

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: CA3642

Product name(s): JOUST PRO

Chemical active substance(s):

Prothioconazole, 150 g/L

Azoxystrobin, 150 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

New Authorisation (Art. 33)

Sponsor: Nufarm Crop Products UK Limited

Applicant: Nufarm Polska Sp. z o. o.

Submission date: 01/02/2023

1st Update: June 2023, 2nd Update: December 2023

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(initial Core Assessment)

October 2024, December 2024 (final Core Assessment)

Version history

When	What
February 2023	Initial dossier submission
June 2023	1 st Update following comments from zRMS PL (May 29 th , 2023)
August 2023	<p>Initial assessment by the zRMS</p> <p>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are struck through and shaded for transparency.</p> <p>Following the evaluation and before sending the document for commenting, all highlighted changes in colour has been removed, from the parts updated by the Applicant, for better legibility.</p>
December 2023	2 nd Update by the Applicant
May 2024	<p>Initial assessment by the zRMS</p> <p>The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are struck through and shaded for transparency.</p> <p>Following the evaluation and before sending the document for commenting, all highlighted changes in colour has been removed, from the parts updated by the Applicant, for better legibility.</p>
October 2024	<p>Final report (Core Assessment updated following the commenting period)</p> <p>Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Not agreed or not relevant information are struck through and shaded for transparency.</p>
December 2024	<p>Final report (Core Assessment updated following the second commenting period)</p> <p>No additional information or assessments after the commenting period.</p>

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Reviewer general comment:

This part of dossier (B6) summarizes data related to the toxicity and NDE assessment for the plant protection product CA3642/ JOUST PRO. This application is submitted for the approval under Art.33 of EU Regulation 1107/2009 of the product coded CA3642, a Suspension concentrate (SC) formulation containing prothioconazole 150 g/L and azoxystrobin 150 g/L.

CA3642 is a fungicide with protective and curative mode of actions that it is intended to be used against a number of foliar and ear diseases.

ZRMS reviewed all elements key to risk assessment and decision-making. The assessment of the toxicity profile of the CA3642/JOUST PRO product and the data presented by the Applicant took into account the hazard classification of the mixtures, which was based on *in vivo* tests, and additionally on the additivity formula taking into account the content of relevant components of the mixture. In accordance with Regulation 1272/2008, *in vivo* tests have priority over the calculation method, therefore the product hazard classification and toxicological profile were agreed by the zRMS Reviewer based on the results of *in vivo* tests.

NDE assessment for operator, workers and B&R has been calculated using the EFSA calculator, on-line version 1.01 considering the worst-case exposure scenario to cover all the intended uses (highest application rate per application as well as the highest application rate per year with the shorter interval between each application). All NDE calculations provided for operator, workers and B&R resulting from use of PPP, considering all tasks according to the critical use(s), identify safe use of the product CA3642/ JOUST PRO.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on CA3642*

Product name and code	CA3642, JOUST PRO
Formulation type	Suspension concentrate [SC]
Active substance(s) (incl. content)	Prothioconazole; 150 g/L Azoxystrobin, 150 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 CA3642 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 CA3642 according to Regulation (EC) No 1272/2008 considering toxicity profile

Hazard class(es), categories	Acute Tox. Cat. 4 Skin Sens. Cat. 1
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 skin reaction
Precautionary statement(s)	P261 Avoid breathing mist/vapours/spray. P264 Wash hands and exposed parts of the body thoroughly after handling P270 Do not eat, drink or smole when using this product P272 Contaminated work clothing should not be allowed out of the work place P280 Wear protective gloves, protective clothing face protection, eye protection P301+P312 IF SWALLOWED: Call a POISON CENTER or a doctor if you feel unwell. P330 Rinse mouth P333+P313 If skin irritation or rash occurs: Get medical advice/attention P302+P352 IF ON SKIN: Wash with plenty of water. P362+P364 Take off contaminated clothing an wash it before reuse
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. To avoid risks to human health and the environment, comply with the instructions for use [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for CA3642

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Operators must wear adequate work wear clothing during mixing/loading
Workers	Acceptable	Worker should use adequate work wear when entering a treated area
Residents	Acceptable	Buffer zone (5 m) or drift reduction technology (50%)*
Bystanders	Acceptable	Buffer zone (5 m) or drift reduction technology (50%)*

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

zRMS Reviewer position (October 2024) reflecting comment made by the cMS: there are no provisions regulating this problem, and no harmonised approach for the quantitative risk assessment of the potentially sensitising hazard of a diluted product to residents/bystanders. Until such an approach is agreed reliable risk management methods will be proposed to minimize the risk. zRMS Reviewer suggest the inclusion of additional phrase on the label of the product: “Treated areas should not be re-entered before spray deposits on leaf surfaces have completely dried”

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

Table 6.1-4 Critical uses and overall conclusion of exposure assessment assumed 100% conversion factor PTZ to PTZ-desthio.

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situ- ation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/syn- ergist (L/ha)) critical gap for operator, worker, resident or by- stander exposure based on [Expo- sure model]	Acceptability of exposure assess- ment			
			Method / Kind (incl. applica- tion technique ***	Max. number (min. interval between ap- plications) a) per use b) per crop/ season	Max. applica- tion rate kg as/ha a) a.s. 1 b) a.s. 2	Water L/ha min / max			Operator	Worker	Residents	Bystander
1-52, 53- 78, 79- 102, 103, 104, 105- 116	Wheat, triticale, rye (BBCH 30- 69), barley, oats (BBCH 30-61), oilseed rape (BBCH 14-18, 20-69), Sun- flower (16-64), flax (BBCH 33 – 51), Mustard (14-18, 20-69)	F	Spraying, LCTM	a) 2 b) 2 (14)	a) 0.210 prothi- oconazole b) 0.210 azoxystrobin	100 - 400	35 - 56	Guidance on the assessment of ex- posure of opera- tors, workers, resi- dents and bystand- ers in risk assess- ment for plant pro- tection products; EFSA Journal 2022; 20(1): 7032				

* 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

Table 6.1-5 Critical uses and overall conclusion of exposure assessment assumed 50% conversion factor PTZ to PTZ-desthio.

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situa- tion (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/syn- ergist (L/ha)) critical gap for operator, worker, resident or by- stander exposure based on [Expo- sure model]	Acceptability of exposure assess- ment			
			Method / Kind (incl. applica- tion technique ***	Max. number (min. interval between ap- plications) a) per use b) per crop/ season	Max. applica- tion rate kg as/ha a) a.s. 1 b) a.s. 2	Water L/ha min / max			Operator	Worker	Residents	Bystander
1-52, 53- 78, 79- 102, 103, 104, 105- 116	Wheat, triticale, rye (BBCH 30- 69), barley, oats (BBCH 30-61), oilseed rape (BBCH 14-18, 20-69), Sun- flower (16-64), flax (BBCH 33 – 51), Mustard (14-18, 20-69)	F	Spraying, LCTM	a) 2 b) 2 (14)	a) 0.210 prothi- oconazole b) 0.210 azoxystrobin	100 - 400	35 - 56	Guidance on the assessment of ex- posure of opera- tors, workers, resi- dents and bystand- ers in risk assess- ment for plant pro- tection products; EFSA Journal 2022; 20(1): 7032				

* 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

Table 6.1-6 Critical uses and overall conclusion of exposure assessment- azoxystrobin

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I**	Application		Application rate		PHI (d)	Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind (incl. application technique ***	Max. number (min. interval between applications) a) per use b) per crop/season	Max. application rate kg as/ha a) a.s. 1 b) a.s. 2	Water L/ha min / max			Operator	Worker	Residents	Bystander
1-52, 53-78, 79-102, 103, 104, 105-116	Wheat, triticale, rye (BBCH 30-69), barley, oats (BBCH 30-61), oilseed rape (BBCH 14-18, 20-69), Sunflower (16-64), flax (BBCH 33-51), Mustard (14-18, 20-69)	F	Spraying, LCTM	a) 2 b) 2 (14)	a) 0.210 prothioconazole b) 0.210 azoxystrobin	100 - 400	35 - 56	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022; 20(1): 7032				

* 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

No data gaps were identified

6.2 Toxicological Information on Active Substance(s)

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

Table 6.2-1: Information on active substances

	Prothioconazole	Prothioconazole-desthio (me- tabolite)*	Azoxystrobin
Common Name	Prothioconazole	Prothioconazole-desthio	Azoxystrobin
CAS-No.	178928-70-6	120983-64-4	131860-33-8
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes, categories: None Code for hazard pictogram: None Signal word: None Hazard statement: None	Hazard classes, categories: None Code for hazard pictogram: None Signal word: None Hazard statement: None	Annex VI CLP (ATP15): Hazard classes, categories: Acute Tox. Cat. 3 ATE _{inhal} = 0,7 mg/L (dust and mist) acc. To Reg. 2020/1182, in prothioconazole Renewal assessment report 2018 from UK, CLH Report Code for hazard pictogram: GHS06

	Prothioconazole	Prothioconazole-desthio (metabolite)*	Azoxystrobin
			Signal word: Danger Hazard statement: H331 Precautionary statement: P261, P273, P280, P304+P340, P311, P321, P405, P501
Additional C&L proposal	None	None	EUH 401
Agreed EU endpoints			
AOEL systemic	0.2 mg/kg bw/d	0.01 mg/kg bw/d	0.2 mg/kg bw/d
Reference (for EU endpoints)	EFSA Scientific Report (2007) 106, 1-98, Conclusion regarding the peer review of the pesticide risk assessment of the active substance prothioconazole	EFSA Scientific Report (2007) 106, 1-98, Conclusion regarding the peer review of the pesticide risk assessment of the active substance prothioconazole	EFSA Scientific Report (2010) 8(4):1542 Conclusion on the peer review of the pesticide risk assessment of the active substance azoxystrobin.
Conditions to take into account/critical areas of concern with regard to toxicology			
According to Review Report/EFSA Conclusion for active substances	The operator safety in spray applications. Conditions of use should include adequate protective measures.	The operator safety in spray applications. Conditions of use should include adequate protective measures.	None
* Prothioconazole-desthio is a relevant metabolite of prothioconazole with a lower AOEL. As such it was considered appropriate to include this metabolite as part of the human non-dietary risk assessments			

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for CA3642 is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of the toxicological evaluation for CA3642 on acute toxicity including irritancy and skin sensitisation for CA3642 based on additive formula

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD50 oral (calculation method)	> 2000 mg/kg bw	results were not taken into account Supplementary*	None	Registration Report - Part C
LD50 dermal (calculation method)	> 2000 mg/kg bw	results were not taken into account Supplementary*	None	Registration Report - Part C
LC50 inhalation (calculation method)	>5 mg/L air	results were not taken into account Supplementary*	None	Registration Report - Part C
Skin irritation (calculation method)	Non-irritant	results were not taken into account Supplementary*	None	Registration Report - Part C
Eye irritation (calculation method)	Irritant	results were not taken into account Supplementary*	Eye Irrit. 2, H319	Registration Report - Part C
Skin sensitisation (calculation method)	Non-sensitising	results were not taken into account Supplementary*	None	Registration Report - Part C

Supplementary studies for combinations of plant protection products	No data – not required	--	--	--
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zRMS Reviewer comment: According to Reg 1272/2008, *in vivo* studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the test results

***zRMS Reviewer comment (October 2024):** During commenting it was noted by the cMS “that 1 out of 5 female rats died after one hour of exposure therefore it is not possible to rule out that classification criteria would have been met, if the animals had been exposed to the aerosolized PPP for the full time period of 4 hour. Therefore, the study data are not sufficient to finally conclude that the plant protection product should not be classified for acute inhalation toxicity” (see Ellis M.; 2020c) considering mentioned above discussion zRMS decided to substantiate outcome of the inhalation study, taking into account calculation method regarding this endpoint.

For the sake of consistency in the toxicological evaluation, zRMS decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the *in vivo* studies remain as primary source of information. Therefore outcome of the Eye irritation study (KCP 7.1.5 Ellis M. 2020e) has precedence to the result of the estimation method (see 1272/2008).

Table 6.3-2: Summary of the toxicological evaluation for CA3642 on acute toxicity including irritancy and skin sensitisation for CA3642 based on *in vivo* studies

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral	1750 mg/kg bw	Yes	Acute Tox. Cat. 4 H302 “Harmful if swallowed”	KCP 7.1.1 [REDACTED] 2020a
LD ₅₀ dermal	> 5000 mg/kg bw	Yes	None	KCP 7.1.2 [REDACTED] 2020b
LC ₅₀ inhalation	>4.96 mg/L air (1 hour) >1.24 mg/L air (4 hours)	Yes	None	KCP 7.1.3 [REDACTED] 2020c
Skin irritation	Non-irritant	Yes	None	KCP 7.1.4 [REDACTED] 2020d
Eye irritation	Non-irritant	Yes	None	KCP 7.1.5 [REDACTED] 2020e
Skin sensitisation	Sensitising	Yes	Skin Sens. Cat. 1 H317 “May cause an allergic skin reaction”	KCP 7.1.6 [REDACTED] 2020f
Supplementary studies for combinations of plant protection products	No data – not required	--	--	--

Table 6.3-3: Additional toxicological information relevant to the active substances and co-formulants of CA3642

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference
Toxicological properties of active substance(s) (relevant for classification of product)	Prothioconazole (14.05% (w/w))	None	COMMISSION DELEGATED REGULATION (EU) 2021/849 MSDS** (2021)

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference
Toxicological properties of active substance(s) (relevant for classification of product)	Azoxystrobin (13.98% (w/w))	H331	COMMISSION DELEGATED REGULATION (eu) 2020/1182 MSDS** (2021)
Toxicological properties of non-active substance(s) (relevant for classification of product)	Polyethoxylated (15EO) Fatty (C16 – C18) at 70% in monopropylene glycol (9-10% (w/w))*	H319 (mixture)	MSDS** (2021)
	20% aqueous solution with dipropylene glycol of sodium salt of 1,2 benzisothiazolin-3- one (<0.1% (w/w))*	H302 H314 H318 H317 (mixture)	MSDS** (2021)
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

The following data on metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites is reported in Part B.10; the submitted toxicological studies are summarised in this document.

6.4.1 R234886

An overview of the results of the accepted toxicological studies for azoxystrobin groundwater metabolite R234886 is given in the following table. The studies were previously submitted and reviewed at EU level, as part of the first active substance renewal process for azoxystrobin. The studies were summarised in the first Renewal Assessment Report (Azoxystrobin – Volume 3, Annex B.6: Toxicology and Metabolism, May 2009) and referenced in the EFSA Conclusion (EFSA Journal 2010; 8(4):1542). As the studies have been previously evaluated, only brief summaries are provided in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4-1: Summary of the results of toxicity studies for R234886

Type of test, species (Guideline)	Result	Acceptability	Reference*
Acute oral toxicity, female rat (OECD 425)	LD ₅₀ > 5000 mg/kg bw	Yes	█, 2005*
Bacterial reverse mutation, <i>S.</i> <i>typhimurium</i> and <i>E. coli</i> (OECD 471)	Negative (non-mutagenic)	Yes	Callander, 2005*

* indicates that a study was reviewed at EU level

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in CA3642 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in CA3642

	Prothioconazole		Prothioconazole-desthio (metabolite)*		Azoxystrobin	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	10%	EFSA Guidance 2017, 4873 default value for concentrate	0.25%	Delobel.M, 2022	0.34%	Delobel.M, 2023
Dilution (0.2%)	50%	EFSA Guidance 2017, 4873 default value for dilution	21%	Delobel.M, 2022	18%	Delobel.M, 2023

* Prothioconazole-desthio is a relevant metabolite with toxicity effects which is formed after foliar spray application of prothioconazole containing products. Diluted prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Although prothioconazole-desthio is not part of the formulation, non-dietary risk assessments were performed for prothioconazole-desthio due to a lower AOEL compared to prothioconazole.

6.5.1 Justification for proposed values - Prothioconazole

No data on dermal absorption for prothioconazole in CA3642 is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for prothioconazole

	Value	Justification for value	Acceptability of justification
Concentrate	10%	CA3642 is a suspension concentrate and the EFSA guidance on dermal absorption indicates a default value of 10% for concentrate for water based formulations.	Justification accepted. Endpoint can be used for current product
Dilution	50%	CA3642 is a suspension concentrate and the EFSA guidance on dermal absorption indicates a default value of 50% for diluted product for water based formulations.	Justification accepted. Endpoint can be used for current product

6.5.2 Justification for proposed values – Prothioconazole-desthio (metabolite)

Proposed dermal absorption rates for prothioconazole-desthio are based on a dermal absorption study on a formulation identical to CA3642. The study results are summarised in the following table. A full summary of the study on the dermal absorption of prothioconazole-desthio that has not previously been evaluated within an EU peer review process is described in detail in Appendix 2.

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

Test	Concentrate	Spray dilution (1: 500)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	0.25%	21%	CA3642	Yes	Not required	Study outcome accepted. Endpoint can be used for current	Delobel, M., 2022

Test	Concentrate	Spray dilution (1: 500)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
						product	

6.5.3 Justification for proposed values - Azoxystrobin

Proposed dermal absorption rates for azoxystrobin are based on dermal absorption studies on a formulation identical to CA3642. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of azoxystrobin that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5-4: Summary of the results of submitted dermal absorption studies for azoxystrobin

Test	Concentrate	Spray dilution (1:500)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.34%	18%	CA3642	Yes	Not required	Study outcome accepted. End-point can be used for current product	Delobel.M, 2023

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

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

Product name and code	CA3642		
Formulation type	SC		
Category	Fungicide		
Active substance(s) (incl. content)	Prothioconazole 150 g/L	Prothioconazole-desthio (a) 136 g/L	Azoxystrobin 150 g/L
AOEL systemic	0.2 mg/kg bw/d	0.01 mg/kg bw/d	0.2 mg/kg bw/d
Inhalation absorption	100%	100%	100%
Oral absorption	100%	100%	100%
Dermal absorption	Concentrate: 10% Dilution: 50% (Default)	Concentrate: 0.25% Dilution: 14% (1.904 g/L) Dilution: 21% (0.272 g/L) (Based on formulation)	Concentrate: 0.34% Dilution: 3.2% (2.1 g/L) Dilution: 18% (0.30 g/L) (Based on formulation)

(a) Calculated assuming 100% conversion of prothioconazole to prothioconazole-desthio. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio).

6.6.1 Selection of critical use(s) and justification

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

Justification

The cGAPs have been based upon a consideration of the maximum use rate and the minimum water volume

(i.e., spray volume). Also, for consideration of the cGAPs for re-entry worker, the minimum spray interval has also been considered.

Prothioconazole-desthio is a relevant metabolite with toxicity effects which is formed during and following foliar spray application of prothioconazole containing products. Diluted prothioconazole can degrade to prothioconazole-desthio in solution, on plant surfaces, clothing or skin. Although prothioconazole-desthio is not part of the formulation, non-dietary risk assessments were included for prothioconazole-desthio due to a lower AOEL compared to prothioconazole.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

Comments of zRMS:	NDE calculations performed by the applicant are acceptable and zRMS agrees to the conclusions. The risk for operators is acceptable under conditions of intended uses and considering below mentioned risk mitigation measures such as Work wear (arms, body and legs covered) during M, L and A
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A summary of the exposure models used for estimation of operator exposure to the active substances during application of CA3642 according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in Appendix 3. No acute exposure assessment is provided as no AAOEL value has been determined for the active substance.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Cereals max. 2 x (0.210 kg prothioconazole/ha + 0.210 kg azoxystrobin/ha) Max application rate: 1.4 L product/ha; equivalent to 0.210 kg prothioconazole/ha (equal to 0.190 kg prothioconazole-desthio/ha, assuming 100% conversion) and 0.210 kg azoxystrobin/ha Water volume: 100 - 400 L/ha
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products; EFSA Journal 2022;20(1):7032 On line calculator: OPEX version 1.0.0

To account for the potential conversion of prothioconazole to prothioconazole-desthio, a conservative approach was used and the following assumptions were made in the exposure calculations:

For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio was assumed. This is taken as the worst possible case and the actual conversion is likely to be lower. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio).

No conversion from prothioconazole to prothioconazole-desthio was considered for the exposure assessment of prothioconazole.

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

		Prothioconazole		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Cereal (2 x 0.210 kg as/ha, 100 L/ha, application equipment: vehicle mounted, downward spraying)					
Application rate		0.210 kg a.s./ha		0.190 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Potential	0.117	58.7	0.0103	103
	Work wear (arms, body and legs covered) M/L and A	0.076	38.1	0.00678	67.8

For prothioconazole the risk assessment indicates that operator exposure is below the AOEL value even if no workwear is worn for all uses.

For prothioconazole-desthio the risk assessment indicates that operator exposure is below the AOEL value if workwear is worn for all uses.

		Azoxystrobin	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Cereal (2 x 0.210 kg a.s./ha, 100 L/ha, application equipment: vehicle mounted, downward spraying)			
Application rate		0.210 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Potential	0.0108	5.4
	Work wear (arms, body and legs covered) M/L and A	0.0072	3.6

For azoxystrobin the risk assessment indicates that operator exposure is below the AOEL value even if no workwear is worn for all uses.

When the combined exposure of prothioconazole-desthio and azoxystrobin is considered (see Section 6.6.5) an acceptable exposure is obtained ($HI = 0.68 + 0.04 = 0.72$).

In addition, calculations are provided to show the risk assessment assuming a 50% conversion of prothioconazole to prothioconazole-desthio (see Appendix 3.4).

		Prothioconazole		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Cereal (2 x 1.4L product/ha PTZ, 100 L/ha, application equipment: vehicle mounted, downward spraying)					
Application rate		0.210 kg a.s./ha, 0.105 kg a.s./ha ¹		0.190 kg a.s./ha, 0.095 kg a.s./ha ²	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Potential	0.107	48.4 + 5.2 = 53.6	0.00461	0.0 + 46.1 = 46.1
	Work wear (arms, body and legs covered) M/L and A	0.0694	31.3 + 3.4 = 34.7	0.00307	0.00 + 30.7 = 30.7
Note the exposure for azoxystrobin remains the same (see above); 3.6% AOEL with Workwear					
1 Exposure to PTZ only during M/L, and 50% PTZ during application					
2 No exposure during M/L, exposure to 50% PTZ-desthio during application					

In section 6.6.5 the combined exposure, considering 50% conversion of prothioconazole, is calculated and demonstrates that an acceptable is obtained ($HI = 0.34 + 0.31 + 0.04 = 0.69$).

6.6.2.2 Measurement of operator exposure

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

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Comments of zRMS:	NDE calculations performed by the applicant are acceptable and zRMS agrees to the conclusions. Exposure for workers (entry into a previously treated area or handling a crop according
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	to the critical uses) is acceptable under conditions of intended uses considering below mentioned risk mitigation measures such as Work wear, (arms, body and legs covered) even in case when 100% conversion factor PTZ to PTZ-desthio has been taken into account.
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Table 6.6-4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with CA3642 according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Cereals max. 2 x (0.210 kg prothioconazole/ha + 0.210 kg azoxystrobin/ha) Max application rate: 1.4 L product/ha; equivalent to 0.210 kg prothioconazole/ha (equal to 0.190 kg prothioconazole-desthio/ha, assuming 100% conversion) and 0.210 kg azoxystrobin/ha Water volume: 100 –400 L/ha
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products; EFSA Journal 2022;20(1):7032 On line calculator: OPEX version 1.0.0

To account for the potential conversion of prothioconazole to prothioconazole-desthio, in the first instance a conservative approach was used and the following assumptions were made in the exposure calculations:

For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio was assumed. This is taken as the worst possible case and the actual conversion is likely to be lower. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio). No conversion from prothioconazole to prothioconazole-desthio was considered for the exposure assessment of prothioconazole.

Table 6.6-5: Estimated worker exposure (longer term exposure)

		Prothioconazole		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereal – Inspection, Irrigation - Outdoor Work rate: 2 hours/day DT50: 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.210 kg a.s./ha		2 x 0.190 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm ² /person/h	0.226	113	0.0860	860
	Work wear (arms, body and legs covered) TC: 1400 cm ² /person/h	0.0252	12.6	0.00963	96.3
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm ² /person/h	0.0226	11.3	0.00860	86.0

For prothioconazole the estimated worker exposure is below the AOEL value for workers wearing standard workwear (this is not considered to be PPE) such that the arms, body and legs are covered.

For prothioconazole-desthio the risk assessment indicates that the estimated worker exposure is below the AOEL value with the use of standard workwear.

		Azoxystrobin	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereal – Inspection, Irrigation - Outdoor Work rate: 2 hours/day DT50: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 14 days			
Number of applications and application rate		2 x 0.210 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm²/person/h	0.0812	40.6
	Work wear (arms, body and legs covered) TC: 1400 cm²/person/h	0.0092	4.6
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm2/person/h	0.0082	4.1

For azoxystrobin the estimated worker exposure is below the AOEL value for workers wearing standard workwear (this is not considered to be PPE) such that the arms, body and legs are covered.

However, when the combined exposure of prothioconazole-desthio and azoxystrobin is considered (see Appendix 3) no acceptable exposure is obtained ($HI = 0.96 + 0.05 = 1.01$) unless gloves are worn ($HI = 0.86 + 0.04 = 0.90$).

To avoid the use of gloves, a refinement of the risk assessment for prothioconazole-desthio was conducted based on the data from two dislodgeable foliar residue (DFR) studies in which levels of prothioconazole-desthio were monitored. Details of the refinement are included in Section 6.6.3.2.

In addition, calculations are provided to show the risk assessment assuming a 50% conversion of prothioconazole to prothioconazole-desthio (see Appendix 3.4).

		Prothioconazole		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereal – Inspection, Irrigation - Outdoor Work rate: 2 hours/day DT50: 30 days DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.210 kg a.s./ha, 0.105 kg a.s./ha assuming 50% conversion		2 x 0.190 kg a.s./ha, 0.095 kg a.s./ha assuming 50% conversion	
Body weight: 60 kg	Potential TC: 12500 cm²/person/h	0.1128	56.4	0.04910	491
	Work wear (arms, body and legs covered) TC: 1400 cm²/person/h	0.0126	6.3	0.00550	55.0
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm²/person/h	0.0112	5.6	0.00491	49.1
Note the exposure for azoxystrobin remains the same (see above), 4.6% with Workwear					

In section 6.6.5 the combined exposure, considering 50% conversion of prothioconazole, is calculated and demonstrates that an acceptable exposure is obtained ($HI = 0.06 + 0.55 + 0.05 = 0.66$) with the use of workwear.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

For prothioconazole-desthio a refinement of the risk assessment was conducted based on the data from two dislodgeable foliar residue (DFR) studies (Stuke, S. 2013 and Stuke, S. 2015), conducted by Bayer Crop-Science, in which levels of prothioconazole and prothioconazole-desthio were monitored. One study was conducted in Northern Germany and one in Northern France and Portugal. Due to issues with analysis of prothioconazole in samples it was concluded that it was appropriate to use the prothioconazole-desthio DFR to refine exposure assessments but not the prothioconazole DFR data. As such, only the prothioconazole-desthio DFR data are used. Table 6.6-6 summarises the application details for the two DFR studies along with a comparison of those for CA3642.

Table 6.6-6: Comparison of application parameters in DFR studies and CA3642 critical GAP

Parameter	Prothioconazole SC 150+150 - Critical GAP CA3642	JAU 6476 & KWG 4168 EC 460 – Northern Germany	Bixafen & Prothioconazole EC 225 – Northern France and Portugal
Active substance	150 g/L prothioconazole (150 g/L azoxystrobin)	160 g/L prothioconazole (300 g/L spiroxamine)	150 g/L prothioconazole (75 g/L bixafen)
Formulation type	SC	EC	EC
Application method	Boom sprayer	Boom sprayer	Boom sprayer
Crop	Field crops such as cereals	Cereal (Wheat)	Cereal (Wheat)
Maximum application rate (prothioconazole)	210 g a.s./ha	200 g a.s./ha	188 g a.s./ha
Number applications	2	2	2

Application interval	14	14	14
Water volume	100 L/ha	150 L/ha	200 L/ha
Growth stage (BBCH)	14 – 69	47 - 61	47 - 65

The above parameters show that overall the applications are comparable and although there are some small differences (water volume, growth stage) it is not considered that these would have a significant effect on DFR levels. It is noted that the formulation type is different, however it is considered that once the product has been diluted with water, applied to the crop and dried on the crop surface that this would not make a significant difference to overall surface levels of prothioconazole-desthio. In addition the application rate in the studies was slightly lower (90 - 95%) than the proposed rate for CA3642. However, as DFR values, expressed as $\mu\text{g}/\text{cm}^2/\text{kg as/ha}$, are corrected for application rate this difference is also considered to be acceptable. As such these DFR studies are considered to be relevant to the intended uses of CA3642 and consequently the likely DFR levels of prothioconazole-desthio.

In both DFR studies, peak residue levels were seen immediately after application of the test item. Based on the Stuke 2015 study conducted in Portugal and France, the highest DFR value for prothioconazole-desthio was found directly after the second application in Portugal and amounted to $0.115 \mu\text{g}/\text{cm}^2$. Based on the Stuke 2013 study conducted in Germany, the highest value for prothioconazole-desthio was found directly after the second application and amounted to $0.125 \mu\text{g}/\text{cm}^2$. Using a pre-cautionary approach the highest DFR value for prothioconazole-desthio from across both studies of $0.125 \mu\text{g}/\text{cm}^2$ (equivalent to $0.691 \mu\text{g}/\text{cm}^2/\text{kg as/ha}$) was used to refine the worker exposure assessment. In fact this value was obtained in the Northern Germany study immediately following the second application, which was conducted at an application rate only slightly below that of the intended use for CA3642.

Full summaries of the studies, provided by the data owner, are submitted in Doc K 7.2-01 and 7.2-02.

DFR study results are additionally used to estimate residential exposure to PTZ-desthio due to entry into treated crops. For details please refer to section 6.6.4.1: Estimation of bystander and resident exposure.

Details of the risk assessment using refined DFR values is presented in Table 6.6-7 (longer term exposure).

Table 6.6-7: Estimated worker exposure (longer term exposure), prothioconazole-desthio (refined DFR)

		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereal – Inspection, Irrigation - Outdoor Work rate: 2 hours/day DT50: 30 days DFR: $0.691 \mu\text{g}/\text{cm}^2/\text{kg a.s./ha}$ Interval between treatments: 14 days			
Number of applications and application rate		0.190 kg equivalent/ha	
Body weight: 60 kg	Potential TC: $12500 \text{ cm}^2/\text{person/h}$	0.0198	198
	Work wear (arms, body and legs covered) TC: $1400 \text{ cm}^2/\text{person/h}$	0.00222	22.2
	Work wear (arms, body and legs covered and gloves) TC: $1250 \text{ cm}^2/\text{person/h}$	0.00198	19.8

Although the exposure assessment is below the AOEL for prothioconazole-desthio, when the combined exposure with azoxystrobin is considered (see Appendix 3) no acceptable exposure is obtained ($\text{HI} = 0.96 + 0.05 = 1.01$) unless gloves are worn ($\text{HI} = 0.86 + 0.04 = 0.90$). To avoid the use of gloves, a refinement of the risk assessment for prothioconazole-desthio was conducted based on the above DFR value. Details

of the refinement are included in Section 6.6.3.2.

When this refinement is considered, for prothioconazole-desthio the estimate of worker exposure is reduced resulting in a combined exposure below the AOEL ($HI = 0.22 + 0.05 = 0.27$) value for workers when wearing standard workwear (this is not considered to be PPE) such that the arms, body and legs are covered.

In addition, calculations are provided to show the risk assessment assuming a 50% conversion of prothioconazole to prothioconazole-desthio and using a refined DFR for prothioconazole-desthio (see Appendix 3.4).

		Prothioconazole		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereal – Inspection, Irrigation - Outdoor Work rate: 2 hours/day DT50: 30 days DFR: 0.691 µg/cm²/kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.210 kg a.s./ha, 0.105 kg a.s./ha assuming 50% conversion		2 x 0.190 kg a.s./ha, 0.095 kg a.s./ha assuming 50% conversion	
Body weight: 60 kg	Potential TC: 12500 cm²/person/h	0.1128	56.4	0.0113	113
	Work wear (arms, body and legs covered) TC: 1400 cm²/person/h	0.0126	6.3	0.00127	12.7
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm²/person/h	0.0112	5.6	0.00113	11.3
Note the exposure for azoxystrobin remains the same (see section 6.6.3.1 above), 4.6% AOEL with Workwear					

In section 6.6.5 the combined exposure, considering 50% conversion of prothioconazole, is calculated and demonstrates that an acceptable and reduced exposure is obtained ($HI = 0.06 + 0.13 + 0.05 = 0.24$).

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

Comments of zRMS:	Justification of waiving acute risk assessment for bystander discussed by the applicant is reliable thus, zRMS agrees to the conclusions. Risk for bystanders and residents is acceptable under conditions of intended uses considering proposed refined risk assessment.
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No bystander risk assessment is required for PPPs that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

Table 6.6-8 shows the exposure model(s) used for estimation of resident and bystander exposure to prothioconazole, prothioconazole-desthio (metabolite) and azoxystrobin. The outcome of the estimation is presented in Table 6.6-9 (longer term resident exposure). Detailed calculations are in Appendix 3.

Table 6.6-8: Exposure models for intended uses

Critical use(s)	Cereals max. 2 x (0.210 kg prothioconazole/ha + 0.210 kg azoxystrobin/ha) Max application rate: 1.4 L product/ha; equivalent to 0.210 kg prothioconazole/ha (equal to 0.190 kg prothioconazole-desthio/ha, assuming 100% conversion) and 0.210 kg azoxystrobin/ha Water volume: 100 L/ha
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products; EFSA Journal 2022;20(1):7032 On line calculator: OPEX version 1.0.0

To account for the potential conversion of prothioconazole to prothioconazole-desthio the following assumptions were made in the exposure calculations.

For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio was assumed. This is taken as the worst possible case and the actual conversion is likely to be lower. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio).

No conversion from prothioconazole to prothioconazole-desthio was considered for the exposure assessment of prothioconazole.

Table 6.6-9: Estimated resident exposure (longer term exposure)

		Prothioconazole		Prothioconazole-desthio (metabolite)	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 2-3 m Drift reduction technology: no DT50: 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.210 kg a.s./ha		2 x 0.190 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0284	14.2	0.0109	109
	Vapour (75 th perc.)	0.0008	0.4	0.00080	8.0
	Deposits (75 th perc.)	0.003	1.5	0.00127	12.7
	Re-entry (75 th perc.)	0.0304	15.2	0.0116	116
	Sum (mean)	0.0428	21.4	0.0169	169
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0068	3.4	0.00257	25.7
	Vapour (75 th perc.)	0.0003	0.1	0.00027	2.7
	Deposits (75 th perc.)	0.0012	0.6	0.00047	4.7
	Re-entry (75 th perc.)	0.017	8.5	0.00645	64.5
	Sum (mean)	0.0178	8.9	0.00696	69.6

		Azoxystrobin	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 2-3 m Drift reduction technology: no DT50: 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days			
Number of applications and application rate		2 x 0.210 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0102	5.1
	Vapour (75 th perc.)	0.0008	0.4
	Deposits (75 th perc.)	0.0012	0.6
	Re-entry (75 th perc.)	0.0110	5.5
	Sum (mean)	0.0160	8.0
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0024	1.2
	Vapour (75 th perc.)	0.0003	0.1
	Deposits (75 th perc.)	0.0004	0.2
	Re-entry (75 th perc.)	0.0060	3.0
	Sum (mean)	0.0066	3.3

For prothioconazole the estimate of resident (and bystander) exposure is below the AOEL value.

For prothioconazole-desthio the estimate of resident exposure is acceptable for adults but is unacceptable for children, due to high exposure through spray drift and re-entry into treated crops.

For azoxystrobin the estimated assessment for resident (longer term) exposure shows that an acceptable exposure is achieved for all cases.

For prothioconazole-desthio a refinement of the risk assessment was conducted based on the data from two dislodgeable foliar residue (DFR) studies (Stuke, S. 2013 and Stuke, S. 2015) in which levels of prothioconazole and prothioconazole-desthio were monitored. Further details of the studies are provided in section 6.6.3.2. A comparison of the application parameters for the two DFR studies along with those for CA3642 are shown in Table 6.6-6 and, as previously mentioned (see section 6.6.3.2) the studies are considered to be relevant to the intended uses of CA3642 and consequently the likely DFR levels of prothioconazole-desthio.

In both DFR studies, peak residue levels were seen immediately after application of the test item. Using a precautionary approach the highest DFR value for prothioconazole-desthio from across both studies of 0.125 µg/cm² (equivalent to 0.691 µg/cm²/kg as/ha) was used to refine the worker exposure assessment. In fact this value was obtained in the Northern Germany study immediately following the second application, which was conducted at an application rate only slightly below that of the intended use for CA3642.

The refined risk assessment is shown in Table 6.6-10.

Table 6.6-10: Estimated resident-child exposure (longer term exposure), prothioconazole-desthio (refined DFR)

		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 2-3 m Drift reduction technology: no			

DT50: 30 days DFR: 0.691 µg/cm²/kg a.s./ha Interval between treatments: 14 days			
Application rate:		2 x 0.190 kg equivalent/ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0109	109
	Vapour (75 th perc.)	0.00080	8.0
	Deposits (75 th perc.)	0.00127	12.7
	Re-entry (75 th perc.)	0.00267	26.7
	Sum (mean)	0.00978	97.8

When this refinement is considered for prothioconazole-desthio the estimate of mean exposure for resident child is not acceptable (109% AOEL for spray drift).

A further refinement of the risk assessment was conducted using a buffer zone (5 m), which is shown in Table 6.6-11.

Table 6.6-11: Estimated resident-child exposure (longer term exposure), prothioconazole-desthio (refined DFR and 5m buffer zone)

		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 5 m Drift reduction technology: no DT50: 30 days DFR: 0.691 µg/cm²/kg a.s./ha Interval between treatments: 14 days			
Application rate:		2 x 0.190 kg equivalent/ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.00724	72.4
	Vapour (75 th perc.)	0.00080	8.0
	Deposits (75 th perc.)	0.00052	5.2
	Re-entry (75 th perc.)	0.00267	26.7
	Sum (mean)	0.00729	72.9

When these refinements are considered for prothioconazole-desthio the estimate of exposure for resident child is acceptable (72.9% AOEL).

A refinement of the risk assessment was conducted using drift reduction, as an alternative to the 5m buffer zone, and is shown in Table 6.6-12.

Table 6.6-12: Estimated resident-child exposure (longer term exposure), prothioconazole-desthio (refined DFR and drift reduction technology)

		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 2 - 3 m Drift reduction technology: 50% DT50: 30 days DFR: 0.691 µg/cm²/kg a.s./ha Interval between treatments: 14 days			

Application rate:		2 x 0.190 kg equivalent/ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.00543	54.3
	Vapour (75 th perc.)	0.00080	8.0
	Deposits (75 th perc.)	0.00063	6.3
	Re-entry (75 th perc.)	0.00267	26.7
	Sum (mean)	0.00636	63.6

When these refinements are considered for prothioconazole-desthio the estimate of exposure for resident child is acceptable (63.6% AOEL).

In section 6.6.5 the combined exposure, considering 100% conversion of prothioconazole, is calculated and demonstrates that an acceptable exposure is obtained (Child HI with 5 m buffer = 0.80, Child HI with drift reduction = 0.70, Adult HI = 0.33).

In addition, calculations are provided to show the risk assessment assuming a 50% conversion of prothioconazole to prothioconazole-desthio and using a refined DFR for prothioconazole-desthio (see Appendix 3.4).

		Prothioconazole		Prothioconazole-desthio (metabolite)	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Cereals - Tractor mounted downward spray application, outdoors Buffer zone: 2-3 m Drift reduction technology: no DT50: 30 days DFR: 3.0 µg/cm ² /kg a.s./ha (PTZ), 0.691 µg/cm ² /kg a.s./ha (PTZ-desthio) Interval between treatments: 14 days					
Number of applications and application rate		2 x 0.210 kg a.s./ha, 0.105 kg a.s./ha assuming 50% conversion		2 x 0.190 kg a.s./ha, 0.095 kg a.s./ha assuming 50% conversion	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0142	7.1	0.00620	62.0
	Vapour (75 th perc.)	0.0008	0.4	0.00080	8.0
	Deposits (75 th perc.)	0.0014	0.7	0.00071	7.1
	Re-entry (75 th perc.)	0.0152	7.6	0.00153	15.3
	Sum (mean)	0.0218	10.9	0.00592	59.2
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0034	1.7	0.00147	14.7
	Vapour (75 th perc.)	0.0002	0.1	0.00027	2.7
	Deposits (75 th perc.)	0.0006	0.3	0.00027	2.7
	Re-entry (75 th perc.)	0.0084	4.2	0.00085	8.5
	Sum (mean)	0.0090	4.5	0.00183	18.3
Note the exposure for azoxystrobin remains the same (see above, Table 6.6-9), Child Sum = 8.0% AOEL, Adult Sum = 3.3% AOEL					

In section 6.6.5 the combined exposure, considering 50% conversion of prothioconazole, is calculated and demonstrates that an acceptable and reduced exposure is obtained (Child HI = 0.78, Adult HI = 0.26).

6.6.4.2 Measurement of resident and/or bystander exposure

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for prothioconazole, prothioconazole-desthio (metabolite) and azoxystrobin will not be exceeded under conditions of intended uses and considering the above mentioned risk mitigation

measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

The product is a mixture of two active substances. During use diluted prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Prothioconazole-desthio is a relevant metabolite with toxicity effects and consequently this metabolite has also been considered in the combined exposure assessments.

6.6.5.1 Exposure assessment of prothioconazole, prothioconazole-desthio (metabolite) and azoxystrobin in CA3642

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

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

A combined exposure assessment is provided, with prothioconazole-desthio included, rather than prothioconazole, along with azoxystrobin. As the Hazard Quotient for prothioconazole-desthio is always significantly higher than prothioconazole, the maximum conversion to the metabolite (ie 100%) is considered as the worst case.

Table 6.6-13: Risk assessment from combined exposure (longer term exposure)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – vehicle mounted outdoors to low crop Standard workwear	Prothioconazole-desthio	0.68
	Azoxystrobin	0.04
	Cumulative risk operators (HI)	0.72
Workers – Cereal, inspection, irrigation Standard Workwear Prothioconazole-desthio DFR refinement	Prothioconazole-desthio	0.22
	Azoxystrobin	0.05
	Cumulative risk workers (HI)	0.27
Resident – child Prothioconazole-desthio DFR refinement	Prothioconazole-desthio	
	Drift	1.09
	Vapour	0.08
	Deposits	0.13
	Re-entry	0.27
	Sum of all pathways	0.98
	Azoxystrobin	
	Drift	0.05
	Vapour	<0.01
	Deposits	0.01
	Re-entry	0.06
	Sum of all pathways	0.08

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Cumulative risk resident – child (HI)	
	Drift	1.14
	Vapour	0.08
	Deposits	0.14
	Re-entry	0.33
	Sum of all pathways	1.06
Resident – adult Prothioconazole-desthio DFR refinement	Prothioconazole-desthio	
	Drift	0.26
	Vapour	0.03
	Deposits	0.05
	Re-entry	0.15
	Sum of all pathways	0.30
	Azoxystrobin	
	Drift	0.01
	Vapour	<0.01
	Deposits	<0.01
	Re-entry	0.03
	Sum of all pathways	0.03
	Cumulative risk resident – adult (HI)	
	Drift	0.27
	Vapour	0.03
	Deposits	0.05
	Re-entry	0.18
	Sum of all pathways	0.33

Table 6.6-14: Risk assessment from combined exposure (longer term exposure) – refined for Resident Child using DFR and 5m buffer zone

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Resident – child Prothioconazole-desthio DFR and buffer zone (5m) refinement	Prothioconazole-desthio	
	Drift	0.72
	Vapour	0.08
	Deposits	0.05
	Re-entry	0.27
	Sum of all pathways	0.73
	Azoxystrobin	
	Drift	0.03
	Vapour	<0.01
	Deposits	<0.01
	Re-entry	0.06
	Sum of all pathways	0.07

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Cumulative risk resident – child (HI)	
	Drift	0.75
	Vapour	0.08
	Deposits	0.05
	Re-entry	0.33
	Sum of all pathways	0.80

The Hazard Index is < 1. Thus, combined exposure to all active substances in CA3642 is not expected to present a risk for operators, workers, residents and bystanders provided a 5 m buffer zone is used. No further refinements of the assessment is required.

Table 6.6-15: Risk assessment from combined exposure (longer term exposure) – refined for Resident Child using DFR and drift reduction technology

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Resident – child Prothioconazole-desthio DFR and drift reduction technology refinements	Prothioconazole-desthio	
	Drift	0.54
	Vapour	0.08
	Deposits	0.06
	Re-entry	0.27
	Sum of all pathways	0.64
	Azoxystrobin	
	Drift	0.03
	Vapour	<0.01
	Deposits	<0.01
	Re-entry	0.06
	Sum of all pathways	0.06
	Cumulative risk resident – child (HI)	
	Drift	0.57
	Vapour	0.08
	Deposits	0.07
	Re-entry	0.33
	Sum of all pathways	0.70

The Hazard Index is < 1. Thus, combined exposure to all active substances in CA3642 is not expected to present a risk for operators, workers, residents and bystanders provided drift reduction technology (50%) is used. No further refinement of the assessment is required.

In addition, for illustration purposes (to show that 100% conversion is the worst case), a combined exposure assessment is provided, with 50% conversion of prothioconazole to prothioconazole-desthio considered during the application phase, along with azoxystrobin. So for operator exposure, during the mixing and loading phase, only prothioconazole and azoxystrobin are considered. During the application phase prothioconazole, prothioconazole and azoxystrobin are considered. For worker and resident exposure prothioconazole, prothioconazole and azoxystrobin are considered. The corresponding substance concentrations are summarised below:

Substance	Concentrations for combined exposure for Operator during mixing and loading (g/L)	Concentrations for combined exposure for Operator during application, Worker and Resident (g/L)
Prothioconazole	150	75
Prothioconazole-desthio	0	67.9
Azoxystrobin	150	150

Exposure values (% AOEL) are taken directly from the calculator excerpts shown in Appendix 3 - Section 3.4.

Table 6.6-16: Risk assessment from combined exposure (longer term exposure) for prothioconazole (50% conversion), prothioconazole-desthio and azoxystrobin

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – vehicle mounted outdoors to low crop Standard workwear (M/L + App)	Prothioconazole (100% M/L, 50% App)	0.31 + 0.03 = 0.34
	Prothioconazole-desthio (0% M/L, 50% A)	0.00 + 0.31 = 0.31
	Azoxystrobin (100%)	0.01 + 0.03 = 0.04
	Cumulative risk operators (HI)	0.69
Workers – Cereal, inspection, irrigation Standard Workwear	Prothioconazole (50%)	0.06
	Prothioconazole-desthio (50%)	0.55
	Azoxystrobin (100%)	0.05
	Cumulative risk workers (HI)	0.66
Workers – Cereal, inspection, irrigation Standard Workwear Prothioconazole-desthio DFR refinement	Prothioconazole (50%)	0.06
	Prothioconazole-desthio (50%)	0.13
	Azoxystrobin (100%)	0.05
	Cumulative risk workers (HI)	0.24
Resident – child Prothioconazole-desthio DFR refinement	Prothioconazole (50%)	
	Drift	0.07
	Vapour	<0.01
	Deposits	0.01
	Re-entry	0.08
	Sum of all pathways	0.11
	Prothioconazole-desthio (50%)	
	Drift	0.62
	Vapour	0.08
	Deposits	0.07
	Re-entry	0.15
	Sum of all pathways	0.59
	Azoxystrobin (100%)	
	Drift	0.05
	Vapour	<0.01
	Deposits	0.01
	Re-entry	0.06
	Sum of all pathways	0.08
	Cumulative risk resident – child (HI)	

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Drift	0.70
	Vapour	0.09
	Deposits	0.08
	Re-entry	0.30
	Sum of all pathways	0.78
Resident – adult Prothioconazole-desthio DFR refinement	Prothioconazole (50%)	
	Drift	0.02
	Vapour	<0.01
	Deposits	<0.01
	Re-entry	0.04
	Sum of all pathways	0.05
	Prothioconazole-desthio (50%)	
	Drift	0.15
	Vapour	0.03
	Deposits	0.03
	Re-entry	0.09
	Sum of all pathways	0.18
	Azoxystrobin (100%)	
	Drift	0.01
	Vapour	<0.01
	Deposits	<0.01
	Re-entry	0.03
	Sum of all pathways	0.03
	Cumulative risk resident – adult (HI)	
	Drift	0.18
	Vapour	0.03
	Deposits	0.03
	Re-entry	0.16
	Sum of all pathways	0.26

The Hazard Index is < 1 when considering 50% conversion of prothioconazole to prothioconazole-desthio. Thus, in this situation, combined exposure to all active substances in CA3642 is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.



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	██████	2020a	Tazer Pro: Acute Oral Toxicity – Up-and-Down Procedure in Rats ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.1.2	██████	2020b	Tazer Pro: Acute Dermal Toxicity in Rats ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.1.3	██████	2020c	Tazer Pro: Acute Inhalation Toxicity in Rats ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.1.4	██████	2020d	Tazer Pro: Primary Skin Irritation in Rabbits ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.1.5	██████	2020e	Tazer Pro: Primary Eye Irritation in Rabbits ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.1.6	██████	2020f	Tazer Pro: Local Lymph Node Assay (LLNA) in Mice ██████ GLP Not published	Y	Nufarm Agriculture Inc.
KCP 7.2-01	Stuke, S.	2013	Determination of the dislodgeable foliar residues (DFR) of prothioconazole in/on wheat after spray application of JAU 6476 & KWG 4168 EC 460 in the field in Germany. Bayer CropScience report No. 12-2901 GLP Not published	N	Bayer AG Crop Science Division

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 7.2-02	Stuke, S.	2015	Determination of the dislodgeable foliar residues (DFR) of prothioconazole and BYF 00587 in/on wheat after spraying of Bixafen & Prothioconazole EC 225 in the field in France (North) and Portugal. Bayer CropScience report No.14-2907 GLP Not published	N	Bayer AG Crop Science Division
KCP 7.3-01	Delobel, M.	2022	Distribution and penetration study in human skin of one concentrated CA3642 test item and 2 dilutions containing ¹⁴ C-prothioconazole-desthio Eurofins ADME Bioanalyses Nufarm Crop Product UK Report No.: 20-0568 GLP Unpublished	N	Nufarm
KCP 7.3-02	Delobel, M.	2023	Distribution and penetration study in human skin of one concentrated CA3642 test item and 2 dilutions containing ¹⁴ C-azoxystrobin with non-labeled prothioconazole Eurofins ADME Bioanalyses Nufarm Crop Product UK Report No.: 21-9194 GLP Unpublished	N	Nufarm

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
KCA 5.8.1/01		2005	Azoxystrobin metabolite R234886: Acute Oral Toxicity Study in The Rat (Up and Down Procedure)  GLP Unpublished	Y	Syngenta

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
KCA 5.8.1/02	Callander, R.	2005	Azoxystrobin metabolite R234886: Bacterial Mutation Assay in S. Typhimurium and E. Coli Report No. YV7083-REG Central Toxicology Laboratory (CTL), Cheshire, UK GLP Unpublished	N	Syngenta

List of data submitted by the applicant and not relied on

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

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

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

CA3642 is a fungicide containing the active substances prothioconazole and azoxystrobin. CA3642 is composed of 150.0 g/L (13.63% w/w) prothioconazole and 150.0 g/L (13.63% w/w) azoxystrobin. Acute toxicity studies were performed on the product CA3642. In vitro dermal absorption studies for prothioconazole-desithio and azoxystrobin were performed on CA3642, therefore, no bridging statement is necessary. In addition to this, classification taking into account Data on the active substances and co-formulants is reported as supportive data in the Part C of this dossier.

Comments of zRMS:	<i>In vivo</i> studies submitted by the applicant to support registration of the product CA3642 / JOUST PRO has been conducted on the same formulation thus bridging approach is not applicable for this registration process.
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A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. (Note: previously deleted text fragments have been restored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. A single co-formulant is classified for acute oral toxicity. The ATE_{mix} is >2000 mg/kg bw and therefore classification of the product is not required (see details in Registration Report - Part C).

Conclusion

According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is not classified for acute oral toxicity.

Comments of zRMS:	Study (██████ 2020a,) has been reviewed for compliance with the current guidelines resulting from scientific progress (OECD 425). Study (██████, 2020a,) implements 3R rules minimizing the number of animals required to estimate the acute oral toxicity of a chemical. No deviation has been noted. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference	KCP 7.1.1/01
Report	Tazer Pro: Acute Oral Toxicity – Up-and-Down Procedure in Rats, ██████, 2020a, ██████
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002)
Deviations	No
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 425
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
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Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	9 females (treated in sequence)
Dose(s)	Sequential treatment: 175; 550; 1750 or 5000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	None; test item administered as received (mixed well prior to use)
Post exposure observation period	14 days
Remarks	<p>The test item was administered in sequence to the animals, using the doses selected above. The decisions to proceed with the next animal and the choice of the tested dose was based on the survival or the death of the previous animal:</p> <ul style="list-style-type: none"> - In case of survival, the next rat was dosed with the following sequential high dose; - In case of death, the next rat was dosed with the following sequential low dose. <p>Statistical analysis was performed for the calculation of the mean density value for dosing, as well it was used for all data analysed including LD50 and confidence limit calculations.</p> <p>The rats were observed for mortality, signs of gross toxicity and behavioral changes approximately 30-mns post dosing during the first several hours post-dosing and at least once daily thereafter for 14 days after dosing or until death occurred.</p> <p>Individual body weights of the rats were recorded prior to the test item administration and again on Days 7 and 14 following dosing or after death.</p> <p>Gross necropsies were performed on all decedents and euthanized rats (via CO₂ inhalation).</p>

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of CA3642

Dose Sequence	Dose level (mg/kg bw)	Short-Term Outcomes	Long-Term Outcomes
1	175	S	S
2	550	S	S
3	1750	D	D
4	550	S	S
5	1750	D	D
6	550	S	S
7	1750	S	S
8	5000	D	D
9	1750	D	D

(S) Survival / (D) Death

Table A 2: Summary of findings of acute oral toxicity study in rats of CA3642

Mortality	<p>175 mg/kg bw (1 animal)</p> <ul style="list-style-type: none"> - No mortality occurred. <p>550 mg/kg bw (3 animals)</p> <ul style="list-style-type: none"> - No mortality occurred. <p>1750 mg/kg bw (4 animals)</p> <ul style="list-style-type: none"> - 3 rats died occurred within one day of test item administration. <p>5000 mg/kg bw (1 animal)</p> <ul style="list-style-type: none"> - 1 rat died occurred within 4.5 hrs of test item administration.
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Clinical signs	175 mg/kg bw (1 animal) <ul style="list-style-type: none"> - No sign of gross toxicity, adverse clinical effects or abnormal behavior. 550 mg/kg bw (3 animals) <ul style="list-style-type: none"> - 1 rat exhibited diarrhea following administration (recovered by Day 1). 1750 mg/kg bw (4 animals) <ul style="list-style-type: none"> - 2 rats with hypoactivities, irregular respiration and/or hunched posture (prior to death), nothing for the third one (prior to death); no clinical signs for the survival one. 5000 mg/kg bw (1 animal) <ul style="list-style-type: none"> - hypoactivities, irregular respiration and/or hunched posture (prior to death).
Body weight	175 mg/kg bw (1 animal) <ul style="list-style-type: none"> - Normal gained body weight. 550 mg/kg bw (3 animals) <ul style="list-style-type: none"> - Normal gained body weight. 1750 mg/kg bw (4 animals) <ul style="list-style-type: none"> - Normal gained body weight for the survival rat. 5000 mg/kg bw (1 animal) <ul style="list-style-type: none"> - Not assessed.
Macroscopic examination	175 mg/kg bw (1 animal) <ul style="list-style-type: none"> - No gross abnormalities at necropsy. 550 mg/kg bw (3 animals) <ul style="list-style-type: none"> - No gross abnormalities at necropsy. 1750 mg/kg bw (4 animals) <ul style="list-style-type: none"> - For the 3 decedents, distension of the stomach and/or intestines; nothing on the survival rat after being euthanized. 5000 mg/kg bw (1 animal) <ul style="list-style-type: none"> - Fluid-filled stomach with a white substance.

Conclusion

Under the experimental conditions, the oral LD₅₀ of CA3642 is estimated to be between 550-1750 mg/kg bw in rats (based on the one dose with a partial response and an assumed sigma of 0.5) with a 95% PL confidence interval of 651.9 mg/kg bw (lower) to 2690 mg/kg bw (upper).

According to Regulation (EC) No. 1272/2008, CA3642 must be classified in Category 4 for oral toxicity.

The signal word “Warning” and hazard statement H302 “Harmful if swallowed” are required.

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

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. (Note: previously deleted text fragments have been restored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. None of the active substances or co-formulants are classified for acute dermal toxicity (see details in Registration Report - Part C).

Conclusion

According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is not classified for acute dermal toxicity.

Comments of zRMS:	Study [REDACTED] (2020b), has been reviewed for compliance with the current guidelines, resulting from scientific progress. OECD 402 procedure is still valid and acceptable. No deviation has been noted from the study protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference	KCP 7.1.2/01
Report	Tazer Pro: Acute Dermal Toxicity in Rats, [REDACTED] 2020b, [REDACTED]
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.1200 (1998)
Deviations	No
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 402
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	5 males and 5 females
Dose(s)	5000 mg/kg bw
Exposure	Once by dermal application, after clipping the dorsal area representing about 10% of the body surface. After an exposure duration of 24 hours, test sites were gently cleansed to remove any residual test item.
Vehicle/Dilution	None; test item administered as received (mixed well prior to use)
Post exposure observation period	14 days
Remarks	The rats were observed for mortality, signs of gross toxicity and behavioral changes during the first several hours post-dosing and at least once daily thereafter for 14 days after dosing or until death occurred.

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of CA3642

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD ₅₀ (mg/kg bw) (14 days)
Male rats				
5000 mg/kg bw	0/5	n.a.	n.a.	> 5000 mg/kg bw
Female rats				
5000 mg/kg bw	0/5	n.a.	n.a.	> 5000 mg/kg bw

* Number of animals which died/number of animals used

n.a. not applicable

Table A 4: Summary of findings of acute dermal toxicity study in rats of CA3642

Mortality	No mortality occurred.
Clinical signs	No clinical signs of toxicity (including dermal irritation) were observed.
Body weight	The body weight gain of the treated animals was normal.
Macroscopic examination	No abnormalities were observed at gross necropsy.

Conclusion

Under the experimental conditions, the dermal LD₅₀ of CA3642 is greater than 5000 mg/kg bw in rats. Thus, no classification for acute dermal toxicity, no signal word or hazard statement is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. (Note: previously deleted text fragments have been restored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. The active substance, azoxystrobin, is classified for acute inhalation toxicity (Acute Tox. 3, H331). The ATEmix is >5 mg/L therefore CA3642 is not classified for Acute Toxicity (see details in Registration Report - Part C).

Conclusion

According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is not classified for acute inhalation toxicity.

Comments of zRMS:	Study [REDACTED] (2020c), has been reviewed for compliance with the current guidelines, resulting from scientific progress, the OECD 403 procedure is still valid and acceptable.. Noted deviation from study protocol has no impact on final study outcome. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference	KCP 7.1.3/01
Report	Tazer Pro: Acute Inhalation Toxicity in Rats, [REDACTED] 2020c, [REDACTED]
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.1300 (1998)
Deviations	Yes, on delay on body weight recording between Days 1 and 2 (no impact)
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 403
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
Species	Rat, Sprague-Dawley derived, albino
No. of animals (group size)	5 males and 5 females
Concentration(s)	4.96 mg/L air (MMAD of 2.69 µm)
Exposure	By inhalation using a nose-only inhalation chamber during 4 hours; animals being individually housed in polycarbonate holding tubes which seal to the chamber with an "O" ring during exposure. NB: the animals were exposed to the targeted chamber concentration for at least 1 hour.
Vehicle/Dilution	Test item was aerosolized as received (kept on a magnetic stirrer during aerosolization)

Post-exposure observation period	14 days
Remarks	The rats were observed for mortality, signs of gross toxicity and behavioral changes during the first several hours post-dosing and at least once daily thereafter for 14 days after dosing or until death occurred.

MMAD Mass Median Aerodynamic Diameter

Results and discussions

Table A 5: Concentration(s) and exposure conditions

Nominal concentration [mg/L air]	Mean actual concentration measured (\pm SD)	Mass median aerodynamic diameter (MMAD)	Geometric standard deviation of MMMAD (GSD)	Inhalation fraction $\leq 4.7 \mu\text{m}$
343.2	$4.96 \pm 0.99 \text{ mg/L}$	$2.69 \mu\text{m}$	2.63	68.1%

Table A 6: Results of acute inhalation toxicity study in rats of CA3642

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC ₅₀ (mg/L air) (14 days)
Male rats				
$4.96 \pm 0.99 \text{ mg/L}$	0/5/5	Day 5	n.a.	> 4.96
Female rats				
$4.96 \pm 0.99 \text{ mg/L}$	1/5/5	Day 7	3 hours on Day 0	> 4.96

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

Table A 7: Summary of findings of acute inhalation toxicity study in rats of CA3642

Mortality	One female died within one day of exposure to the test atmosphere
Clinical signs	Clinical signs observed were hypoactivity, exhibited irregular respiration, hunched posture, nasal discharge and/or ano-genital staining. The rats recovered by Day 7 the latest.
Body weight	The treated animals gained body weight over the 14-day observation period.
Macroscopic examination	No abnormalities were observed at gross necropsy.

Conclusion

Under the experimental conditions, the inhalation LC₅₀ of CA3642 is greater than $4.96 \pm 0.99 \text{ mg/L}$ air in rats for a 1-hour exposure. The equivalent 4-hour exposure concentration was calculated to be 1.24 mg/L . Thus, no classification for acute toxicity by inhalation, no signal word or hazard statement is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. (Note: previously deleted text fragments have been restored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. A single co-formulant is classified for Skin Corrosion in Category 1A. The amount of co-formulant present in CA3642 is below the concentration that triggers classification of the mixture, and therefore classification is not required (see details in Registration Report - Part C).

Conclusion

According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is not classified for skin irritation/corrosion.

Comments of zRMS:	Study [REDACTED] (2020d), has been reviewed for compliance with the current guidelines, resulting from scientific progress the OECD 404 procedure is still valid and acceptable. There is no deviation from studies protocol, Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference	KCP 7.1.4/01
Report	Tazer Pro: Primary Skin Irritation in Rabbits, [REDACTED] 2020d, [REDACTED]
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.2500 (1998)
Deviations	No
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 404
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
Species	Rabbit New Zealand albino
No. of animals (group size)	3 females
Initial test using one animal	No
Exposure	On the day before application, the animals were prepared by clipping the dorsal area of the trunk. 0.5 mL of the test item was applied to one 6-cm ² intact dose site of each rabbit (before being covered and wrapped). After 4 hours of exposure, the dose sites were gently cleansed to remove any residual test item.
Vehicle/Dilution	Test item was applied as received (mixed well prior to use)
Post-exposure observation period	3 days after exposure
Remarks	Individual dose sites were scored according to the Draize scoring system at about 30-60 mins, 24, 48 and 72 hours after patch removal. Observations were done for signs of gross toxicity and behavioral changes at least once daily during the test period; as well body weights were recorded at both initial and terminal stages of the test.

Results and discussions

Table A 8: Skin irritation of CA3642

Animal No.		Scores after treatment				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema	0	0	0	0	0.0	Not concerned
	Oedema	0	0	0	0	0.0	
2	Erythema	0	0	0	0	0.0	Not concerned
	Oedema	1	0	0	0	0.0	
3	Erythema	0	0	0	0	0.0	Not concerned
	Oedema	1	0	0	0	0.0	

Clinical signs:	No clinical signs of toxicity were observed; normal body weights were gained during the study.
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Conclusion

Under the experimental conditions, CA3542 is not a skin irritant. Thus, no classification for skin irritation is required according to Regulation (EC) No. 1272/2008. No signal word or hazard statement is required.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. Therefore outcome of the Eye irritation study (KCP 7.1.5 Ellis M. 2020e) has precedence to the result of the estimation method (see 1272/2008). (Note: previously deleted text fragments have been re-stored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. One co-formulant is classified for Eye Irritation in Category 2, and one co-formulant is classified for Eye Damage in Category 1. These co-formulants trigger classification of the product as Eye Irritation Category 2, H319 (see details in Registration Report - Part C).

Conclusion

~~According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is classified as Eye Irrit. 2, H319.~~

zRMS Reviewer comment (Octobert 2024): Under the experimental conditions, CA3642 is not an eye irritant. Thus, no classification for eye irritation, no signal word or hazard statement is required according to Regulation (EC) No. 1272/2008. *In vivo* studies remain as primary source of information. Therefore outcome of the Eye irritation study (KCP 7.1.5 Ellis M. 2020e) has precedence to the result of the estimation method (see 1272/2008).

Comments of zRMS:	Study [REDACTED] (2020e), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 405 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference	KCP 7.1.5/01
Report	Tazer Pro: Primary Eye Irritation in Rabbits, [REDACTED] 2020e, [REDACTED]
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.2400 (1998)
Deviations	No
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 405
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
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Species	Rabbit New Zealand albino
No. of animals (group size)	3 females
Initial test using one animal	No
Exposure	0.1 mL of the test item was instilled into the conjunctival sac of the right eye of each rabbit, the other eye remaining untreated and serving as a control.
Irrigation (time point)	No
Vehicle/Dilution	Test item was applied as received (mixed well prior to use)
Post exposure observation period	3 days after exposure
Remarks	Ocular irritation was evaluated using a white light source with the Draize method of scoring at 1, 24, 48 and 72 hours post-instillation. The fluorescein dye evaluation procedure was used in the treated eye at 24 hours to verify the absence of corneal damage. Observations were done for signs of gross toxicity and behavioral changes at least once daily during the test period; as well body weights were recorded at both initial and terminal stages of the test.

Results and discussions

Table A 9: Eye irritation of CA3642

Animal No.		Scores after treatment				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	0	0	0	0.00	Day 2
	Iritis	0	0	0	0	0.00	
	Redness conjunctivae	2	1	0	0	0.33	
	Chemosis conjunctivae	1	0	0	0	0.00	
2	Corneal opacity	0	0	0	0	0.00	Day 1
	Iritis	0	0	0	0	0.00	
	Redness conjunctivae	1	0	0	0	0.00	
	Chemosis conjunctivae	1	0	0	0	0.00	
3	Corneal opacity	0	0	0	0	0.00	Day 2
	Iritis	0	0	0	0	0.00	
	Redness conjunctivae	1	1	0	0	0.33	
	Chemosis conjunctivae	1	0	0	0	0.00	

Clinical signs:	No clinical signs of toxicity were observed; normal body weights were gained during the study for two rabbits and a slight reduction was recorded for the third one.
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Conclusion

Under the experimental conditions, CA3642 is not an eye irritant. Thus, no classification for eye irritation, no signal word or hazard statement is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	According to Reg 1272/2008, <i>in vivo</i> studies take precedence over the calculation method, therefore hazard classification for the product also toxicological profile, has been agreed by the zRMS Reviewer based on the <i>in vivo</i> test results. zRMS comment (October 2024): Reflecting comments made by the cMS, zRMS Reviewer for the sake of consistency in the toxicological evaluation decided to accept the results of the calculation method as supplementary data, but it should be keep in mind that the results of the <i>in vivo</i> studies remain as primary source of information. (Note: previously deleted text fragments have been restored and marked in yellow.)
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Reliable data on the components of the product CA3642 from studies and MSDSs are available. One co-formulant is classified as a Skin Sensitiser in Category 1. The amount of co-formulant present in CA3642

is below the concentration that triggers classification of the mixture and below the SCL for that substance, therefore classification is not required (see details in Registration Report - Part C).

Conclusion

According to the classification rules laid down in Regulation (EC) No 1272/2008 (CLP), the product CA3642 is not classified for skin sensitisation.

Comments of zRMS:	Study [REDACTED], (2020f), has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 429 procedure is valid and acceptable. Study is in line with the suggestions of point 5 of Regulation 284/2013 and Annex VII to REACH REG (EC) No 1907/2006. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted
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Reference	IIIA 7.1.6/01
Report	Tazer Pro: Local Lymph Node Assay (LLNA) in Mice, [REDACTED] 2020f, [REDACTED]
Guideline(s)	US EPA Health Effects Test Guidelines, OPPTS 870.2600 (2003)
Deviations	No
GLP	Yes
Acceptability	Yes, this OPPTS Guideline is in conformity with OECD Guideline N. 429
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Tazer Pro (code: CA3642), batch No. A20022
Species	Mouse, CBA/J
No. of animals (group size)	Preliminary test: - Irritation (4 groups): 2 per group Main test: - Test (3 groups): 5 per group - Vehicle (Negative) Control: 5 - Positive Control: 5
Preliminary Toxicity testing	Three test item concentrations (25%, 50% and 100%) and the vehicle control were used: 25 µL of the appropriate concentration of the test item and the vehicle were applied to the dorsum of both ears of each mouse for 3 consecutive days. No treatment on Days 4 and 5. On Day 6, the sites for each mouse were evaluated for local reactions (erythema and edema). Animal were observed daily for signs of toxicity in order to select the 3 concentrations for the main test: 25%, 50% and 100%.
Exposure (concentration(s), no. of applications)	Day 1, 2, 3: topical application of 25 µL test item, positive and negative control Three concentrations were tested: 25, 50 and 100% test item.
Vehicle	1% Pluronic L92
Pre-treatment prior to topical application	No
Reliability check	Positive control: α -hexyl cinnamic aldehyde (25% v/v)
Remarks	Prior to each application (Days 1, 2, and 3) and on Day 6, the ears were evaluated for erythema and edema. On Day 6, 250 µL of PBS containing 20 µCi of ^3H -methyl thymidine was injected <i>i.v.</i> via the tail vein of each mouse. After 4 hours, mice were sacrificed and their draining auricular lymph nodes excised in order to extract

	<p>the DNA from the lymph node cells.</p> <p>Once each individual samples per mouse prepared, incorporation of ³H-methyl thymidine was measured by beta-scintillation (expressed as disintegrations per mn).</p> <p>The mean and standard deviation of the dpm values were calculated for each dose group, and a Stimulation Index (SI) was derived for each experimental group. Any group with SI ≥ 3 is normally considered as positive for skin sensitisation.</p>
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Results and discussions

Table A 10: Results of skin sensitisation study of CA3642 - Stimulation indices

Group		Mean DPM (minus background)	SI	Sensitisation Response
Vehicle control	1	1827.44	-	N/A
Positive Control (25% HCA)	2	9132.32	5.00	Positive – Valid study
25% test item	3	10269.54	5.62	Sensitiser
50% test item	4	12176.88*	6.66	Sensitiser
100% test item	5	16191.01**	8.86	Sensitiser

N/A Not Applicable

* Statistically significant difference from vehicle control at p < 0.05 by Dun's Multiple Comparisons test

** Statistically significant difference from vehicle control at p < 0.01 by Dun's Multiple Comparisons test

NB: EC3 can't be estimated

Clinical signs:	No clinical signs of toxicity were observed. Very slight erythemas were observed at Day 2 or Day 3 in both treated and positive control groups with desquamation at Day 6. A few mice lost body weight during the study, all the other mice gained.
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Conclusion

Under the experimental conditions, CA3642 is considered as a skin sensitiser. According to Regulation (EC) No. 1272/2008, **CA3642 must be classified in Category 1 for Skin Sensitisation. The signal word "Warning" and hazard statement H317 "May cause an allergic skin reaction" are required.**

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

The product CA3642 is not intended to be used in combination with other plant protection products.

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)

No dermal absorption study was conducted on prothioconazole and default values were used for risk assessment. However, a dermal absorption study was conducted on the main metabolite, prothioconazole-desthio, in which prothioconazole was replaced to mimic a worst case 100% conversion of the active substance to the metabolite. A dermal absorption study was also conducted on azoxystrobin.

A 2.10.1 Prothioconazole-desthio in CA3642

Comparative dermal absorption, in vitro using rat and human skin

Comments of zRMS:	Study has been performed according to OECD 428 and is considered acceptable. The dermal absorption values as proposed by the applicant are acceptable. The dermal penetration estimates for prothioconazole-desthio to be used for risk assessment were set at 0.25% and 21% (worst case) for the formulation concentrate and the spray dilutions based on the EFSA guidance criteria. Values of the tested doses and proposed ones in the GAP (applications rate, spray dilution) are comparable thus Pro-rata correction is not needed.
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Reference	KCP 7.3/01
Report	Distribution and penetration study in human skin of one concentrated CA3642 test item and 2 dilutions containing ¹⁴ C-prothioconazole-desthio, Delobel, M., 2022, report No 21-0568
Guideline(s)	OECD Guideline 428: Skin Absorption: In Vitro Method (2004), Guidance on dermal Absorption (EFSA Journal 2017; 15(6): 4873)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication	No

Executive summary

An *in vitro* study was performed to assess the rate and extent of absorption of [¹⁴C]-prothioconazole-desthio through human skin following topical application using the commercial formulation CA3642, in a suspension concentrate (SC), and two in-use dilutions, covering the entire intended in-use concentration range. For the purpose of this study, prothioconazole was replaced by prothioconazole-desthio to mimic 100% conversion of the active substance into its metabolite. Replacement was achieved by mixing blank CA3642 with the appropriate amount of prothioconazole-desthio to obtain concentrated (136 g/L) and diluted test items (1.904 and 0.272 g/L). Twelve split-thickness human skin samples from 4 donors were used; a tritiated water barrier integrity test was performed prior to the main study.

Percutaneous absorption was assessed by collecting receptor fluid in fractions from 0 to 24 hour post application. Exposure was terminated at 8 hours post application by washing the skin surface and at 24 hours post application the skin was then removed from the flow through diffusion cells. All samples were analysed by liquid scintillation counting.

Following topical application of [¹⁴C]-prothioconazole-desthio in Concentrate (136 g/L), Dilution 1 (1.904 g/L) and Dilution 2 (0.272 g/L) to human skin *in vitro*, the absorbable dose was 0.25% (not complete), 14.34% (not complete) and 20.82% (complete) of the applied dose, respectively.

The mean total recovery for each condition was within the acceptance criteria (95-110%) validating the results obtained. Based on the EFSA guidance criteria, the amount of applied dose penetrating within 24 hours (mean + k * SD) was determined to be:

- 0.25% for Concentrated test item (136 g/L)
- 14% for Dilution 1 at 1.4% v/v (1.904 g/L)
- 21% for Dilution 2 at 0.2% v/v (0.272 g/L)

The dermal penetration estimates for prothioconazole-desthio to be used for risk assessment were set at 0.25% and 21% (worst case) for the formulation concentrate and the spray dilutions based on the EFSA guidance criteria.

The BfR Excel Spreadsheet is provided



efs24873-BfR_CA36
42_PTZ-desthio_v1.x

Materials and methods

Test material

- Non-radiolabelled test item

Name (as used in the report):	Prothioconazole-desthio
Supplier:	LGC Standards, Germany
Lot No(s).:	G1043839
Purity:	99.55%
Expiry date:	21 November 2025

- Radiolabelled test item

Name (as used in the report):	[triazole-U- ¹⁴ C]-Prothioconazole-desthio
Supplier:	Selcia, UK
Lot No(s).:	11990JYC001-1
Purity:	99.5%
Specific activity:	6.201 MBq/mg (undiluted)
Expiry date:	Not applicable. The test item was stable over the course of the experiment

- Blank product

Name (as used in the report): CA3642 blank (containing azoxystrobin at 150 g/L)
Supplier: Nufarm Crop Product UK
Batch No.: A21053A
Expiry date: 31 January 2024

Test system

Four samples of full-thickness human female skin (abdomen) were obtained from donors aged 39 to 68 years old. Split-thickness membranes were prepared equivalent to 300-400 µm depth.

An automated flow-through diffusion cell apparatus (Bronaugh), none occluded, was used. The flow-through diffusion cells were placed in a static water bath calibrated to maintain the skin surface temperature at 32°C ± 1°C. The receptor fluid was collected continuously passing through the dynamic system at a flow rate of 1.5 mL/h. The surface area of exposed skin within the cells was 1.0 cm². The receptor fluid (phosphate buffered saline 0.01M, pH7.4 + 3% polyoxyethylene 20 oleyl ether) was chosen based on solubility and compatibility with the test substance and test system.

Application

The test items were prepared by isotopic dilution of ¹⁴C-prothioconazole-desthio with prothioconazole-desthio and incorporation into the blank product. The test concentrations are summarised in Table A 11.

Table A 11: Summary of prothioconazole-desthio concentrations and application rates in test preparations

Tested doses	Concentrate	Spray dilution 1 (1.4%)	Spray dilution 2 (0.2%)
Target concentration [mg/ml]	136	1.904	0.272
Area dose [µg/cm ²]	1360	19.04	2.75
Total dose [µg/cell]	1360	19.04	2.75
No. of donors	4	4	4
No of cells used/valid cells	12/12	12/12	12/12

Study Design and Methods

The experimental work was conducted between 02 March 2022 and 08 April 2022.

The dermal penetration and absorption of prothioconazole-desthio was measured *in vitro* in human donor skin exposed to the formulation CA3642 (136 g a.i./L and also containing 150 g a.i. /L azoxystrobin) and to two in-use dilutions (1.904 and 0.272g/L).

Samples of the prepared split-thickness skin were mounted on to an automated flow-through diffusion cell apparatus calibrated to maintain the skin surface temperature at 32°C ± 1°C. Measurement of Trans Epidermal Water Loss (TEWL) was used to assess the barrier integrity of the skin in the individual cells prior to the initiation of the study. The human skin samples were included in the study if the TEWL was between 0.5 and 13 g/m²/h.

Each test preparation was applied to 12 individual cells and left open to the atmosphere. Test preparations were applied at 10 µL/cm² (10 µL/cell). Aliquots of each test preparation were collected and analysed to determine accuracy of dosing. Receptor fluid was collected continuously with a flow rate of 1.5 mL/hour and sampling intervals after 1, 2, 4, 8, 12 and 24 hours post dose. All the receptor fluid samples were mixed with scintillation fluid and analysed by liquid scintillation counting.

At 8 h post dose, the exposure period was terminated by rinsing with commercial hand-wash soap (1 mL 10% Sanex®). The skin was then rinsed with nine aliquots (1 mL) of water and the skin was dried with 3 half cotton swabs. At 24 h post dose, each flow-through cell was disconnected from the receptor fluid lines. The donor and receptor compartments were separately washed with acetonitrile. Each skin sample was taken using tweezers and placed on aluminium foil. A seal was put on the skin and tape strips were taken from the skin sample using tape. Stripped samples were placed separately in vials. Using a scalpel blade, the skin corresponding to the application area was separated from the remaining (surrounding) skin and placed in vials. The donor and receptor chambers, tissue swabs, rinses and skin were retained. All samples were analysed for total radioactivity by dissolution, if necessary, then liquid scintillation counting.

Results and discussions

Application

The mean recoveries for each formulation dilution were within the acceptance criteria (95-110%) therefore validating the experimental findings.

Dermal absorption

The results of the dermal absorption are shown in Table A 12. The majority of the applied doses was recovered in the 8 hour wash with little remaining in or on the skin or on the tape strips at 24 hours.

Absorption was calculated as: receptor fluid + receptor chamber washes + skin sample + tape strips. The first two tape strips were considered to represent material that would not be bioavailable, due to desquamation. As such the first two individual strips from all cells was included as non-absorbed material. If absorption was essentially complete at the end of the study (>75% of total absorption occurring within half of the sampling period), all other tape strips were excluded from the calculation of the absorbable fraction. If absorption was not complete, tape strips, after strips 1 and 2, were considered as part of the absorbable fraction.

The mean relative absorption is shown in Table A 12 and was complete only for Dilution 2. Based on the EFSA guidance criteria, the amount of applied dose penetrating within 24 hours (mean + k * SD) was determined to be:

- 0.25% for Concentrated test item
- 14% for Dilution 1 at 1.4% v/v
- 21% for Dilution 2 at 0.2% v/v

Table A 12: In-vitro dermal penetration of prothioconazole-desthio formulated as CA3642 through human skin - Recovery data

Dose group	High dose		Mid dose		Low dose	
	Formulation concentrate		Dilution 1, 1.4%		Dilution 2, 0.2%	
Target concentration [mg/mL]	136		1.904		0.272	
Target dose [µg/cm²]	1360		19.04		2.72	
Mean actual applied dose [µg/cm²]	1360		19.04		2.75	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose						
Skin excess ^a	99.74	2.58	84.47	13.07	70.68	11.40
Dose associated to skin						
Tape strips: 1 st sample, strips 1 + 2	0.03	0.05	3.57	3.16	5.32	3.02
Tape strips: 2 nd sample; strips 3 - n	0.04	0.07	4.79	5.22	6.03	4.41
Skin preparation	0.02	0.01	1.97	2.26	4.93	4.25
Absorbed dose						
Receptor fluid + chamber wash	0.12	0.07	2.36	1.17	11.13	3.59
Total recovery¹	99.95	2.64	97.17	5.09	98.10	3.05
Absorption essentially complete at end of study (>75% absorption within half the study duration) [% Absorption at t _{0.5} – k*SD]	No [66.86%]		No [72.80%]		Yes [75.48%] ^b	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) ²	0.18	0.11	9.12	8.15	NA	NA
If yes: Absorption estimates = absorbed dose + skin preparation	NA	NA	NA	NA	16.06	7.43
Absorption estimate normalised ³	-	-	-	-	-	-
Relevant absorption estimate ⁴	0.25 [0.18 + (0.64 x 0.11)]		14.34 [9.12 + (0.64 x 8.15)]		20.82 (16.06 + 0.64 x 7.43)	
Absorption estimates used for risk assessment⁵	0.25		14		21	

- ^a Skin excess corresponds to: washings + donor compartment rinsing + remaining skin
- ^b Mean $t_{0.5} - (k \times SD) = 79.85 - (0.64 \times 6.82) = 75.48$, so absorption considered complete
- ¹ Values may not calculate exactly due to rounding of figures
- ² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. In addition, the skin preparation is also considered potentially absorbable.
- ³ According to the EFSA Guidance on Dermal Absorption, cells with insufficient recovery (< 95%) can be corrected by normalisation of absorption estimate to 100% recovery; explanation should be included.
- ⁴ In accordance with the EFSA Guidance on Dermal Absorption, a multiplication factor k of the standard deviation is added to the mean. In this case there were 12 replicates therefore the k factor is 0.64.
- ⁵ Relevant absorption estimate was rounded to the required number of significant figures.
- NA: not applicable

Remarks

Absorption was considered to be incomplete for the Concentrate and Dilution. Absorption was considered to be complete for Dilution 2.

Conclusion/endpoint:

The dermal penetration of prothioconazole-desthio, formulated in product CA3642 in place of prothioconazole, through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating within 24 hours was determined to be $0.18\% \pm 0.11$ for the formulation concentrate and $9.12\% \pm 8.15$, $16.06\% \pm 7.43$ for the 1.4%, and 0.2% spray dilutions respectively. The dermal penetration estimates to be used for risk assessment were set at 0.25%, 14% and 21% for the formulation concentrate (136 g/L) and the 1.4% (1.904 g/L) and 0.2% (0.272 g/L) spray dilutions respectively based on the EFSA guidance criteria.

A 2.10.2 Azoxystrobin in CA3642

Comments of zRMS:	Study has been performed according to OECD 428 and is considered acceptable. The dermal absorption values as proposed by the applicant are acceptable. The dermal penetration estimates for azoxystrobin to be used for risk assessment were set at 0.34% and 18% (worst case) for the formulation concentrate and the spray dilutions based on the EFSA guidance criteria. Values of the tested doses and proposed ones in the GAP (applications rate, spray dilution) are comparable thus Pro-rata correction is not needed.
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Reference	KCP 7.3/02
Report	Distribution and penetration study in human skin of one concentrated CA3642 formulation and 2 dilutions containing ¹⁴ C-azoxystrobin with non-labelled prothioconazole, Delobel, M., 2023, report No 21-9194
Guideline(s)	OECD Guideline 428: Skin Absorption: In Vitro Method (2004), Guidance on dermal Absorption (EFSA Journal 2017; 15(6): 4873)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication	No

Executive summary

An *in vitro* study was performed to assess the rate and extent of absorption of [¹⁴C]-azoxystrobin through human skin following topical application using the commercial formulation CA3642, in a suspension concentrate (SC), and two in-use dilutions, covering the entire intended in-use concentration range. Blank

CA3642 was mixed with the appropriate amount of azoxystrobin to obtain concentrated (150 g/L) and diluted test items (2.1 and 0.30 g/L). Twelve split-thickness human skin samples from 4 donors were used; a tritiated water barrier integrity test was performed prior to the main study.

Percutaneous absorption was assessed by collecting receptor fluid in fractions from 0 to 24 hour post application. Exposure was terminated at 8 hours post application by washing the skin surface and at 24 hours post application the skin was then removed from the flow through diffusion cells. All samples were analysed by liquid scintillation counting.

Following topical application of [¹⁴C]-azoxystrobin in Concentrate (150 g/L), Dilution 1 (2.1 g/L) and Dilution 2 (0.30 g/L) to human skin *in vitro*, the absorbable dose was 0.34% (not complete), 3.22% (not complete) and 17.67% (not complete) of the applied dose, respectively.

The mean total recovery for each condition was within the acceptance criteria (95-110%) validating the results obtained. Based on the EFSA guidance criteria, the amount of applied dose penetrating within 24 hours (mean + k * SD) was determined to be:

0.34% for Concentrated test item (150 g/L)
3.2% for Dilution 1 at 1.4% v/v (2.1 g/L)
18% for Dilution 2 at 0.2% v/v (0.30 g/L)

The dermal penetration estimates for azoxystrobin to be used for risk assessment were set at 0.34% and 18% (worst case) for the formulation concentrate and the spray dilutions based on the EFSA guidance criteria.

The BfR Excel Spreadsheet is provided



efs24873-BfR_CA36
42_Azoxy.xlsx

Materials and methods

Test material

- Non-radiolabelled test item

Name (as used in the report):	Azoxystrobin
Supplier:	LGC Standards, Germany
Lot No(s).:	G1049128
Purity:	98.72%
Expiry date:	23 January 2024

- Radiolabelled test item

Name (as used in the report):	[cyanophenyl-U- ¹⁴ C]-azoxystrobin
Supplier:	Selcia, UK
Lot No(s).:	12951AKV006-3
Purity:	98.3%
Specific activity:	5.32 MBq/mg (undiluted)
Expiry date:	Not applicable. The test item was stable over the duration of the experiment

- Blank product

Name (as used in the report):	CA3642 placebo (containing prothioconazole at 150 g/L)
Supplier:	Nufarm Crop Product UK
Batch No.:	A21053B
Expiry date:	31 January 2024

Name (as used in the report):	CA3642 placebo (containing azoxystrobin at 150 g/L)
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Supplier: Nufarm Crop Product UK
Batch No.: A21053A
Expiry date: 31 January 2024

Test system

Four samples of full-thickness human female skin (abdomen) were obtained from donors aged 53 to 61 years old. Split-thickness membranes were prepared equivalent to 300-400 µm depth.

An automated flow-through diffusion cell apparatus (Bronaugh), none occluded, was used. The flow-through diffusion cells were placed in a static water bath calibrated to maintain the skin surface temperature at $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$. The receptor fluid was collected continuously passing through the dynamic system at a flow rate of 1.5 mL/h. The surface area of exposed skin within the cells was 1.0 cm². The receptor fluid (phosphate buffered saline 0.01M, pH7.4 + 3% polyoxyethylene 20 oleyl ether) was chosen based on solubility and compatibility with the test substance and test system.

Application

The test items were prepared by isotopic dilution of ¹⁴C-azoxystrobin with azoxystrobin and incorporation into the blank product. The test concentrations are summarised in Table A 3.

Table A 13: Summary of azoxystrobin concentrations and application rates in test preparations

Tested doses	Concentrate	Spray dilution 1 (1.4%)	Spray dilution 2 (0.2%)
Target concentration [mg/ml]	150	2.1	0.30
Mean Area dose [µg/cm ²]	1527	21.16	3.00
Mean Total dose [µg/cell]	1527	21.16	3.00
No. of donors	4	4	4
No of cells used/valid cells	12/12	12/12	12/12

Study Design and Methods

The experimental work was conducted between 05 September 2022 and 25 October 2022.

The dermal penetration and absorption of azoxystrobin was measured *in vitro* in human donor skin exposed to the formulation CA3642 (150 g a.i./L and also containing 150 g a.i. /L prothioconazole) and to two in-use dilutions (2.1 and 0.30 g/L).

Samples of the prepared split-thickness skin were mounted on to an automated flow-through diffusion cell apparatus calibrated to maintain the skin surface temperature at $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$. Measurement of Trans Epidermal Water Loss (TEWL) was used to assess the barrier integrity of the skin in the individual cells prior to the initiation of the study. The human skin samples were included in the study if the TEWL was between 0.5 and 13 g/m²/h.

Each test preparation was applied to 12 individual cells and left open to the atmosphere. Test preparations were applied at 10 µL/cm² (10 µL/cell). Aliquots of each test preparation were collected and analysed to determine accuracy of dosing. Receptor fluid was collected continuously with a flow rate of 1.5 mL/hour and sampling intervals after 1, 2, 4, 8, 12 and 24 hours post dose. All the receptor fluid samples were mixed with scintillation fluid and analysed by liquid scintillation counting.

At 8 h post dose, the exposure period was terminated by rinsing with commercial hand-wash soap (1 mL 10% Sanex®). The skin was then rinsed with nine aliquots (1 mL) of water and the skin was dried with 3 half cotton swabs. At 24 h post dose, each flow-through cell was disconnected from the receptor fluid lines. The donor and receptor compartments were separately washed with acetonitrile. Each skin sample was taken using tweezers and placed on aluminium foil. A seal was put on the skin and tape strips were taken from the skin sample using tape. Stripped samples were placed separately in vials. Using a scalpel blade, the skin corresponding to the application area was separated from the remaining (surrounding) skin and placed in vials. The donor and receptor chambers, tissue swabs, rinses and skin were retained. All samples were analysed for total radioactivity by dissolution, if necessary, then liquid scintillation counting.

Results and discussions

Application

The mean recoveries for each formulation dilution were within the acceptance criteria (95-110%) therefore validating the experimental findings.

Dermal absorption

The results of the dermal absorption are shown in Table A 4. The majority of the applied doses was recovered in the 8 hour wash with little remaining in or on the skin or on the tape strips at 24 hours.

Absorption was calculated as: receptor fluid + receptor chamber washes + skin sample + tape strips. The first two tape strips were considered to represent material that would not be bioavailable, due to desquamation. As such the first two individual strips from all cells was included as non-absorbed material. If absorption was essentially complete at the end of the study (>75% of total absorption occurring within half of the sampling period), all other tape strips were excluded from the calculation of the absorbable fraction. If absorption was not complete, tape strips, after strips 1 and 2, were considered as part of the absorbable fraction.

The mean relative absorption is shown in Table A 4 and was incomplete in all cases. Based on the EFSA guidance criteria, the amount of applied dose penetrating within 24 hours (mean + k * SD) was determined to be:

- 0.34% for Concentrated test item
- 3.2% for Dilution 1 at 1.4% v/v
- 18% for Dilution 2 at 0.2% v/v

Table A 14: In-vitro dermal penetration of azoxystrobin formulated as CA3642 through human skin - Recovery data

Dose group	High dose		Mid dose		Low dose	
	Formulation concentrate		Dilution 1, 1.4%		Dilution 2, 0.2%	
Target concentration [mg/mL]	150		2.1		0.30	
Target dose [µg/cm²]	1500		21.0		3.00	
Mean actual applied dose [µg/cm²]	1443		21.0		3.0	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose						
Skin excess ^a	96.58	3.59	95.99	4.07	80.51	12.58
Dose associated to skin						
Tape strips: 1 st sample, strips 1 + 2	0.26	0.20	1.04	1.49	6.43	4.91
Tape strips: 2 nd sample; strips 3 - n	0.15	0.08	0.89	1.44	5.28	4.21
Skin preparation	0.08	0.06	0.52	0.97	4.75	4.63
Absorbed dose						
Receptor fluid + chamber wash	0.10 0.02	0.07 0.06	0.75 0.23	1.22 0.25	6.11 1.36	5.57 1.14
Total recovery¹	97.05	3.69	98.60	1.56	97.46	2.04
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at t _{0.5} – k*SD]	No [58.42%]		No [68.35%]		No [67.27%]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) ²	0.25	0.13	1.57	2.59	11.71	9.31
If yes: Absorption estimates = absorbed dose + skin preparation	NA	NA	NA	NA	NA	NA
Absorption estimate normalised ³	-	-	-	-	-	-
Relevant absorption estimate ⁴	0.34 [0.25 + (0.64 x 0.13)]		3.22 [1.57 + (0.64 x 2.59)]		17.67 (11.71 + 0.64 x 9.31)	
Absorption estimates used for risk assessment^{1,5}	0.34		3.2		18	

- ^a Skin excess corresponds to: washings + donor compartment rinsing + remaining skin
- ¹ Values may not calculate exactly due to rounding of figures
- ² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. In addition, the skin preparation is also considered potentially absorbable.
- ³ According to the EFSA Guidance on Dermal Absorption, cells with insufficient recovery (< 95%) can be corrected by normalisation of absorption estimate to 100% recovery; explanation should be included.
- ⁴ In accordance with the EFSA Guidance on Dermal Absorption, a multiplication factor k of the standard deviation is added to the mean. In this case there were 12 replicates therefore the k factor is 0.64.
- ⁵ Relevant absorption estimate was rounded to the required number of significant figures.

NA: not applicable

Remarks

Absorption was considered to be incomplete for the Concentrate and both Dilution 1 and 2 .

Conclusion/endpoint:

The dermal penetration of azoxystrobin, formulated in product CA3642, through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating within 24 hours was determined to be 0.25% ± 0.13 for the formulation concentrate and 1.57% ± 2.59, 11.71 ± 9.31 for the 1.4%, and 0.2% spray dilutions respectively. The dermal penetration estimates to be used for risk assessment were set at 0.34%, 3.2% and 18% for the formulation concentrate (150 g/L) and the 1.4% (2.1 g/L) and 0.2% (0.30 g/L) spray dilutions respectively based on the EFSA guidance criteria.

A 2.11 Other/Special Studies

The below studies were evaluated at EU level for the first renewal of the active substance; endpoints were agreed in the EFSA Conclusion for azoxystrobin (EFSA Journal 2010; 8(4):1542).

A 2.11.1 R234886 Acute Oral Toxicity

Comments of zRMS:	zRMS agree with outcome and conclusion of the study.
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Reference	CA 5.8.1/01
Report	Azoxystrobin metabolite R234886: Acute Oral Toxicity Study In The Rat (Up and Down Procedure [REDACTED]. (2005) [REDACTED]
Guideline(s)	Yes (OECD 425)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Azoxystrobin metabolite R234886, batch ASJ10063-01S
Species	Rat, HanRcc:WIST (SPF)
No. of animals (group size)	3 female rats
Dose(s)	5000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	Corn oil, dose volume of 20 mL/kg
Post exposure observation period	14 days

Remarks	None
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Results and discussions

Table A 15: Results of acute oral toxicity study in rats of R234886

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD ₅₀ (mg/kg bw) (14 days)
Female rats				
5000	0/3/3	7 days	-	> 5000

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

Table A 16: Summary of findings of acute oral toxicity study in rats of R234886

Mortality	No mortality occurred
Clinical signs	Slightly ruffled fur in all animals from 0.5 h reading to test Day 5 or 6. Hunched posture in 2 animals from the 2-5 h examination. One animal showed slight sedation at the 2 and 3 hour reading. All animals were normal from Day 7.
Body weight	Body weight gain was considered to be normal.
Macroscopic examination	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the oral LD₅₀ of R234886 is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.11.2 R234886 Bacterial Reverse Mutation

Comments of zRMS:	zRMS agree with outcome and conclusion of the study.
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Reference	CA 5.8.1/02
Report	Azoxystrobin Metabolite R234886: Bacterial Mutation Assay in <i>S. typhimurium</i> and <i>E. coli</i> , Callander, R. (2005), Report No. CTL/YV7083-REG
Guideline(s)	Yes (OECD 471, EPA 870.5100/EC, EC B13/B14)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Azoxystrobin metabolite R234886, batch ASJ10063-01S
Test organisms	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537 <i>Eschericia coli</i> WP2 <i>uvrA</i> (pKM101), WP2 (pKM101)
Mammalian metabolic system	S9 derived from rat liver induced with β -naphthoflavone and phenobarbitol
Test concentrations	100, 200, 500, 1000, 2500, and 5000 μ g/plate
Solvent and positive controls	Yes
Assay type	Standard plate test (both experiments without S9, initial experiment with S9) Pre-incubation (60 minutes) (second experiment with S9)

Results and discussions

In two separate assays with each strain, the test substance did not induce any significant, reproducible increases in the observed number of revertant colonies in any of the tester strains used, either in the presence or absence of S9-mix.

Conclusion

Under the conditions of this assay, R234886 was non-mutagenic both in the presence and absence of metabolic activation.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for prothioconazole

Estimation of longer term operator exposure towards prothioconazole according to EFSA guidance (excerpt from calculator report)

3.1. Use 1 : Field crops

		Short term exposure		Prothioconazole (% AOEL)	
Mixing/loading		Application		Normal & vehicle-mounted	
				58.7	
				38.1	

3.1.1. Scenario 1 : Outdoor, normal, downward spraying, vehicle-mounted


3.1.1.1. Summary data - Short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of syst emic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption (concentrate): 10 % Dermal absorption (in-use dilution): 50 %			
Prothioconazole	M/L: Workwear App: Workwear	0.08	38.1

A 3.1.2 Calculations for prothioconazole-desthio and azoxystrobin

Estimation of longer term operator exposure towards prothioconazole-desthio and azoxystrobin according to EFSA guidance (excerpt from calculator report)

3.1. Use 1 : Field crops

		Short term exposure		
Mixing/loading		Azoxystrobin (% AOEL)	Prothioconazole-desthio (% AOEL)	Combined (hazard index)
		Normal & vehicle-mounted		
		5.4	103	1.08
		3.6	67.8	0.714

3.1.1. Scenario 1 : Outdoor, normal, downward spraying, vehicle-mounted

3.1.1.1. Summary data - Short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Azoxystrobin	Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption (concentrate): 0.34 % Dermal absorption (in-use dilution): 18 %		
	M/L: Workwear App: Workwear	0.007	3.6
Prothioconazole-desthio	Number of applications and application rate: 2 x 0.19047 kg a.s./ha Dermal absorption (concentrate): 0.25 % Dermal absorption (in-use dilution): 21 %		
	M/L: Workwear App: Workwear	0.007	67.8
Combined exposure			Hazard index
			M/L: Workwear App: Workwear
			0.7

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for prothioconazole

Estimation of longer term worker exposure towards prothioconazole according to EFSA guidance (excerpt from calculator report)

4. Worker

4.1. Use 1 : Field crops

4.1.1. Scenario 1 : Outdoor, normal

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 14 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h			
Number of applications & application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.2	113	6
Workwear	0.03	12.6	0
Workwear and gloves	0.02	11.3	0
Hands covered, no workwear			

A 3.2.2 Calculations for prothioconazole-desthio and azoxystrobin

Estimation of longer term worker exposure towards prothioconazole-desthio and azoxystrobin according to EFSA guidance (assuming 100% conversion to prothioconazole-desthio) (excerpt from calculator report)

4. Worker

4.1. Use 1 : Field crops

4.1.1. Scenario 1 : Outdoor, normal

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 14 days Body weight: 60 kg TC (potential): 12500 cm ² /h TC (workwear (arms, body and legs covered)): 1400 cm ² /h TC (workwear (arms, body and legs covered) and gloves): 1250 cm ² /h TC (gloves): NA cm ² /h			
Number of applications & application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.09	860	94
Workwear	0.01	96.3	0
Workwear and gloves	0.009	86	0
Hands covered, no workwear			
Number of applications & application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.08	40.6	0
Workwear	0.009	4.6	0
Workwear and gloves	0.008	4.1	0
Hands covered, no workwear			
Combined		Hazard index	
potential		9	96
Workwear		1	1
Workwear and gloves		0.9	0
Hands covered, no workwear			0

Estimation of longer term worker exposure towards prothioconazole-desthio and azoxystrobin according to EFSA guidance assuming 100% conversion to prothioconazole-desthio with DFR refinement (excerpt from calculator report)

4. Worker

4.1. Use 1 : Field crops

4.1.1. Scenario 1 : Outdoor, normal

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 14 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h			
Number of applications & application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 0.69 µg/cm² foliage per kg a.s./ha DT50 Foliar: 30 days DT50 Air: 30 days DT50 Soil: 30 days			
Potential	0.02	198	30
Workwear	0.002	22.2	0
Workwear and gloves	0.002	19.8	0
Hands covered, no workwear			
Azoxystrobin Number of applications & application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.08	40.6	0
Workwear	0.009	4.6	0
Workwear and gloves	0.008	4.1	0
Hands covered, no workwear			
Combined		Hazard index	
potential		2.4	38
Workwear		0.3	0
Workwear and gloves		0.2	0
Hands covered, no workwear			0

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for prothioconazole

Estimation of longer term resident exposure towards prothioconazole according to EFSA guidance (excerpt from calculator report)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole	Drift (75th perc.)	0.03	14.2
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.003	1.5
	Re-entry (75th perc.)	0.03	15.2
	Sum (mean)	0.04	21.4
Resident child Body weight: 10 kg	Drift (75th perc.)	0.007	3.4
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.001	0.6
	Re-entry (75th perc.)	0.02	8.5
	Sum (mean)	0.02	8.9

A 3.3.2 Calculations for prothioconazole-desthio and azoxystrobin

Estimation of longer term resident exposure towards prothioconazole-desthio and azoxystrobin according to EFSA guidance (100% conversion, excerpt from calculator)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Number of applications and application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole-desthio			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	109
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.001	12.7
	Re-entry (75th perc.)	0.01	116
	Sum (mean)	0.02	169
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.003	25.7
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0005	4.7
	Re-entry (75th perc.)	0.006	64.5
	Sum (mean)	0.007	69.6
Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Azoxystrobin			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	5.1
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.001	0.6
	Re-entry (75th perc.)	0.01	5.5
	Sum (mean)	0.02	8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.002	1.2
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0004	0.2
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.007	3.3

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		1.1
	Vapour (75th perc.)		0.08
	Deposits (75th perc.)		0.1
	Re-entry (75th perc.)		1.2
	Sum (mean)		1.8
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.3
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.05
	Re-entry (75th perc.)		0.7
	Sum (mean)		0.7

Estimation of longer term resident exposure towards prothioconazole-desthio according to EFSA guidance (100% conversion and refined DFR, excerpt from calculator)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Prothioconazole-desthio (refined dfr)		Number of applications and application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 0.69 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	109
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.001	12.7
	Re-entry (75th perc.)	0.003	26.7
	Sum (mean)	0.01	97.8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.003	25.7
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0005	4.7
	Re-entry (75th perc.)	0.001	14.8
	Sum (mean)	0.003	30
Azoxystrobin		Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	5.1
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.001	0.6
	Re-entry (75th perc.)	0.01	5.5
	Sum (mean)	0.02	8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.002	1.2
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0004	0.2
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.007	3.3

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		1.1
	Vapour (75th perc.)		0.08
	Deposits (75th perc.)		0.1
	Re-entry (75th perc.)		0.3
	Sum (mean)		1.1
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.3
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.05
	Re-entry (75th perc.)		0.2
	Sum (mean)		0.3

Estimation of longer term resident exposure towards prothioconazole-desthio according to EFSA guidance (100% conversion, refined DFR and 5 m buffer zone, excerpt from calculator)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 5 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Prothioconazole-desthio (refined dfr)		Number of applications and application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 0.69 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.007	72.4
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.0005	5.2
	Re-entry (75th perc.)	0.003	26.7
	Sum (mean)	0.007	72.9
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	13.2
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0002	1.9
	Re-entry (75th perc.)	0.001	14.8
	Sum (mean)	0.002	22.6
Azoxystrobin		Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.007	3.4
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.0005	0.3
	Re-entry (75th perc.)	0.01	5.5
	Sum (mean)	0.01	6.8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	0.6
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0002	0.09
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.006	2.9

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		0.8
	Vapour (75th perc.)		0.08
	Deposits (75th perc.)		0.05
	Re-entry (75th perc.)		0.3
	Sum (mean)		0.8
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.1
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.02
	Re-entry (75th perc.)		0.2
	Sum (mean)		0.3

Estimation of longer term resident exposure towards prothioconazole-desthio according to EFSA guidance (100% conversion, refined DFR and drift reduction technology, excerpt from calculator)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 50 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Prothioconazole-desthio (refined dfr)	Number of applications and application rate: 2 x 0.19047 kg a.s./ha Dermal absorption: 21 % DFR: 0.69 µg/cm ² foliage per kg a.s./ha DT50: 30 days		
	Drift (75th perc.)	0.005	54.3
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.0006	6.3
	Re-entry (75th perc.)	0.003	26.7
Sum (mean)		0.006	63.6
Resident child Body weight: 10 kg	Drift (75th perc.)	0.001	12.9
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0002	2.3
	Re-entry (75th perc.)	0.001	14.8
	Sum (mean)	0.002	22.3
Azoxystrobin	Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days		
	Drift (75th perc.)	0.005	2.6
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.0006	0.3
	Re-entry (75th perc.)	0.01	5.5
Sum (mean)		0.01	6.4
Resident child Body weight: 10 kg	Drift (75th perc.)	0.001	0.6
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0002	0.1
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.006	2.9
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	0.6
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0002	0.1
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.006	2.9





Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		0.6
	Vapour (75th perc.)		0.08
	Deposits (75th perc.)		0.07
	Re-entry (75th perc.)		0.3
	Sum (mean)		0.7
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.1
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.02
	Re-entry (75th perc.)		0.2
	Sum (mean)		0.3

A 3.4 Combined exposure calculations for prothioconazole, prothioconazole-des-thio (metabolite) and azoxystrobin

Details of combined exposure are summarised in section 6.6.5. Extracts from the EFSA calculator showing model outputs are included below.

Estimation of operator exposure towards prothioconazole and azoxystrobin according to EFSA guidance during mixing and loading (0% PTZ conversion, excerpt from calculator)

3.1. Use 1 : Field crops

		<i>Short term exposure</i>		
Mixing/loading	Application	Prothioconazole (% AOEL) Normal & vehicle-mounted	Azoxystrobin (% AOEL)	Combined (hazard index)
		48.4	1.7	0.501
		31.3	1.2	0.325





3.1.1. Scenario 1 : Outdoor, normal, downward spraying, vehicle-mounted

3.1.1.1. Summary data - Short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Prothioconazole	Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption (concentrate): 10 % Dermal absorption (in-use dilution): 0 %		
	M/L: Workwear App: Workwear	0.06	31.3
Azoxystrobin	Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption (concentrate): 0.34 % Dermal absorption (in-use dilution): 0 %		
	M/L: Workwear App: Workwear	0.002	1.2
Combined exposure			Hazard index
M/L: Workwear App: Workwear			0.3

Estimation of operator exposure towards prothioconazole, prothioconazole-desthio and azoxystrobin according to EFSA guidance during application (50% PTZ conversion, excerpt from calculator)

3.1. Use 1 : Field crops

		Short term exposure			
		Prothioconazole (% AOEL)	Prothioconazole-desthio (% AOEL)	Azoxystrobin (% AOEL)	Combined (hazard index)
		Normal & vehicle-mounted			
Mixing/loading	Application				
		5.2	46.1	3.8	0.551
		3.4	30.7	2.5	0.367

3.1.1. Scenario 1 : Outdoor, normal, downward spraying, vehicle-mounted

3.1.1.1. Summary data - Short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Prothioconazole	Number of applications and application rate: 2 x 0.105 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 50 %		
	M/L: Workwear App: Workwear	0.007	3.4
Prothioconazole-desthio	Number of applications and application rate: 2 x 0.09506 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 24.040404040404 %		
	M/L: Workwear App: Workwear	0.003	30.7
Azoxystrobin	Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 18 %		
	M/L: Workwear App: Workwear	0.005	2.5
Combined exposure			Hazard index
			M/L: Workwear App: Workwear
			0.4

Estimation of worker exposure towards prothioconazole, prothioconazole-desthio and azoxystrobin according to EFSA guidance (50% PTZ conversion, excerpt from calculator)

4. Worker

4.1. Use 1 : Field crops

4.1.1. Scenario 1 : Outdoor, normal

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 14 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h			
Number of applications & application rate: 2 x 0.105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.1	56.4	0
Workwear	0.01	6.3	0
Workwear and gloves	0.01	5.6	0
Hands covered, no workwear			
Number of applications & application rate: 2 x 0.09506 kg a.s./ha Dermal absorption: 24.0404040404 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.05	491	69
Workwear	0.006	55	0
Workwear and gloves	0.005	49.1	0
Hands covered, no workwear			
Number of applications & application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.08	40.6	0
Workwear	0.009	4.6	0
Workwear and gloves	0.008	4.1	0
Hands covered, no workwear			

Estimation of worker exposure towards prothioconazole, prothioconazole-desthio and azoxystrobin according to EFSA guidance (50% PTZ conversion, DFR refinement, excerpt from calculator)

4. Worker

4.1. Use 1 : Field crops

4.1.1. Scenario 1 : Outdoor, normal

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: 14 days Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h			
Number of applications & application rate: 2 x 0.105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.1	56.4	0
Workwear	0.01	6.3	0
Workwear and gloves	0.01	5.6	0
Hands covered, no workwear			
Number of applications & application rate: 2 x 0.095235 kg a.s./ha Dermal absorption: 23.989920201596 % DFR: 0.69 µg/cm² foliage per kg a.s./ha DT50 Foliar: 30 days DT50 Air: 30 days DT50 Soil: 30 days			
Potential	0.01	113	6
Workwear	0.001	12.7	0
Workwear and gloves	0.001	11.3	0
Hands covered, no workwear			
Number of applications & application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.08	40.6	0

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Workwear	0.009	4.6	0
Workwear and gloves	0.008	4.1	0
Hands covered, no workwear			
Combined		Hazard index	
potential		2.8	33
Workwear		0.3	0
Workwear and gloves		0.3	0
Hands covered, no workwear			0

Estimation of resident exposure towards prothioconazole, prothioconazole-desthio and azoxystrobin according to EFSA guidance (50% PTZ conversion, excerpt from calculator)

5. Resident

5.1. Use 1 : Field crops

5.1.1. Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 14 days Minimum volume of water: 100 l			
Number of applications and application rate: 2 x 0.105 kg a.s./ha Dermal absorption: 50 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	7.1
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.001	0.7
	Re-entry (75th perc.)	0.02	7.6
	Sum (mean)	0.02	10.9
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.003	1.7
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0006	0.3
	Re-entry (75th perc.)	0.008	4.2
	Sum (mean)	0.009	4.5
Number of applications and application rate: 2 x 0.095235 kg a.s./ha Dermal absorption: 23.989920201596 % DFR: 0.69 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole-desthio (refined dfr)			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.006	62
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.0007	7.1
	Re-entry (75th perc.)	0.002	15.3
	Sum (mean)	0.006	59.2
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	14.7
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0003	2.7
	Re-entry (75th perc.)	0.0008	8.5
	Sum (mean)	0.002	18.3

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Azoxystrobin Number of applications and application rate: 2 x 0.21 kg a.s./ha Dermal absorption: 18 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	5.1
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.001	0.6
	Re-entry (75th perc.)	0.01	5.5
	Sum (mean)	0.02	8
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.002	1.2
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0004	0.2
	Re-entry (75th perc.)	0.006	3
	Sum (mean)	0.007	3.3
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		0.7
	Vapour (75th perc.)		0.09
	Deposits (75th perc.)		0.08
	Re-entry (75th perc.)		0.3
	Sum (mean)		0.8
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.2
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.03
	Re-entry (75th perc.)		0.2
	Sum (mean)		0.3

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)

The DFR studies referred to in this dRR were conducted by Bayer Crop Science and full summaries are provided in Doc K 7.2. Nufarm has agreed access to these studies with the data owner.