~ ~~GHS05, GSH07, GSH08~~ ~~Signal word: Danger~~ ~~Hazard statement(s):~~ ~~H302 "Harmful if swallowed"~~ ~~H332 "Harmful if inhaled"~~ ~~H317 "May cause an allergic skin reaction"~~ ~~H318 "Causes serious eye damage"~~ ~~H335 "May cause respiratory irritation"~~ ~~H373 "May cause damage to organs through prolonged or repeated exposure"~~ # Repr. 2 H361d Acute Tox. 4 H332 Acute Tox. 4 H302 STOT SE 3 H335 STOT SE 3 H336 STOT RE 2 H373 (nervous system, eyes, lungs) Skin Irrit. 2 H315 Eye Dam. 1 H318 Skin Sens. 1 H317
Additional C&L proposal	None	None	None
Agreed EU endpoints			
AOEL systemic	0.2 mg/kg bw/d (based on the (combined developmental NOAEL 20 mg/kg bw and the critical effects with retarded ossification, reduced fetal weights, total litter losses, abortions, microphtalmia (rat))	0.01 mg/kg bw/d (desthioprothioconazole (JAU 6476-desthio)* (based on the rat developmental study NOAEL 1 mg/kg bw and the critical effects with increased rudimentary supernumerary ribs)	0.02 mg/kg bw/d (based on NOAEL 2 mg/kg bw of 1-year dog study and the critical effects with increased liver weight, hypertrophy of hepatocytes, spinal cord demyelination)
	~~0.01 mg/kg bw/d (desthioprothioconazole (JAU 6476-desthio)* (based on the rat developmental study NOAEL 1 mg/kg bw and the critical effects with increased rudimentary supernumerary ribs)~~		

	Prothioconazole	**Prothioconazole-desthio** (Toxicological relevant metabolite of active substance prothioconazole*)	**Fenpropidin**
Reference	EFSA Scientific Report (2007) 106, 1-98		EFSA Scientific Report (2007) 124, 1-84; # Committee for Risk Assessment RAC Opinion proposing harmonised classification and labelling at EU level of fenpropidin (ISO); CLH-O-0000007218-72-01/F Adopted 1 December 2022
	Conditions to take into account/critical areas of concern with regard to toxicology		
Review Report/EFSA Conclusion for active substance	EFSA Scientific Report (2007) 106, 1-98: The metabolite prothioconazole-desthio is more toxic than prothioconazole in the rat and rabbit developmental studies		None

*as stated in DAR (2005), B.6.15.1 Operator exposure (III 7.2.1), p.327: “It has been found that JAU 6476-desthio (SXX 0665) may be formed in diluted prothioconazole formulations. This may happen on clothing, skin or certain plant surfaces during the drying process. The degradation product, JAU 6476-desthio, is known to have an embryotoxic potential in experimental animals.”
**MSDS of fenpropidin (see KCP 1.4.3-09)

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for ADM.03502.F.1.A 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. All other data are confidential and are submitted in Part C.

Table 6.3-1: Summary of evaluation of the data on acute toxicity including irritancy and skin sensitisation for ADM.03502.F.1.A - based on alternative or adverse study data

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
Acute oral toxicity (Alternative approach acc. to Reg. 1272/2008)	LD_{50} (calculated): > 2000 mg/kg bw	Yes	None	Refer to Part C
Acute dermal toxicity (Alternative approach acc. to Reg. 1272/2008)	None of the ingredients is classified for dermal toxicity	Yes	None	Refer to Part C
Acute inhalation toxicity (Alternative approach acc. to Reg. 1272/2008)	LC_{50} (calculated): 3.94 mg/L	No*	Acute Tox. 4 H332 “Harmful if inhaled”	Refer to Part C
Skin irritation Reconstructed human epidermis EpiDermTM (OECD 439)	Irritant	No**	Skin Irrit. 2 H315 “Causes skin irritation”	KCP 7.1.4/01 Groß, C., 2021
Eye irritation, BCOP assay, isolated corneas of bovine eyes (OECD 437)	No prediction can be made on irritation potential	No**	n.a.	KCP 7.1.5/01 Julienne, S., 2020
Eye irritation, rabbit tiered approach (OECD 405)	Irritant[1]	Yes	Eye Irrit. 1 H318 “Causes serious eye damage”	…
Skin sensitisation (Alternative approach acc. Reg. 1272/2008)	Sensitising (based on data on ingredients)	Yes	Skin Sens. 1 H317 “May cause an allergic skin reaction”	Refer to Part C
Supplementary studies for combinations of plant protection products	No data – not required			

n.a. = not applicable

[1] Eye irritation - An in vivo study was performed (to satisfy the regulatory requirements of countries outside of the EUin accordance with OECD 405, after an initial in vitro study failed to give a conclusive result. Thus, a tiered approach is considered according to Regulation (EC) No 1272/2008. The results of this in vivo study show eye irritation properties and is thus considered as “adverse data” as outlined in Article 56 of Reg (EC) No. 1107/2009. For this reason, the study is included as part of this application.

* **zRMS comment:** Results of In vivo study (refer Table 6.3-2, KCP 7.1.3/01 … 2021) has been considered as relevant data to ADM.03502.F.1.A and required for classification and labelling since results of the study deviates from predicted classification based on the properties of the individual components in ADM.03502.F.1.A.

** **zRMS comment:** detailed discussion regarding this data point has been provided by the reviewer in commenting box pp. 6, 7.

Table 6.3-2: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for ADM.03502.F.1.A – based on study data

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
Acute oral toxicity, rat (OECD 423)	LD_{50} > 2000 mg/kg bw[1]	~~Supporting information~~ Yes	None	~~Available on request~~ ~~…~~
Acute dermal toxicity, rat (OECD 402)	LD_{50} > 2000 mg/kg bw[2]	~~Supporting information~~ Yes	None	~~Available on request~~ ~~…~~
Acute inhalation toxicity, rat (OECD 403)	LC_{50} > 5.36 mg/L (analysed conc.)[3]	Yes	None	…
Skin irritation, rabbit (OECD 404)	No study available	n.a.* Based on WoE	~~n.a.~~ Skin Irrit. 2 H315 “Causes skin irritation”	n.a.
Eye irritation, rabbit (OECD 405)	Irritant[4]	Yes	Eye Irrit. 1 H318 “Causes serious eye damage	…
Skin sensitisation, mouse (OECD 429, LLNA)	Weak sensitizer[5]	~~Supporting information~~ Yes	Skin Sens. 1 H317 “May cause an allergic skin reaction”	~~Available on request~~ ~~…~~
Supplementary studies for combinations of plant protection products	No data – not required			

n.a. = not applicable

[1] Acute oral - This in vivo study was not performed with intention for use within the EU. It was however performed to satisfy the regulatory requirements of countries outside of the EU. However, as the study data show the formulation to result in a LD_{50} above 2000 mg/kg bw, this is in line with the alternative calculation method. ~~Therefore, this study has not been presented as part of this application in the EU, although the study report is available upon request.~~

[2] Acute dermal - This in vivo study was not performed with intention for use within the EU. It was however performed to satisfy the regulatory requirements of countries outside of the EU. However, as the study data show the formulation to result in a LD_{50} above 2000 mg/kg bw, this is in line with the alternative calculation method. ~~Therefore, this study has not been presented as part of this application in the EU, although the study report is available upon request.~~

[3] Inhalation - An in vivo study was performed (to satisfy the regulatory requirements of countries outside of the EU, in accordance with OECD 403. The study resulted in a LC_{50} of > 5.36 mg/L (analysed concentration). Based on the study data, no classification is required and thus the classification from the vertebrate study is not in line with the proposed classification from the alternative approach. As the study data are used as basis for non-classification, the study is included as part of this application.

[4] Eye irritation - An in vivo study was performed (to satisfy the regulatory requirements of countries outside of the EU, in accordance with OECD 405, after an initial in vitro study failed to give a conclusive result. This study is classed as “adverse data” as outlined in Article 56 of Reg (EC) No. 1107/2009. For this reason, the study is included as part of this application.

[5] Skin Sensitization – This in vivo study was not performed with intention for use within the EU. It was however performed to satisfy the regulatory requirements of countries outside of the EU. The results show the formulation to be a weak sensitizer (EC3 value >2%). This is generally in line with the alternative approach based on the available data of the ingredients. Thus, classification as “Skin Sens. 1” is required according to Reg. No. 1272/2008 and subsequent regulations. ~~Therefore, the study is not considered as “adverse data” as outlined in Article 56 of Reg (EC) No. 1107/2009 and has thus not been presented as part of this application in the EU, although the study report is available upon request.~~

* **zRMS comment:** detailed discussion regarding this data point has been provided by the reviewer in commenting box pp. 6, 7.

Taking the available information into account, and considering the principles of the CLP Regulation, the classification for toxicological properties for ADM.03502.F.1.A are considered to be:

H315 Causes skin irritation
H317 May cause an allergic reaction
H318 Causes serious eye damage
H335 May cause respiratory irritation
H373 May cause damage to organs through prolonged or repeated exposure (nervous system, eyes, lungs)

Table 6.3-3: Additional toxicological information relevant for classification/labelling of ADM.03502.F.1.A

	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)	Fenpropidin (CAS no. 67306-00-7, 23-26 % (v/v))*	STOT-SE 3 H335 (criteria ≥ 20 %) STOT-RE 2 H373 (criteria ≥ 10 %)	MSDS 07-03-2018*	STOT-SE 3 H335 (> 20 %) STOT-RE 2 H373 (> 10 %)
Toxicological properties of non-active substance(s) (relevant for classification of product)	No data – not required, for overall CLP proposal of ADM.03502.F.1.A please refer to confidential data submitted in Part C			
Further toxicological information	~~19% of the mixture consists of ingredient of unknown acute toxicity~~			

* Material safety data sheet by the applicant

Taking the available additional information into account, and considering the principles of the CLP Regulation, the additional classification for toxicological properties for ADM.03502.F.1.A are considered to be:

H335 May cause respiratory irritation
H373 May cause damage to organs (central nervous system) through prolonged or repeated exposure

6.4 Toxicological Evaluation of Groundwater Metabolites

All metabolite concentrations are predicted to be 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 ADM.03502.F.1.A (MCW-2091) and the toxicological relevant metabolite prothioconazole-desthio is presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in ADM.03502.F.1.A and the relevant metabolite

	Prothioconazole		Fenpropidin		Prothioconazole-desthio	
	Value	**Reference**	**Value**	**Reference**	**Value**	**Reference**
Concentrate	25 %	Default values according to EFSA Guidance on dermal absorption (2017)*	0.78%	Maas, W.J.M. (2021b) reported in Appendix 2	~~n.a.**~~	
Dilution	70 %		17%		~~6.9%~~ 9,2%	Maas, W.J.M. (2021a) reported in Appendix 2

* EFSA Guidance on dermal absorption (2017), EFSA Journal 2017; 15(6):4873, 60 pp.
~~** not applicable; prothioconazole-desthio is a degradation product which does not exist in the concentrate~~

6.5.1 Justification for proposed values - prothioconazole

Data on dermal absorption for prothioconazole in ADM.03502.F.1.A are not available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, 60pp.) are presented in the following table.

Table 6.5-2: Default dermal absorption values for prothioconazole

	Value	Justification for value	Acceptability of justification
Concentrate	25 %	The active substance is present in the plant protection product at a concentration higher than 50 g/L.	Justification accepted. Endpoint can be used for current product
Dilution	70 %	The active substance is present in the plant protection product at a concentration lower than or equal to 50 g/L.	Justification accepted. Endpoint can be used for current product

6.5.2 Justification for proposed values - fenpropidin

Proposed dermal absorption rate for fenpropidin is based on a dermal absorption study on ADM.03502.F.1.A (MCW-2091). The study results are summarized in the following table. Full summary of study on the dermal absorption of fenpropidin in ADM.03502.F.1.A (MCW-2091) that have not previously been evaluated within an EU peer review process is described in detail in Appendix 2.

Table 6.5-3: Summary of the results of submitted dermal absorption study for fenpropidin

Test	Concentrate	Spray dilution (1:533 0.469 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	~~17%~~ 0.78 %	~~0.78%~~ 17 %	ADM.03502.F.1.A	Yes	Not required	Endpoint can be used for current product	Maas, W.J.M. (2021b)

6.5.3 Justification for proposed values - prothioconazole-desthio

Proposed dermal absorption rate for prothioconazole-desthio is based on a dermal absorption study on ADM.03502.F.1.A (MCW-2091). The study results are summarized in the following table. Full summary of study on the dermal absorption of prothioconazole-desthio in ADM.03502.F.1.A (MCW-2091) that have not previously been evaluated within an EU peer review process is described in detail in Appendix 2.

Table 6.5-4: Summary of the results of submitted dermal absorption study for prothioconazole-desthio

Test	Spray dilution (1:533 0.328 g/L)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	~~6.9%~~ 9.2%	ADM.03502.F.1.A	Yes	Not required	Endpoint can be used for current product	Maas, W.J.M. (2021a)

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Reviewer comment:

The NDE calculations performed by the applicant using EFSA Operator Model (75th quantile regression) are acceptable and zRMS agrees to the conclusions.
The risk assessment/calculated exposure for operators, workers and B&R are acceptable under conditions of intended uses.
All changes regarding NDS assessment which reflects comments made by cMS countries has been included in this revised RR. Additional calculations for each exposed group are placed in separate boxes highlighted in yellow and turquoise (Appendix 3) colour. In case of exposure to PTZ-desthio it has been considered into the assessment 50% conversion factor. Buffer zones accepted for NDE calculations are 2-3 m and 5 m.

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

Product name and code	ADM.03502.F.1.A		
Formulation type	Emulsifiable Concentrate (EC)		
Category	Fungicide		
Container size(s), short description	Please refer to Section 4.1 for further information on containers		
Active substance(s) (incl. content)	Prothioconazole 175 g/L	Prothioconazole-desthio (Toxicological relevant metabolite of active substance prothioconazole*)	Fenpropidin 250 g/L
AOEL systemic	0.2 mg/kg bw/d (1)	0.01 mg/kg bw/d (1)	0.02 mg/kg bw/d (2)
AAOEL systemic	Not set in the 1st EU review of prothioconazole		Not set in the 1st EU review of fenpropidin
Inhalation absorption	100 %	100 %	100 %
Oral absorption	100 %	100 %	100 %
Dermal absorption	Concentrate: 25 % Dilution: 70 % (Default values) (3)	Concentrate and dilution: ~~6.9%~~ 9,2% (Dilution rate: 1:533, 0.328 g/L) (Based on product (Maas, W.J.M. (2021a), reported in A 2.10)	Concentrate: 0.78 % Dilution: 17 % (Based on product (Maas, W.J.M. (2021b), reported in A 2.10))
Vapour pressure	<<4 × 10-7 Pa at 20°C (1), <<4 × 10-7 Pa at 25°C (1), i.e. classified as low volatile substance according to EFSA Guidance (4)	Parent value	1.7 × 10-2 Pa at 25°C (2) for the non-protonated form, based on the justification provided below, classified as low volatile substance.

(1) EFSA (2007). Conclusion regarding the peer review of the pesticide risk assessment of the active substance prothioconazole. EFSA Journal 2007; 5(8): RN-106, 1-98. doi:10.2903/j.efsa.2007.106r.
(2) EFSA (2008). Conclusion on the peer review of the pesticide risk assessment of the active substance fenpropidin. EFSA Journal 2008; 6(1): RN-124, 1-84. doi: 10.2903/j.efsa.2008.124r.
(3) EFSA (2017). Guidance on dermal absorption. EFSA Journal 2017;15(6):4873. doi.org/10.2903/j.efsa.2017.4873.

(4) EFSA (2014). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp. doi:10.2903/j.efsa.2014.3874.

* In addition to the risk assessment of the active substance prothioconazole, the risk of the metabolite prothioconazole-desthio is assessed (based on the EFSA conclusion for prothioconazole).

Acute AOEL

According to the Commission Guidance Document1, for the approval of active substances under Regulation (EC) No 1107/2009, "Consideration of acute exposure should only be made where an AAOEL has been established during an approval, review or renewal evaluation of an active substance, i.e. no acute operator, worker and bystander exposure assessments can be performed with the OPEX model where no AAOEL has been set". Since AAOELs are not available for the relevant substances, acute exposure assessments for operators and bystanders are currently not required.

Vapour pressure of fenpropidin

The vapour pressure (VP) of pure fenpropidin reported in the EFSA conclusion (2007) is 1.7 × 10-2 Pa at 25°C (extrapolated, purity 99.3 %). This value is above the trigger value for moderately volatile substances according to the EFSA Guidance (2014) and exposure estimations for a substance with such a vapour pressure are not covered by this guidance.

However, fenpropidin is a strong base (p*K*a is 10.1 (Pesticide manual (1997)[2])) and can be protonated in aqueous solutions. The vapour pressure of protonated fenpropidin is considered to be negligible based on the fact that the vapour pressure of the protonated ionic form is lower than the vapour pressure of the parent molecule since in protonated fenpropidin the ionic bond strength is significantly higher compared with the Van-der-Waals interactions present in the non-protonated parent molecule. It is assumed that fenpropidin is predominately protonated under real use conditions and that volatilisation is negligible. This is in agreement with the following conclusions:

- The p*H* of the product (1 % *v/v*) in deionized water was determined at 7.3 (see dRR part B Section 2 (KCP 2.4.2)). According to the GAP, the highest application rate of ADM.03502.F.1.A is 1 L product/ha in 100 – 400 L water/ha. This results in concentrations of 0.25 – 1.0 % *(v/v)* in aqueous solution. Since during application, a higher dilution rate may be possible, compared to the dilution rate used in the study, the p*H* of the spray dilution is predicted being comparable to the p*H* value in the study, *i.e.,* at neutral p*H* and well below p*H* 10.
- As reported in the conclusions on the peer review of fenpropidin (EFSA (2007)) *"Only the neutral form of fenpropidin is potentially volatile. pKa is 10.1 and at environmentally relevant pH fenpropidin will predominantly be present in protonated, non-volatile form."*

These assumptions are supported by the measurement of evaporation after spray application in field studies with fenpropidin EC formulations. In these field studies, presence of low concentrations of fenpropidin in air was measured: A 24 h time weighted average air concentration of 1.06 µg fenpropidin/m^3 was measured after application of 750 g fenpropidin/ha to grassland of 0.6 to 0.7 m height (*i.e*, the height of the grass was similar to spring barley) in a field trial located in North Yorkshire, UK (KCP 7.2.2.2/01, DEFRA Project PS2023 (2010)[3]), and a 24 h time weighted average air concentration of less than 0.7 µg fenpropidin/m^3 was recorded after application of 450 g fenpropidin/ha in a field trial located in Paris Basin, Northern France (KCP 7.2.2.2/02, Bedos *et. al.* (2010)[4]). In both studies, EC formulations were applied with higher application rates compared to ADM.03502.F.1.A (DEFRA study: 750 g fenpropidin/ha and Bedos study: 450 g fenpropidin/ha *vs*. GAP: 250 g fenpropidin/ha). It is noted that concentrations of fenpropidin in air measured in these studies are comparable to the value used in the EFSA calculator for low volatile substances (*i.e.,* 1 µg/m³). Thus, read-across of the results of the field studies to the intended GAP use of

[1] Commission Guidance Document. SANTE-10832-2015 rev. 1.7, 24 January 2017. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products.

[2] Tomlin, C.D.S. (Editor) (1997). The pesticide manual.: A World compendium, 11th edition, British Crop Production Council, 1997.

[3] DEFRA Project PS202 (2010). Development of air sampling methodology in support of determining risk of bystander and resident exposure to pesticides. Food and Environment Research Agency (FERA), Sand Hutton, York, YO411LZ.

[4] Bedos, C.; Rouseaue-Djabri, M.-F.; Loubet, B.; Durand, B.; Flura, D.; Briand, O. and Barriuso, E. (2010). Fungicide Volatilization Measurements: Inverse Modeling, Role of Vapor Pressure, and State of Foliar Residue, Environ. Sci. Technol. 44, 7, 2522-2528. doi.org/10.1021/es9030547.

ADM.03502.F.1.A of 250 g fenpropidin/ha is considered feasible and are conservative air concentrations for fenpropidin since even 3-fold lower value for the DEFRA study and 1.8-fold lower value for the Bedos study can be expected after application of ADM.03502.F.1.A, respectively. Summaries of the studies are provided under Appendix 4 as supportive information.

Thus, due to the reasons given above, the input parameter *"low volatile substances with a vapour pressure < 5*10^{-3}Pa"* was used in the EFSA calculator and is considered appropriate.

Overall considerations in the exposure assessment of ADM.03502.F.1.A

According to the DAR (2005)[5], diluted prothioconazole can degrade to the metabolite prothioconazole-desthio:

"It has been found that JAU 6476-desthio (SXX 0665) may be formed in diluted prothioconazole formulations. This may happen on clothing, skin or certain plant surfaces during the drying process. The degradation product, JAU 6476-desthio, is known to have an embryotoxic potential in experimental animals."

According to the EFSA conclusion of prothioconazole[6], the degradation product prothioconazole-desthio is more toxic than the parent compound and is therefore considered in the risk assessments of all relevant population groups. The content of prothioconazole-desthio in the concentrate is however assumed to be very low. This assumption is based on the Commission Implementing Regulation (EU) No 540/2011 (amending Regulation (EU) No 1107/2009), in which it is declared that the amount of prothioconazole-desthio may not exceed 0.5 g/kg, *i.e.* 0.05 % (*w/w*) in the technical material[7]. To reflect this non-availability of prothioconazole-desthio when handling the concentrate, *i.e.* during mixing and loading, the value for the dermal absorption of prothioconazole-desthio in the concentrate was set to 0 %.

In a conservative approach, two exposure assessments are conducted for each relevant exposure group. One this assessment reflects exposure to 100 % 50% prothioconazole and 50% prothioconazole-desthio when handling the concentrate, the dilution or the dried formulation, while the other assessment reflects exposure to 100 % prothioconazole-desthio when handling the dilution or the dried formulation. For the estimation of the amount of prothioconazole-desthio that may be formed when handling the product, a conversion factor is calculated based of the molecular weights of prothioconazole-desthio and prothioconazole (Equation 1):

$$\frac{MW_{prothioconazole-desthio}}{MW_{prothioconazole}} = \frac{312.2\ \text{g/mol}}{344.26\ \text{g/mol}} = 0.907 \qquad \text{Equation 1}$$

- $MW_{prothioconazole-desthio}$ = Molecular weight of prothioconazole-desthio (EFSA, 2007)
- $MW_{prothioconazole}$ = Molecular weight of prothioconazole (EFSA, 2007)

Taking the above calculated conversion factor of 0.907 into account and a 50% conversion factor of prothioconazole to prothioconazole-dethio, 0.159 kg 0.0875 hg/ha prothioconazole and 0.0793 kg prothioconazole-desthio/ha is to be are considered for an application rate of 1.0 L prod./ha, containing 0.175 kg prothioconazole/ha.

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 zone is given in Part B, Section 0.

[5] DAR (2005). B.6.15.1 Operator exposure (III 7.2.1), p. 327.
[6] EFSA (2007). Conclusion regarding the peer review of the pesticide risk assessment of the active substance prothioconazole. EFSA Journal 2007; 5(8): RN-106, 1-98. doi:10.2903/j.efsa.2007.106r.
[7] dRR Part B Section 1: Identity, Section 2: Physical and chemical properties, Section 4: Further information, 2021

Justification

ADM.03502.F.1.A is a fungicide applied as spray in cereals. All applications are done *via* tractor-mounted downward spraying. The highest application rate of 1 L prod./ha in a minimum water volume of 100 L/ha in cereals is considered as worst case for all intended uses.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

Since AAOELs are not available for fenpropidin, prothioconazole and prothioconazole-desthio, acute exposure assessments for operators are currently not required.

A summary of the exposure models used for estimation of operator exposure to prothioconazole, prothioconazole-desthio and fenpropidin during application of ADM.03502.F.1.A according to the critical use is presented in Table 6.6-2. Outcome of the estimation is presented in Table 6.6-3. Detailed calculations are in Appendix 3. For information on combined toxicity, please refer to Section 6.6.5.

Table 6.6-2: Exposure models for intended uses

Critical use	**Cereals** (max. 1 L product/ha applied by tractor-mounted downward spraying in a minimum water volume of 100 L/ha)
Model	EFSA Guidance (2014) [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874] EFSA calculator [Latest version: 30 Mar 2015 - Version produced to support guidance document published 23/10/2014]

Table 6.6-3: Estimated operator exposure

		Prothioconazole		Fenpropidin		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(1)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(2)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(3)
Tractor-mounted boom spray application outdoors to cereals Application rate: 1 L prod/ha (0.175 kg prothioconazole/ha or 0.159 kg prothioconazole-desthio/ha in a worst-case approach, 0.250 kg fenpropidin/ha)							
EFSA calculator (75th percentile, long-term exposure)	No PPE: Work wear(5) during M/L and A	0.1260	63.00	0.0102	50.95	0.0016	15.73
	Work wear(5) during M/L and A + gloves during M/L	0.0191	9.55	0.0058	29.00	0.0016	15.73

Bold = Above the AOEL; M/L = Mixing and loading, A = Application
(1) = AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) = AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) = AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(4) = Potential exposure = Operator wearing shorts and T-shirt
(5) = No PPE: Work wear = arms, body and legs covered

~~Conclusions of critical GAP uses in cereals~~

~~According to the model calculations, the use of ADM.03502.F.1.A results in exposure levels of 63.00 % of the AOEL for prothioconazole, 50.95 % of the AOEL of fenpropidin and 15.73 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs during mixing/loading and application.~~

~~Due to the classification of the product with H315, H317 and H318 protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.~~

Product-specific data for the dermal absorption of prothioconazol-desthio are available. The value of 9.2% obtained from the tested dilution of 0.328 g/L prothioconazole-desthio is considered appropriate to use for calculation of systemic exposure estimates during mixing and loading as a worst case assumption and during application in the risk assessment.

Table 6.6-4: Estimated operator exposure taking into account 50% conversion of prothioconazole to prothioconazole-desthio

		50% Prothioconazole		**Fenpropidin**		**50% Prothioconazole-desthio**	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(1)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(2)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(3)**
Tractor mounted boom spray application outdoors to cereals Application rate: 1 L prod/ha (0.0875 kg prothioconazole/ha, 0.0793 kg prothioconazole-desthio/ha, 0.250 kg fenpropidin/ha)							
EFSA calculator (75th percentile, long-term exposure)	No PPE: Work wear(5) during M/L and A	0.0724	36.18	0.0102	50.95	**0.0230**	**230.11**
	Work wear(5) during M/L and A + gloves during M/L	0.0097	4.85	0.0058	29.00	0.0016	16.35

Bold = Above the AOEL; M/L = Mixing and loading, A = Application
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(4) Potential exposure – Operator wearing shorts and T-shirt
(5) No PPE: Work wear – arms, body and legs covered

Conclusions of critical GAP uses in cereals

According to the model calculations, the use of ADM.03502.F.1.A results in exposure levels of 4.85 % of the AOEL for prothioconazole, 29.0 % of the AOEL of fenpropidin and 16.35 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs during mixing/loading and application and gloves during mixing/loading.

Due to the classification of the product with H315, H317 and H318 protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.

6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure levels (AOELs) for fenpropidin, prothioconazole and prothioconazole-desthio will not be exceeded under conditions of intended uses and considering 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)

6.6.3.1 Estimation of worker exposure

Table 6.6-5 shows the exposure models used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with ADM.03502.F.1.A according to the critical use. Outcome of the estimation is presented in
Table 6.6-6. Detailed calculations are in Appendix 3. For information on combined toxicity, please refer to Section 6.6.5.

Table 6.6-5: Exposure models for intended uses

Critical use	**Cereals** (max. 1 L product/ha applied by tractor-mounted downward spraying in a minimum water volume of 100 L/ha)
Model	EFSA Guidance (2014) [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874] EFSA calculator [Latest version: 30 Mar 2015 - Version produced to support guidance document published 23/10/2014]

Table 6.6-6: Estimated worker exposure

		Prothioconazole		Fenpropidin		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(1)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(2)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(3)
Application rate:		0.175 kg a.s./ha		0.250 kg a.s./ha		0.159 kg prothioconazole-desthio/ha	
EFSA calculator 2 hours/day for inspection or irrigation activities DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	No PPE: Work wear(5)	0.0172	8.58	0.0060	29.75	0.0015	15.33

Bold = Above the AOEL
(1) = AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) = AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) = AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(4) = Potential exposure: Worker wearing shorts and T-shirt
(5) = No PPE: Work wear = arms, body and legs covered, but no gloves

Conclusions of critical GAP uses in cereals

According to the model calculations, the use of ADM.03502.F.1.A results in exposure levels of 8.58 % of the AOEL for prothioconazole, 29.75 % of the AOEL of fenpropidin and 15.33 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs.

Thus, the use of ADM.03502.F.1.A in cereals is acceptable for re-entry workers wearing work wear covering arms, body and legs.

Table 6.6-7: Estimated worker exposure taking into account 50% conversion of prothioconazole to prothioconazole-desthio

		50% Prothioconazole		Fenpropidin		50% Prothioconazole-desthio	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(1)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(2)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(3)**
Application rate:		0.0875 kg a.s./ha		0.250 kg a.s./ha		0.0793 kg prothioconazole-desthio/ha	
EFSA calculator 2 hours/day for inspection or irrigation activities DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	No PPE: Work wear(5)	0.0086	4.29	0.0060	29.75	0.0010	10.21

Bold = Above the AOEL
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(4) Potential exposure: Worker wearing shorts and T-shirt
(5) No PPE: Work wear – arms, body and legs covered, but no gloves

Conclusions of critical GAP uses in cereals

According to the model calculations, the use of ADM.03502.F.1.A results in exposure levels of 4.29 % of the AOEL for prothioconazole, 29.75 % of the AOEL of fenpropidin and 10.21 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs.

Thus, the use of ADM.03502.F.1.A in cereals is acceptable for re-entry workers wearing work wear covering arms, body and legs.

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 levels (AOELs) for fenpropidin, prothioconazole and prothioconazole-desthio will not be exceeded under conditions of intended uses and considering above mentioned PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.4 Bystander and resident exposure (KCP 7.2.2)

6.6.4.1 Estimation of bystander and resident exposure

Since AAOELs are not available for fenpropidin, prothioconazole and prothioconazole-desthio, acute exposure assessments for bystanders are currently not required. Instead, the long-term exposure assessment for residents as provided in the EFSA Guidance/model covers bystander exposure.

In all Tier I assessments, the default dissipation half-life of 30 days was used.Table 6.6-8 shows the exposure model used for estimation of bystander and resident exposure to fenpropidin, prothioconazole and prothioconazole-desthio. Outcome of the estimation is presented in Table 6.6-9. Detailed calculations are in Appendix 3. For information on combined toxicity, please refer to Section 6.6.5.

Table 6.6-8: Exposure models for intended uses

Critical use	**Cereals** (max. 1 L product/ha applied by tractor-mounted downward spraying in a minimum water volume of 100 L/ha)
Model	EFSA Guidance (2014) [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874] EFSA calculator [Latest version: 30 Mar 2015 - Version produced to support guidance document published 23/10/2014]

Table 6.6-9: Estimated bystander and resident exposure

	Prothioconazole		Fenpropidin		Prothioconazole-desthio	
Model data	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(1)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(2)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(3)**
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 2-3 m (standard) Application rate: 1 L prod/ha (0.175 kg prothioconazole/ha or 0.159 kg prothioconazole-desthio/ha in a worst-case approach, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0329	16.44	0.0115	57.25	0.0030	29.72
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70
Surface deposits	0.0019	0.96	0.0008	4.11	0.0003	2.88
Entry into treated crops	0.0207	10.34	0.0072	35.86	0.0018	18.48
Sum of all pathways	**0.0371**	**18.54**	**0.0137**	**68.53**	**0.0044**	**43.98**
Adult (body weight 60 kg)						
Spray drift	0.0079	3.94	0.0027	13.67	0.0007	7.06
Vapour	0.0002	0.12	0.0002	1.15	0.0002	2.30
Surface deposits	0.0008	0.42	0.0003	1.45	0.0001	0.75
Entry into treated crops	0.0115	5.74	0.0040	19.92	0.0010	10.27
Sum of all pathways	**0.0137**	**6.87**	**0.0049**	**24.59**	**0.0014**	**14.40**
Refinement using a buffer strip of 5 m						
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 5 m Application rate: 1 L prod/ha (0.175 kg prothioconazole/ha or 0.159 kg prothioconazole-desthio/ha in a worst-case approach, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0219	10.94	0.0076	38.11	0.0020	19.80
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70
Surface deposits	0.0008	0.40	0.0003	1.69	0.0001	1.18
Entry into treated crops	0.0207	10.34	0.0072	35.86	0.0018	18.48
Sum of all pathways	**0.0302**	**15.12**	**0.0113**	**56.35**	**0.0037**	**37.36**
Adult (body weight 60 kg)						
Spray drift	0.0040	1.99	0.0014	6.93	0.0004	3.59
Vapour	0.0002	0.12	0.0002	1.15	0.0002	2.30
Surface deposits	0.0003	0.17	0.0001	0.59	0.0000	0.31
Entry into treated crops	0.0115	5.74	0.0040	19.92	0.0010	10.27
Sum of all pathways	**0.0117**	**5.86**	**0.0042**	**21.08**	**0.0013**	**12.59**

	Prothioconazole		Fenpropidin		Prothioconazole-desthio	
Model data	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(1)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(2)	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL(3)
Refinement using drift reduction nozzles						
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 2-3 m (standard) and drift reduction nozzles Application rate: 1 L prod/ha (0.175 kg prothioconazole/ha or 0.159 kg prothioconazole-desthio/ha in a worst-case approach, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0164	8.22	0.0057	28.63	0.0015	14.86
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70
Surface deposits	0.0010	0.48	0.0004	2.05	0.0001	1.44
Entry into treated crops	0.0207	10.34	0.0072	35.86	0.0018	18.48
Sum of all pathways	**0.0273**	**13.66**	**0.0102**	**51.23**	**0.0035**	**34.71**
Adult (body weight 60 kg)						
Spray drift	0.0039	1.97	0.0014	6.84	0.0004	3.53
Vapour	0.0002	0.12	0.0002	1.15	0.0002	2.30
Surface deposits	0.0004	0.21	0.0001	0.72	0.0000	0.37
Entry into treated crops	0.0115	5.74	0.0040	19.92	0.0010	10.27
Sum of all pathways	**0.0116**	**5.78**	**0.0042**	**20.81**	**0.0012**	**12.44**

(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day

Conclusions of critical GAP uses in cereals

The calculations above show that the exposure of residents of any age is below 100 % of the AOELs for all substances. Thus, according to the model calculations, the use of ADM.03502.F.1.A in cereals results in acceptable exposure levels for fenpropidin, prothioconazole and prothioconazole-desthio without consideration of risk management measures.

Table 6.6-10: Estimated bystander and resident exposure taking into account 50% conversion of prothioconazole to prothioconazole-desthio

	50% Prothioconazole		Fenpropidin		50% Prothioconazole-desthio	
Model data	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(1)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(2)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(3)**
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 2-3 m (standard) Application rate: 1 L prod/ha (0.0875 kg prothioconazole/ha, 0.0793 kg prothioconazole-desthio/ha, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0164	8.22	0.0115	57.25	0.0020	1974
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70
Surface deposits	0.0010	0.48	0.0008	4.11	0.0002	1.71
Entry into treated crops	0.0103	5.17	0.0072	35.86	0.0012	12.31
Sum of all pathways	**0.0191**	**9.54**	**0.0137**	**68.53**	**0.0033**	**32.67**
Adult (body weight 60 kg)						
Spray drift	0.0039	1.97	0.0027	13.67	0.0005	4.70
Vapour	0.0002	0.12	0.0002	1.15	0.0002	2.30
Surface deposits	0.0004	0.21	0.0003	1.45	0.0000	0.50
Entry into treated crops	0.0057	2.87	0.0040	19.92	0.0007	6.84
Sum of all pathways	**0.0070**	**3.49**	**0.0049**	**24.59**	**0.0010**	**10.35**
Refinement using a buffer strip of 5 m						
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 5 m Application rate: 1 L prod/ha (0.0875 kg prothioconazole/ha, 0.0793 kg prothioconazole-desthio/ha, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0109	5.47	0.0076	38.11	0.0013	13.15
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70
Surface deposits	0.0004	0.20	0.0003	1.69	0.0001	0.70
Entry into treated crops	0.0103	5.17	0.0072	35.86	0.0012	12.31
Sum of all pathways	**0.0157**	**7.83**	**0.0113**	**56.35**	**0.0028**	**28.35**
Adult (body weight 60 kg)						
Spray drift	0.0020	1.00	0.0014	6.93	0.0002	2.38
Vapour	0.0002	0.12	0.0002	1.15	0.0002	2.30
Surface deposits	0.0002	0.12	0.0001	0.59	0.0000	0.20
Entry into treated crops	0.0057	2.87	0.0040	19.92	0.0007	6.84
Sum of all pathways	**0.0060**	**2.99**	**0.0042**	**21.08**	**0.0009**	**9.15**

	50% Prothioconazole		Fenpropidin		50% Prothioconazole-desthio	
Model data	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(1)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(2)**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL(3)**
Refinement using drift reduction nozzles						
EFSA calculator (75th percentile and mean values in case of all pathways, long-term exposure): Tractor-mounted spray application outdoors to cereals, buffer: 2-3 m (standard) and drift reduction nozzles Application rate: 1 L prod/ha (0.0875 kg prothioconazole/ha, 0.0793 kg prothioconazole-desthio/ha, 0.250 kg fenpropidin/ha)						
Child (body weight 10 kg)						
Spray drift	0.0082	4.11	0.0057	28.63	0.0010	9.87%
Vapour	0.0011	0.54	0.0011	5.35	0.0011	10.70%
Surface deposits	0.0005	0.24	0.0004	2.05	0.0001	0.85%
Entry into treated crops	0.0103	5.17	0.0072	35.86	0.0012	12.31%
Sum of all pathways	**0.0142**	**7.10**	**0.0102**	**51.23**	**0.0027**	**26.59%**
Adult (body weight 60 kg)						
Spray drift	0.0020	0.98%	0.0014	6.84	0.0002	2.35%
Vapour	0.0002	0.12%	0.0002	1.15	0.0002	2.30%
Surface deposits	0.0002	0.10%	0.0001	0.72	0.0000	0.25%
Entry into treated crops	0.0057	2.87%	0.0040	19.92	0.0007	6.84%
Sum of all pathways	**0.0059**	**2.95%**	**0.0042**	**20.81**	**0.0009**	**9.05%**

(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of fenpropidin: 0.02 mg/kg bw/day
(3) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day

Conclusions of critical GAP uses in cereals

The calculations above show that the exposure of residents of any age is below 100 % of the AOELs for all substances. Thus, according to the model calculations, the use of ADM.03502.F.1.A in cereals results in acceptable exposure levels for fenpropidin, prothioconazole and prothioconazole-desthio without consideration of risk management measures.

6.6.4.2 Measurement of bystander and/or resident exposure

Since the resident exposure estimations carried out indicated that the acceptable operator exposure levels (AOELs) for fenpropidin, prothioconazole and prothioconazole-desthio will not be exceeded under conditions of intended uses, a study to provide measurements of bystander/resident exposure was not necessary and was therefore not performed.

However, studies for verifying the low volatility and concentrations of fenpropidin in air after spray applications are considered in the Appendix (KCP 7.2.2.2/01, DEFRA Project PS2023 (2010)) and KCP 7.2.2.2/02, Bedos *et. al.* (2010)) as supportive information.

6.6.5 Combined exposure

The product is a mixture of two active substances, prothioconazole and fenpropidin, whereas the diluted prothioconazole, as contained in the product ADM.03502.F.1.A, can degrade to the metabolite prothioconazole-desthio. In a conservative approach, two combined exposure assessments have therefore been performed for each relevant exposure group. One assessment reflects exposure to 100 % prothioconazole when handling the concentrate, the dilution or the dried formulation, while the other assessment reflects exposure to 100 % prothioconazole-desthio when handling the dilution or the dried formulation. Since exposure cannot occur to 100 % prothioconazole and 100 % prothioconazole-desthio simultaneously, a summation of

~~the results is considered appropriate by calculation of the combined effects of fenpropidin and 100 % prothioconazole as well as of fenpropidin and 100 % prothioconazole-desthio.~~

~~As a first tier assessment, combined exposure was calculated by use of the Hazard Index (HI) concept provided in chapter 6.6.5.1. An acceptable risk for the operator, worker, bystander and resident adult is concluded (*i.e.* HI below 1) except for the calculated combined exposure of (i) operators wearing work wear (but no specific PPE such as protective gloves) exposed to fenpropidin and prothioconazole (HI = 1.14) and (ii) child residents exposed to fenpropidin and prothioconazole-desthio (HI = 1.13).~~

~~Therefore, as a second tier assessment, the toxicity effects and the target organs of the active substances and the metabolite relevant to the combined exposure assessment are taken into account to investigate the potential for acting combined.~~

Taking into account a conversion rate of 50% of prothioconazole to prothioconazole -desthio as requested by cMS, a combined exposure of prothioconazole, prothioconazole-desthio and fenpropidin is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for prothioconazole, prothioconazole-dethio and fenpropidin by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from Table 6.6-3,

Table 6.~~6-6~~ and Table 6.6-9 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

6.6.5.1 Exposure Assessment of fenpropidin and prothioconazole in ADM.03502.F.1.A taking into account 50% conversion of prothioconazole to prothioconazole-desthio

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

~~**First tier assessment**~~

~~At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from Table 6.6-3 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.~~

~~**Table 6.6-11: Risk assessment (overview) from combined exposure**~~

~~Application scenario~~	~~Exposure scenario~~	~~Active Ingredient~~	~~Estimated exposure / AOEL (HQ)~~
~~Operators – tractor-mounted downward spraying, wearing work wear [1] during M/L and A[2]~~ ~~*For details, please refer to 6.6.2.*~~	~~No formation of degradation product is present~~	~~prothioconazole~~	~~0.63~~
		~~fenpropidin~~	~~0.51~~
		~~**Cumulative risk Operators (HI)**~~	~~**1.14**~~
	~~Prothioconazole is completely transformed into prothioconazole-desthio~~	~~prothioconazole-desthio~~	~~0.16~~
		~~fenpropidin~~	~~0.51~~
		~~**Cumulative risk Operators (HI)**~~	~~**0.67**~~

Application scenario	Exposure scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
Operators – tractor-mounted downward spraying, wearing work wear [1] during M/L and A and gloves during M/L [2] *For details, please refer to 6.6.2.*	No formation of degradation product is present	prothioconazole	0.10
		fenpropidin	0.29
		Cumulative risk Operators (HI)	**0.39**
	Prothioconazole is completely transformed into prothioconazole-desthio	prothioconazole-desthio	0.16
		fenpropidin	0.29
		Cumulative risk Operators (HI)	**0.45**
Workers – inspection and irrigation, wearing work wear *For details, please refer to 6.6.3.*	No formation of degradation product is present	prothioconazole	0.09
		fenpropidin	0.30
		Cumulative risk Worker (HI)	**0.38**
	Prothioconazole is completely transformed into prothioconazole-desthio	prothioconazole-desthio	0.15
		fenpropidin	0.30
		Cumulative risk Worker (HI)	**0.45**
Resident – Child (all pathways) [2] *For details, please refer to 6.6.4.*	No formation of degradation product is present	Prothioconazole	0.19
		Fenpropidin	0.69
		Cumulative risk Resident – Child (HI)	**0.87**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.44
		Fenpropidin	0.69
		Cumulative risk Resident – Child (HI)	**1.13**
Resident – Adult (all pathways) [2] *For details, please refer to 6.6.4*	No formation of degradation product is present	Prothioconazole	0.07
		Fenpropidin	0.25
		Cumulative risk Resident – Adult (HI)	**0.31**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.14
		Fenpropidin	0.25
		Cumulative risk Resident – Adult (HI)	**0.39**
Resident – Child (all pathways) [2] Buffer: 5 m *For details, please refer to 6.6.4.*	No formation of degradation product is present	Prothioconazole	0.15
		Fenpropidin	0.56
		Cumulative risk Resident – Child (HI)	**0.71**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.37
		Fenpropidin	0.56
		Cumulative risk Resident – Child (HI)	**0.94**
Resident – Adult (all pathways) [2] Buffer: 5 m *For details, please refer to 6.6.4*	No formation of degradation product is present	Prothioconazole	0.06
		Fenpropidin	0.21
		Cumulative risk Resident – Adult (HI)	**0.27**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.13
		Fenpropidin	0.21
		Cumulative risk Resident – Adult (HI)	**0.34**

Application scenario	Exposure scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
Resident – Child (all pathways) (2) Drift reduction nozzles + standard buffer: 2-3 m *For details, please refer to 6.6.4.*	No formation of degradation product is present	Prothioconazole	0.14
		Fenpropidin	0.51
		Cumulative risk Resident – Child (HI)	**0.65**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.35
		Fenpropidin	0.51
		Cumulative risk Resident – Child (HI)	**0.86**
Resident – Adult (all pathways) (2) Drift reduction nozzles + standard buffer: 2-3 m *For details, please refer to 6.6.4*	No formation of degradation product is present	Prothioconazole	0.06
		Fenpropidin	0.21
		Cumulative risk Resident – Adult (HI)	**0.27**
	Prothioconazole is completely transformed into prothioconazole-desthio	Prothioconazole-desthio	0.12
		Fenpropidin	0.21
		Cumulative risk Resident – Adult (HI)	**0.33**

(1) – Work wear – arms, body and legs covered
(2) – M = Mixing, L = Loading, A = Application

As can be seen in the table above, the Hazard Index is < 1, except for

- operators wearing work wear during mixing/loading and application when considering combined exposure of fenpropidin and prothioconazole; and
- child residents, when considering combined exposure of fenpropidin and prothioconazole-desthio.

Thus, a second tier assessment taking into account the toxicological effects of fenpropidin, prothioconazole and prothioconazole-desthio was performed.

Table 6.6-12: Risk assessment (overview) from combined exposure

Application scenario	Exposure scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
Operators – tractor-mounted downward spraying, wearing work wear (1) during M/L and A and gloves during M/L(2) *For details, please refer to 6.6.2, Table 6.6-3.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.05
		fenpropidin	0.29
		prothioconazole-desthio	0.16
		Cumulative risk Operators (HI)	**0.50**
Workers - inspection and irrigation, wearing work wear *For details, please refer to 6.6.3, Table 6.6-5.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.04
		fenpropidin	0.30
		prothioconazole-desthio	0.10
		Cumulative risk Operators (HI)	**0.44**
Resident - Child (all pathways) *For details, please refer to 6.6.4, Table 6.6-7.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.10
		fenpropidin	0.69
		prothioconazole-desthio	0.33
		Cumulative risk Operators (HI)	***1.12***
Resident - Adult (all pathways) *For details, please refer to 6.6.4, Table 6.6-7.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.03
		fenpropidin	0.25
		prothioconazole-desthio	0.10
		Cumulative risk Operators (HI)	**0.38**

Application scenario	Exposure scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
Resident - Child (all pathways) Buffer: 5 m *For details, please refer to 6.6.4, Table 6.6-7.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.08
		fenpropidin	0.56
		prothioconazole-desthio	0.28
		Cumulative risk Operators (HI)	**0.92**
Resident - Adult (all pathways) Buffer: 5 m *For details, please refer to 6.6.4, Table 6.6-7*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.03
		fenpropidin	0.21
		prothioconazole-desthio	0.09
		Cumulative risk Operators (HI)	**0.33**
Resident - Child (all pathways) Drift reduction nozzles + standard buffer: 2-3 m *For details, please refer to 6.6.4, Table 6.6-7.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.07
		fenpropidin	0.51
		prothioconazole-desthio	0.27
		Cumulative risk Operators (HI)	**0.85**
Resident - Adult (all pathways) Drift reduction nozzles + standard buffer: 2-3 m *For details, please refer to 6.6.4, Table 6.6-7.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.03
		fenpropidin	0.21
		prothioconazole-desthio	0.09
		Cumulative risk Operators (HI)	**0.33**

Bold cursive = Above the Hazard Index (HI) of 1
(1) Work wear – arms, body and legs covered
(2) M = Mixing, L = Loading, A = Application

According to the risk assessment by taking into account a combined exposure of prothioconazole, fenpropidin and prothioconazole-desthio, the risk is acceptable with Hazard Index <1 for operators wearing regular work wear during application during mixing/loading and application and gloves during mixing/loading, and for workers without considering specific PPE, and for bystanders and residents with risk mitigation measures as buffer strip of 5 m or drift reduction nozzles.

~~**Reviewer comment:**~~

~~Detailed discussion regarding second tier assessment which took into account key target organ and the critical effects for setting the systemic AOELs of fenpropidin, prothioconazole and prothioconazole-desthio has been accepted by the zRMS.~~
~~zRMS supports conclusions that organs and the critical effects for setting TRV's (systemic AOELs) are different and the additivity of doses does not need to be considered.~~
~~1) For PTZ TRV has been derived from original & supplementary rat developmental studies combined~~
~~Developmental target / critical effect:~~
~~pups: retarded ossification , reduced fetal weights, total litter losses, abortions, microphtalmia (rat) [Wistar Hanover rats (Crl:WI(HAN) is sensitive to this malformation, up to maternally toxic doses, not sufficient to warrant classification)[a, b].~~
~~2) For PTZ desthio TRV has been derived from supplementary rat developmental studies:~~
~~Developmental target / critical effect:~~
~~pups: Extranumerary ribs/supernumerary rudimentary ribs (rat) [this effect has been considered by the EChA associated with delayed foetal development and are not sufficient to warrant classification][a, b].~~
~~3) For fenpropidin TRV has been derived from 1 year dog study.~~
~~Developmental target / critical effect:~~
~~Local irritation, body weight, liver (hypertrophy), spinal, chord demyelination, corneal opacity [c].~~

~~[a] Committee for Risk Assessment RAC; Opinion proposing harmonised classification and labelling at EU level of Prothioconazole; CLH-O-0000001412-86-269/F Adopted 15 March 2019~~
~~[b] EFSA Scientific Report (2007) 106, 1-98, Conclusion on the peer review of prothioconazole, 12 July 2007~~
~~[c] EFSA Scientific Report (2007) 124, 1-84, Conclusion on the peer review of fenpropidin, 17 December 2007~~

Second tier assessment (exposure to fenpropidin and prothioconazole)

The AOEL of fenpropidin is based on the NOAEL from the 1-year dog study and the critical effects noted were increased liver weight, hypertrophy of hepatocytes and spinal chord demyelination. The AOEL of prothioconazole is based on the NOAEL of a rat developmentary study and the increased incidence of microphthalmia. Thus, the key target organ and the critical effects for setting the systemic AOELs of fenpropidin and prothioconazole, respectively, are different.
Therefore, in the non-dietary risk assessment of ADM.03502.F.1.A, the additivity of doses does not need to be considered and an acceptable risk for the operator, worker, bystander and resident is concluded without the need of PPE or risk mitigation measures.

Second tier assessment (exposure to fenpropidin and prothioconazole-desthio)

The AOEL of fenpropidin is based on the NOAEL from the 1-year dog study and the critical effects noted were increased liver weight, hypertrophy of hepatocytes and spinal chord demyelination. The AOEL of prothioconazole-desthio is based on the NOAEL of the supplementary rat developmentary study and the increased rudimentary supernumerary ribs. Thus, the key target organ and the critical effects for setting the systemic AOELs of fenpropidin and prothioconazole-desthio, respectively, are different.
Therefore, in the non-dietary risk assessment of ADM.03502.F.1.A, the additivity of doses does not need to be considered and an acceptable risk for the operator, worker, bystander and resident is concluded without the need of risk mitigation measures.

Conclusion

According to the tiered assessment of fenpropidin, prothioconazole and prothioconazole-desthio, combined exposure to the active substances in ADM.03502.F.1.A is not expected to present an unacceptable risk for operators, workers, bystanders and residents even without considering specific PPE or risk mitigation measures.

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
KCP 7.1.1/01	…	2020a	Acute oral toxicity (Acute Toxic Class Method) in the Rat with ADM.3502.F.1.A Report no.: … … GLP Unpublished	Y	ADM
KCP 7.1.2/01	….	2020b	Acute dermal toxicity (Acute Toxic Class Method) in the Rat with ADM.3502.F.1.A Report no.: … … GLP Unpublished	Y	ADM
~~KCP 7.1.3/01~~	~~…~~	~~2021~~	~~Acute inhalation toxicity study in Wistar rats – OECD 403 Report no.: G19710; sponsor no.: … … GLP Unpublished~~	~~Y~~	~~ADM~~
~~KCP 7.1.4/01~~	~~Groß, C.~~	~~2021~~	~~*In vitro* skin irritation: Human Skin Model Test (EpiDerm™) with ADM.3502.F.1.A Test Guideline: OECD 439, report no. STUGC20AA1348-2, sponsor no.: 000104837 Eurofins BioPharma Product Testing Munich GmbH, Planegg, Germany GLP Unpublished~~	~~N~~	~~ADM~~
KCP 7.1.5/01	Julienne, S.	2020	Bovine corneal opacity and permeability assay for identifying test item inducing serious eye damage and test item not requiring classification – OECD 437 Report no.: B20 0481; sponsor no.: 000104835 Eurofins BioPharma Product Testing Munich GmbH, Planegg, Germany GLP Unpublished	N	ADM
KCP 7.1.5/02	…	2021	Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A Report no.: … …	Y	ADM

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
			GLP Unpublished		
KCP 7.1.6/01	…	2021	Prothioconazole 175 g/L + Fenpropidin 250 g/L EC (ADM.03502.F.1.A): Local Lymph Node Assay (LLNA) in CBA/Ca MICE Report no.: … … GLP Unpublished	Y	ADM
KCP 7.2.2.2/01	Anonymous	2010	Development of air sampling methodology in support of determining risk of bystander and resident exposure to pesticides SID 5 (Rev. 07/10), DEFRA Project PS2023 Non-GLP Published	N	Not applicable
KCP 7.2.2.2/02	Bedos, C.; Rouseaue-Djabri, M.-F.; Loubet, B.; Durand, B.; Flura, D.; Briand, O. and Barriuso, E.	2010	Fungicide Volatilization Measurements: Inverse Modeling, Role of Vapor Pressure, and State of Foliar Residue Environmental Science and Technology, 44, 7, 2522-2528 Non-GLP Published	N	Not applicable
KCP 7.3/01	Maas, W.J.M.	2021a	The i*n vitro* percutaneous absorption of radiolabelled Prothioconazole-desthio in one in-use dilution of the Prothioconazole 175 g/L + Fenpropidin 250 g/L EC formulation (ADM.03502.F.1.A) through human split-thickness skin. Report no.: 20275164; sponsor no.: 000107008 Charles River Laboratories Den Bosch BV, DD ‘s-Hertogenbosch, The Netherlands GLP Unpublished	N	ADM
KCP 7.3/02	Maas, W.J.M.	2021b	The i*n vitro* percutaneous absorption of radiolabelled Fenpropidin in a concentrate formulation and one in-use dilution of the Prothioconazole 175 g/L + Fenpropidin 250 g/L EC formulation (ADM.03502.F.1.A) through human split-thickness skin. Report no.: 20275166; sponsor no.: 000107009 Charles River Laboratories Den Bosch BV, DD ‘s-Hertogenbosch, The Netherlands GLP Unpublished	N	ADM

ADM = Property of ADAMA Agricultural Solutions and all affiliates.

Under Article 59 of Regulation 1107/2009/EC, the Sponsor Company claims data protection for all ADM studies. For details on country specific data protection, refer to Part A.

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
-	-	-	-	-	-

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
KCP 7.1.3/01	…	2021	Acute inhalation toxicity study in Wistar rats - OECD 403 Report no.: … … GLP Unpublished	Y	ADM
KCP 7.1.4/01	Groß, C..	2021	*In vitro* skin irritation: Human Skin Model Test (EpiDerm™) with ADM.3502.F.1.A Test Guideline: OECD 439, report no. STUGC20AA1348-2, sponsor no.: 000104837 Eurofins BioPharma Product Testing Munich GmbH, Planegg, Germany GLP Unpublished	N	ADM

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

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
-	-	-	-	-	-

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Bridging was not necessary.

Comments of zRMS:	Bridging is not applicable. Hazard classification via the application of bridging principles is not possible since data on a similar mixture are not available. *In vivo* studies has been provided using currently registered product (ADM.03502.F.1.A).

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	~~Hazard assessment and proposed classification of the product based on content of ingredients of the mixture has been accepted (for details see Part C).~~ Acute Oral toxicity study … (2020a), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol. The OECD 423 procedure implements the 3R rules thus study is in line with the suggestions of point 5 of Regulation 284/2013. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

A 2.2.1 Study 1

Classification via the application of bridging principles is not possible since data on a similar mixture are not available. Thus, in a first approach, classification based on the complete composition of the plant protection product is taken into account for classification purpose. Since the composition of the plant protection product is confidential, this approach is presented in the confidential part C of this dossier.

Conclusion

Based on the alternative approach by using the calculation method, ADM.03502.F.1.A has a calculated LD_{50} of ~~2938 mg/kg bw~~ 1667 mg/kg bw and should ~~not~~ be classified as acutely toxic via the oral route as Acute Tox. 4 with H302. ~~However, any possible effects of components of unknown toxicity on the toxic potential of mixture cannot be predicted. Therefore, additional labelling is considered to be required as follows: "19% of the mixture consists of ingredient of unknown acute oral toxicity".~~

~~Thus, no classification of ADM.03502.F.1.A for acute toxicity via the oral route is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.~~

However, a vertebrate study is available for acute toxicity of ADM.03500.F.1.A via the oral route. This study was not performed with intention for use within the EU, but it was performed to satisfy the regulatory requirements of countries outside of the EU. As requested by the zRMS, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.1/01
Report	Acute oral toxicity (Acute Toxic Class Method) in the Rat with ADM.3502.F.1.A, … (2020a), report no. …
Guideline(s):	OECD guideline 423 (2001); EC 440/2008 Method B.1 tris (2008); EPA OPPTS 870.1100 (2002)
Deviations:	No
GLP:	Yes

Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.03502.F.1.A, Batch no. 1191-101219-01
Species	Rat *(Rattus norvegicus)* / WISTAR rats Crl: WI(Han) (full barrier)
No. of animals (group size)	Step 1: 3 females; step 2: 3 females (total number of animals: 6 females)
Dose(s)	2000 mg/kg bw
Exposure	Once by gavage using a feeding tube
Vehicle/Dilution	None (undiluted)
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in female rats of ADM.03502.F.1.A

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Step 1				LD_{50} > 2000 -5000 LD_{50} cut-off: 5000 mg/kg bw
2000	0/3/3	Day 1**	n.a.	
Step 2				
2000	0/3/3	Day 1**	n.a.	

* Number of animals which died/number of animals with clinical signs/number of animals used
** Day of test item administration
n.a. not applicable

Table A 2: Summary of findings of acute oral toxicity study in female rats of ADM.03502.F.1.A

Mortality:	None
Clinical signs:	Yes, the most relevant clinical findings in the animals treated with the test item at a dose of 2000 mg/kg bw were slightly to greatly reduced spontaneous activity, slight piloerection, hunched posture and half closed eyes. All animals recovered within up to 4 hours post-dose.
Body weight:	Throughout the 14-day observation period, the body weight gain of the surviving animals was within the normal range of variation for this strain.
Macroscopic examination:	At necropsy, no treatment-related macroscopic findings were observed in any surviving animals.

Conclusion

Under the conditions of the present study and according to OECD Guideline 423, EC 440/2008 Method B.1 tris and OPPTS 871.1100, the median lethal dose of ADM.03502.F.1.A after a single oral administration to female rats, observed over a period of 14 days is > 2000 mg/kg bw, with a LD_{50} cut-off (rat): 5000 mg/kg bw. Thus, no classification for acute toxicity via the oral route is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.

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

Comments of zRMS:	~~Hazard assessment and proposed classification of the product based on content of ingredients of the mixture has been accepted (for details see Part C).~~

	Acute percutaneous study … 2020b has been reviewed for compliance with the current guidelines, resulting from scientific progress. OECD 402 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

A 2.3.1 Study 1

Classification via the application of bridging principles is not possible since data on a similar mixture are not available. Thus, in a first approach, classification based on the complete composition of the plant protection product is taken into account for classification purpose. Since the composition of the plant protection product is confidential, this approach is presented in the confidential part C of this dossier.

Conclusion

Based on the available data ADM.03502.F.1.A should not be classified as acutely toxic via the dermal route. ~~However, any possible effects of components of unknown toxicity on the toxic potential of mixture cannot be predicted. Additional labelling is considered to be required: "**19% of the mixture consists of ingredients of unknown acute dermal toxicity**".~~

Thus, **no classification** of ADM.03502.F.1.A for acute toxicity via the dermal route is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.
In addition, a vertebrate study is available for acute toxicity of ADM.03500.F.1.A via the dermal route. This study was not performed with intention for use within the EU, but it was performed to satisfy the regulatory requirements of countries outside of the EU. As requested by the zRMS, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.2/01
Report	Acute Dermal Toxicity (Fixed Dose Procedure) in the Rat with ADM.3501.F.1.A, …., 2020b, report no. …
Guideline(s):	OECD guideline 402 (2017); EC 440/2008 Method B.3 (2008)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.03502.F.1.A, Batch no. 1191-101219-01-01
Species	rat (*Rattus norvegicus*) / WISTAR rats Crl: WI(Han)
No. of animals (group size)	3 female rats (1 (dose range finding test) plus 2 (main study))
Dose(s)	2000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	None, used undiluted
Post exposure observation period	14 days
Remarks	Scratches were observed at the application site in all animals starting 7 days after removal of patches, but not further explained in the study report.

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of ADM.03502.F.1.A

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
2000	0/0/3	Day 3 – day 15	n.a.	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used
n.a. not applicable

Table A 4: Summary of findings of acute dermal toxicity study in rats of ADM.03502.F.1.A

Mortality:	No mortality occurred.
Clinical signs:	None of the animals showed signs of acute dermal toxicity. Signs of skin irritation were assessed using the scoring system described in OECD TG 404: Erythema grade 1 was observed at the application site in animal no. 3 on day 3, 4 and 5. Small red spots Ø 1-2 mm were observed at the application site in animal no. 1 on day 6, 7 and 8 and in animal no. 2 on day 4. None of the animals showed any oedema. Furthermore small scratches were observed in all animals at the application site: In animal no. 1 (Ø 1-2 mm) on day 9 until day 15, in animal no. 2 (Ø 2 mm) on day 8 until day 15 and in animal no. 3 (Ø 1 mm) on day 7 until day 9. There were no other adverse clinical findings recorded for any animal over the course of the study.
Body weight:	Body weight gain was considered to be normal.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the dermal LD_{50} of ADM.03502.F.1.A is higher than 2000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	…. (2021) Acute inhalation toxicity study in Wistar rats - OECD 403 and assessment based ATEmix/additivity formula and components content gave the different outcome. Based on the alternative approach by using the calculation method, ADM.03502.F.1.A has a calculated LC50 of 3.94 mg/L and classified as acutely toxic via the inhalation route would be required. However, based on the results of the acute inhalation toxicity study, the acute LC50 is > 5.0 mg/L. Thus, classification of ADM.03502.F.1.A is not required according to Regulation (EC) No. 1272/2008 and subsequent regulations. Thus, the relying on the results of an acute inhalation toxicity study is considered justified for adequate classification of the product. Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. In the study (…. 2021) animals are exposed to one limit concentration for a pre-determined duration (4 hours) and obtain sufficient information on the acute toxicity of test article to enable its classification and to provide lethality data (LC_{50}) for both sexes as needed for quantitative risk assessments. Noted deviation from TG OECD 403 procedure has no critical impact on study outcome. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

A 2.4.1 Study 1

Reference:	KCP 7.1.3/01
Report	Acute inhalation toxicity study in Wistar rats - OECD 403, …. (2021), Report no.: G19710; sponsor no.: 000104833
Guideline(s):	OECD guideline 403 (2009)
Deviations:	None

GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3502.F.1.A (1191-101219-01)
Species	Rat, Wistar
No. of animals (group size)	5 rats/sex/dose
Concentration(s)	5.36 ± 0.05 mg/L (Limit test)
Exposure	4 hours (nose only)
Vehicle/Dilution	Clean air
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Concentration(s) and exposure conditions

Nominal conc. (mg/L air)	Actual conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
20.76	5.36 ± 0.05	2.32	1.73

* MMAD = Mass Median Aerodynamic Diameter
** GSD = Geometric Standard Deviation

Table A 6: Results of acute inhalation toxicity study in rats of ADM.3502.F.1.A

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Male rats				
5.36 ± 0.05	0/5/5	Day 0** - Day 4	n.a.	LC_{50} > 5 mg/L
Female rats				
5.36 ± 0.05	0/5/5	Day 0** - Day 4	n.a.	LC_{50} > 5 mg/L

* Number of animals which died/number of animals with clinical signs/number of animals used
** removal from the exposure tube
n.a. = not applicable

Table A 7: Summary of findings of acute inhalation toxicity study in rats of ADM.3500.F.2.B

Mortality:	No animals died.
Clinical signs:	Clear nasal discharge, slight / moderate salivation and hypoactivity was observed in treated rats. All animals were normal from day 4 onwards.
Body weight:	There was slight reduction in body weight observed on days 2 and 4 in all rats, however all these rats gained body weight on day 8 and terminal weighing when compared to their initial bodyweight.
Macroscopic examination:	No abnormality was detected at necropsy in any of the rats.

Conclusion

Based on the results of the acute inhalation (4 hours) toxicity study, the median Lethal Concentration (LC_{50}) value is more than 5.36 mg/L air in male and female Wistar rats. Thus, **classification** of ADM.03502.F.1.A is not required according to Regulation (EC) No. 1272/2008 and subsequent regulations.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Regarding *in vitro* study Groß, C. (2021), (*In vitro* skin irritation: Human Skin Model Test (EpiDerm™) with ADM.3502.F.1.A) zRMS reviewer draws attention to the following information available in GD OECD 439 revision 14 June 2021 INITIAL CONSIDERATIONS AND LIMITATIONS Subsection 8: p.2 (..) data indicates a lack of applicability of the RhE based *in vitro* skin irritation test for agrochemical formulations (47). (..). See also: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). Regulatory accepted but out of domain: *In vitro* skin irritation tests for agrochemical formulations. Regul. Toxicol. Pharmacol 89, 125-130. Thus, taking into account mentioned above information zRMS decided to conclude assessment in this hazard category for the ADM.03502.F.1.A taking into account outcome of the *in vivo* study … (2021) *Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A.* and classify product ADM.03502.F.1.A with hazard category H315 "Causes skin irritation" as a precautionary approach. However, for the purpose of classification the study method is not sufficient to distinguish between skin corrosion category 1 and skin irritation category 2. Therefore a weight-of evidence approach is applied. Relevant and reliable data derived from other *in vivo* and *in vitro* toxicity studies of dermal exposure provide additional information regarding the skin effects of ADM.03502F.1.A. Acute dermal toxicity study in rats, LLNA-test in mice and *in vitro* dermal absorption study on human skin are taken into account: In the acute dermal toxicity study according to OECD 402 (see Chapter A.2.3 Acute dermal toxicity (KCP 7.1.2/01)), using the undiluted PPP, none of the animals showed erythema or oedema, except for one animal. Animal no. 3 showed grade 1 erythema on day 3, 4 and 5. Two animals showed small red spots Ø 1-2 mm at the application site on day 6 through day 8, and on day 4, respectively. These skin reactions were reversible. In addition, scratches at the application site were observed in all rats from day 7 after removal of the patches. The study report does not elaborate on the appearance of the scratches. However, in general, scratches are considered to be damage to the skin surface due to physical injury. Considering the skin sensitizing potential of fenpropidin classified as Skin Sens. Cat. 1B and a 25% concentration of fenpropidin in ADM.03502F.1.A, an allergic reaction with responding skin effects must be also considered likely. In the study slight skin irritant effects were observed, however, any corrosive reactions as typified by ulcers, bleeding, bloody scabs, and, then leading to discolouration due to blanching of the skin, complete areas of alopecia, and scars were not noted. In the LLNA test in mice according to OECD 429 (see Chapter A.2.7 Skin sensitisation (KCP 7.1.6/01)), the undiluted test substance does not elicited any skin irritation or skin corrosive reaction under the conditions of the study. In the dermal absorption study of fenpropidin in ADM.03502F.1.A according to OECD 428 (see Chapter A.2.10 Study on dermal absorption (KCP 7.3/02)), the results derived from the applied concentrate on human skin samples showed less than 0.5% of a.s. in the receptor fluid (0.38%±0.18%) and therefore, does not give any evidence on damaging effects on the skin barrier due to corrosive properties of the PPP. Overall, in the existing *in vivo* and *in vitro* OECD toxicity studies, dermal exposure to undiluted ADM.03502F.1.A showed no corrosive effects on rat and mouse skin and human skin samples, respectively. In a weight of evidence approach it is concluded that the data are sufficient for classification and no further testing for assessing corrosivity is necessary. **Thus, classification as Skin Irrit. Cat.2 with hazard statement H315 "Causes skin irritation" is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.**

A 2.5.1 Study 1

Reference:	KCP 7.1.4/01
Report	*In vitro* skin irritation: Human Skin Model Test (EpiDerm™) with

	ADM.3502.F.1.A Test Guideline: OECD 439, Groß, C. (2021), report no. STUGC20AA1348-2, sponsor no.: 000104837
Guideline(s):	OECD guideline 439 (2020); EU method B.46 (EC No. 440/2008)
Deviations:	None
GLP:	Yes
Acceptability:	No
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3502.F.1.A (1191-101219-01)
Test system:	Reconstituted three-dimensional human skin model EpiDerm™ (MatTek)
Vehicle/Dilution	None
Negative control	Dulbecco's phosphate buffered saline (DPBS)
Positive control	5% sodium dodecyl sulfate (TC-SDS-5%)
No. of tissues per group	3 EpiDerm™ tissues
Exposure	30 µL of undiluted test item, negative control or positive control, all plates were transferred to the incubator for 35 ± 1 min. Afterwards all plates were removed from the incubator and placed under the sterile flow for the remaining time until the 60 ± 1 min incubation time of the first dosed tissue was over.
Washing and post-incubation	The tissues were washed by filling and emptying the inserts 15 times with DPBS using a constant stream in about 1.5 cm distance from the tissue surface, this process also occurred sequentially, e.g. in one-minute intervals. Subsequently, the inserts were completely submerged three times in 150 mL DPBS and shaken to remove rests of the test item. Finally, the inserts were rinsed once from the inside and the outside with sterile DPBS. Excess DPBS was removed by blotting the bottom with blotting paper. The inserts were placed in prepared new 6-well plates containing 0.9 mL pre-warmed fresh assay medium per well and the tissue surface was dried using a sterile cotton tip. The plates were post-incubated at 37 ± 1 °C, 5.0% CO_2, humidified to 95%, for 24 ± 2 h. Following this incubation the tissues were transferred to new wells containing 0.9 mL fresh assay medium and incubated for additional 18 ± 2 h.
MTT reduction assay	The bottom of the inserts were blotted on sterile blotting paper and the inserts were transferred in a prepared 24-well plate containing 300 µL pre-warmed MTT medium. This plate was incubated for 3 h ± 5 min at 37 ± 1 °C, 5.0% CO_2, humidified to 95%. Cytotoxicity is expressed as the reduction of mitochondrial dehydrogenase activity measured by formazan production from MTT after test item exposure plus post-treatment incubation period and compared to those of the concurrent negative controls. Formazan was extracted by using isopropanol.
Optical density measurement	Per tissue 2 x 200 µL aliquots of the extract were transferred to a plate and the optical density (OD) was measured at 570 nm without reference wavelength in a plate spectrophotometer.
Evaluation	Prediction on irritant potential: UN GHS Category 2: mean tissue viability ≤ 50% of negative control UN GHS no category: mean tissue viability > 50% of negative control The reconstructed human epidermis (RhE) test method cannot resolve between UN GHS Categories 1 and 2, further information are required to decide on final classification
Acceptance criteria	The test meets acceptance criteria if: - mean absolute $OD_{570\ nm}$ of the three negative control tissues is ≥ 0.8 and ≤ 2.8

	- mean relative tissue viability of the three positive control tissues is ≤ 20% - standard deviation (SD) of relative tissue viability obtained from each three concurrently tested tissues is ≤ 18%.
Remarks	In preliminary tests the test substance was not soluble in aqua dest., even after centrifugation a turbidity was observable. However, the mixture showed no relevant colouring detected by unaided eye-assessment. Thus, the no additional test with viable tissues and the quantitative corrections were necessary. After washing, it was not possible to completely wash off the test material resulting in little remaining test material of the skin tissue surface. As these little residues were only on small parts of the tissues, the impact on the results are presumably negligible.

Results and discussions

Table A 8: *In vitro* Skin irritation of ADM.3502.F.1.A

Dose group	Treatment interval	Mean absolute OD570	Mean OD570 of the duplicates (blank-corrected) Tissue 1	Mean OD570 of the duplicates (blank-corrected) Tissue 2	Mean OD570 of the duplicates (blank-corrected) Tissue 3	Total mean OD570 of 3 replicate tissues (blank-corrected) ± SD OD570	Mean relative tissue viability (%) ± SD*** tissue viability	Cell viability [% viabilities]
Negative control	60 ± 1 min.	2.279****	2.427	2.034	2.237	2.233* ± 0.196	100.0 ± 8.8	8.8
Positive control	60 ± 1 min.	0.109	0.065	0.057	0.066	0.063 ± 0.005	2.8** ± 0.2	7.8
Test substance	60 ± 1 min.	0.504	0.491	0.684	0.201	0.459 ± 0.243	20.5 ± 10.9	53.0

* Blank-corrected mean OD570 of the negative control corresponds to 100% absolute tissue viability.
** Mean relative tissue viability of the three positive control tissues is ≤ 20%
*** Standard deviation (SD) of relative tissue viability obtained from each three concurrently tested tissues is ≤ 18%
***

Table A 9 Historical control data for negative and positive control (generated from 2015 to 2021)

	Mean absolute OD570 ± 30 nm Negative control (DPBS)	Mean relative viability [%] Positive control (5% SDS)	SD viability Negative control, positive control, and test item [%]
mean	1.806	4.1	4.4
SD	0.242	2.0	4.6
Range of LCL - UCL	1.322 – 2.290	0.2 – 8.0	0.0 – 13.7
n	79	78	376

LCL = Lower control limit (95%, mean – 2*SD)
UCL = Upper control limit (95%, mean + 2*SD)
n = number of control values

The controls confirmed the validity of the study. The mean absolute OD570 of the three negative control tissues was ≥ 0.8 and ≤ 2.8 (2.279). The mean relative tissue viability (% negative control) of the positive control was ≤ 20% (2.8%). The maximum standard deviation of viability of replicate tissues of all dose groups was ≤ 18% (8.8, 0.2 and 10.9%).

Conclusion

Under the experimental conditions, the test item showed irritant effects. Thus, classification as Skin Irrit. Cat.2 with hazard statement H315 “Causes skin irritation” is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.
Final conclusion regarding hazard classification “skin irritation” see zRMS comment in the commenting box. zRMS additional discussion reflects cMS comments submitted during commenting period.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Regarding *in vitro* study Julienne, S. (2020), (Bovine corneal opacity and permeability assay for identifying test item inducing serious eye damage and test item not requiring classification – OECD 437), zRMS reviewer draws attention to the following information available in the paper: Kolle S.N., van Cott A., van Ravenzwaay B. and Landsiedel R. (2017): Lacking applicability of *in vitro* eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS. Regulatory Toxicology and Pharmacology 85 (2017) 33-47. Thus, taking into account mentioned above information zRMS decided to conclude assessment in this hazard category for the ADM.03502.F.1.A based on *in vivo* study.

A 2.6.1 Study 1

Reference:	KCP 7.1.5/01
Report	Bovine corneal opacity and permeability assay for identifying test item inducing serious eye damage and test item not requiring classification – OECD 437, Julienne, S. (2020), Report no.: B20 0481; sponsor no.: 000104835
Guideline(s):	OECD guideline 437 (2017)
Deviations:	Yes With minor deviations in reporting (details of historical control data and data on measured cornea diameter are missing)
GLP:	Yes
Acceptability:	No
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.03502.F.1.A, Batch no. 1191.101219.01
Test system:	Corneas of calvers aged less than 8 months
Vehicle/Dilution	Diluted at 10% with 0.9% NaCl
Negative control	Physiological saline 0.9% NaCl
Positive control	Dimethylformamide 100%
No. of corneas per group	3 corneas
Exposure	750 µL for 10 minutes, 32 ± 1 °C
Irrigation	After treatment the corneas were washed with EMEM containing phenol red followed by washing with EMEM without phenol red. Then, the corneas were incubated in EMEM without phenol red for another 2 hours (32 ± 1 °C).
Measurements	(1) Corneal opacity: Initial and final measurement of corneal opacity before treatment and after 2 hour incubation period; (2) Corneal permeability: Treatment with sodium fluorescein for 90 minutes (32 ± 1 °C) and measurement of optical density at 490 nm after treatment.
Evaluation	Calculation of mean opacity and mean OD490 values of each treatment groups and the *in vitro* irritation score: *In vitro* irritation score (IVIS) = mean opacity value + (15 × mean permeability OD490 value) for assessing the prediction on irritant potential.

	The IVIS cut-off values for identifying test substances as inducing serious eye damage (Category 1) and test substances not requiring classification for eye irritation or serious eye damage are as follows: Category 1: IVIS > 55 No category: IVIS ≤ 3 No prediction can be made: IVIS > 3; IVIS ≤ 55
Validity criteria	Negative control: The test was considered acceptable if the negative control gives the opacity OP < 3 and the optical density OD <0.021 Study results of negative control: OP = 1.0, OD = 0.019 Positive control: The test was considered acceptable if the positive control gives an IVIS that fall within two standard deviations of the current historical mean (69.8 < IVIS < 107.9) Study results of positive control: 97.0 ± 4.0 .

Results and discussions

Table A 10: *In vitro* eye irritation of ADM.03502.F.1.A

Test group	Corrected opacity value (OPT2 – OPT0)		Corrected OD490		In vitro irritancy score (IVIS)
		Mean ± SD		Mean	
Negative control NaCl 0.9%	2	1.0 ± 1.0	0.014	0.019 ± 0.004	0.3 ± 0.1
	1		0.021		
	0		0.021		
Positive control Dimethylformamide	79	82.7 ± 4.5	1.311	0.959 ± 0.331	97.0 ± 4.0
	84		0.654		
	88		0.910		
Test substance 10% ADM.03502.F.1.A in NaCl 0.9%	6	4.0 ± 1.0	-0.002	-0.001 ± 0.005	4.0 ± 1.0
	5		-0.003		
	4		-0.006		

SD = standard deviation

The corneas treated with ADM.03502.F.1.A showed slight epithelium detachment. The cornea treated with the positive control showed oedema and high epithelium detachment. The mean *in vitro* irritation score of the test item is 4.0. As the positive control falls within the two standard deviations of the current historical control mean, the validity criteria according to study guideline is fulfilled.

The negative control responses resulted in opacity and permeability values that are less than the established upper limits for background bovine corneas treated with the respective negative control.

Conclusion

The potential of undiluted ADM.03502.F.1.A to induce ocular corrosivity or severe irritancy was investigated in the bovine corneal opacity and permeability assay (*in vitro* test). Based on the results of the *in vitro* study, no prediction can be made for the classification of ADM.03502.F.1.A concerning classification as eye irritant. As stated in Section 7 (Toxicological studies) point 7.1.5 Eye irritation of Regulation (EU) 284/2013 the testing strategy shall follow a tiered approach:
(1) the use of an in vitro dermal irritation/corrosion test to predict eye irritation/corrosion;
(2) the performance of a validated or accepted in vitro eye irritation study to identify severe eye irritants/corrosives, and where negative results are obtained;
(3) the assessment of eye irritation using an available, in vitro test method validated for plant production products for identification of non-irritants or irritant, and when not available;
(4) and initial in vivo eye irritation study using one animal, and where no adverse effects are noted;
(5) confirmatory testing using one or two animals are recommended. Thus, further testing is needed. An *in vivo* GLP OECD study with ADM.03502.F.1.A is available and summarised below. The study data are reliable and adequate for classification purpose.

Comments of zRMS:	*In Vivo* studies has been considered as primary source of information regarding hazard classification, thus classification based on the complete composition of the plant protection or alternative method (*in vitro*) has not been taken into account (please refer zRMS detailed consideration in the preface to this dRR). Study (… 2021) has been reviewed for compliance with the current guidelines resulting from scientific progress (OECD 405 rev 2017). The update from 2012 mainly focused on the use of analgesics and anesthetics without impacting the basic concept and structure of the TG. ICCVAM (*Interagency Coordinating Committee on the Validation of Alternative Methods*) reviewed the usefulness and limitations of routinely using topical anesthetics, systemic analgesics, during *in vivo* ocular irritation safety testing. The review concluded that the use of topical anesthetics and systemic analgesics could avoid most or all pain and distress without affecting the outcome of the test, and recommended that these substances should always be used. In the discussed study (… 2021) topical anesthetics has been used. One hour before the application of the test item, 0.01 mg/kg of buprenorphine (Indivior) was administered subcutaneously in order to achieve a therapeutic level of systemic analgesia. Approximately 5 minutes prior to the application of the test item, 1–2 drops of an ocular anaesthetic (proparacaine hydrochloride ophthalmic 0.5% solution, URSAPHARM Arzneimittel) were administered in both the treated and the control eye of the animal. To prevent pain and distress after the application of the test item the animal was treated with the following doses of buprenorphine and meloxicam. Considering mentioned information in the Reviewer opinion study implements 3R rules and humane endpoints minimizing pain and distress of animals. In the mentioned study degree of eye irritation/serious eye damage were evaluated by scoring lesions of conjunctiva, cornea, and iris, at specific intervals. Duration of the study was sufficient to evaluate the reversibility or irreversibility of the effects. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

A 2.6.2 **Study 2**

Reference:	KCP 7.1.5/02
Report	Acute Eye Irritation/Corrosion in the Rabbit with ADM.03502.F.1.A, … (2021), Report no.: …
Guideline(s):	OECD guideline 405 (2017); EPA OPPTS 870.2400 (1998); EU method B.5 (EC No. 440/2008)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.03502.F.1.A, Batch no. 1191-101219-01
Species	Rabbit, New Zealand albino
No. of animals (group size)	1 female
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in one conjunctival sac. The (untreated) contralateral eye served as a control.)
Irrigation (time point)	No
Vehicle/Dilution	None

Post exposure observation period	21 days
Remarks	None

Results and discussions

Table A 11: Eye irritation of ADM.03502.F.1.A

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	1	1	1	1	1	not fully reversible within 21 days post-administration
	Iritis	1	1	1	1	1	
	Redness conjunctivae	2	2	1	1	1.33	
	Chemosis conjunctivae	4	2	2	2	2	

* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	The animal showed clinical findings such as reduced spontaneous activity, half eyelid closure, hypersecretion, crust and hairless area. After 21 days post-application the following effects were persistent: redness grade 1, chemosis grade 1, iris lesion grade 1 and cornea opacity grade 1. Upon fluorescein examinations starting 24 hours post-application corneal lesions were found in the animal. The body weight development of all animals was within the expected range.

Conclusion

Under the experimental conditions, ADM.03502.F.1.A is a severe irritant to the eye. Thus, classification in Serious Eye Damage Cat. 1 with hazard statement H318: “Causes serious eye damage” is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	~~Hazard assessment and proposed classification of the product based on content of ingredients of the mixture has been accepted (for details see Part C).~~ Skin sensitisation study …. (2021) 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.

A 2.7.1 Study 1

Classification via the application of bridging principles is not possible since data on a similar mixture are not available. Thus, in a first approach, classification based on the complete composition of the plant protection product is taken into account for classification purpose. Since the composition of the plant protection product is confidential, this approach is presented in the confidential part C of this dossier.

Conclusion

~~Based on the available data of ingredients, ADM.03502.F.1.A is a skin sensitiser. Thus, ADM.03502.F.1.A requires classification in Skin Sensitisation Category 1 with hazard statement H317: “May cause an allergic skin reaction” according to Regulation (EC) No. 1272/2008 and subsequent regulations.~~

In addition, a vertebrate study is available for skin sensitisation of ADM.03500.F.1.A. This study was not performed with intention for use within the EU, but it was performed to satisfy the regulatory requirements of countries outside of the EU. As requested by the zRMS, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.6/01
Report	Prothioconazole 175 g/L + Fenpropidin 250 g/L EC (ADM.03502.F.1.A): Local Lymph Node Assay (LLNA) in CBA/Ca MICE, …. (2021), Report no. …
Guideline(s):	OECD guideline 429 (2010); EPA OPPTS 870.2600 (2003); EU method B.42 (EC No. 440/2008)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	… (Batch no. …)
Species	Mouse, CBA/Ca
No. of animals (group size)	Preliminary test: 1 female/concentration Test substance groups: 6 female mice/ concentration Vehicle control group: 6 female mice Positive control group: 6 female mice
Vehicle/negative control	Methyl-ethyl ketone (MEK)
Positive control	Positive control: α-hexylcinnamaldehyde (25% in MEK)
Range finding:	Yes In the irritation screen, the vehicle MEK, concentrations of 5, 25, 50 and 75% v/v in MEK and 100% (undiluted) test item were evaluated for irritation potential (1 mouse/group), as measured by erythema of the ears.
Exposure (concentration(s), no. of applications)	25, 50 and 100 % (undiluted) 25 µL of the appropriate concentration was applied to the ears of each mouse once per day for three consecutive days
Procedures	Both ears were observed for skin reaction prior to application of the test item and on day 1, 2, 3 and on day 6. All mice were weighed on Days 1 and 6. Ear thickness was measured using Digimatic micrometer (Mitutoyo, Japan) prior to dosing on Days 1 and 3 and on day 6. Additionally, on Day 6, ear thickness was determined by ear punch weight determination after animals were euthanized.
Evaluations	Erythema scores, ear thickness and body weight data following the test item applications were compared to the response of the animals treated with vehicle alone.
Proliferation Assay	On day 6, a volume of 250 µL (20 µCi) of ^{3}H-TdR in PBS was administered to each mouse via the lateral tail vein. Approximately five hours post injection of ^{3}H-TdR, animals were euthanized using isoflurane anaesthesia. The auricular lymph nodes (bilateral) were excised and placed in PBS, processed and the radioactivity was counted by using a ß-scintillation counter.

Results and discussions

In the irritation screen test (1 animal) and in the main test (6 animals), the animals treated with three different dose concentrations of the test substance of up to 100% test substance (undiluted) showed no topical effects; no erythema were observed on the application sites (both ears) or any significant increase in the ear thickness or ear punch weights. Thus, the undiluted test substance does not elicited any skin irritation reaction under the conditions of the study.

Table A 12: Results of skin sensitisation study of ADM.03502.F.1.A

Groups	No. of animals	Concentration (%)	DPM / group (± SD)	Stimulation index (SI) ± SD	EC3 value
ADM.03502.F.1.A	6	25	2697.50 ± 278.02	2.82 ± 0.29	25.80%.
	6	50	8119.33 ± 1867.76	8.48 ± 1.95	
	6	100	12182 ± 2600.02	12.73 ± 2.72	
Vehicle control	6	0	957.17 ± 171.35	1.00 ± 0.18	n.a.
Positive control	6	25	7742.00 ± 2170.15	8.09 ± 2.27	n.a.

SD = standard deviation
n.a. = not applicable

The sensitivity of this LLNA test was demonstrated via the response from the positive control (25% HCA in MEK), which elicited a stimulation index (SI) of 8.09, in comparison with the vehicle-treated mice.

There were no clinical signs, no erythema at the site of application and no significant effect on body weight gains. The Mean SI values for 25, 50% v/v test item in MEK and 100% undiluted test item were 2.82, 8.48 and 12.73, respectively (Table A 12). The EC_3 value was 25.80%.

Conclusion

Under the experimental conditions, ADM.03502.F.1.A is a weak skin sensitizer based on the EC3 value of 25.80%. Thus, classification as Skin Sensitisation Category 1B with hazard statement H317: "May cause an allergic skin reaction" is required according to Regulation (EC) No. 1272/2008.

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

No further studies are necessary.

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)

In the EFSA Scientific Report (2007) 106, 1-98 the metabolite prothioconazole-desthio is concluded to be more toxic than prothioconazole in the rat and rabbit developmental studies. As stated in DAR (2005), B.6.15.1 Operator exposure (III 7.2.1), p.327: "It has been found that JAU 6476-desthio (SXX 0665) may be formed in diluted prothioconazole formulations. This may happen on clothing, skin or certain plant surfaces during the drying process. The degradation product, JAU 6476-desthio, is known to have an embryotoxic potential in experimental animals." Thus, for assessment of non-dietary exposure to the toxicologically relevant metabolite a new dermal absorption study with prothioconazole-desthio in intended spray dilution of ADM.03502.F.1.A (MCW-2091) is available and submitted with this dossier (refer to KCP

7.3/01).

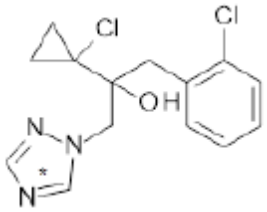
A new dermal absorption study with the active substance fenpropidin in MCW-2091 (ADM.03502.F.1.A) is available and submitted with this dossier (refer to KCP 7.3/02).

Comments of zRMS:	Dermal absorption study on prothioconazole-desthio has been conducted according to the OECD TG 428 revision 2004. For testing human split thickness skin has been used. There were no deviations from the TG. The absorbed dose of Prothioconazole-desthio from the ADM.03500.F.2.B spray dilution has been calculated based on EFSA GD 2017. Applying a dermal absorption rate for prothioconazole-desthio in formulation (ADM.03502.F.1.A) of 6.9% for the intended spray dilution of 0.328 g/L (1:533) is considered appropriate to use according to EFSA Guidance on Dermal Absorption (2017). In-use dilution is covered by the dilution tested in the study then no pro-rata correction is required. Results of the DA study and conclusions are adequate for risk assessment (NDE) Study accepted

A 2.10.1 **Study 1**

Reference:	KCP 7.3/01
Report	The i*n vitro* percutaneous absorption of radiolabelled Prothioconazole-desthio in one in-use dilution of the Prothioconazole 175 g/L + Fenpropidin 250 g/L EC formulation (ADM.03502.F.1.A) through human split-thickness skin. Maas, W.J.M., 2021, Report no.: 20275164; sponsor no.: 000107008
Guideline(s):	OECD 428 (2004), EU method B.45 (Reg (EC) 440/2008)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	Not applicable

Materials and methods

Test material, purity (Lot/Batch No.)	Prothioconazole-desthio, 99.83% (625-050-00, Code CC-711)
Radiolabeled test material (Lot No.) **Structure** (*position of radiolabel)	[^{14}C] Prothioconazole-desthio, [1, 2, 4-triazole-U-^{14}C] Prothioconazole-desthio (XXIV/5/C/2) 
Formulation, type of formulation (Batch No.)	Prothioconazole 175 g/L + Fenpropidin 250 g/L EC, ADM.03502.F.1.A, emulsifiable concentrate
Concentration of relevant metabolite in the spray dilution (analytical), [g/L]	Prothioconazole-desthio: 0.328 (0.26, CV: 13.2%)
Amount of spray dilutions applied on human skin [µL/cm^2]	10 (ca. 6.4 µL)
Skin sample source	Human skin derived from abdomen of four female donors aged 27 to 60
Skin preparation used	Split-thickness skin membrane

Test system	Automated flow through diffusion cell apparatus (McGregor/Toner cells), exposure area: 0.64 cm^2, receptor chamber volume: 0.25 mL, flow rate: 1.5 mL/h, temperature: 32 ± 1°C
Exposure time	8 hours
Sampling duration	0 to 24 hours: 0 to 2 hours 1 hour intervals followed by 2 hours interval until 24 hours after application
Integrity of skin samples	Yes, was checked by measuring the permeability coefficient of skin samples
No. of replicates per dose group	Human skin: 8 (2 samples from 4 donors)
Receptor fluid composition	Phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, ca 6%, w/v), sodium azide (ca 0.01%, w/v), streptomycin (ca 0.1 mg/mL) and penicillin (ca 100 units/mL), pH 7.4
Swabbing	Concentrated commercial hand wash soap was applied to the skin and the soap gently rubbed onto the skin with a tissue swab. The skin was then rinsed with 5 mL of a ca 2% (v/v) commercial soap solution. The soap solution was applied in aliquots and each aliquot was aspirated three times with a pipette. The skin was dried with a tissue swab. The process was repeated and the skin was dried with an additional tissue swab.
Mass balance samples	Receptor fluid samples, skin wash, tissue swab, pipette tip, receptor compartment wash, donor compartment wash, tape strips and digested skin
Analytical method	Liquid scintillation counting

Results and discussions

Solubility of prothioconazole-desthio in receptor fluid was determined and found to be 47 ± 8 µg/mL. The maximum absorption rate (flux) into the receptor fluid was 85.8 ng.equiv./cm^2/h (Cell 24), which corresponds to (0.086 µg × 0.64)/(1 h×1.5 mL/h) = 0.04 µg/mL. Therefore, the solubility of the test item in the receptor fluid was demonstrated to be adequate and not rate-limiting to the absorption process.
Furthermore, in the flow-through cells used, the volume of the receptor fluid in the receptor chamber beneath the skin was ca. 0.25 mL. At a flow rate of ca. 1.5 mL/h, this volume was replenished continuously (6 times per hour) such that the rate of diffusion into the receptor fluid did not become a rate-limiting step (*i.e.* sink conditions were maintained).

At the time of preparation the stock solution and at dosing the stability of prothioconazole-desthio was analysed in duplicate by determining the radiochemical purity with the HPLC method (stock solution, mean value: 97.6.8%, dilution, mean value : 96.2%). The results of the radiochemical purity assessment confirmed that the test item was stable upon dosing of the test preparations.

A tritiated water barrier integrity test was performed. The integrity of all human skin samples was within the acceptability criteria (absorption ≤1.6% of applied dose of tritiated water).

A total of 8 samples of human split-thickness skin membranes obtained from 4 different donors were dosed topically with the test preparation. Overall, the absorption profiles looked similar for all samples (Figure 1). One replicate (Cell 24) was excluded from the calculations of the mean values since it showed an uncharacteristically higher absorption into the receptor fluid compared to the other replicates (Dixon's Q-test at 95% confidence level).

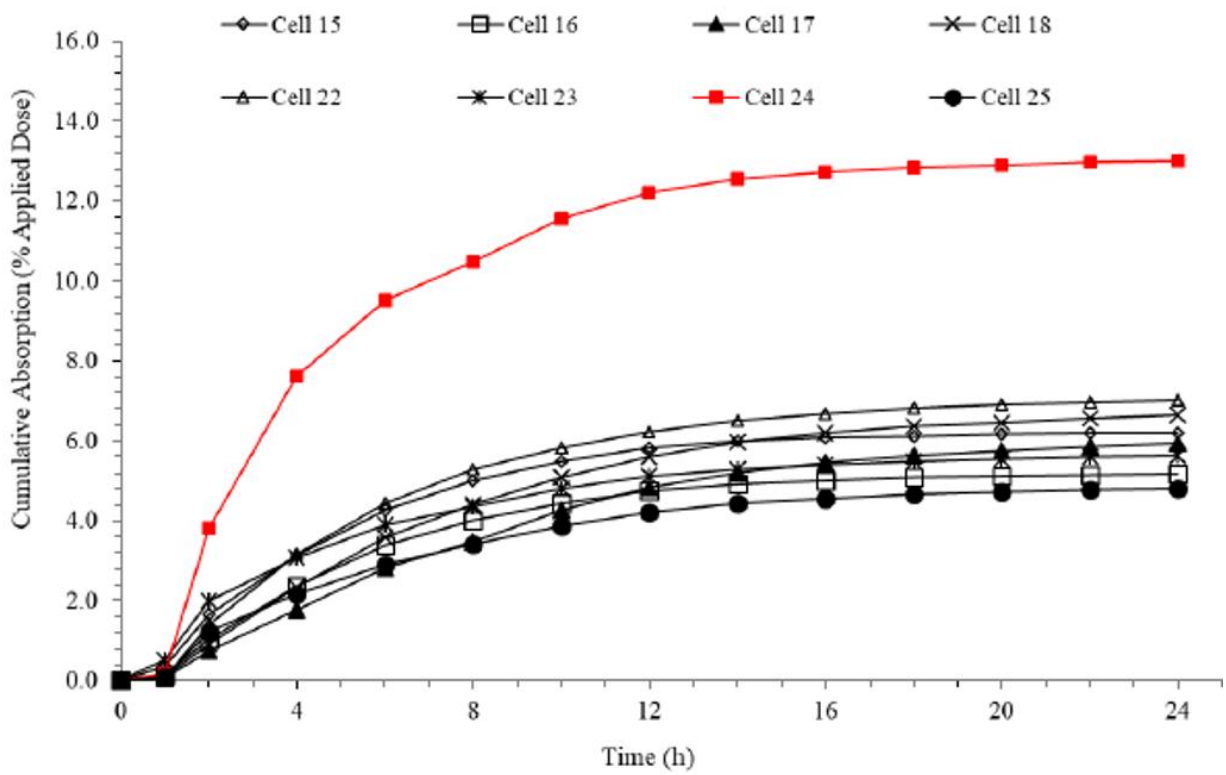


Figure 1: Individual absorption profiles for [^{14}C]PTZ-desthio (% of applied dose) in receptor fluid following topical application in the test preparation (0.328 g/L) to human split-thickness skin

However, zRMS considers that cell#24 should not be excluded from the calculation, due to statistical criteria only and requests recalculation of the dermal absorption value including cell#24.

The required mean total recovery rate of ≥ 95% was met for dilution with ~~99.69%~~ 100.14% of the applied dose. For the spray dilution tested more than 75 % of the absorption of prothioconazole-desthio in the receptor fluid over 24 hours occurred within half of the study duration (*i.e.* 12 hours) and the calculated t0.5 value is with ~~84.64~~ 85.52 over the threshold of 75. According to the EFSA guidance on dermal absorption (2017), the absorption is considered essentially complete within half the duration of the study and the amount in the lower stratum corneum is not taken into account. The calculated values are listed below in the summary table. To address variability between replicates, the multiplication factor k=~~0.92~~ 0,84 corresponding to the number of replicates with n=~~7~~ 8 was applied to the standard deviation and the value was added to the mean potentially absorbed dose as proposed in Chapter 5.3. "Variability within the results and outliers" of EFSA Guidance (2017). The calculation of dermal absorption values is carried out with the recommended calculation template provided by BfR and published as supporting information to current EFSA Guidance.

Details of study results and the evaluation are summarised in the Table A 13 below.

Table A 13: Results of dermal absorption of [^{14}C]prothioconazole-desthio in dilution of ADM.03502.F.1.A through human skin

~~Results and discussion~~

		~~Dilution~~	
-		~~(1:533)~~	
~~Target concentration [mg/mL]~~		~~0.328~~	
~~Target dose [µg/cm²]~~		~~3.28~~	
~~Recovery [%]~~		~~Mean~~	~~SD~~
~~Dislodgeable dose~~	-	-	

~~Skin wash after 8 hours~~	~~90.85~~	~~4.38~~
~~Skin associated dose~~		
~~Tape strips 1-2~~	~~0.63~~	~~0.59~~
~~Tape strips 3-x~~	~~1.10~~	~~0.66~~
~~Skin preparation~~	~~0.17~~	~~0.10~~
~~Absorbed dose~~		
~~Receptor fluid~~	~~6.80~~	~~2.61~~
~~Receptor chamber wash~~	~~0.04~~	~~0.02~~
~~Total recovery~~	~~99.69~~	~~3.49~~
~~LLC of t_0.5 absorption~~	~~84.64~~	~~3.79~~
~~Absorption complete?~~	~~Yes~~	
~~Measured absorption, if LLC of t_0.5<=75%~~	~~N/A~~	~~N/A~~
~~Measured absorption, if LLC of t_0.5>75%~~	~~7.02~~	~~2.64~~
~~Measured absorption corrected~~	~~6.12~~	~~0.85~~
~~Relevant absorption estimate~~	~~6.905~~	
~~**Final estimate (rounded)**~~	~~**6.9**~~	

~~N/A = Not applicable~~

Results and discussion

	Dilution 1 (1:533)	
Target concentration [mg/mL]	0.328	
Target dose [µg/cm^2]	3.28	
Recovery [%]	Mean	SD
Dislodgeable dose		
Skin wash after 8 hours	90.85	4.38
Donor chamber wash	0.55	0.13
Skin associated dose		
Tape strips 1-2	0.63	0.59
Tape strips 3-x	1.10	0.66
Skin preparation	0.17	0.10
Absorbed dose		
Receptor fluid	6.80	2.61
Receptor chamber wash	0.04	0.02
Total recovery	100.14	3.47
LLC of t_0.5 absorption	85.52	3.58
Absorption complete?	Yes	
Measured absorption, if LLC of t_0.5<=75%	N/A	N/A
Measured absorption, if LLC of t_0.5>75%	7.02	2.64
Measured absorption corrected	7.02	2.64
Relevant absorption estimate	9.235	
Final estimate (rounded)	**9.2**	

N/A = Not applicable

Conclusion

Under the experimental conditions and applying the criteria of the EFSA Guidance on dermal absorption (2017), the estimated dermal absorption values of prothioconazole-desthio is ~~6.9%~~ 9,2% for the intended spray dilution of 0.328 g/L (1:533)

Applying a dermal absorption rate for prothioconazole-desthio in ADM.03502.F.1.A of 6.9% for spray dilution diluted 1:533 and for concentrate, as a conservative approach, in non-dietary risk assessments is

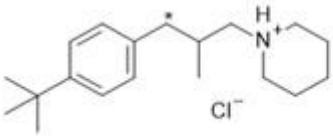
considered appropriate to use according to EFSA Guidance on Dermal Absorption (2017).

Comments of zRMS:	Dermal absorption study on fenpropidin has been conducted according to the OECD TG 428 revision 2004. For testing human split thickness skin has been used. Noted deviations from TG has no impact on final study outcome. The absorbed dose of fenpropidin from the ADM.03502.F.1.A spray dilution has been calculated based on EFSA GD 2017. Applying a dermal absorption rate for fenpropidin in formulation (ADM.03502.F.1.A) of 17% for the intended spray dilution of 0.469 g/L (1:533) is considered appropriate to use according to EFSA Guidance on Dermal Absorption (2017). In-use dilution is covered by the dilution tested in the study then no pro-rata correction is required. Results of the DA study and conclusions are adequate for risk assessment (NDE) Study accepted. zRMS: The dermal absorption study of fenpropidin and the additional volatility tests are conclusive and indicate that the missing portion should be considered unabsorbed and therefore has no effect on the dermal absorption value. Under the conditions of the study, the higher temperature of 32°C in the test system could also have relevantly increased the vapor pressure and volatility behaviour of fenpropidin.

A 2.10.2 **Study 2**

Reference:	KCP 7.3/02
Report	The i*n vitro* percutaneous absorption of radiolabelled Fenpropidin in a concentrate formulation and one in-use dilution of the Prothioconazole 175 g/L + Fenpropidin 250 g/L EC formulation (ADM.03502.F.1.A) through human split-thickness skin. Maas, W.J.M., 2021b, Report no.: 20275166; sponsor no.: 000107009
Guideline(s):	OECD 428 (2004), EU method B.45 (Reg (EC) 440/2008)
Deviations:	Yes Minor deviations not affecting the integrity of the results: Due to concern about (limited) volatility of the test item, three extra membranes were dosed. The donor chambers of the diffusion cells were occluded using a charcoal filter to trap test item possibly evaporating from the skin surface. The results obtained show that the missing % recovery was lost due to evaporation and should therefore not be considered as being absorbed.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	Not applicable

Materials and methods

Test material, (Lot/Batch No.)	Fenpropidin, 99.80% (644-019-01)
Radiolabeled test material (Lot/Batch No.) **Structure** (*position of radiolabel)	Fenpropidin hydrochloride, [propyl-3-^{14}C] HCL (CC-652/XXVI/57/B/1)  * denotes the position of C-14 Radiochemical purity: 98.31%
Formulation, type of formulation	Prothioconazole 175 g/L + Fenpropidin 250 g/L EC, ADM.03502.F.1.A, emulsifiable concentrate

Concentration(s) of active substance(s) in the formulation (measured), [g/L]	Prothioconazole: 175 (not determined) Fenpropidin: 250 (251 ± 1)
Concentration(s) of active substance(s) in the field dilution [g/L]	Prothioconazole: 0.328 (not determined) Fenpropidin: 0.469 (0.42 ± 1.8)
Dilution rate	533
Applied dose of fenpropidin [analytical µg/cm^2]	Concentrate: 2513 ± 0; Spray Dilution: 4.21 ± 0.37
Amount of spray dilutions applied on human skin [µL/cm^2]	10 (ca. 6.4 µL)
Skin sample source	Human skin derived from breast and abdomen of four female donors aged 16 to 55
Skin preparation used	Split-thickness skin membrane
Test system	Automated flow through diffusion cell apparatus (McGregor/Toner cells), exposure area: 0.64 cm^2, receptor chamber volume: 0.25 mL, flow rate: 1.5 mL/h, temperature: 32 ± 1°C
Exposure time	8 hours
Sampling duration	0 to 24 hours: 0 to 2 hours 1 hour intervals followed by 2 hours interval until 24 hours after application
Integrity of skin samples	Yes, was checked by measuring the absorption of tritiated water of all skin samples
No. of replicates per dose group	Human skin: 8 (2 samples from 4 donors)
Receptor fluid composition	Phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, ca 6%, w/v), sodium azide (ca 0.01%, w/v), streptomycin (ca 0.1 mg/mL) and penicillin (ca 100 units/mL), pH 7.4
Swabbing	Concentrated commercial hand wash soap was applied to the skin and the soap gently rubbed onto the skin with a tissue swab. The skin was then rinsed with 5 mL of a ca 2% (v/v) commercial soap solution. The soap solution was applied in aliquots and each aliquot was aspirated three times with a pipette. The skin was dried with a tissue swab. The process was repeated and the skin was dried with an additional tissue swab.
Mass balance samples	Receptor fluid samples, skin wash, tissue swab, pipette tip, receptor compartment wash, donor compartment wash, tape strips and digested skin
Analytical method	Liquid scintillation counting
Remark	Testing of additional replicates under occlusive conditions, in which the donor chamber was (semi-)occluded using a charcoal filter

Results and discussions

Solubility of fenpropidin in receptor fluid was determined and found to be 94.9 ± 1.5 µg/mL. The maximum absorption rate (flux) into the receptor fluid was 1.76 µg.equiv./cm^2/h (Cell 4, concentrate), which corresponds to (1.76 µg × 0.64)/(1 h×1.5 mL/h) = 0.75 µg/mL. Therefore, the solubility of the test item in the receptor fluid was demonstrated to be adequate and not rate-limiting to the absorption process. Furthermore, in the flow-through cells used, the volume of the receptor fluid in the receptor chamber beneath the skin was ca. 0.25 mL. At a flow rate of ca. 1.5 mL/h, this volume was replenished continuously (6 times per hour) such that the rate of diffusion into the receptor fluid did not become a rate-limiting step (*i.e.* sink conditions were maintained).

The radiochemical purity of a stock solution of [^{14}C]Fenpropidin was determined in duplicate upon arrival and compared to the authentic non-labelled Fenpropidin. The radiochemical purity was confirmed again shortly before dose preparation (single injection). The (mean) radiochemical purity was determined to be 96.1% in the initial stock solution (95.8% shortly before dose preparation). The radiochemical purity of [^{14}C]Fenpropidin in the test preparations was determined in duplicate following dose application. The mean radiochemical purity was >96% (concentrate: 96.8%; dilution: 96.1%). The results of the radiochemical

purity assessment confirmed that the test item was stable upon dosing of the test preparations.

A tritiated water barrier integrity test was performed. The integrity of all human skin samples was within the acceptability criteria (absorption ≤1.6% of applied dose of tritiated water).

A total of 8 samples of human split-thickness skin membranes obtained from 4 different donors were dosed topically with both test preparations. Overall, the absorption profiles of concentrate and dilution were comparable for all samples, respectively.

The required mean total recovery rate of ≥ 95% was met for the concentrate (98.2% of the applied dose) but not for the dilution (87.9% of the applied dose). For assessing if losses are derived from potential volatility of active substance an additional volatility test was carried out. Three additional replicates per test preparation were tested under occlusive conditions. In this test system the donor chamber was (semi-)occluded using a charcoal filter. The skin membranes kept in the occluded cells were analyzed as one fraction, i.e. no tape-stripping and no separation of exposed and non-exposed skin was performed. The purpose of these cells was to identify the amount of material lost to evaporation. The charcoal filters were extracted using tetrahydrofuran (THF) before analysis of a sub-sample of the extract by LSC. The results show that a mean of 0.12% and 2.61% of the applied dose was trapped in the charcoal filter on top of the donor compartment of the cells dosed with test preparation 1 (concentrate) or 2 (spray dilution), respectively. For test preparation 1, evaporation is minor and appeared not to play a major role in obtaining an adequate mass balance. For test preparation 2 (spray dilution), (semi-)occlusion did result in an adequate recovery (mean: 96.7 ± 3.2% of the applied dose). At the same time, for test preparation 2 (spray dilution), occlusion also resulted in a notably higher absorption into the receptor fluid (mean: 27.7 ± 2.8% of the applied dose) compared to non-occlusion in the major study (mean: 14.14 ± 2.73% of the applied dose, see Table A 16, below). As a result, the amount on the skin that was available to potentially evaporate was lower under occluded conditions, which explains why only about 2.6% is recovered in the filters and not ca. 10% (i.e. the missing mass balance under non-occluded conditions). Nevertheless, the results show that the missing recovery resulted from evaporative losses. As stated in the EFSA Guidance on dermal absorption (2017), 5.2 Recovery, p.13, “Losses that are considered to be from non-absorbed material will have no impact on the results.” Thus, the dermal absorption from test preparation 2 (spray dilution) does not need to be corrected for any losses.

Details of results of additional testing on volatility are presented in the tables below.

Table A 14: Distribution of Radioactivity (% Applied Dose) at 24 h After Dosing Following Topical Application of Test Preparation 1 (250 g/L) to Human Split-Thickness Skin under Occluded Conditions

Test preparation 1 (concentrate)	Cell Number and Donor Number				
Donor:	Cell 12 H20-15B	Cell 13 H21-01	Cell 14 H21-05	Mean	SD
8h Dislodgeable Dose	92.6	98.5	96.9	96.0	3.1
Filter (8 h + 24 h)	0.10	0.11	0.13	0.12	0.02
Donor Wash	0.02	0.02	0.11	0.05	0.05
Total Dislodgeable Dose	92.7	98.6	97.2	96.2	3.1
Skin [1]	0.05	0.07	0.29	0.14	0.13
Receptor Fluid	0.20	0.23	0.25	0.23	0.02
Receptor Wash	<0.002	0.003	0.004	0.003	0.001
Mass Balance	92.9	98.9	97.7	96.5	3.2

1 Skin was not tape-stripped and no separation of exposed and non-exposed skin was performed.
<: value below LoD

Table A 15: Distribution of Radioactivity (% Applied Dose) at 24 h After Dosing Following Topical Application of Test Preparation 2 (0.469 g/L) to Human Split-Thickness Skin under Occluded Conditions

Test preparation 2 (dilution)	Cell Number and Donor Number				
Donor:	Cell 26 H20-15B	Cell 27 H21-01	Cell 28 H21-05	Mean	SD
8h Dislodgeable Dose	59.4	69.4	61.6	63.5	5.2
Filter (8 h + 24 h)	3.42	3.07	1.33	2.61	1.12
Donor Wash	1.82	0.48	0.54	0.95	0.75
Total Dislodgeable Dose	64.6	72.9	63.5	67.0	5.1
Skin [1]	2.28	1.28	2.41	1.99	0.62
Receptor Fluid	28.0	24.7	30.3	27.7	2.8
Receptor Wash	0.08	0.04	0.06	0.06	0.02
Mass Balance	95.0	99.0	96.3	96.7	2.0

1 Skin was not tape-stripped and no separation of exposed and non-exposed skin was performed.
<: value below LoD

For test preparation 1 (concentrate), the distribution of radioactivity (% applied dose) showed that following the skin wash at 8 h post application, 97.3% of the applied dose was washed off, i.e. the 8 h dislodgeable dose. At 24 h post dose, a further 0.17% was recovered with the donor compartment wash. Therefore, the total dislodgeable dose was 97.5% of the applied dose. The total absorbed dose (0.39%) was the sum of the receptor fluid (0.38%) and the receptor wash (0.015%). The exposed skin contained 0.059% of the applied dose. Dermal delivery (0.45%) was the sum of the total absorbed dose and the exposed skin. The mass balance, total dislodgeable dose, total absorbed dose and dermal delivery were 2468, 2449, 9.87 and 11.3 µg equiv./cm^2, respectively.

For test preparation 2 (spray dilution), the distribution of radioactivity (% applied dose) showed that following the skin wash at 8 h post application, 68.5% of the applied dose was washed off, i.e. the 8 h dislodgeable dose. At 24 h post dose, a further 2.12% was recovered with the donor compartment wash. Therefore, the total dislodgeable dose was 70.6% of the applied dose. The total absorbed dose (14.2%) was the sum of the receptor fluid (14.1%) and the receptor wash (0.085%). The exposed skin contained 0.43% of the applied dose. Dermal delivery (14.6%) was the sum of the total absorbed dose and the exposed skin. The mass balance, total dislodgeable dose, total absorbed dose and dermal delivery were 3.70, 2.98, 0.60 and 0.62 µg equiv./cm^2, respectively.

For the concentrate tested less than 75 % of the absorption of fenpropidin in the receptor fluid over 24 hours occurred within half of the study duration (*i.e.* 12 hours) and the calculated t0.5 values is with 57.69 below the threshold of 75. According to the EFSA guidance on dermal absorption (2017), the absorption of fenpropidin in the concentrate is not essentially complete within half the duration of the study and the amount in the lower stratum corneum is considered as potentially absorbable and added to the absorbed dose. For the dilution more than 75 % of the absorption of fenpropidin in the receptor fluid over 24 hours occurred within half of the study duration (*i.e.* 12 hours) and the calculated t0.5 values is with 89.96 above the threshold of 75.

The calculated values are listed below in the summary table. To address variability between replicates, for the concentrate and the spray dilution the multiplication factor k=0.84 corresponding to the number of replicates with n=8 was applied to the standard deviation and the value was added to the mean potentially absorbed dose as proposed in Chapter 5.3. “Variability within the results and outliers” of EFSA Guidance (2017). The calculation of dermal absorption values is carried out with the recommended calculation template provided by BfR and published as supporting information to current EFSA Guidance.

Details of study results and the evaluation are summarised in the Table A 16 below.

Table A 16: Results of dermal absorption of [^{14}C]fenpropidin in ADM.03502.F.1.A through human skin

Results and discussion

	Concentrate		Dilution 1 (1:533)	
Target concentration [mg/mL]	250		0.469	
Target dose [µg/cm^2]	2500		4.69	
Mean actual applied dose [µg/cm^2]	2513		4.21	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 hours	97.31	0.81	68.54	7.15
Donor chamber wash	0.17	0.07	2.12	0.72
Skin associated dose				
Tape strips 1-2	0.19	0.10	1.14	0.38
Tape strips 3-x	0.11	0.06	1.50	0.87
Skin preparation	0.06	0.03	0.45	0.36
Absorbed dose				
Receptor fluid	0.38	0.18	14.14	2.73
Receptor chamber wash	0.02	0.01	0.09	0.08
Total recovery	98.23	0.75	87.97	4.54
LLC of t_0.5 absorption	57.69	7.80	89.96	2.98
Absorption complete?	No		Yes	
Measured absorption, if LLC of t_0.5<=75%	0.57	0.25	N/A	N/A
Measured absorption, if LLC of t_0.5>75%	N/A	N/A	14.67	2.74
Measured absorption corrected	0.57	0.25	14.67	2.74
Relevant absorption estimate	0.776		17.41	
Final estimate (rounded)	**0.78**		**17**	

N/A = Not applicable

Conclusion

By applying the criteria of the EFSA Guidance on dermal absorption (2017), the estimated dermal absorption values of fenpropidin are 0.78% and 17% for the concentrated product (250 g/L actual concentration) and the intended spray dilution of 0.469 g/L (1:533), respectively.

Applying a dermal absorption rate for fenpropidin in ADM.03502.F.1.A of 0.78% for the concentrate and 17% for the spray dilution in non-dietary risk assessments is considered appropriate to use according to EFSA Guidance on Dermal Absorption (2017).

A 2.11 Other/Special Studies

Not relevant.

Appendix 3 Exposure calculations

A 3.1 Operator, worker and resident exposure calculations (KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

A 3.1.1 Calculations for prothioconazole

Table A 17: Input parameters considered for the estimation of operator, worker and resident exposure to prothioconazole

Substance name	Prothioconazole	
Product name	ADM.03502.F.1.A	
Reference value non acutely toxic active substance (RVNAS)	0.2	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	100	L/ha
Maximum application rate of active substance	0.175	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	25.00%	
Dermal absorption of in-use dilution	70.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Substance name	Prothioconazole	
Product name	ADM.03502.F.1.A	
Reference value non acutely toxic active substance (RVNAS)	0.2	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	100	L/ha
Maximum application rate of active substance	0.0875	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	25.00%	
Dermal absorption of in-use dilution	70.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Table A 18: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to prothioconazole

Substance	Prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.175 kg a.s. /ha	Spray dilution = 1.75 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 25	Dermal for in use diluation = 70	Oral = 100	Inhalation = 100	
RVNAS	0.2 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.2018	% of RVNAS	100.91%
	Acute systemic exposure mg/kg bw/day		1.1518	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.1260	% of RVNAS	63.00%
	Acute systemic exposure mg/kg bw/day		0.5505	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.1531	% of RVNAS	76.56%
	Working clothing mg/kg bw/day	0.0172	% of RVNAS	8.58%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0329	% of RVNAS	16.44%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0019	% of RVNAS	0.96%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0207	% of RVNAS	10.34%
	All pathways (mean) mg/kg bw/day	0.0371	% of RVNAS	18.54%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0079	% of RVNAS	3.94%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0008	% of RVNAS	0.42%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0115	% of RVNAS	5.74%
	All pathways (mean) mg/kg bw/day	0.0137	% of RVNAS	6.87%

Substance	Prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0875 kg a.s. /ha	Spray dilution = 0.875 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 25	Dermal for in use diluation = 70	Oral = 100	Inhalation = 100	
RVNAS	0.2 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	
Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.1181	% of RVNAS	59.03%
	Acute systemic exposure mg/kg bw/day		0.8018	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0724	% of RVNAS	36.18%
	Acute systemic exposure mg/kg bw/day		0.3222	% of RVAAS	
Worker - Inspection, irrigation	Potential exposure mg/kg bw/day		0.0766	% of RVNAS	38.28%
	Working clothing mg/kg bw/day		0.0086	% of RVNAS	4.29%
	Working clothing and gloves mg/kg bw/day			% of RVNAS	
Resident - child	Spray drift (75th percentile) mg/kg bw/day		0.0164	% of RVNAS	8.22%
	Vapour (75th percentile) mg/kg bw/day		0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day		0.0010	% of RVNAS	0.48%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0103	% of RVNAS	5.17%
	All pathways (mean) mg/kg bw/day		0.0191	% of RVNAS	9.54%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day		0.0039	% of RVNAS	1.97%
	Vapour (75th percentile) mg/kg bw/day		0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day		0.0004	% of RVNAS	0.21%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0057	% of RVNAS	2.87%
	All pathways (mean) mg/kg bw/day		0.0070	% of RVNAS	3.49%

Table A 19: Screenshot of the summary table in the EFSA calculator for the estimation of operator exposure to prothioconazole considering gloves (during mixing and loading)

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.2018	% of RVNAS	100.91%
	Acute systemic exposure mg/kg bw/day		1.1518	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0191	% of RVNAS	9.55%
	Acute systemic exposure mg/kg bw/day		0.1563	% of RVAAS	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.1181	% of RVNAS	59.03%
	Acute systemic exposure mg/kg bw/day		0.8018	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0097	% of RVNAS	4.85%
	Acute systemic exposure mg/kg bw/day		0.0918	% of RVAAS	

Table A 20: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure to prothioconazole considering a buffer strip of 5 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0219	% of RVNAS	10.94%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0008	% of RVNAS	0.40%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0207	% of RVNAS	10.34%
	All pathways (mean) mg/kg bw/day	0.0302	% of RVNAS	15.12%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0040	% of RVNAS	1.99%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	0.17%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0115	% of RVNAS	5.74%
	All pathways (mean) mg/kg bw/day	0.0117	% of RVNAS	5.86%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0109	% of RVNAS	5.47%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	0.20%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0103	% of RVNAS	5.17%
	All pathways (mean) mg/kg bw/day	0.0157	% of RVNAS	7.83%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	1.00%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.09%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0057	% of RVNAS	2.87%
	All pathways (mean) mg/kg bw/day	0.0060	% of RVNAS	2.99%

Table A 21: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure to prothioconazole considering drift reduction nozzles and a buffer strip of 2-3 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0164	% of RVNAS	8.22%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	0.48%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0207	% of RVNAS	10.34%
	All pathways (mean) mg/kg bw/day	0.0273	% of RVNAS	13.66%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0039	% of RVNAS	1.97%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	0.21%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0115	% of RVNAS	5.74%
	All pathways (mean) mg/kg bw/day	0.0116	% of RVNAS	5.78%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0082	% of RVNAS	4.11%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	0.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0103	% of RVNAS	5.17%
	All pathways (mean) mg/kg bw/day	0.0142	% of RVNAS	7.10%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	0.98%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.10%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0057	% of RVNAS	2.87%
	All pathways (mean) mg/kg bw/day	0.0059	% of RVNAS	2.95%

A 3.1.2 Calculations for fenpropidin

Table A 22: Input parameters considered for the estimation of operator, worker and resident exposure to fenpropidin

Substance name	Fenpropidin	
Product name	ADM.03502.F.1.A	
Reference value non acutely toxic active substance (RVNAS)	0.02	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	100	L/ha
Maximum application rate of active substance	0.25	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.78%	
Dermal absorption of in-use dilution	17.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Table A 23: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to fenpropidin

Substance	Fenpropidin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0,25 kg a.s. /ha	Spray dilution = 2,5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 0,78	Dermal for in use diluation = 17	Oral = 100	Inhalation = 100	
RVNAS	0,02 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0158	% of RVNAS	78.78%
	Acute systemic exposure mg/kg bw/day		0.0941	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0102	% of RVNAS	50.95%
	Acute systemic exposure mg/kg bw/day		0.0599	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0531	% of RVNAS	265.63%
	Working clothing mg/kg bw/day	0.0060	% of RVNAS	29.75%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0115	% of RVNAS	57.25%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	5.35%
	Surface deposits (75th percentile) mg/kg bw/day	0.0008	% of RVNAS	4.11%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0072	% of RVNAS	35.86%
	All pathways (mean) mg/kg bw/day	0.0137	% of RVNAS	68.53%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0027	% of RVNAS	13.67%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.15%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	1.45%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0040	% of RVNAS	19.92%
	All pathways (mean) mg/kg bw/day	0.0049	% of RVNAS	24.59%

Table A 24: Screenshot of the summary table in the EFSA calculator for the estimation of operator exposure to fenpropidin, considering gloves (during mixing and loading)

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0158	% of RVNAS	78.78%
	Acute systemic exposure mg/kg bw/day		0.0941	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0058	% of RVNAS	29.00%
	Acute systemic exposure mg/kg bw/day		0.0436	% of RVAAS	

Table A 25: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure to fenpropidin considering a buffer strip of 5 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0076	% of RVNAS	38.11%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	5.35%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	1.69%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0072	% of RVNAS	35.86%
	All pathways (mean) mg/kg bw/day	0.0113	% of RVNAS	56.35%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0014	% of RVNAS	6.93%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.15%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.59%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0040	% of RVNAS	19.92%
	All pathways (mean) mg/kg bw/day	0.0042	% of RVNAS	21.08%

Table A 26: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure fenpropidin considering drift reduction nozzles and a buffer strip of 2-3 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0057	% of RVNAS	28.63%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	5.35%
	Surface deposits (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	2.05%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0072	% of RVNAS	35.86%
	All pathways (mean) mg/kg bw/day	0.0102	% of RVNAS	51.23%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0014	% of RVNAS	6.84%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.15%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.72%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0040	% of RVNAS	19.92%
	All pathways (mean) mg/kg bw/day	0.0042	% of RVNAS	20.81%

A 3.2 Calculations for prothioconazole-desthio

Table A 27: Input parameters considered for the estimation of operator, worker and resident exposure to prothioconazole-desthio

Substance name	Prothioconazole-desthio	
Product name	ADM.03502.F.1.A	
Reference value non acutely toxic active substance (RVNAS)	0.01	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	100	L/ha
Maximum application rate of active substance	0.159	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.00%	
Dermal absorption of in-use dilution	6.90%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Substance name	Prothioconazole-desthio	
Product name	ADM.03502.F.1.A	
Reference value non acutely toxic active substance (RVNAS)	0.01	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)		mg/kg bw/day
Crop type	Cereals	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	100	L/ha
Maximum application rate of active substance	0.079	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	9.20%	
Dermal absorption of in-use dilution	9.20%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Buffer strip	2-3	m
Number of applications	1	
Interval between multiple applications	365	days
Season (upward spraying orchards only)	not relevant	

Table A 28: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to prothioconazole-desthio

Substance	Prothioconazole-desthio	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.158725 kg a.s. /ha	Spray dilution = 1.58725 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 0	Dermal for in use diluation = 6.9	Oral = 100	Inhalation = 100	
RVNAS	0.01 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0023	% of RVNAS	23.09%
	Acute systemic exposure mg/kg bw/day		0.0167	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0016	% of RVNAS	15.73%
	Acute systemic exposure mg/kg bw/day		0.0128	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0137	% of RVNAS	136.90%
	Working clothing mg/kg bw/day	0.0015	% of RVNAS	15.33%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0030	% of RVNAS	29.72%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	2.88%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0018	% of RVNAS	18.48%
	All pathways (mean) mg/kg bw/day	0.0044	% of RVNAS	43.98%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0007	% of RVNAS	7.06%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.75%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	10.27%
	All pathways (mean) mg/kg bw/day	0.0014	% of RVNAS	14.40%

Substance	Prothioconazole-desthio	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0793 kg a.s. /ha	Spray dilution = 0.793 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 9.2	Dermal for in use diluation = 9.2	Oral = 100	Inhalation = 100	
RVNAS	0.01 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0378	% of RVNAS	377.82%
	Acute systemic exposure mg/kg bw/day		0.2592	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0230	% of RVNAS	230.11%
	Acute systemic exposure mg/kg bw/day		0.0927	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0091	% of RVNAS	91.20%
	Working clothing mg/kg bw/day	0.0010	% of RVNAS	10.21%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	19.74%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.71%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0012	% of RVNAS	12.31%
	All pathways (mean) mg/kg bw/day	0.0033	% of RVNAS	32.67%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	4.70%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.50%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0007	% of RVNAS	6.84%
	All pathways (mean) mg/kg bw/day	0.0010	% of RVNAS	10.35%

Table A 29: Screenshot of the summary table in the EFSA calculator for the estimation of operator exposure to prothioconazole-desthio, considering gloves (during mixing and loading)

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0023	% of RVNAS	23.09%
	Acute systemic exposure mg/kg bw/day		0.0167	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0016	% of RVNAS	15.73%
	Acute systemic exposure mg/kg bw/day		0.0128	% of RVAAS	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0378	% of RVNAS	377.82%
	Acute systemic exposure mg/kg bw/day		0.2592	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0016	% of RVNAS	16.35%
	Acute systemic exposure mg/kg bw/day		0.0142	% of RVAAS	

Table A 30: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure to prothioconazole-desthio considering a buffer strip of 5 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	19.80%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	1.18%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0018	% of RVNAS	18.48%
	All pathways (mean) mg/kg bw/day	0.0037	% of RVNAS	37.36%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	3.59%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.31%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	10.27%
	All pathways (mean) mg/kg bw/day	0.0013	% of RVNAS	12.59%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0013	% of RVNAS	13.15%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.70%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0012	% of RVNAS	12.31%
	All pathways (mean) mg/kg bw/day	0.0028	% of RVNAS	28.35%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.38%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.20%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0007	% of RVNAS	6.84%
	All pathways (mean) mg/kg bw/day	0.0009	% of RVNAS	9.15%

Table A 31: Screenshot of the summary table in the EFSA calculator for the estimation of resident exposure to prothioconazole-desthio considering drift reduction nozzles and a buffer strip of 2-3 m

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0015	% of RVNAS	14.86%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	1.44%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0018	% of RVNAS	18.48%
	All pathways (mean) mg/kg bw/day	0.0035	% of RVNAS	34.71%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	3.53%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.37%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	10.27%
	All pathways (mean) mg/kg bw/day	0.0012	% of RVNAS	12.44%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	9.87%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.85%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0012	% of RVNAS	12.31%
	All pathways (mean) mg/kg bw/day	0.0027	% of RVNAS	26.59%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.35%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.25%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0007	% of RVNAS	6.84%
	All pathways (mean) mg/kg bw/day	0.0009	% of RVNAS	9.05%

A 3.3 Combined exposure calculations for fenpropidin, prothioconazole and prothioconazole-desthio

Please refer to Chapter 6.6.5.

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)

A 4.1 Detailed evaluation of fenpropidin in air (published data)

Experimental data on the concentration of fenpropidin in air as a result of evaporation after spray application are available from published data (DEFRA Project PS2023, 2010 and Bedos *et. al.*, 2010) which are summarised as supportive information.

A 4.1.1 DEFRA Project PS2023, 2010

Reference:	KCP 7.2.2.2/01
Report	Development of air sampling methodology in support of determining risk of bystander and resident exposure to pesticides SID 5 (Rev. 07/10), DEFRA Project PS2023
Guideline(s):	Not applicable
Deviations:	Not applicable
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

Material and methods

Test item:	750 g fenpropidin/L, EC formulation applied as tank mix with an epoxiconazole SC product
Application rate (fenpropidin):	750 g a.s./ha
Crop:	Grassland

In a field study carried out in 2009 in North Yorkshire, UK, a tank mix[8] also containing Alpha Fenpropidin formulated as an EC with 750 g a.s./L was applied at a rate of 750 g fenpropidin/ha to grass land of 0.6 – 0.7 m height at time of treatment. The spray volume was 200 L/ha. The application was achieved using a tractor mounted boom (20 m width) sprayer and the timing was in October.

Air sampling pumps connected via Tygon tubing to absorbent tubes containing XAD-2 and polyurethane foam (PUF) fitted with a glass fibre filter were used to monitor the air concentrations around the treated area. Air sampling media were set at a sampling height of 0.7 m above the ground.

Sampling commenced after the application was completed, such that the sprayer was 4 spray passes (80 m) downwind of the sampling station to avoid any contamination by particulate spray drift. The sampling station was positioned in the centre of a 10 m × 10 m unsprayed

block, to give a minimum of 5 m between the sprayed area and the sampling station. Sampling periods were gradually extended following the application from 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 12 hours up to a maximum of 24 hour periods from days 2 to 21 after application. The results for fenpropidin are summarised in Table A 32.

The analytical method involved solvent elution of active substances from the sample tubes followed by determination with gas chromatography tandem quadrupole mass spectrometry (GC-MS/MS). For details of the method validation please refer to dRR part B5, Appendix 2, A.2.1.1.

[8] Tank mix of an epoxiconazole SC and a fenpropidin EC formulation

Results and discussion

Table A 32: Summary of air concentration measurements for fenpropidin

Sample time after application	Concentration in air (ng a.s./m^3)	Maximum temperature (°C)	Maximum wind speed (m/sec)
30 minutes	11127	14.7	2.5
1 hour	9394		
2 hours	8077		
4 hours	2040		
6 hours	285		
8 hours	249		
12 hours	229		
24 hours	95.7	15.1	5.2
36 hours	72.4		
48 hours	13.0	15.7	6.9
3 days	7.8	14.7	3.4
4 days	20.3	15.6	2.0
5 days	7.47	15.6	2.4
6 days	5.43	18.5	3.3
7 days	9.10	13.2	1.8
8 days	0.41	15.0	2.9
9 days	1.70	14.0	3.2
10 days	1.59		

For the resident exposure assessment with the EFSA calculator, the time-weighted average (TWA) air concentration during the first 24 hours after application is of relevance. For this period, the measured data are the following:

Table A 33: Field trial data with concentrations in air of fenpropidin during 24 h after application

Sample time after application	Concentration in air (ng/m^3)	Sampling duration (h)	Portion per 24 h (ng/m^3)
0.5	11127	0.5	231.81
1	9394	0.5	195.71
2	8077	1	336.54
4	2040	2	170.00
6	285	2	23.75
8	249	2	20.75
12	229	4	38.17
24	95.7	12	47.85
		24 h TWA concentration	**1064.58**

Laboratory studies with the sorbent tubes and a range of pesticides confirmed that there was no breakthrough of pesticide through the sampling media of the sorbent tubes. The solvent elution method was found to result in good recovery of the pesticide compounds and stability of the pesticide compounds was demonstrated over a 21-day period in storage.

Detectable residues of pesticide vapour were found up to 10 days after treatment (DAT), with a peak concentration for fenpropidin within an hour of treatment. The highest 24-hour time weighted average (TWA) air concentration of fenpropidin occurred within the first 24 hours post application and was recorded at 1.06 $\mu g/m^3$ (Table A 33).

Conclusion

After application of an EC formulation with fenpropidin at a rate of 750 g/ha to grassland, the 24-hour time weighted average (TWA) air concentration was determined at 1.06 $\mu g/m^3$. The highest 24 h TWA air concentration occurred within the first 24 hours post application. Subsequent 24-hour air concentrations declined thereafter, suggesting the use of this TWA value to assess exposure for residents is precautionary.

Fenpropidin in ADM.03502.F.1.A is applied also as EC formulation and at a 3.75-fold lower rate (250 g/ha) than in the DEFRA field trial. A similar water volume (minimum of 100 L/ha according to intended GAP *vs*. 100 L/h in the field trial) was applied, and application to cereals at BBCH 31-61 or grassland of 0.6 to 0.7 m height is comparable with regard to volatilisation. Thus, extrapolation of the results of the field study to the intended GAP use of ADM.03502.F.1.A is considered feasible. Based on this, an **air concentration of 1.06 $\mu g/m^3$/24 h TWA value for fenpropidin** can be regarded as conservative estimate since an even 3.75-fold lower value can be expected after application of ADM.03502.F.1.A.

A 4.1.2 **Bedos et. al. (2010)**

Further data on the concentration of fenpropidin in air as a result of evaporation after spray application were measured in a field trial in Northern France (Paris Basin) in which fenpropidin was sprayed to winter wheat at growth stage BBCH 30-31:

Reference:	**KCP 7.2.2.2/02**
Report	Fungicide Volatilization Measurements: Inverse Modeling, Role of Vapor Pressure, and State of Foliar Residue, Bedos, C.; Rouseaue-Djabri, M.-F.; Loubet, B.; Durand, B.; Flura, D.; Briand, O. and Barriuso, E. (2010), Environ. Sci Technol. 44: 2522-2528
Guideline(s):	Not applicable
Deviations:	Not applicable
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

Material and methods

Test item:	Fenpropidin EC formulation (Gardian supplied by Syngenta)
Application rate (fenpropidin):	450 g a.s./ha
Crop:	Winter wheat, growth stage BBCH 30-31 at time of application

In the field study carried out in 2006 measurements of fenpropidin and chlorothalonil volatilisation on a wheat field using the aerodynamic gradient (AG) method and an inverse dispersion modelling approach was reported. Measured application dose, crop interception, plant foliage residue, upwind concentration and meteorological conditions necessary to run volatilisation models were also reported.

The trial site was located in the Paris Basin (Norther France) and the field was cropped with winter wheat sown on 28th October 2005. The wheat was at growth stage BBCH 30-31 at time of application which was done in the morning of May 4, 2006 (DOY 124; DOY = day-of-year).

Fenpropidin formulated as EC product was applied by tractor mounted spray application (tractor velocity of 7 to 7.5 km h^{-1}, median diameter of the spray droplets 268 µm) at around 1 m above the crop canopy. The application rate was 450 g a.s./ha and the spray volume was 150 L/ha. After application, the sampling station was immediately positioned in the centre of the field to optimise fetch conditions.

Weather conditions during the two first days after application were predominantly sunny, without rainfall, with maximum air temperature at 1.5 m above the crop of about 24 °C around noon on day 1 and 19 °C on day 2 after application.

Air sampling tubes were set up at four heights (0.68, 0.88, 1.23 and 1.98 m above the ground). Sampling periods were gradually extended following the application from days 1 to 6 after application. The pesticide concentrations in the air were estimated by pumping ambient air through stainless steel tubes (L110 × ID 4 mm) fixed on the air sampling mast and filled with Tenax TA (250 mg, Supelco). The air flow rate was driven by pumps (HX1 6902, Piot & Tirouflet-France). The air volume sampled was measured with volumetric controllers (Gallius, Schlomberger). Preliminary tests showed a good stability of the flow rate for all tubes (average 1.29 L/149 min, CV 12 %, n=131). Because it was not possible to carry out multiple analysis of the samples (trapped pesticides being extracted by thermal desorption which destroys the sample during the analysis), a reference tube was set up 0.88 m above the soil to select the best analysis range for the other samples. In addition, when volatilisation was expected to be high (for the first sampling periods), a second tube was placed in series behind the reference tube to control breakthrough. The trapping efficiency of Tenax appeared to be satisfactory for chlorothalonil and fenpropidin as chlorothalonil was never detected, and if fenpropidin could be detected, it was in very small quantities compared to those in the first tube.

Pesticides trapped in Tenax tubes were extracted on a thermal desorption unit (ACEM 900, Dynatherm inc.) and analysed by GC/MS (VARIAN, 3800/Saturn 2000).

Results and discussion

Just after application, concentrations of fenpropidin in the air at 0.68 m above the soil were about 1.33 µg/m^3. Concentrations decreased rapidly. From day 2 to day 4 after application, air was sampled at only one level (1.23 m) over 12 h sampling periods. Even with a longer sampling period, the fenpropidin concentration could not be quantified. During the period when vertical gradients of concentrations were measured, a typical gradient of emission was observed for fenpropidin and chlorothalonil (Figure 2).

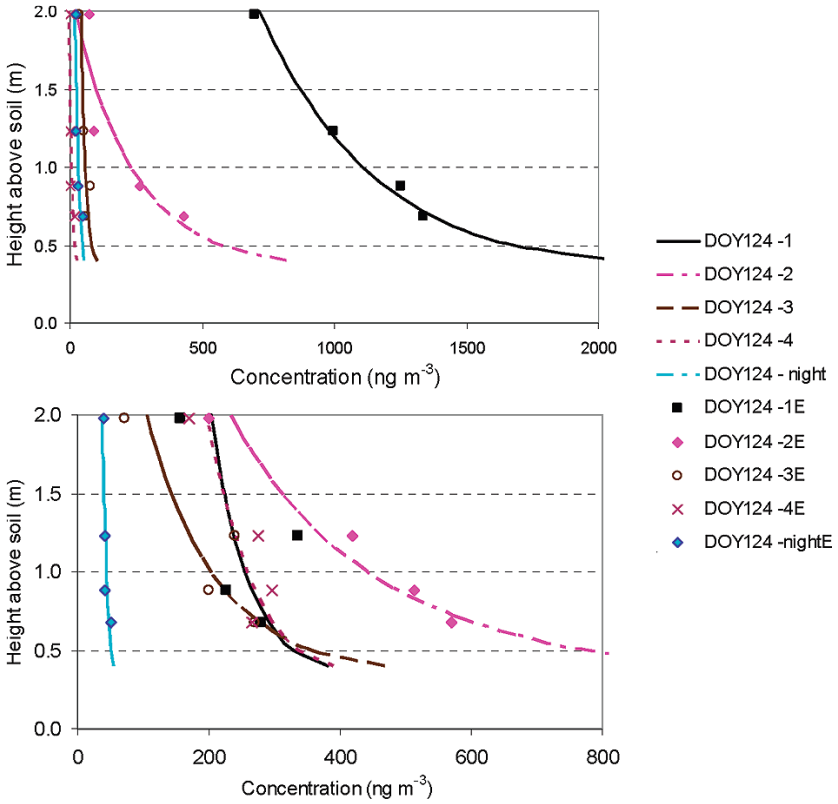


Figure 2: Vertical profiles of pesticide concentrations in the air above the field on day 1 (ng/m^3). Concentrations of fenpropidin in the top, chlorothalonil in the bottom. Symbols represent measured concentrations and lines represent the interpolation obtained given aerodynamic gradient method calculation.

Conclusion

In the field trial of Bedos *et al.* 2010, the measured concentration in air of fenpropidin was 1.33 µg/m^3 in 0.68 m height just after application of 450 g fenpropidin/ha. Fenpropidin concentrations in air decreased rapidly to level below 0.1 µg/m^3 within the first 12 hours after application.

Fenpropidin in ADM.03502.F.1.A is applied also as EC formulation and at a 1.8-fold lower rate (250 g/ha) than in the field trial of Bedos *et al.* 2010. The same water volume range (minimum of 100 L/ha according to intended GAP; 200 L/ha in the field trial) was applied, and application was done to cereals, the same crop as for which authorisation of ADM.03502.F.1.A is applied for. Thus, extrapolation of the field study results obtained in cereals is considered feasible. The initial measured air concentration of 1.33 µg/m^3 followed by a rapid decrease to negligible levels 12 hours after application indicates an **24 h time weighted average air concentration below 0.7 µg/m^3** which can still be regarded as conservative value after the use of ADM.03502.F.1.A according to the critical GAP.