REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: ADM.03500.F.2.B
(alternative codes: ADM.3500.F.2.B; MCW-2075)

Product name(s): see part A

Chemical active substance:

Prothioconazole, 250 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorisation)

Applicant: Country organisation / representative
as specified in Part A

Submission date: June 2021, updated November 2022

MS Finalisation date: November 2022 (initial Core Assessment)

March 2023 (final Core Assessment)

Version history

When	What
2021/06	Version 1 Applicant
November 2022	Applicant's update
November 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~~.
March 2023	Final report (Core Assessment updated following the commenting period) Additional information/assessments included by the zRMS in the report in response to comments recieved 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.03500.F.2.B. Under Article 59, Regulation 1107/2009/EC, on behalf of the Sponsor Company the applicant claims data protection for the studies conducted with ADM.03500.F.2.B. 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The summaries and evaluations contained in this document may be based on unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory authority that prepared it.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authorities should not grant, amend, or renew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this document unless they have received the data on which the summaries and evaluation are based, either –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:

1) This dossier has been prepared to support registration of ADM.03500.F.2.B/ SORATEL 250 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 SORATEL 250 EC (developmental code ADM.03500.F.2.B), an emulsifiable concentration (EC) formulation containing prothioconazole 250 g/L. ADM.03500.F.2.B is a fungicide intended to be used on cereals and oilseed rape (GAP details see 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 with regard to the formulation studies. Therefore, relevant data on the plant protection product ADM.03500.F.2.B had to be generated for authorization purposes.
2) zRMS (the Reviewer) analyzed all available data regarding the hazard classification based on ATEmix, composition-relevant ingredients, *in vitro* and *in vivo* studies. The Reviewer noticed several differences between outcomes of discussed assessments, thus considering expert judgement and fact that Reg. 1272/2008 clearly indicated priority of the *in vivo* studies, ZRMS decided to conclude hazard classification based on *in vivo* studies as most valuable source of information.

NOTE:
Table below was initially provided as part of the Article 33 application for ADM.03500.F.2.B submitted in Central zone in July 2021 (justifications for new studies (Article 33.3c)).
Applicant, in response to the ZRMS request regarding the availability of reports from existing *in vivo* studies, updated the information contained in the table below. Amended text in the November 2022 version is highlighted in grey). Also Applicant clarified that all *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
KCP 7.1.1/01	xxxxxxxxxx (2019a) Acute oral toxicity – Up-and Down procedure in rats; Report no.: 51286; sponsor no.: 000102245; xxxxxxxxxx, GLP, Unpublished	Data relevant to ADM.03500.F.2.B 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.03500.F.2.B.
KCP 7.1.2/01	xxxxxxxxxx (2019) ADM.3500.F.2.B: Acute dermal toxicity – fixed dose procedure in rats. Report no.: 51287; sponsor no.: 000102246 xxxxxxxxx, USA, GLP, Unpublished	Data relevant to ADM.03500.F.2.B and required for classification and labelling Study was submitted following request from ZRMS.
KCP 7.1.3/01	xxxxxxxxxx (2019b) ADM.3500.F.2.B: Acute inhalation toxicity in rats; Report no.: 51288; sponsor no.: 000102247; xxxxxxxxxxx, Dayton, NJ, USA; GLP; Unpublished	Data relevant to ADM.03500.F.2.B and required for classification and labelling since the classification and labelling cannot be reliable predicted based on the properties of the individual components in ADM.03500.F.2.B. Regulatory authorities outside of the EU, also request data for classification purposes.
KCP 7.1.4/01	xxxxxxxxxx (2019) ADM.3500.F.2.B: Primary skin irritation in rabbits. Report no.: 51290; sponsor no.: 000102248 xxxxxxxxxx, Dayton, NJ, USA; GLP; Unpublished	Data relevant to ADM.03500.F.2.B and required for classification and labelling Study was submitted following request from ZRMS.
KCP 7.1.5/01	xxxxxxxxxx (2019) ADM.3500.F.2.B: Primary eye irritation in rabbits. Report no.: 51289; sponsor no.: 000102250 xxxxxxxxxxx, Dayton, NJ, USA; GLP Unpublished	Data relevant to ADM.03500.F.2.B and required for classification and labelling Study was submitted following request from ZRMS.
KCP 7.1.6/01	xxxxxxxxxx (2019f) ADM.3500.F.2.B: Local lymph node assay	Data relevant to ADM.03500.F.2.B and required for classification and labelling since results of the study

	(LLNA) in mice; Report no.: 51291; sponsor no.: 000102249; xxxxxxxxxx, Dayton, NJ, USA; GLP; Unpublished	deviates from predicted classification based on the properties of the individual components in ADM.03500.F.2.B.

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

- KCP 7.1.4/01 xxxxxxxxxxx., 2019 (Skin irritation, Reconstructed human epidermis EpiDermTM (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 based on *in vivo* study.
- KCP 7.1.5/01 Regarding *in vitro* study xxxxxxxxxxx., 2019 (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.

Regarding studies on acute inhalation toxicity ZRMS decided as follow:

- KCP 7.1.3/01 xxxxxxxxx (2019b) ADM.3500.F.2.B: Acute inhalation toxicity in rats and assessment based ATEmix/additivity formula and components content gave the similar outcome however significant percentage of the mixture consists of ingredients of unknown acute inhalation toxicity (refer Part C), the available data are not considered sufficient to justify classification of the product for acute inhalation toxicity applying the calculation method. Thus, the relying on the results of an acute inhalation toxicity study is considered justified for adequate classification of the product ZRMS decided to conclude assessment in this hazard category for the ADM.03500.F.2.B based on *in vivo* study Xxxxxxxxxxx (2019b).

NDE assessment for operator, workers and B&R exposure to the PTZ and PTZ-desthio considering all critical use(s) and all tasks, identify safe use of the product ADM.03500.F.2.B/Soratel 250EC
Based on the results of the acute toxicity and non-dietary risk assessments conducted for ADM.03500.F.2.B/ SORATEL 250 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 mixing/loading and application.

Additional NDE estimation taking into account a conversion rate of 50% of prothioconazole to prothioconazole - desthio reflecting cMS comments has been added.

Note: precautionary measures based on classification & labelling:
Due to the classification of the product with H317 and H319, 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.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on ADM.03500.F.2.B*

Product name and code	ADM.03500.F.2.B
Formulation type	Emulsifiable concentrate [Code: EC]
Active substance(s) (incl. content)	Prothioconazole; 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.03500.F.2.B 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 according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	Acute Tox. 4 Eye Irrit. 2 Skin Sens. 1B
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS07
Signal word:	Warning
Hazard statement(s):	H302 Harmful if swallowed H317 May cause an allergic reaction H319 Causes serious eye irritation H332 Harmful if inhaled
Precautionary statement(s):	P102 Keep out of reach of children P261 Avoid breathing spray P270 Do not eat, drink or smoke when using this product P280 Wear protective gloves/protective clothing/eye protection/face protection P302 + P352 IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower P305 + P 351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rising P304 + P340 IF INHALED: Remove person to fresh air and keep comfortable for breathing. P501 Dispose of contents/container to an approved waste disposal plant
Additional labelling phrases:	To avoid risks to human health 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]

*Additional hazard classification (acute inhalation toxicity) has been added to reflects cMS comments and discussion regarding outcome of the Acute inhalation toxicity, rat (OECD 403) study, Xxxxxxxxxxx, 2019b

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for ADM.03500.F.2.B

	Result	PPE / Risk mitigation measures
Operators	Acceptable	**Results of risk assessment:** Operator wearing protective gloves during mixing and loading and wearing workwear covering arms, body and legs during mixing/loading and application* ~~Operator wearing workwear covering arms, body and legs during mixing/loading and application.~~ **Precautionary measures based on classification & labelling:** Due to the classification of the product with H317 and H319, protective gloves, protective clothing and eye protection/face protection should be worn when handling the product.
Workers	Acceptable	Workwear covering arms, body and legs
Bystanders	Acceptable	None
Residents	Acceptable	None

*Adjusted RMM has been added to reflects cMS comments and discussion regarding NDE outcome assuming 50% conversion rate PTZ to PTZ-desthio.

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 *Additional hazard classification (acute inhalation toxicity) has been added to reflects cMS comments and discussion regarding outcome of the Acute inhalation toxicity, rat (OECD 403) study, Xxxxxxxxxxx, 2019b

Table 6.1-3 are applied. Due to the classification of the product with H317 as well as with H319, 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.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, bystander or resident exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha** **a) per use** **b) per crop/ season**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
1-4, 6-9, 11-15, 17-21, 28-31, 33-36, 38-40, 42-43, 45-46, 52-54, 169	**Cereals** [Winter and spring barley (BBCH 30-65 spring), winter and spring wheat (BBCH 30-69 spring), oats (BBCH 30-65 spring), rye (BBCH 30-65 spring), triticale (BBCH 30-69 spring)]	F	Foliar spraying, overall, LCTM	1; 1	a) 0.200 b) 0.200	100 - 400	-	Operators, workers, bystanders and residents [EFSA calculator]				

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

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

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

Explanation for column 10 "Acceptability of exposure assessment"

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

Data gaps

Noticed data gaps are:

- None.

6.2 Toxicological Information on Active Substance(s)

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

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

	Prothioconazole
Common Name	Prothioconazole
CAS-No.	178928-70-6
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	None
Additional C&L proposal	H317 ~~None~~
Agreed EU endpoints	
AOEL systemic	0.2 mg/kg bw/d
AOEL systemic desthio- prothioconazole (JAU 6476-desthio)*	0.01 mg/kg bw/d
Reference	EFSA Scientific Report (2007) 106, 1-98
Conditions to take into account/critical areas of concern with regard to toxicology	
EFSA Scientific Report (2007) 106, 1-98	The metabolite prothioconazole-desthio is 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."

Evaluation meeting (24-26/04/2007): the impurity JAU-(xxxxxx), shown to be a skin sensitizer, is increased above the trigger value for classification in the technical specification of the large scale production. In the absence of a new skin sensitization test for the new technical specification, the classification (R43) H317 is proposed. For details refer ***EFSA Scientific Report* **(2007) 106, 1-98, Conclusion on the peer review of prothioconazole.**

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for ADM.03500.F.2.B 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.
Further details are provided in Part C.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for ADM.03500.F.2.B – 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, rat (OECD 425)	LD_{50} 1030 mg/kg bw (approx. 95% confidence interval: 550 – 1750 mg/kg bw)[1]	See table 6.3-2 See ZRMS detailed discussion in the preface to the dRR	Acute Tox. 4 H302 "Harmful if swallowed"	KCP 7.1.1/01 xxxxxxxxx 2019a
Acute dermal toxicity, rat (Calculated acc. to Reg. 1272/2008)	~~n.a.~~ None of the ingredients of ADM.03500.F.2.B is classified as acutely toxic via dermal route and needs to be considered in the calculation.	No See ZRMS detailed discussion in the preface to the dRR	None	Refer to Part C
Acute inhalation toxicity, rat (OECD 403)	LC_{50} ~~>~~ < 5 mg/L (calculated)[2]	See table 6.3-2 See ZRMS detailed discussion in the preface to the dRR See additional consideration below the table.	Acute Tox. 4 H332 Harmful if inhaled [#] ~~None~~	KCP 7.1.3/01 xxxxxxxxx. 2019b
Skin irritation, Reconstructed human epidermis EpiDerm™ (OECD 439)[6]	Irritant	No See detailed discussion below table	No adequate data for classification	KCP 7.1.4/01 xxxxxxxxxxx., 2019
Skin irritation, rabbit (Alternative approach acc. to Reg. 1272/2008)	~~Non-irritant~~[3] Irritant	No	Skin Irritant Cat 1B H314 "Causes severe skin burns and eye damage"	Refer to Part C
Eye irritation, BCOP assay, isolated corneas of bovine eyes (OECD 437)[7]	No prediction can be made	No See detailed discussion below table	No adequate data for classification	KCP 7.1.5/01 xxxxxxxxx., 2019
Eye irritation, rabbit (Alternative approach acc. to Reg. 1272/2008))	Irritant[4]	No	Eye Irritation Cat. 1 H318 "Causes serious eye damage"	Refer to part C
Skin sensitisation, mouse (OECD 429, LLNA)	Sensitising[5]	See table 6.3-2 See ZRMS detailed discussion in the preface to the dRR	Skin Sens. 1B H317 "May cause an allergic skin reaction"	KCP 7.1.6/01 xxxxxxxxx 2019c
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} below 2000 mg/kg bw, this study is 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.

[2] Acute 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 5.02 mg/L, with confidence interval of 4.24 – 5.95 mg/L calculated by Probit analysis based on the study results. For this reason, the study is included as part of this application.

[#]Following discussion has been accepted by the zRMS as base for adjusted hazard classification:

1) (..) It is recognised that the calculated LC_{50} is slightly above 5 mg/L (5.02 mg/L) based on the statistical Probit analysis. However, no justification or explanation is given why 7.0 mg/L would correspond to a mortality rate of 100%. In case this assumed

number would be slightly different, the statistically calculated LC_{50} might be lower than 5.02 mg/L and therefore classification would be warranted. (..)
2) (..) According to the OECD TG 403, a Probit analysis should be conducted if multiple concentrations and/or multiple durations of exposure have been assessed in the study (C x t protocol). However, this is not the case, as only two concentrations have been used. Consequently, suitable data to conclude on dose-response is lacking. Assuming a simple linear correlation, the estimated LC_{50} is lower than 5 mg/L (as it was done in the dRR/study description: it was predicted that 10/10 animals would be dead at 7 mg/L, which is based on linear extrapolation). Thus, the product should be classified as Acute Tox 4, H332(..).
[3] Skin irritation - Consideration of the content and the classification of the individual components in ADM.03500.F.2.B would lead to a classification with H314.
[4] Eye irritation - Consideration of the content and the classification of the individual components in ADM.03500.F.2.B would lead to a classification with H318, but this is already considered by H314" Causes severe skin burns and eye damage" and does therefore not appear as hazard statement in the label.
[5] Skin Sensitisation - This 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 results show the formulation to be a sensitiser, despite none of the individual ingredients being classified as such, 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.
[6] 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 based on composition and using the criteria given in 1272/2008.
[7] ZRMS for this endpoint (eye corrosion/irritation) decided to take into account for hazard assessment predictions for eye corrosion/irritation based on in vivo study . Outcome of this study gave more sevier This approach is supported by following 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.
Based on the eye irritation of the individual components, estimation trigger classification H318. Composition and calculation details are provided in dRR Part C is relevant and sufficient for hazard evaluation.

Table 6.3-2: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for ADM.03500.F.2.B – 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 425)	LD_{50}: 1030 mg/kg bw[1] (approx. 95% confidence interval: 550 – 1750 mg/kg bw)	Yes	Acute Tox. 4 H302 "Harmful if swallowed"	KCP 7.1.1/01 Xxxxxxxxxx, 2019a
Acute dermal toxicity, rat (OECD 402)	LD_{50} >2000 mg/kg bw[2]	Yes	None	~~Available on request~~ KCP 7.1.2/01 xxxxxxxxx (2019) Already existing study has been included into consideration on ZRMS request
Acute inhalation toxicity, rat (OECD 403)	LC_{50} ~~>~~ < 5 mg/L[3]	Yes See additional consideration below the table.	Acute Tox. 4 H332 Harmful if inhaled [#] ~~None~~	KCP 7.1.3/01 Xxxxxxxxxx, 2019b
Skin irritation, rabbit (OECD 404)	Non-irritant[4]	Yes	None	~~Available on request~~ KCP 7.1.4/01 xxxxxxxxx (2019) Already existing study has been included into consideration on ZRMS request
Eye irritation, rabbit (OECD 405)	Irritant[5]	Yes	Eye Irritation Cat. 2 H319 "Causes serious eye irritation"	~~Available on request~~ KCP 7.1.5/01 xxxxxxxxx (2019) Already existing study has been included into consideration on ZRMS request
Skin sensitisation, mouse (OECD 429, LLNA)	Sensitising[6]	Yes	Skin Sens. 1B H317 "May cause an allergic skin reaction"	KCP 7.1.6/01 xxxxxxxxx M., 2019c
Supplementary studies for combinations of plant protection products	No data – not required			

[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 results show the formulation to result in a LD_{50} below 2000 mg/kg bw, this study is 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.

[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. Under the experimental conditions, the dermal LD_{50} of ADM.03500.F.2.B is higher than 2000 mg/kg bw in rats, which does not require a classification according to Regulation (EC) No. 1272/2008. The classification based on experimental data is in line with the alternative approach and the study is not considered as "adverse data" as outlined in Article 56 of Reg (EC) No. 1107/2009 and has not been presented as part of this application into the EU, although the study report is available upon request.

Note: ZRMS: Already existing study has been included into current consideration on ZRMS request.

[#]Following discussion has been accepted by the zRMS as base for adjusted hazard classification:

1) (..) It is recognised that the calculated LC_{50} is slightly above 5 mg/L (5.02 mg/L) based on the statistical Probit analysis. However, no justification or explanation is given why 7.0 mg/L would correspond to a mortality rate of 100%. In case this assumed number would be slightly different, the statistically calculated LC_{50} might be lower than 5.02 mg/L and therefore classification would be warranted. (..),

2) (..) According to the OECD TG 403, a Probit analysis should be conducted if multiple concentrations and/or multiple durations of exposure have been assessed in the study (C x t protocol). However, this is not the case, as only two concentrations have been used. Consequently, suitable data to conclude on dose-response is lacking. Assuming a simple linear correlation, the estimated LC_{50} is lower than 5 mg/L (as it was done in the dRR/study description: it was predicted that 10/10 animals would be dead at 7 mg/L, which is based on linear extrapolation). Thus, the product should be classified as Acute Tox 4, H332(..).

[3] Acute 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 5.02 mg/L, with confidence interval of 4.24 – 5.95 mg/L calculated by Probit analysis based on the study results. For this reason, the study is included as part of this application.
[4] Skin irritation – An in vivo study was performed (to satisfy the regulatory requirements of countries outside of the EU), in accordance with OECD 404, after an initial in vitro study failed to give a conclusive result. The results of the in vitro and in vivo tests show no conformity, as the in vivo study showed no skin irritation potential for ADM.03500.F.2.B. Considering the principles of the CLP Regulation (EC) 1272/2008 and the results of the animal study ADM.03500.F.2.B does not need to be classified as skin irritant according to CLP Regulation (EC) 1272/2008. The results of the in vitro study are included as part of this application in the EU. The in vivo study is not included in the application but is available on request.
Note: ZRMS: Already existing study has been included into current consideration on ZRMS request.
[5] 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. The results of this study show eye irritation properties and is thus in line with the alternative approach based on available data on ingredients which require classification as eye irritant according to CLP Regulation (EC) 1272/2008. Taking all information together classification "Eye Irritation Cat. 2 H319 "Causes serious eye irritation" is applied. The in vivo study has not been presented as part of this application in the EU, although the study report is available upon request.
Note: ZRMS: Already existing study has been included into current consideration on ZRMS request.
[6] Skin Sensitisation - This 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 results show the formulation to be a sensitiser, despite none of the individual ingredients being classified as such, 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.

Taking the available information into account, and considering the principles of the CLP Regulation, the classification for toxicological properties for ADM.03500.F.2.B are considered to be:

H302 Harmful if swallowed
H317 May cause an allergic reaction
H319 Causes serious eye irritation

Table 6.3-3: Additional toxicological information relevant for classification/labelling of ADM. 03500.F.2.B

	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)	No data – not required, for overall CLP proposal of ADM.03500.F.2.B please refer to confidential data submitted in Part C			
Toxicological properties of non-active substance(s) (relevant for classification of product)	No data – not required, for overall CLP proposal of ADM.03500.F.2.B please refer to confidential data submitted in Part C			
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10 % or > 1 %) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

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

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substance in ADM.03500.F.2.B and the toxicological relevant metabolite prothioconazole-desthio is presented in the following table.

Table 6.5-1: Dermal absorption rates for the active substance in ADM.03500.F.2.B and the relevant metabolite

	Prothioconazole		Prothioconazole-desthio	
	Value	**Reference**	**Value**	**Reference**
Concentrate	25 %	Default values according to EFSA Guidance on dermal absorption (2017)*	n.a.**	-
Dilution 1 (1:188)	70 %		11 %	Finlayson, Z. (2020), reported in Appendix 2
Dilution 2 (1:667)			13 %	

* 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 and prothioconazole-desthio

Data on dermal absorption for prothioconazole in ADM.03500.F.2.B 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 rates 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

The proposed dermal absorption rates for prothioconazole-desthio are based on a dermal absorption study on ADM.03500.F.2.B. The study results are summarized in the following table. Full summaries of studies on the dermal absorption of prothioconazole-desthio that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5-3: Summary of the results of submitted dermal absorption studies for prothio-conazole-desthio

Test	Dilution 1 (1:188)	Dilution 2 (1:667)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	11 %	13 %	ADM.03500.F.2.B	Yes	Not required	Endpoint can be used for current product	Finlayson, Z. (2020)

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.

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

Product name and code	ADM.03500.F.2.B	
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)	Active substance Prothioconazole 250 g/L	Toxicological relevant metabolite of active substance* Prothioconazole-desthio
AOEL systemic	0.2 mg/kg bw/d (1)	0.01 mg/kg bw/d (1)

AAOEL systemic	Not set in the 1st EU review of prothioconazole	
Inhalation absorption	100 %	100 %
Oral absorption	100 %	100 %
Dermal absorption	Concentrate: 25 % Dilution: 70 % (Default values based on the Guidance on dermal absorption) (2)	Concentrate: 0 % Dilution: 13 % (Dilution rate: 1:667) (Based on product (formulation), Finlayson, Z. (2020) reported in Appendix 2)
Vapour pressure	<<4 x 10-7 Pa at 20°C (1), <<4 x 10-7 Pa at 25°C (1), i.e. low volatile substances having a vapor pressure of <5 x 10-3 at 25°C	Parent value

(1) 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) Guidance on dermal absorption. EFSA Journal 2017;15(6):4873
* 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.

Overall considerations in the exposure assessment of ADM.03500.F.2.B

According to the DAR (2005)2, 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[3], 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.[4] 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 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. 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):

[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] DAR (2005), B.6.15.1 Operator exposure (III 7.2.1), p. 327
[3] 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
[4] dRR Part B Section 1: Identity, Section 2: Physical and chemical properties, Section 4: Further information, 2020

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

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

Taking the above calculated conversion factor of 0.907 into account, 0.1814 kg prothioconazole-desthio/ha is to be considered for an application rate of 0.8 L prod./ha, containing 0.2 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.

Justification

ADM.03500.F.2.B is a fungicide applied as spray in cereals and oilseeds. All applications are done via tractor-mounted downward spraying. The highest application rate of 0.8 L prod./ha in a minimum water volume of 100 L/ha in cereals is considered as worst case for all intended uses, and therefore also considered to cover the use in oilseeds.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

Since AAOELs are not available for 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 and prothioconazole-desthio during application of ADM.03500.F.2.B 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.

Table 6.6-2: Exposure models for intended uses

Critical use	Cereals (max. 1 x 0.8 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		**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)**
Tractor mounted boom spray application outdoors to cereals Application rate: 0.8 L prod/ha (0.2 kg prothioconazole/ha or 0.1814 kg prothioconazole-desthio/ha in a worst-case approach)					
EFSA calculator (75th percentile,	Potential exposure(3)	0.2239	**111.95**	0.0048	47.93
	No PPE: Work wear(4)	0.1402	70.12	0.0032	32.08

long-term exposure)	during M/L and A				

Bold = Risk is not acceptable, M/L = Mixing and loading, A = Application
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(3) Potential exposure – Operator wearing shorts and T-shirt
(4) No PPE: Work wear – arms, body and legs covered

According to the model calculations, the use of ADM.03500.F.2.B results in exposure levels of 70.12 % of the AOEL for prothioconazole and 32.08 % of the AOEL for prothioconazole-desthio in consideration of regular work wear covering arms, body and legs during mixing/loading and application. Thus, the use of ADM.03500.F.2.B in cereals and oilseeds is acceptable for operators wearing work wear (arms, body and legs covered) during mixing/loading and application. Due to the classification of the product with H317 as well as with H319, protective gloves, protective clothing and eye protection/face protection should additionally be worn when handling the product.

zRMS: This additional estimations of non-dietary exposure reflects comments made by the cMS. This new calculation took into account a conversion factor of 50% of prothioconazole to prothioconazole-desthio. New calculations on operator exposure estimates are presented below:

Applying a conversion rate of 50% of prothioconazole to its desthio-metabolite, 0.1 kg prothioconazole /ha is to be considered for an application rate of 0.8 L prod./ha and for prothioconazole-desthio an amount of 0.0907 kg prothioconazole-desthio/ha by the following equation:

Application rate prothioconazole-desthio = application rate of prothioconazole x MW prothioconazole-desthio / MW prothioconazole x conversion rate (%)

Thus, the calculated application rate of prothioconazole-desthio in 0.8 L prod./ha is 0.1 kg a.s./ha x 312.2 g/mol / 344.3 g/mol x 1 = 0.0907 kg prothioconazole-desthio/ha.

Product-specific data for the dermal absorption of prothioconazol-desthio is available, the value of 11 % obtained from the tested dilution of 1.33 g/L prothioconazole-desthio is considered appropriate to use for this risk assessment.

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

		50% Prothioconazole		**50% Prothioconazole-desthio**	
Dermal absorption		Concentrate: 25 % Dilution: 70 % (Default values)		Concentrate: 11 % Test concentration: 1.33 g/L) Dilution: 13 % (Test concentration: 0.375 g/L) (Based on product (formulation), Finlayson, Z. (2020) reported in Appendix 2)	
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)**
Tractor mounted boom spray application outdoors to cereals					
Application rate: 0.8 L prod/ha in 100 L/ha		0.1 kg prothioconazole/ha		0.0907 kg prothioconazole-desthio/ha	
EFSA calculator (75th percentile, long-term exposure)	No PPE: Work wear(3) during M/L and A	0.0805	40.25	0.0308	**307.63**
	PPE during M/L: Work wear during M/L and A + gloves during M/L(4)	0.0111	5.53	0.0024	24.18

Bold = Risk is not acceptable, M/L = Mixing and loading, A = Application
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(3) No PPE: Work wear – arms, body and legs covered
(4) PPE during M/L: Work wear – arms, body and legs covered during mixing and loading and application, additional protective gloves during mixing and loading

According to the model calculations and assuming a conversion factor of 50% of prothioconazole to prothioconazole-desthio, the use of ADM.03500.F.2.B results in exposure levels of 5.53 % of the AOEL for prothioconazole and 24.18 % of the AOEL for prothioconazole-desthio in consideration of protective gloves and regular work wear covering arms, body and legs during mixing/loading and regular work wear during application.

Due to the classification of the product with H317 as well as with H319, protective gloves, protective clothing and eye protection/face protection should additionally 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) 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 model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with ADM.03500.F.2.B according to the critical use. Outcome of the estimation is presented in Table 6.6-6. Detailed calculations are in Appendix 3.

Table 6.6-5: Exposure models for intended uses

Critical use	Cereals (max. 1 × 0.8 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		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)**
Number of applications and application rate:		1 × 0.2 kg a.s./ha		1 × 0.1814 kg prothioconazole-desthio/ha in a worst-case approach	
EFSA calculator 2 hours/day for inspection or irrigation activities DT50: 30 days DFR: 3 µg/cm²/kg a.s./ha	Potential exposure(3)	0.1750	87.50	0.0295	**294.78**
	No PPE: Work wear(4)	0.0196	9.80	0.0033	33.01

Bold = Risk is not acceptable
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(3) Potential exposure: Worker wearing shorts and T-shirt
(4) No PPE: Work wear – arms, body and legs covered, but no gloves

According to the model calculations, the use of ADM.03500.F.2.B results in exposure levels of 9.80 % of the AOEL for prothioconazole and 33.01 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs. Thus, the use of ADM.03500.F.2.B in cereals and oilseeds is acceptable for re-entry workers wearing work wear covering arms, body and legs.

Additional estimation of worker exposure taking into account a conversion factor of 50% of prothioconazole to prothioconazole -desthio reflecting cMS comments are presented below:

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

		50% Prothioconazole		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)**
Number of applications and application rate:		0.1 kg prothioconazole/ha		0.0907 kg prothioconazole-desthio/ha	
EFSA calculator 2 hours/day for inspection or irrigation activities DT50: 30 days DFR: 3 µg/cm²/kg a.s./ha	Potential exposure(3)	0.0875	43.75	0.0147	**147.39**
	No PPE: Work wear(4)	0.0098	4.90	0.0017	16.51

Bold = Risk is not acceptable
(1) AOEL (RVNAS) of prothioconazole: 0.2 mg/kg bw/day
(2) AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
(3) Potential exposure: Worker wearing shorts and T-shirt
(4) No PPE: Work wear – arms, body and legs covered, but no gloves

According to the model calculations and assuming a conversion factor of 50% of prothioconazole to prothioconazole-desthio, the use of ADM.03500.F.2.B results in exposure levels of 4.90 % of the AOEL for prothioconazole and 16.51 % of the AOEL for prothioconazole-desthio in consideration of work wear covering arms, body and legs. Thus, the use of ADM.03500.F.2.B in cereals and oilseeds 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) will not be exceeded under conditions of intended uses and considering work wear, 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 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.

Table 6.6-8 shows the exposure model(s) used for estimation of bystander and resident exposure to prothioconazole and prothioconazole-desthio. Outcome of the estimation is presented in Table 6.6-9. Detailed calculations are in Appendix 3.

Table 6.6-8: Exposure models for intended uses

Critical use	Cereals (max. 1 × 0.8 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		**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)**
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: 0.8 L prod/ha (1 × 0.2 kg prothioconazole/ha or 1 × 0.1814 kg prothioconazole-desthio/ha in a worst-case approach)				
Child (body weight 10 kg)				
Spray drift	0.0376	18.79	0.0064	63.63
Vapour	0.0011	0.54	0.0011	10.70
Surface deposits	0.0022	1.10	0.0005	4.91
Entry into treated crops	0.0236	11.81	0.0040	39.79

	Prothioconazole		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)**
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: 0.8 L prod/ha (1 × 0.2 kg prothioconazole/ha or 1 × 0.1814 kg prothioconazole-desthio/ha in a worst-case approach)				
Sum of all pathways	**0.0422**	**21.11**	**0.0081**	**81.14**
Adult (body weight 60 kg)				
Spray drift	0.0090	4.50	0.0015	15.18
Vapour	0.0002	0.12	0.0002	2.30
Surface deposits	0.0010	0.48	0.0002	1.61
Entry into treated crops	0.0131	6.56	0.0022	22.11
Sum of all pathways	**0.0157**	**7.83**	**0.0028**	**28.32**

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

According to the model calculations, the use of ADM.03500.F.2.B results in exposure levels of up to 21.11 % of the AOEL for prothioconazole and up to 81.14 % of the AOEL for prothioconazole-desthio for residents of any age.

Additional estimation of resident and bystander exposure taking into account a conversion factor of 50% of prothioconazole to prothioconazole -desthio reflecting cMS comments are presented below:

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

	50% Prothioconazole		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)**
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: 0.8 L prod/ha (1 × 0.1 kg prothioconazole/ha and 1 × 0.0907 kg prothioconazole-desthio/ha)				
Child (body weight 10 kg)				
Spray drift	0.0188	9.40	0.0032	31.82
Vapour	0.0011	0.54	0.0011	10.70
Surface deposits	0.0011	0.55	0.0003	2.45
Entry into treated crops	0.0118	5.91	0.0020	19.90

	50% Prothioconazole		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)**
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: 0.8 L prod/ha (1 × 0.1 kg prothioconazole/ha and 1 × 0.0907 kg prothioconazole-desthio/ha)				
Sum of all pathways	**0.0216**	**10.82**	**0.0046**	**45.92**
Adult (body weight 60 kg)				
Spray drift	0.0045	2.25	0.0008	7.59
Vapour	0.0002	0.12	0.0002	2.30
Surface deposits	0.0005	0.24	0.00008	0.80
Entry into treated crops	0.0066	3.28	0.0011	11.05
Sum of all pathways	**0.008**	**3.97**	**0.0015**	**15.31**

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

According to the model calculations and assuming a conversion factor of 50% of prothioconazole to prothioconazole-desthio, the use of ADM.03500.F.2.B results in exposure levels of up to 10.82 % of the AOEL for prothioconazole and up to 45.92 % of the AOEL for prothioconazole-desthio for residents of any age.

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 prothioconazole and prothioconazole-desthio will not be exceeded under conditions of intended uses, a study to provide measurements of /resident exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

Diluted prothioconazole, as contained in the product ADM.03500.F.2.B, can degrade to the metabolite prothioconazole-desthio. In a conservative approach, two 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 not considered appropriate and the risk is considered being acceptable if exposure to either substance is below the respective AOEL.

Taking into account a conversion rate of 50% of prothioconazole to prothioconazole -desthio combined exposure of prothioconazole and prothioconazole-desthio 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 and prothioconazole-desthio 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 6.6-3a,

Table 6.6-6a and

Table 6.6-9a 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	50% Prothioconazole is transformed into prothio-	prothioconazole	0.06
		prothioconazole-desthio	0.24

Application scenario	Exposure scenario	Active Ingredient	Estimated exposure / AOEL (HQ)
work wear (1) during M/L and A and gloves during M/L(2) *For details, please refer to 6.6.2, Table 6.6-3a.*	conazole-desthio	**Cumulative risk Operators (HI)**	**0.30**
Workers - inspection and irrigation, wearing work wear *For details, please refer to 6.6.3, Table 6.6-5a.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.05
		prothioconazole-desthio	0.17
		Cumulative risk Operators (HI)	**0.22**
Resident - Child (all pathways) *For details, please refer to 6.6.4, Table 6.6-7a.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.11
		prothioconazole-desthio	0.46
		Cumulative risk Operators (HI)	**0.57**
Resident - Adult (all pathways) *For details, please refer to 6.6.4, Table 6.6-7a.*	50% Prothioconazole is transformed into prothioconazole-desthio	prothioconazole	0.04
		prothioconazole-desthio	0.15
		Cumulative risk Operators (HI)	**0.19**

(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 and prothioconazole-desthio, the risk is acceptable for operators wearing gloves and regular work wear during mixing/loading and regular work wear during application and for workers without considering specific PPE and for bystanders and residents without any 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	xxxxxxxxxx	2019a	Acute oral toxicity – Up-and Down procedure in rats Report no.: 51286; sponsor no.: 000102245 xxxxxxxxxxxx, Dayton, NJ, USA GLP Unpublished	Y	ADM
KCP 7.1.2/01	xxxxxxxxxx	2019	ADM.3500.F.2.B: Acute dermal toxicity – Fixed dose procedure in rats Report no. 51287; sponsor no.: 000102246 xxxxxxxxxxx Dayton, NJ, USA GLP Unpublished	Y	ADM
KCP 7.1.3/01	xxxxxxxxxx	2019b	ADM.3500.F.2.B: Acute inhalation toxicity in rats Report no.: 51288; sponsor no.: 000102247 xxxxxxxxxxxx, Dayton, NJ, USA GLP Unpublished	Y	ADM
KCP 7.1.4/02	xxxxxxxxxx	2019	ADM.3500.F.2.B: Primary skin irritation in rabbits Report no. 51290; sponsor no.: 000102248 xxxxxxxxxx, Dayton, NJ, USA GLP Unpublished	Y	ADM
KCP 7.1.5/02	xxxxxxxxxx	2019	ADM.3500.F.2.B: Primary eye irritation in rabbits Report no. 51289; sponsor no.: 000102250 xxxxxxxxxxx, Dayton, NJ, USA GLP Unpublished	Y	ADM
KCP 7.1.6/01	xxxxxxxxxx	2019c	ADM.3500.F.2.B: Local lymph node assay (LLNA) in mice Report no.: 51291; sponsor no.: 000102249 xxxxxxxxxxx, Dayton, NJ, USA GLP Unpublished	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
KCP 7.3/01	Finlayson, Z..	2020	The i*n vitro* percutaneous absorption of radiolabelled Prothioconazole-desthio in two in-use dilutions of the Prothioconazole 250 g/L EC Formulation (ADM.03500.F.2.B) through human split-thickness skin Report no.: 786166; sponsor no.: 000105848 Charles River Laboratories Edinburgh Ltd., Tranent, UK 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 7.1.4/01	xxxxxxxxxxx.	2019	In vitro skin iritation: Human skin model test (EpiDerm™) with ADM.3500.F.2.B Report no.: STUGC19AA0974-1; sponsor no.: 000102242 xxxxxxxxxxxxx, Planegg, Germany GLP Unpublished	N	ADM
KCP 7.1.5/01	xxxxxxxxxxx	2019	Screening for the eye irritancy potential using the Bovine corneal opacity and permeability assay with ADM.3500.F.2.B Report no.: STUGC19AA0974-2; sponsor no.: not stated	N	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
			xxxxxxxxxxxxxxxxxx, Planegg, Germany GLP Unpublished		

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. *In vivo* studies has been provided with currently registered product (ADM.03500.F.2.B)

A 2.2 Acute oral toxicity (KCP 7.1.1)

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). Data has been reviewed for compliance with the current guidelines resulting from scientific progress (OECD 425 rev 2022). Study (xxxxxxxxxxxxx) implements 3R rules minimizing the number of animals required to estimate the acute oral toxicity of a chemical. Limit test at 5000 mg/kg has been accepted by the zRMS based on expert judgement confirms significant clinical signs of toxicity tested up to Category 4 values such irregular respiration, abnormal posture, abnormal gait, reduced fecal (except for diarrhea, piloerection or an ungroomed appearance). Noted deviation from TG OECD 425 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 2.2.1 Study 1

Justification for vertebrate study:
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.

In addition, a vertebrate study is available for acute toxicity of ADM.03500.F.2.B 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. For transparency reasons, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.1/01
Report	Acute oral toxicity – Up-and-Down procedure in rats, xxxxxxxx. (2019a), report no. 51286
Guideline(s):	OECD guideline 425 (2008); EPA OPPTS 870.1100 (2002)
Deviations:	Yes Rationale for initial dose level selection, dose progression factor and for follow-up dose levels was missing.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	175 mg/kg bw: 1 female 550 mg/kg bw: 3 females 1750 mg/kg bw: 3 females 5000 mg/kg bw: 1 female (total number of animals: 8 females)
Dose(s)	175, 550, 1750, and 5000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of ADM.3500.F.2.B

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD50 (mg/kg bw) (14 days)
Female rats				
175	0/0/1	n.a.	n.a.	1030 (approx. 95% C.I.: 550 – 1750 mg/kg bw)
550	0/1/3	Day 0**	n.a.	
1750	3/3/3	Day 0 – Day 1**	Day 1 – Day 2	
5000	1/1/1	Day 0**	Day 1	

* Number of animals which died/number of animals with clinical signs/number of animals used
** Day of test item adminstration
n.a. not applicable
C.I. Confidence interval

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

Mortality:	Yes, mortality occurred at the 1750 and 5000 mg/kg bw dose levels. At the 1750 mg/kg bw dose level all animals died within two days of test substance administration. At the 5000 mg/kg bw dose level, the animal died within one day of test substance administration.
Clinical signs:	Yes, clinical signs were observed for all dose levels, except for the lowest dose level. Following administration of 550 mg/kg bw, one animal was hypoactive and exhibited irregular respiration. However, the animal recovered by Day 1 and along with the remaining animals appeared active an healthy for the remainder of the 14-day observation period. At the 1750 mg/kg bw dose level, one animal was hypoactive prior to death and all animals exhibited irregular respiration, abnormal posture, abnormal gait, reduced fecal volume and/or diarrhoea. Lastly, at the 5000 mg/kg bw dose level the animal exhibited irregular respiration, abnormal gait, prone posture and oral discharge.
Body weight:	All animals of the 175 and 550 mg/kg bw dose groups gained body weight during the study. However, the animals of the 1750 and 5000 mg/kg bw dose groups lost weight prior to death.
Macroscopic examination:	No gross abnormalities were noted for the animals of the 175 and 550 mg/kg bw dose groups when necropsied at the conclusion of the 14-day observation period. Gross necropsy of the decedents of the 1750 m/kg bw dose group revealed distention of the stomach and/or a fluid filled stomach and/or a fluid filled intestines. Furthermore, gross necropsy of the decedent of the 5000 mg/kg bw dose group revealed distention of the stomach and intestines and a fluid-filled stomach.

Conclusion

Under the experimental conditions, the oral LD_{50} of ADM.3500.F.2.B is 1030 mg/kg bw (approx. 95% confidence interval: 550 – 1750 mg/kg bw) in rats. Thus, classification as Acute Tox. 4 with hazard statement H302 “Harmful if swallowed” 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:	*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). Already existing study (xxxxxxxxxx)) has been included into consideration on ZRMS request. Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. In the study (KCP 7.1.2/01 xxxxxxxxxxxxxx (2019) tested material has not been administered at doses which cause pain and distress due to potential corrosive or severely irritant actions (see animal welfare discussion). There is no deviation from studies protocol. 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. None of the ingredients of ADM.03500.F.2.B is classified as acutely toxic via dermal route and needs to be considered in the calculation. However, the acute dermal toxicity of two ingredients is unknown and therefore an alternative approach using the calculation method was applied.~~

~~**Conclusion:**~~
~~Based on the result derived using the calculation method, ADM.03500.F.2.B 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.~~
~~Thus, no classification of ADM.03500.F.2.B for acute toxicity via the dermal route is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.~~

Reference:	KCP 7.1.2/01
Report	ADM.3500.F.2.B: Acute dermal toxicity – Fixed dose procedure in rats, xxxxxxxxxx (2019), report no. 51287
Guideline(s):	OECD guideline 402 (2017)
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	Range-finding study: 1 female Main study: 2 females
Dose(s)	Range-finding study: 2000 mg/kg bw Main study: 2000 mg/kg bw
Exposure	Topical application
Vehicle/Dilution	None

Post exposure observation period	14 days
Remarks	None

Summary

An acute dermal toxicity test (Fixed Dose Procedure) was conducted with rats to determine the potential for ADM.3500.F.2.B to produce toxicity from a single topical application. Under the conditions of this study, the single dose acute dermal LD50 of the test substance is greater than 2000 mg/kg bw (body weight) in female rats.

Initially, two thousand milligrams of the test substance per kilogram of body weight was moistened with distilled water and applied to the skin of one healthy rat for 24 hours. Due to the absence of toxicity or death, two additional animals were tested for the main test at 2000 mg/kg bw. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males. The animals were observed for mortality, signs of gross toxicity and behavioral changes at least once daily for 14 days. Body weights were recorded prior to application (initial) and again on Days 7 and 14 (terminal). Necropsies were performed on all animals at terminal sacrifice.

All animals survived test substance administration and gained body weight during the study. Other than the dermal irritation noted at the dose site of one animal on Day 2, there were no other adverse clinical findings recorded for any animal over the course of the study. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

Animal Welfare

This study complied with all applicable sections of the Guidelines from the Guide for the Care and Use of Laboratory' Animals (NRC 2011). All studies conducted for PSL adhere to the following principles:

• The Sponsor ensures that the study described in this report does not unnecessarily' duplicate previous experiments, and is in compliance with the PSL Policy on Animal Testing.

• Whenever possible, procedures used in this study have been designed to implement a reduction, replacement, and/or refinement in the use of animals in an effort to avoid or minimize discomfort, distress or pain to animals. All methods are described in this study report or in written laboratory standard operating procedures.

• Animals experiencing severe pain or distress that cannot be relieved are painlessly euthanized, as deemed appropriate by the veterinary staff and study director or appropriate designee. The principles of OECD Guidance Document No. 19: Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation was followed.

• Methods of euthanasia used during this study were in conformance with the above referenced regulation and the recommendations of the American Veterinary Medical Association (AVMA), 2013 Guidelines on Euthanasia.

• Animals were provided with species-appropriate environmental enrichment. Product Safety Labs is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International

Results and discussions

Table 1: Results of acute dermal toxicity study in rats of ADM.3500.F.2.B

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Female rats				
Range-finding study				> 2000
2000	0/0/1	-	-	
Main study				

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
2000	0/1/2	-	-	

* Number of animals which died/number of animals with clinical signs/number of animals used

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

Mortality:	No mortality occurred.
Clinical signs:	Except for the dermal irritation noted at the dose site of one animal of the main study on Day 2, no other signs of gross toxicity, dermal irritation, adverse clinical effects or abnormal behaviour were observed.
Body weight:	Body weight gain was considered to be normal.
Macroscopic examination:	No gross abnormalities were noted for any of the animals when necropsied at the end of the 14-day observation period.

Conclusion
Based on the present study results, the acute dermal LD50 of ADM.3500.F.2.B is more than 2000 mg/kg body weight in female Sprague-Dawley rats.
Therefore, classification of the formulation for acute dermal toxicity is not required according to the Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

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). Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. In the study (Xxxxxxxxxx (2019c)) animals are exposed to one limit concentration for a predetermined 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

Justification for vertebrate study:
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.

In addition, a vertebrate study is available for acute toxicity of ADM.03500.F.2.B via the inhalational 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. For transparency reasons, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.3/01
Report	ADM.3500.F.2.B: Acute inhalation toxicity in rats, Xxxxxxxxxx (2019c), report no. 51288
Guideline(s):	OECD guideline 403 (2009); EPA OPPTS 870.1300 (1998); EU method B.2 (EC No. 440/2008)
Deviations:	Yes

3 test animals per sex per concentration step is foreseen by the guideline, however, in this study 5 animals per sex per test concentration were used; ~~an aerosol test concentration of 1 mg/L air is recommended instead of 2 mg/L~~ air

GLP: Yes

Acceptability: Yes

Duplication (if vertebrate study): No

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	5 rats/sex/dose
Concentration(s)	2.10 ± 0.08 and 5.13 ± 0.36 mg/L
Exposure	4 hours (nose only)
Vehicle/Dilution	Clean air
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 3: Concentration(s) and exposure conditions

Nominal conc. (mg/L air)	Actual conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
13.49	2.10 ± 0.08	1.80	2.25
43.75	5.13 ± 0.36	1.83	2.13

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

Table A 4: Results of acute inhalation toxicity study in rats of ADM.3500.F.2.B

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Male rats				
2.10	0/5/5	Day 0** - Day 7	n.a.	2 mg/L < LC_{50} ≤ 5 mg/L
5.13	3/5/5	Day 0** – Day 11	Day 2	
Female rats				
2.10	0/5/5	Day 0** - Day 7	n.a.	2 mg/L < LC_{50} ≤ 5 mg/L
5.13	3/5/5	Day 0** – Day 13	Day 1 – Day 2	

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

Table A 5: Summary of findings of acute inhalation toxicity study in rats of ADM.3500.F.2.B

Mortality:	No mortality was observed at the 2.10 mg/L concentration level. However, three males and three females died within two days following exposure to 5.13 mg/L of the test substance.
Clinical signs:	Following exposure to 2.10 mg/L of the test substance, two animals were hypoactive and all animals exhibited abnormal respiration. However, all animals recovered by day 8 and appeared active and healthy for the remainder of the 14-day observation period.

	Prior to death, all animals of the 5.13 mg/L group were hypoactive and exhibited abnormal respiration, moist rales, gasping, ano-genital staining and/or prone posture. Following exposure to 5.13 mg/L, the surviving animals exhibited similar clinical signs.
Body weight:	All animals of the 2.10 mg/L group gained body weight during the study. Furthermore, two male animals of the 5.13 mg/L group lost body weight (one animal >10%), the remaining two female animals gained body weight during the study.
Macroscopic examination:	No gross abnormalities were noted for any of the animals of the 2.10 mg/L group when necropsied at the conclusion of the 14-day observation period. Gross necropsy of the decedents of the 5.13 mg/L group revealed distention of the stomach and intestines and/or discolouration of the lungs. Furthermore, gross necropsy for two of the euthanized animals revealed distention of the stomach and/or intestines. No gross abnormalities were noted for the remaining two euthanized animals when necropsied at the conclusion of the 14-day observation period.

Conclusion

Based on the study results, a LC_{50} of 5.02 mg/L with a 95% confidence interval of 4.24 – 5.95 mg/L was derived using the Probit analysis. A worst-case value of 7.0 mg/L with an assumed mortality rate of 100% was applied in the calculation. The result is slightly above the requirement for classification in Category 4 for dusts and mists ($1.0 < LC_{50} \leq 5.0$) and therefore no classification is required.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Regarding *in vitro* study xxxxxxxxxxx., 2019 (Skin irritation, Reconstructed human epidermis EpiDermTM (OECD 439)) 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.03500.F.2.B based on *in vivo* study.

A 2.5.1 Study 1

~~Reference:~~ ~~KCP 7.1.4/01~~

~~Report~~ ~~*In vitro* skin irritation: Human skin model test (EpiDerm™) with ADM.3500.F.2.B, Zuckerstätter, V. (2019), report no. STUGC19AA0974-1~~

~~Guideline(s):~~ ~~OECD guideline 439 (2019); EU method B.46 (EC No. 440/2008)~~

~~Deviations:~~ ~~No~~

~~GLP:~~ ~~Yes~~

~~Acceptability:~~ ~~Yes~~

~~Duplication (if vertebrate study)~~ ~~No~~

~~**Materials and methods**~~

~~**Test material (Lot/Batch No.)**~~	~~ADM.3500.F.2.B (3178-010519-01)~~
~~**Skin model**~~	~~Reconstructed three-dimensional human skin model EpiDerm™ (MatTek)~~
~~**Vehicle/Dilution**~~	~~None~~

Negative control	Dulbecco's phosphate buffered saline (DPBS)
Positive control	5% sodium dodecyl sulfate solution
No. of tissues per group	3 tissues
Exposure	30 µL for 60 ± 1 minutes; incubator for 35 ± 1 minutes followed by placing the plates under the sterile flow for the remaining time
Post-treatment incubation period	42 ± 2 hour (37 ± 1 °C)
MTT reduction assay	3 hours ± 5 minutes (37 ± 1 °C) (0.3 mg MTT/mL) 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
Acceptance criteria	The test meets acceptance criteria if: - mean absolute OD570 nm of the three negative control tissues ≥ 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 showed reduction of MTTcompared to the solvent, but no relevant colouring potential after mixture with aqua dest. and with isopropanol. Therefore, no additional controls for correction of possible false-negative results were necessary.

Results and discussions

Table A 6: *In vitro* Skin irritation of ADM.3500.F.2.B

Dose group	Treatment interval	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	Mean relative tissue viability [%] – NSMTT*** corrected
Negative control	60 ± 1 min.	1.680	1.730	1.389	1.600* ± 0.184	100.0 ± 11.5	—
Positive control	60 ± 1 min.	0.102	0.115	0.136	0.118 ± 0.017	7.4 ± 1.1	—
Test substance	60 ± 1 min.	0.092	0.092	0.094	0.093 ± 0.002**	5.8 ± 0.1	3.2 ± 0.1

* Blank-corrected mean OD_{570} of the negative control corresponds to 100% absolute tissue viability.
** TOD_{IT} (true MTT metabolic conversion) was 0.052 for the test item treated living tissues
*** NSMTT = non-specific reduction of MTT

Table A 7 Historical control data (generated from 2015 to 2018)

	Mean absolute OD570 ± 30 nm Negative control	Mean relative viability [%] Positive control	SD viability Negative control, positive control, and test item [%]
mean	1.808	3.8	4.1
SD	0.239	1.6	4.1
Range of LCL – UCL	1.330 – 2.287	0.5 – 7.1	0.0 – 12.2
n	47	47	223

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. The mean relative tissue viability (% negative control) of the positive control was ≤ 20% (7.4%). The maximum standard deviation of viability of replicate tissues of all dose groups was ≤ 18% (0.1% – 11.5%). The mean relative tissue viability of the positive control (7.4 ± 1.1) slightly exceeds the range observed in the historical control data generated from 2015-2018 (0.5-7.1 %). However, this is not considered to have an impact on the reliability of the results or conclusion of the test.~~

~~**Conclusion**~~
~~Under the experimental conditions, the *in vitro* study results trigger a classification for skin irritation of Cat 1 or Cat 2.~~

A 2.5.2 **Study 2**

Classification via the application of bridging principles is not possible since data on a similar mixture are not available. In consideration of the content and the classification of the individual components in the formulation ADM.03500.F.2.B, a classification of ADM.03500.F.2.B with H314 would be required. Since the composition of the plant protection product is confidential, this approach is presented in the confidential part C of this dossier.

However, an *in vivo* skin irritation study according to OECD guideline 404 (2015) was conducted but not performed with intention for use within the EU, but to satisfy the regulatory requirements of countries outside of the EU. The study was conducted to clarify the results of the *in vitro* study, since the results of the *in vitro* study does not enable an exact prediction on the classification for skin irritation to Category 1 or 2. Considering the results of the animal study the product does not need to be classified as skin irritant according to CLP Regulation (EC) 1272/2008. ~~The study is thus 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.~~

Conclusion
In a weight of evidence approach based on the ~~*in vitro* and~~ *in vivo* data, ADM.03500.F.2.B requires no classification as a skin irritant according to Regulation (EC) No. 1272/2008 and subsequent regulations.

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). Already existing study (Xxxxxxxxxx (2019)) has been included into consideration on ZRMS request. As it was mentioned and explained in the our general comment *in vitro* study (Zuckerstätter, V., 2019) based on OECD 439 is not applicable for agrochemical formulations thus already existed *in vivo* study has been accepted and considered by the ZRMS as reliable for the hazard assessment. Test product was applied in a single dose to the skin of an experimental animal; untreated skin areas of the test animal serve as the control. The degree of irritation/corrosion was read and scored at specified intervals in order to provide a complete evaluation of the effects. The duration of the study was sufficient to evaluate the reversibility or irreversibility of the effects observed. There was no deviation from studies protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

Reference:	KCP 7.1.4/02
Report	ADM.3500.F.2.B: Primary skin irritation in rabbits, Xxxxxxxxxx (2019), report no. 51290
Guideline(s):	OECD guideline 404 (2015); EPA OPPTS 870.2500 (1998); EU method B.4 (EC No. 440/2008)

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

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Species	Rabbit, New Zealand albino
No. of animals (group size)	3 females
Initial test using one animal	No
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	7 days
Remarks	None

Summary

A primary skin irritation test was conducted with rabbits to determine the potential for ADM.3500.F.2.B to produce irritation after a single topical application. Under the conditions of this study, the test substance is classified as moderately irritating to the skin.

Five-tenths of a millilitres of the test substance was applied to the skin of three healthy rabbits for 4 hours. Following exposure, dermal irritation was evaluated by the Draize method of scoring.

Within 30-60 minutes of patch removal, all three treated sites exhibited very slight to well-defined erythema and/or very slight to slight oedema. The overall incidence and severity of irritation decreased gradually with time. All animals were free of dermal irritation by Day 7 (study termination).

The incidence, severity and reversibility of irritation are detailed below:

The Primary Dermal Irritation Index (PDII) calculated for this test substance was 2.4

Results and discussions

Table 1: Skin irritation of ADM.3500.F.2.B

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema Oedema	1 0	1 0	0 0	0 0	0.33 0	2
2	Erythema Oedema	2 2	2 2	2 1	2 1**	2 1.33	7
3	Erythema Oedema	2 1	2 2	2 1	2 1**	2 1.33	7

* scores in the range of 0 to 4; ** desquamation at the dose site

Clinical signs:	No clinical signs of toxicity were observed, except for dermal irritation. Within 30 – 60 minutes of patch removal, all three treated sites exhibited very slight to well-defined erythema and/or very slight to slight oedema. The overall incidence and severity of irritation decreased gradually with time. Two animals also showed desquamation at the dose site at the 72-hour observation. All animals were free of dermal irritation by Day 7 (study termination). All animal gained body weight during the study.

Conclusion

Under the experimental conditions, ADM.3500.F.2.B is not a skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008 and subsequent regulations.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Regarding *in vitro* study_xxxxxxxxxx 2019 (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.

A 2.6.1 Study 1

Reference:	KCP 7.1.5/01
Report	Screening for the eye irritancy potential using the Bovine corneal opacity and permeability assay with ADM.3500.F.2.B, Niklas, V. (2019), report no. STUGC19AA0974-2
Guideline(s):	OECD guideline 437 (2017); EPA OPPTS 870.1000 (2002); EU method B.47 (EC No. 440/2008)
Deviations:	Yes Historical control data of the negative control were missing. Furthermore, corneal diameter as a measure of age of the source animal and suitability for the assay were not stated.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Test system:	Isolated corneas of bovine
Vehicle/Dilution	None
Negative control	Physiological saline 0.9% NaCl
Positive control	Ethanol 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 MEM (containing phenol red) followed by washing with complete RPMI 1640 medium (without phenol red).Then, the corneas were incubated in complete RPMI 1640 medium for another 2 hours (32 ± 1 °C).
Measurements	Initial and final measurement of opacity before treatment and after 2 hour incubation period; treatment with sodium fluoroescein 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 x 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	The BCOP assay is considered to be valid if the *in vitro* irritation score obtained with the positive control falls within the two standard deviations of the current historical mean. The negative control responses should result in opacity and permeability values that are less than the established upper limits for background bovine corneas treated with the respective negative control.

Results and discussions

Table A 8: *In vitro* eye irritation of ADM.3500.F.2.B

Test group	Corrected opacity value (t130 – t0)		Corrected OD490		In vitro irritancy score (IVIS)
		Mean ± SD		Mean	
Negative control	1.58	1.20 ± 0.90	0.009	0.012 ± 0.005	1.38
	0.17		0.017		
	1.86		0.009		
Positive control	23.94	23.03 ± 2.38	1.403	1.508 ± 0.575	45.65
	20.33		0.992		
	24.82		2.128		
Test substance	6.08	7.50 ± 1.72	-0.008	-0.007 ± 0.002	7.39
	7.00		-0.009		
	9.41		-0.006		

SD = standard deviation

Table A 9: Historical mean *in vitro* irritation score of the positive control

	IVIS Positive control
Mean value (MV)	48.04
Standard deviation (SD)	8.76
MV – 2xSD	30.51
MV + 2xSD	65.56
Number of replicates providing historical mean: 65	

Positive controls are updated after every single experiment or at least every 3 months

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.3500.F.2.B to induce ocular corrosivity or severe irritancy was investigated in the bovine corneal opacity and permeability assay (*in vitro* test). Under the experimental conditions, ADM.3500.F.2.B induced an IVIS of 7.39. Based on the result of the study, no prediction can be made regarding the classification of the test substance according to the BCOP classification criteria as described in the OECD 437 guideline (threshold for no prediction: IVIS > 3; IVIS ≤ 55).

A 2.6.2 **Study 2**

~~Classification via the application of bridging principles is not possible since data on a similar mixture are not available. In consideration of the content and the classification of the individual components in the formulation, a classification of ADM.03500.F.2.B with H314 (and H318) would be required. Since the composition of the plant protection product is confidential, this approach is presented in the confidential part C of this dossier.~~

An *in vivo* eye irritation study according to OECD guideline 405 (2017) was conducted but not performed with intention for use within the EU, but to satisfy the regulatory requirements of countries outside of the EU to clarify the results of the *in vitro* study. ~~The study results of the *in vivo* are in line with the alternative approach and the study has not been presented as part of this application into the EU, although the study report is available upon request.~~

Conclusion

Based on the available information, ADM.3500.F.2.B is an eye irritant. Thus, classification as Eye irritation Category 2 with hazard statement H319 "Causes serious eye irritation" is required according to Regulation (EC) No. 1272/2008.

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). Already existing study (Xxxxxxxxxx (2019)) has been included into consideration on ZRMS request. Study (Xxxxxxxxxx (2019)) 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 (Xxxxxxxxxx (2019)) topical anesthetics has been used. Prior to instillation, 1-2 drops of ocular anesthetic (Tetracaine Hydrochloride Ophthalmic Solution VSP, 0.5%) were placed into both the treated and control eye of each. 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.

Reference:	KCP 7.1.5/02
Report	ADM.3500.F.2.B: Primary eye irritation in rabbits, Xxxxxxxxxx (2019), report no. 51289
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

Executive summary:

A primary eye irritation test was conducted with rabbits to determine the potential for ADM.3500.F.2.B to produce irritation from a single instillation via the ocular route. Under the conditions of this study, the test substance is classified as moderately irritating to the eye.
One-tenth of a milliliter of the test substance was instilled into the right eye of three healthy rabbits. The left eye remained untreated and served as a control. Ocular irritation was evaluated by the Draize method of scoring
Within 24 hours after test substance instillation, all three treated eyes exhibited corneal opacity and 'positive' conjunctivitis. There was no iritis observed in any treated eye during this study. The overall incidence and severity of irritation decreased gradually with time. Positive irritation cleared from all three treated eyes by Day 4. All animals were free of ocular irritation by Day 7 (study termination).

The incidence of positive effects, severity and reversibility are detailed below:

Time post installation	Incidence of Positive Effects		
	Corneal opacity	Iritis	Conjunctivitis
1 hour	0/3	0/3	3/3
24 hours	3/3	0/3	2/3
48 hours	2/3	0/3	1/3
72 hours	2/3	0/3	0/3
Day 1	0/3	0/3	0/3
Day 2	0/3	0/3	0/3

Time post installation	Severity of Irritation – Mean Score
1 hour	12.0
24 hours	15.7
48 hours	9.7
72 hours	5.3
Day 1	1.3
Day 2	0.0

Procedure
Prior to test initiation, both eyes of a group of animals were examined using a white light source and a fluorescein dye procedure. One drop of ophthalmic fluorescein sodium dye was instilled into both eyes of each rabbit. The eyes were rinsed with physiological saline (0.9% NaCl) after instillation of the fluorescein and then evaluated for corneal damage using an ultraviolet light source. Prior to test substance instillation, the eyes were re-examined and scored for abnormalities according to the "Scale for Scoring Ocular Lesions" Three healthy, naive animals (riot previously tested) without pre-existing ocular irritation were selected for test. A systemic analgesic (Buprenorphine SR) was administered to relieve potential discomfort associated with eye irritation which provides therapeutic relief for periods of up to 76 hours. Prior to test substance instillation. 0.1 mg/kg of body weight of the analgesic was administered to the animals and at appropriate intervals to maintain therapeutic blood levels.

Preparation of Test Substance
The test substance was instilled as received and mixed well prior to use. The pH was determined for the test substance prior to the instillation and was within a pH range of 2 and 11.5, therefore testing proceeded. The procedure used and the results are retained in the raw data.

Instillation
Prior to instillation, 1-2 drops of ocular anesthetic (Tetracaine Hydrochloride Ophthalmic Solution VSP, 0.5%) were placed into both the treated and control eye of each animal One-tenth of a milliliter of the test substance was then instilled into the conjunctival sac of the right eye of each rabbit by pulling the lower lid away from the eyeball. The upper and lower lids were then gently held together for about one second before releasing to minimize loss of the test substance. The other eye of each rabbit remained untreated with the test substance and served as a control. The rabbits were then returned to their designated cages

Ocular scoring

Ocular irritation was evaluated using a white light source in accordance with the Draize method of scoring (Draize et al., 1944; see Table 4) at I, 24, 48, and 72 hours and at 4 and 7 days post instillation. The fluorescein dye evaluation procedure described in Section 5.A. was used in the treated eye at 24 hours and as needed at subsequent scoring intervals to evaluate the extent of comeal damage or to verij reversal of effects. Individual scores were recorded for each animal. In addition to observations of the cornea, iris and conjunctivae, any other observed lesions were noted. The average score for all rabbits at each scoring period was calculated to aid in data interpretation

Results and discussions

Table 7.5.1/02-01: Eye irritation of ADM.3500.F.2.B

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	1**	1**	1**	1	7
	Iritis	0	0	0	0	0	
	Redness conjunctivae	1	2	1	1	1.33	
	Chemosis conjunctivae	2***	1	0	0	0.33	
2	Corneal opacity	0	1**	1**	1**	1	7
	Iritis	0	0	0	0	0	
	Redness conjunctivae	1	2	2	1	1.67	
	Chemosis conjunctivae	2***	2***	2***	1	1.67	
3	Corneal opacity	0	1**	0	0	0.33	3
	Iritis	0	0	0	0	0	
	Redness conjunctivae	1	1	1	0	0.67	
	Chemosis conjunctivae	2***	1	0	0	0.33	

* 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
** ophthalmic fluorescein sodium dye was used to evaluate the extent or verify the absence of corneal opacity
*** Discharge with moistening of lids and hairs, and considerable area around the eye was observed for all animals (animal no. 2 also showed discharge with moistening of lids and hairs just adjacent to lids at the 24-hour observation and an amount of discharge above normal at the 48-hour observation)

Clinical signs:
No clinical signs of toxicity were observed, except for eye irritation. Within 24 hours after test substance instillation, all three treated eyes exhibited corneal opacity, conjunctival redness and chemosis. There was no iritis observed in any treated eye during this study. The overall incidence and severity of irritation decreased gradually with time. Discharge with moistening of lids and hairs, and considerable area around the eye was observed for all animals. One animal also showed discharge with moistening of lids and hairs just adjacent to lids at the 2- hour observation and an amount of discharge above normal at the 48-hour observation. All animals were free of ocular irritation by Day 7 (study termination). All animals gained body weight during the study.

Results:
Within 24 hours after test substance instillation, all three treated eyes exhibited corneal opacity and 'positive' conjunctivitis. There was no iritis observed in any treated eye during this study. The overall incidence and severity of irritation decreased gradually with time. Positive irritation cleared from all three treated eyes by Day 4. All animals were free of ocular irritation by Day 7 (study termination). The Maximum Mean Total Score of ADM.3500.F.2. B is 15.7.

Conclusion

Under the experimental conditions, ADM.3500.F.2.B is an eye irritant. Thus, classification as Eye irritation Category 2 with hazard statement H319 "Causes serious eye irritation" is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

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 protec-

	tion or alternative method (*in vitro*) has not been taken into account (please refer ZRMS detailed consideration in the preface to this dRR). Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. Study is in line with the suggestions of point 5 of Regulation 284/2013 and Annex VII to REACH REG (EC) No 1907/2006. Noted deviation from TG OECD 429 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 2.7.1 **Study 1**

Justification for vertebrate study:
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.

In addition, a vertebrate study is available for skin sensitisation of ADM.03500.F.2.B. 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. For transparency reasons, the study is provided with this dossier and summarised hereafter.

Reference:	KCP 7.1.6/01
Report	ADM.3500.F2.B: Local lymph node assay (LLNA) in mice, Xxxxxxxxxx (2019f), report no. 51291
Guideline(s):	OECD guideline 429 (2010); EPA OPPTS 870.2600 2003); EU method B.42 (EC No. 440/2008)
Deviations:	With minor deviations: Body weights were recorded in the main study (Day 1 and Day 6) but not during the pre-test. The ear thickness was not measured.
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ADM.3500.F.2.B (3178-010519-01)
Species	Mouse, CBA/J strain
No. of animals (group size)	Preliminary test: 2 females/concentration Test substance group: 5 female mice/ concentration Vehicle control group: 5 female mice Positive group: 5 female mice
Range finding:	Yes The concentrations of 25%, 50%, and 100% as well as a vehicle control group were tested during the preliminary test.
Exposure (concentration(s), no. of applications)	25%, 50%, and 100 % 25 µL of the appropriate concentration was applied to the ears of each mouse once per day for three consecutive days.
Vehicle	1% Pluronic® L92
Pretreatment prior to topical application	Not applicable
Reliability check	25% Hexyl cinnamic aldehyde

Remarks	None

Results and discussions

Table A 10: Results of skin sensitisation study of ADM.3500.F.2.B

	No. of animals	Concentration (%)	DPM / group (SD)	Stimulation index (SI)	EC3 value
ADM.3500.F.2.B	5	25	10865.82 (4310.13)	1.80	88.1%
	5	50	8627.25 (2849.23)	1.43	
	5	100	21055.32 (10435.79)	3.49	
Vehicle Control Group	5	1	6030.62 (1152.96)	---	---
Positive control	5	25	28770.96 (13388.17)	4.77	---

SD = standard deviation

Clinical signs:	All animals appeared active and healthy throughout the study. One mouse of the vehicle control group and of the positive control group and three mice of the test groups lost body weight (< 3%) during the study. All other mice gained body weight during the study. No dermal irritation was observed for any of the vehicle control group sites. Very slight erythema was evident at all positive control sites between Days 2 and 6. Slight oedema was present at three sites on Day 3 and at one site on Day 6. No dermal irritation was observed after the application of the 25% test item concentration. Very slight erythema was evident at two sites on Day 2 and at three sites on Day 3 after the application of the 50% test item concentration. Very slight erythema was evident at four test sites on Day 2, at all sites on Day 3 and at one site on Day 6. The EC3 value calculated for the test substance was 88.1%.

Conclusion

Under the experimental conditions, ADM.3500.F.2.B is a skin sensitizer. 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 spray dilutions of Prothioconazole 250 g/L EC Formulation (ADM.03500.F.2.B) is available and submitted with this dossier.

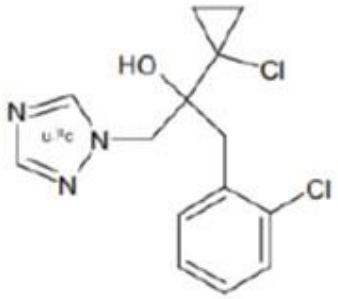
Comments of zRMS:	Dermal absorption study on prothioconazole-desthio has been conducted according to the OECD TG 428 revision 2004. For testing human split thickness skin has been used. There were no deviations from the TG. The absorbed dose of Prothioconazole-desthio from the ADM.03500.F.2.B spray dilution has been calculated based on EFSA GD 2017 also BfR Calculator. Applying a dermal absorption rate for prothioconazole-desthio in Prothioconazole 250 g/L EC Formulation (ADM.03500.F.2.B) of 11% for spray dilution diluted 1:188 and of 13% for spray dilution diluted 1:667 in non-dietary risk assessments is considered appropriate to use according to EFSA Guidance on Dermal Absorption (2017). Thus, it is concluded then the 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 *in vitro* percutaneous absorption of radiolabelled Prothioconazole-desthio in two in-use dilutions of the Prothioconazole 250 g/L EC Formulation (ADM.03500.F.2.B) through human split-thickness skin, Finlayson, Z., 2020, report no. 786166, sponsor no. 000105848
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, 99.7% (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/B/2)

	
Formulation, type of formulation (Batch No.)	Prothioconazole 250 g/L EC, ADM.03500.F.2.B, emulsifiable concentrate (3178-010519-01)
Highest concentration of relevant metabolite in the spray dilution (analytical), [g/L]	Prothioconazole-desthio: 1.33 (1.35, CV: 1.02%)
Lowest concentration of relevant metabolite in the spray dilution (analytical), [g/L]	Prothioconazole-desthio: 0.375 (0.377, CV: 1.16%)
Amount of spray dilutions applied on human skin [µL/cm²]	10 (ca. 6.4 µL)
Skin sample source	Human skin derived from abdomen of four female donors aged 48 to 64
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 8 hours 1 hour intervals followed by 2 hours interval until 24 hours after application
Integrity of skin samples	Yes, was checked by measuring the electrical resistance of skin samples, a rejection criterion of less than 7.7 kΩ was applied
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 7.42
Swabbing	Concentrated commercial hand wash soap was applied to the skin and the soap gently rubbed onto the skin with atissue 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 0.00413 g/L. The target concentration (0.00397 g/L) represented the maximum possible concentration of prothioconazole-desthio in the receptor fluid based on 70% of the applied dose being absorbed into a single 1 h receptor fluid collection. As > 100% of the target concentration was achieved in the receptor fluid the solubility was considered sufficient. Furthermore, the individual data of the highest concentration spray dilution 1 show that the receptor fluid was not rate-limiting to absorption with a mean receptor fluid value of 6.19%. Immediately after dosing the stability of prothioconazole-desthio in both test preparations was analysed by determining the radiochemical purity with the HPLC method (dilution 1: 92.8%, dilution 2: 95.3%).

The radiochemical purity of prothioconazole-desthio in dilution 2 with 95.2% confirmed stability over the dosing period in the preparation. The radiochemical purity of prothioconazole-desthio in dilution 1 with 92.8% was slightly low. As dilution 2 was made by taking an aliquot of dilution 1 and diluting with water, the varied purity value is most likely due to the low concentration of radiochemical. This is justifiable, as prothioconazole-desthio is a breakdown product, there would be varied concentrations in a realistic scenario.

For skin integrity assessment the electrical resistances of skin samples were measured and a cut-off value of < 7.7 kΩ was applied in the study.

The required mean total recovery rate of ≥ 95% was met for high and low concentration dilutions with 98.29% and 96.70% of the applied dose, respectively. For both spray dilutions tested less 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 values of spray dilution 1 and spray dilution 2 are with 69.54 and 73.74 below the threshold of 75. According to the EFSA guidance on dermal absorption (2017), the absorption 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. The calculated values are listed below in the summary table. To address variability between replicates, 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 15 below.

Table A 11: Results of dermal absorption of [^{14}C]prothioconazole-desthio in ADM.03500.F.2.B through human skin

	Dilution 1		Dilution 2	
	high dose		low dose	
Target concentration [mg/mL]	1.33		0.375	
Target dose [µg/cm^2]	13.3		3.75	
Mean actual applied dose [µg/cm^2]	13.5		3.77	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Swash after 8 h incl. donor chamber wash	87.82	2.36	85.58	4.04
Skin associated dose				
Tape strips 1-2	0.44	0.58	0.21	0.13
Tape strips 3-x	1.04	1.18	0.74	0.63
Skin preparation	2.24	0.89	2.09	1.32
Absorbed dose				
Receptor fluid	6.19	2.51	7.65	3.79
Receptor chamber wash	0.55	0.23	0.43	0.18
Total recovery	98.29	2.23	96.70	2.02
LLC of t_0.5 absorption	69.54	7.73	73.74	7.41
Absorption complete?	No		No	
Measured absorption. if LLC of t_0.5<=75%	10.02	1.58	10.91	2.79
Measured absorption. if LLC of t_0.5>75%	N/A	N/A	N/A	N/A
Measured absorption corrected	10.02	1.58	10.91	2.79
Relevant absorption estimate	11.350		13.251	
Final estimate (rounded)	11		13	

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 are 11% for the high concentrated spray dilution of 1.33 g/L and 13% for the low concentrated spray dilution of 0.375 g/L

Applying a dermal absorption rate for prothioconazole-desthio in Prothioconazole 250 g/L EC Formulation (ADM.03500.F.2.B) of 11% for spray dilution diluted 1:188 and of 13% for spray dilution diluted 1:667 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 12: Input parameters considered for the estimation of operator, worker and resident exposure to prothioconazole, use in cereals

Substance name	Prothioconazole	
Product name	ADM.03500.F.2.B	
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	0.2	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 13: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to prothioconazole, use in cereals

Substance	Prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.2 kg a.s. /ha	Spray dilution = 2 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		0.2239	% of RVNAS	111.95%
	Acute systemic exposure mg/kg bw/day		1.2395	% 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		0.1402	% of RVNAS	70.12%
	Acute systemic exposure mg/kg bw/day		0.6105	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.1750	% of RVNAS	87.50%
	Working clothing mg/kg bw/day	0.0196	% of RVNAS	9.80%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0376	% of RVNAS	18.79%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0022	% of RVNAS	1.10%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0236	% of RVNAS	11.81%
	All pathways (mean) mg/kg bw/day	0.0422	% of RVNAS	21.11%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0090	% of RVNAS	4.50%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0010	% of RVNAS	0.48%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0131	% of RVNAS	6.56%
	All pathways (mean) mg/kg bw/day	0.0157	% of RVNAS	7.83%

A 3.1.2 Calculations for prothioconazole-desthio

Table A 14: Input parameters considered for the estimation of operator, worker and resident exposure to prothioconazole-desthio, use in cereals

Substance name	Prothioconazole-desthio	
Product name	ADM.03500.F.2.B	
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	0.1814	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	13.00%	
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	

A 3.1.3 Calculations for prothioconazole considering a conversion rate of 50%

Table A 15: Input parameters considered for the estimation of operator, worker and resident exposure to 50% prothioconazole, use in cereals

Substance name	Prothioconazole	
Product name	ADM.03500.F.2.B	
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	0.1	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 16: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to 50% prothioconazole, use in cereals

Substance	Prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1 kg a.s. /ha	Spray dilution = 1 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		0.1309	% of RVNAS	65.44%
	Acute systemic exposure mg/kg bw/day		0.8577	% 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		0.0111	% of RVNAS	5.53%
	Acute systemic exposure mg/kg bw/day		0.1016	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0875	% of RVNAS	43.75%
	Working clothing mg/kg bw/day	0.0098	% of RVNAS	4.90%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0188	% of RVNAS	9.40%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.54%
	Surface deposits (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.55%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0118	% of RVNAS	5.91%
	All pathways (mean) mg/kg bw/day	0.0216	% of RVNAS	10.82%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0045	% of RVNAS	2.25%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.12%
	Surface deposits (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	0.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0066	% of RVNAS	3.28%
	All pathways (mean) mg/kg bw/day	0.0079	% of RVNAS	3.97%

A 3.1.4 Calculations for prothioconazole-desthio considering a conversion rate of 50%

Table A 17: Input parameters considered for the estimation of operator, worker and resident exposure to prothioconazole-desthio, to 50% prothioconazole, use in cereals

Substance name	Prothioconazole-desthio	
Product name	ADM.03500.F.2.B	
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	0.0907	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	11.00%	
Dermal absorption of in-use dilution	13.00%	
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-desthio, use in cereals

Substance	Prothioconazole-desthio	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0907 kg a.s. /ha	Spray dilution = 0.907 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 = 11	Dermal for in use diluation = 13	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		0.0503	% of RVNAS	503.17%
	Acute systemic exposure mg/kg bw/day		0.3331	% 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		0.0024	% of RVNAS	24.18%
	Acute systemic exposure mg/kg bw/day		0.0210	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0147	% of RVNAS	147.39%
	Working clothing mg/kg bw/day	0.0017	% of RVNAS	16.51%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0032	% of RVNAS	31.82%
	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	2.45%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	19.90%
	All pathways (mean) mg/kg bw/day	0.0046	% of RVNAS	45.92%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0008	% of RVNAS	7.59%
	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	0.80%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	11.05%
	All pathways (mean) mg/kg bw/day	0.0015	% of RVNAS	15.31%

Table A 19: Screenshot of the summary table in the EFSA calculator for the estimation of operator, worker and resident exposure to prothioconazole-desthio, use in cereals

Substance	Prothioconazole-desthio	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1814 kg a.s. /ha	Spray dilution = 1.814 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 = 13	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		0.0048	% of RVNAS	47.93%
	Acute systemic exposure mg/kg bw/day		0.0343	% 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		0.0032	% of RVNAS	32.08%
	Acute systemic exposure mg/kg bw/day		0.0260	% of RVAAS	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0295	% of RVNAS	294.78%
	Working clothing mg/kg bw/day	0.0033	% of RVNAS	33.01%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0064	% of RVNAS	63.63%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	10.70%
	Surface deposits (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	4.91%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0040	% of RVNAS	39.79%
	All pathways (mean) mg/kg bw/day	0.0081	% of RVNAS	81.14%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0015	% of RVNAS	15.18%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	2.30%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.61%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0022	% of RVNAS	22.11%
	All pathways (mean) mg/kg bw/day	0.0028	% of RVNAS	28.32%

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

Not relevant.