

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GPF515 / FGE03

Product name: Boscalid / Prothioconazole 350 / 200 WG

Chemical active substances:

Boscalid, 350 g/kg

Prothioconazole, 200 g/kg

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(Article 33 application for a new product registration)

Applicant: UPL Holdings Coöperatief U.A.

Submission date: November 2024

MS Finalisation date: April 2025 (initial Core Assessment)

August 2025, update April 2026 (final Core Assessment)

Version history

When	What
November 2024	V01 – Version from applicant for submission to z-RMS Poland in the frame of the PPP Authorization according to Article 33 of Regulation (EC) No 1107/2009.
April 2025	Initial zRMS assessment The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through~~ and shaded for transparency.
August 2025	Final report (Core Assessment updated following the commenting period) Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Not agreed or not relevant information are ~~struck through~~ and shaded for transparency.
April 2026	Updated final report prepared following the comments submitted by the Ministry of Agriculture. All additional information and revisions have been highlighted in green.

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Reviewer general comment:

This part of dossier (B6) summarizes data related to the toxicity profile and NDE assessment for the plant protection product Patton Boost. This application is submitted for the approval under Art.33 of EU Regulation 1107/2009 of the product coded GPF515/FGE03, water dispersible granule (WG) formulated fungicide containing 350 g/kg of the active substance boscalid and 200 g/kg active substance prothioconazole. It is intended to be used as fungicide to control Sclerotinia in oilseed rape. (for details refer Part A).

zRMS reviewed all elements key to risk assessment and decision-making. The assessment of the toxicity profile of the GPF515/FGE03 product and the data presented by the Applicant took into account the hazard classification of the mixtures, which was based on the additivity formula taking into account the content of "relevant components" of the mixture.

NDE assessment for operator, workers and B&R has been calculated using the EFSA calculator, on-line version 1.02 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 GPF515/FGE03.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on GPF515/FGE03 *

Product name and code	GPF515 / FGE03
Formulation type	WG
Active substance(s) (incl. content)	Boscalid, 350 g/kg Prothioconazole, 200 g/kg
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 - This submission is for a new product registration

* Information on the detailed composition of GPF515 / FGE03 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 GPF515/FGE03 according to Regulation (EC) No 1272/2008

Hazard class(es), categories	~~None (regarding human health); Skin Irrit Cat 2 Eye damage Cat 1~~ None
Hazard pictograms or Code(s) for hazard pictogram(s)	~~None (regarding human health);~~  None
Signal word	~~None (regarding human health); Danger~~ None
Hazard statement(s)	~~None (regarding human health); H315 Causes skin irritation H318 Causes serious eye damage~~ None
Precautionary statement(s)	~~None (regarding human health); P280 Wear protective gloves/eye protection/face protection. P264 Wash ... thoroughly after handling. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310 Immediately call a POISON CENTER/ doctor/... P302 + P352 IF ON SKIN: Wash with plenty of water/... P332 + P313 If skin irritation occurs: Get medical advice/attention. P362 + P364 Take off contaminated clothing and wash it before reuse.~~ None
Additional labelling phrases	To avoid risks to ~~man~~ human and the environment, comply with the instructions for use. [EUH401]
	None.

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for GPF515/ FGE03

	Result	PPE / Risk mitigation measures
Operators	Acceptable	None ²⁵
Workers	Acceptable	Normal work wear
Residents	Acceptable	10 m buffer zone, 50% drift reduction (Prothioconazole-desthio)
Bystanders	Acceptable	10 m buffer zone, 50% drift reduction (Prothioconazole-desthio)

²⁵zRMS comment: Regarding CLP classification it is strongly recommended to use by the operators protective goggles and protective gloves

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

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

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

1	2	3	4	5	6	7	8	9	10			
Use- No.*	Crops and situation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safen- er/synergist (L/ha)) critical gap for operator, worker, resident or by- stander exposure based on [Expo- sure model]	Acceptability of exposure as- sessment			
			Method / Kind (incl. applica- tion technique ***	Max. number (min. interval between applications) 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
#2	Oil seed rape ^s (BBCH 61-73)	F	Spraying, LCTM	a) 2 b) 2	a) 0.245 b) 0.140	100 - 400	35	Guidance on the assessment of exposure of opera- tors, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032			#	#
Minor uses according to Article 51 (zonal uses)												
#3	Spring rape gold of pleasure, winter turnip rape, mustard, sunflower, poppy linseed, flax, hemp, borage (BBCH 61-73)	F	Spraying, LCTM	a) 2 b) 2	a) 0.245 b) 0.140	100 - 400	35	Use covered by use n.2			#	#

* 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

\$ Critical use worst case covering use n.1 and also minor uses number 3 of the GAP of section B0

[#]zRMS Reviewer comment regarding NDE assessment:

Considering outcome of risk assessment from **combined exposure** (longer term exposure) for PTZ-desithio (refer table 6.6-12) additional RMM for Resident – child has been proposed (10 m, 50% drift reduction). Refinement has been accepted by the zRMS.

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 substance(s)

	Boscalid	Prothioconazole	Prothioconazole-Desthio
Common Name	Boscalid	Prothioconazole	Prothioconazole-Desthio
CAS-No.	188425-85-6	178928-70-6	120983-64-4
Index No:		613-337-00-9	
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: Not classified Code(s) for hazard pictogram(s): None Signal word: None Hazard statement(s): None Precautionary statement(s): Nne	Hazard classes (s), categories: Not classified Code(s) for hazard pictogram(s): None Signal word: None Hazard statement(s): None Precautionary statement(s): None	No harmonised classification according to Regulation (EC) 1272/2008
Additional C&L proposal	Not required	Not required	Not applicable
Agreed EU endpoints			
AOEL systemic	0.1 mg/kg bw/d (corrected for 44% oral absorption)	0.2 mg/kg bw/d (with a 100-fold correction factor, no correction for oral absorption)	0.01 mg/kg (with a 100-fold correction factor)
AOEL systemic desthio-prothioconazole	n.a.	0.01 mg/kg bw/d	
Reference	Review Report SANCO/3919 /2007-rev. 5, 21 January 2008	EFSA Scientific Report (2007) 106, 1-98	EFSA Scientific Report (2007) 106, 1-98
Conditions to take into account/critical areas of concern with regard to toxicology			
According to Review Report for Boscalid/EFSA Scientific Report (2007) for Prothioconazole*	Operator safety	The metabolite prothioconazole-desthio is more toxic than prothioconazole in the rat and rabbit developmental studies.	The metabolite prothioconazole-desthio is more toxic than prothioconazole in the rat and rabbit developmental studies.

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

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for GPF515 / FGE03 is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for GPF515 / FGE03

Type of test, species, model system (Guideline)	Result		Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ -oral, rat	Not submitted, not necessary. Justification presented in Appendix 2			
LD ₅₀ -dermal, rat	Not submitted, not necessary. Justification presented in Appendix 2			

LC ₅₀ inhalation, rat	Not submitted, not necessary. Justification presented in Appendix 2			
Skin irritation	Not submitted, not necessary. Justification presented in Appendix 2			
Eye irritation	Not submitted, not necessary. Justification presented in Appendix 2			
Skin sensitisation	Not submitted, not necessary. Justification presented in Appendix 2			
Skin sensitisation, mouse (OECD 429/LLNA)	Not submitted, not necessary. Justification presented in Appendix 2			
Supplementary studies for combinations of plant protection products	No data – not required			

zRMS Reviewer comment regarding content of table 6.3-1:

In the Reviewer opinion wording ” (..) Not submitted, not necessary” however is in proposed in dRR template is misleading, toxicity profile of the mixture should be always discussed and summarized even in case when data on toxicity has been gathered considering ATEmix approach, therefore zRMS decided to adjust point 6.3 table 6.3-1.

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
oral toxicity (LD ₅₀) calculation method for classification; 1272/2008	The plant protection product GPF515 / FGE03 does not contain any component classified for acute oral toxicity	Yes	None	Refer Part C
dermal toxicity (LD ₅₀) calculation method for classification; 1272/2008	The plant protection product GPF515 / FGE03 does not contain any component classified for acute dermal toxicity	Yes	None	Refer Part C
inhalation toxicity (LC ₅₀) calculation method for classification; 1272/2008	Content of component classified as “May cause respiratory irritation” does not trigger classification of the mixture	Yes	None	Refer Part C
Skin irritation; calculation method for classification; 1272/2008	~~Irritant~~ Content of component classified as “Causes skin irritation” trigger classification of the mixture Content of component classified as “Causes skin irritation” does not trigger classification of the mixture	Yes	~~H315~~ None	Refer Part C
Eye irritation; calculation method for classification; 1272/2008	~~Irritant~~ Content of component classified as “Causes serious eye damage” trigger classification of the mixture Content of component classified as “Causes serious eye damage” does not trigger classification of the mixture	Yes	~~H318~~ None	Refer Part C
Skin sensitisation; calculation method for classification; 1272/2008	Non-sensitising The plant protection product GPF515 / FGE03 does not contain any component classified for skin sensitisation	Yes	None	Refer Part C
Supplementary studies for	No data – not required	-	-	-

combinations of plant protection products				
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Table 6.3-2: Additional toxicological information relevant for classification/labelling of GPF515/ FGE03

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Boscalid (35% (w/w))	Not classified	Reg. 1272/2008 / MSDS** / EFSA conclusion	None
Toxicological properties of active substance(s) (relevant for classification of product)	Prothioconazole (20% (w/w))	Not classified	Reg. 1272/2008 / MSDS** / EFSA conclusion	None
Toxicological properties of non-active substance(s) (relevant for classification of product)	None	Not applicable (n.a.)	n.a.	n.a.
Further toxicological information	No data – not required			

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

** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

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

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in GPF515/ FGE03 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GPF515/ FGE03

	Boscalid		Prothioconazole		Prothioconazole-desthio	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	0.11%	New study reported in Appendix 2	0.77%	New study reported in Appendix 2	N/A	N/A
Dilution (1:100)	1.5%	New study reported in Appendix 2	2.9%	New study reported in Appendix 2	7.6%	New study reported in Appendix 2
Dilution (1:574) (1:571)	3.1%	New study reported in Appendix 2	14%	New study reported in Appendix 2	27%	New study reported in Appendix 2

6.5.1 Justification for proposed values - Boscalid

Proposed dermal absorption rates for Boscalid are based on dermal absorption studies on a formulation identical to GPF515/ FGE03. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of Boscalid that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2..

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

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	0.11%	1.5% (1:100) 3.1% (~~1:574~~ 1:571)	GPF515/ FGE03	Yes	Not required as the test item is the current formulation.	Justification accepted. Endpoint can be used for current product	Nagane (2023)

Boscalid 350 g/kg + Prothioconazole 200 g/kg WG (FGE03) was tested at three target concentrations of Boscalid:

- Test preparation I - as the commercial concentrate. The concentrate formulation was mixed with water in a 1:1 ratio (w/w) to generate a 'paste' which was applied to the skin. This exposure scenario was considered to be representative of a person being exposed to the concentrate formulation which in turn mixes with sweat. Therefore, the concentration of Boscalid in the 1:1 mixture was ≈ 175 g Boscalid/kg,
- Test preparation II - as an aqueous spray dilution-1 representing the lowest in-use dilution (highest concentration) of 1 kg product in 100 L water [Boscalid: 3.5 g/L],
- Test preparation III - as an aqueous spray dilution-2 representing the highest in-use dilution (lowest concentration) of 0.7 kg product in 400 L water allowed in the GAP [Boscalid: 0.61 g/L]

6.5.2 Justification for proposed values - Prothioconazole

Proposed dermal absorption rates for Prothioconazole are based on dermal absorption studies on a formulation identical to GPF515/ FGE03. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of Prothioconazole that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

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

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	0.77%	2.9% (1:100) 14% (~~1:574~~ 1:571)	GPF515/ FGE03	Yes	Not required as the test item is the current formulation.	Justification accepted. Endpoint can be used for current product.	Desai (2024)

Boscalid 350 g/kg + Prothioconazole 200 g/kg WG (FGE03) was tested at three target concentrations of Prothioconazole:

- Test preparation I - as the commercial concentrate. The concentrate formulation was mixed with water in a 1:1 ratio (w/w) to generate a 'paste' which was applied to the skin. This exposure scenario was considered to be representative of a person being exposed to the concentrate formulation which in turn mixes with sweat. Therefore, the concentration of Prothioconazole in the 1:1 mixture was ≈ 100 g Prothioconazole /kg,

b) Test preparation II - as an aqueous spray dilution-1 representing the lowest in-use dilution (highest concentration) of 1 kg product in 100 L water [Prothioconazole: 2.0 g/L],

c) Test preparation III - as an aqueous spray dilution-2 representing the highest in-use dilution (lowest concentration) of 0.7 kg product in 400 L water allowed in the GAP [Prothioconazole: 0.35 g/L]

6.5.3 Justification for proposed values – Prothioconazole-desthio

Proposed dermal absorption rates for Prothioconazole-desthio are based on dermal absorption studies on a formulation identical to GPF515/ FGE03. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of Prothioconazole-desthio that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5-2: Summary of the results of submitted dermal absorption studies for Prothioconazole-desthio

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	N/A	7.6% (1:100) 27% (1:574) 1:571	GPF515/ FGE03	Yes	Not required as the test item is the current formulation.	Justification accepted. Endpoint can be used for current product	Desai (2023)

Boscalid 350 g/kg + Prothioconazole 200 g/kg WG (FGE03) was tested at two target concentrations of Prothioconazole-desthio:

a) Test Preparation I - as an aqueous spray dilution-1 representing the lowest in-use spray dilution (higher concentration) of 1.0 kg product in 100 L water [Prothioconazole-desthio: 2.0 g/L],

b) Test Preparation II - as an aqueous spray dilution-2 representing the highest in-use dilution (lowest concentration) of 0.7 kg product in 400 L water allowed in the GAP [Prothioconazole-desthio: 0.35 g/L]

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	GPF515/ FGE03	
Formulation type	WG	
Category	Fungicide	
Active substance(s) (incl. content)	Boscalid 350 g/kg	Prothioconazole 200 g/kg
AOEL systemic	0.1 mg/kg bw/d	0.2 mg/kg bw/d
Inhalation absorption	100%	100%
Oral absorption	44%	100%
Dermal absorption	Concentrate: 0.11% Dilution: 3.1% (0.61 g/L) (Based on product (formulation))	Concentrate: 0.77% Dilution: 14% (0.35 g/L) (Based on product (formulation))
Active substance(s) (incl. content)	n.a.	Desthio-prothioconazole
AOEL systemic	n.a.	0.01 mg/kg bw/d
Inhalation absorption	n.a.	100%

Oral absorption	n.a.	100%
Dermal absorption	n.a.	Concentrate: 0% Dilution: 27% (0.35 g/L) (Based on product (formulation))

Table 6.6-1a: Additional parameters used in risk assessment

	Molecular weight [g/mol]	Vapour pressure [Pa]	Reference
Boscalid	343.21	7.2×10^{-7}	SANCO/3919/2007 – rev. 5
Prothioconazole	344.26	4×10^{-7}	EFSA LoEP, 2007
Prothioconazole-desthio	312.2	1×10^{-10}	EFSA LoEP, 2007 (see part B.8)

6.6.1 Selection of critical use(s) and justification

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

Justification

The use no. 2 in oilseed rape represents the worst case in respect to maximum application rate and the in use concentration of active substances revealing highest dermal absorption values for operator, worker and resident exposure.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

Comments of zRMS:	NDE calculation (EFSA on-line model OPEX ver. 1.02) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. The risk for operators is acceptable under conditions of intended uses and considering below mentioned risk mitigation measures such as Work wear (arms, body and legs covered) during M, L and A.
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A summary of the exposure models used for estimation of operator exposure to the active substances during application of GPF515/ FGE03 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 for the active substances (longer term exposure) and Table 6.6-4 considering the degradation product Prothioconazole-desthio (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Oilseed rape (max. 0.7 kg product/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 Online calculator version: 1.0.2

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

Estimated operator exposure (longer term exposure)					
		Boscalid		Prothioconazole	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to field crops					
Application rate		0.245 kg a.s./ha		0.140 kg a.s./ha	
Spray application outdoor (AOEM;	Potential exposure (no work wear, no PPE)	0.003	2.9	0.006	3.1

95 th percentile) Body weight: 60 kg	Work wear (arms, body and legs covered) M/L and A	0.002	2.3	0.004	2.1
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As the assessment of resident exposure for Boscalid considering the degradation product Prothioconazole-desthio requires risk mitigation measures to demonstrate a safe use, the calculations for the respective operator exposure assessment presented already reflect this.

Table 6.6-4: Estimated operator exposure (longer term exposure) - desthio

Table 6.3-4: Estimated operator exposure (longer term exposure) - deslino					
		Boscalid		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
Tractor mounted boom spray application outdoors to field crops, 50% drift reduction					
Application rate		0.245 kg a.s./ha		0.127 kg a.s./ha**	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Potential exposure (no work wear, no PPE)	0.002	1.9	0.003	30.3
	Work wear (arms, body and legs covered) M/L and A	0.002	1.7	0.003	26.8

* Exposure only relevant for in-use dilution during application

** A conversion of 100% is assumed. Based on a molecular weight of 344.26 g/mol for Prothioconazole and 312.19 g/mol for Prothioconazole-desthio a factor of 0.907 was applied.

Using the AOEM model, potential operator exposure is predicted to be in a range of 0.003 mg/kg bw/d and 0.006 mg/kg bw/d equal to approximately 2.9% and 3.1% of the AOEL for Boscalid and Prothioconazole for tractor-mounted spraying to field crops.

Potential operator exposure for the degradation product Prothioconazole-desthio, formed during application, is predicted at 0.003 mg/kg bw/d, equal to ca. 30% of the AOEL.

Thus, no risk for the operator using GPF515/ FGE03 is anticipated for all intended uses even without personal protective equipment.

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 calculation (EFSA on-line model OPEX ver. 1.02) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. Exposure for workers (entry into a previously treated area or handling a crop according to the critical uses) is acceptable under conditions of intended uses considering below mentioned risk mitigation measures such as Work wear, (arms, body and legs covered).
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Table 6.6-5 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GPF515/ FGE03 according to the critical use(s). Outcome of the estimation is presented in Table 6.6-6 for the active substances (longer term exposure) and

Table 6.6-7 considering the degradation product Prothioconazole-desthio (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-5: Exposure models for intended uses

Critical use(s)	Oil seed rape (max. 2×0.7 kg product/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 Online calculator version: 1.0.2

Table 6.6-6: Estimated worker exposure (longer term exposure)

Table 6.3-6: Estimated worker exposure (longer term exposure)					
		Boscalid		Prothioconazole	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Inspection, irrigation Outdoor Work rate: 2 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 × 0.245 kg a.s./ha		2 × 0.140 kg a.s./ha	
Body weight: 60 kg	Potential TC: 12500 cm ² /person/h	0.02	16.3	0.04	21.1
	Work wear (arms, body and legs covered) TC: 1400 cm ² /person/h	0.002	1.8	0.005	2.4
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm ² /person/h	0.002	1.6	0.004	2.1

Table 6.6-7: Estimated worker exposure (longer term exposure) - desthio

Table 6.6 %: Estimated worker exposure (longer term exposure) - deslino					
		Boscalid		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
Inspection, irrigation Outdoor Work rate: 2 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 × 0.245 kg a.s./ha		2 × 0.127 kg a.s./ha**	
Body weight: 60 kg	Potential TC: 12500 cm ² /person/h	0.02	16.3	0.07	735
	Work wear (arms, body and legs covered) TC: 1400 cm ² /person/h	0.002	1.8	0.008	82.4
	Work wear (arms, body and legs covered) and gloves TC: 1250 cm ² /person/h	0.002	1.6	0.007	73.5

* Exposure only relevant for in-use dilution during application

** A conversion of 100% is assumed. Based on a molecular weight of 344.26 g/mol for Prothioconazole and 312.19 g/mol for Prothioconazole-desthio a factor of 0.907 was applied.

Potential worker exposure is estimated at 0.02 mg/kg bw/d equal to approximately 16% of the AOEL for Boscalid and 0.04 mg/kg bw/d equal to approximately 21% of the AOEL for Prothioconazole for inspection/irrigation re-entry activities in field crops.

As Prothioconazole-desthio is formed during application, normal work wear should be worn with exposure estimated at 0.008 mg/kg bw equal to 82% of the AOEL.

Thus, overall, no risk for workers upon re-entry is anticipated if normal work wear is worn.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

In view of worker exposure assessment results, no studies were deemed necessary.

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

Comments of zRMS:	Justification of waiving acute risk assessment discussed by the applicant is reliable thus, zRMS agrees to the conclusions. Also no AAOEL has been set for active substances, therefore in line with EFSA, 2022. <i>Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products</i>. EFSA, Journal 2022;20(1):7032, 134 pp. exposure assessment for residents also covers bystander exposure refer point 2.3.1 Step 1; Table 2. Risk for bystanders is acceptable under conditions of intended uses. Considering outcome of risk assessment from <u>combined exposure</u> (longer term exposure) for PTZ-desthio (refer table 6.6-12) additional RMM for Resident – child has been proposed (10 m, 50% drift reduction). Refinement has been accepted by the zRMS.
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The acute exposure assessment for bystanders covers the exposure that a resident could reasonably be expected to incur in a single day. Therefore, there is no need for a separate acute risk assessment for residents.

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

Table 6.6-8 shows the exposure model(s) used for estimation of resident and bystander exposure to Boscalid and Prothioconazole. The outcome of the estimation is presented Table 6.6-9 (longer term resident exposure) and 10 for the degradation product Prothioconazole-desthio. Detailed calculations are in Appendix 3.

Table 6.6-8: Exposure models for intended uses

Critical use(s)	Oil seed rape (max. 2×0.7 kg product/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 Online calculator version: 1.0.2

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

		Boscalid		Prothioconazole	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to field crops Buffer zone: 2-3 m Drift reduction technology: no DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 × 0.245 kg a.s./ha		2 × 0.140 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.002	2.1	0.005	2.7
	Vapour (75 th perc.)	8 × 10 ⁻⁵	0.08	8 × 10 ⁻⁸	4 × 10 ⁻⁵
	Deposits (75 th perc.)	0.0003	0.3	0.0007	0.3
	Re-entry (75 th perc.)	0.002	2.2	0.006	2.8
	Sum (mean)	0.003	3.2	0.008	4
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0005	0.5	0.001	0.6
	Vapour (75 th perc.)	3 × 10 ⁻⁵	0.03	3 × 10 ⁻⁸	1 × 10 ⁻⁵
	Deposits (75 th perc.)	9 × 10 ⁻⁵	0.09	0.0002	0.1
	Re-entry (75 th perc.)	0.001	1.2	0.003	1.6
	Sum (mean)	0.001	1.3	0.003	1.6

In order to present an acceptable risk for resident exposure assessment, risk mitigation measures are required when considering exposure to the degradation product Prothioconazole-desthio, that may be formed in the field dilution, the final outcome is presented below.

Table 6.6-10: Estimated resident exposure (longer term exposure) - desthio

		Boscalid		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Tractor mounted boom spray application outdoors to field crops Buffer zone: 10 m Drift reduction technology: yes (50%) DT ₅₀ : 30days DFR: 3 µg/cm ² /kg a.s./ha Interval between treatments: 14 days					
Number of applications and application rate		2 × 0.245 kg a.s./ha		2 × 0.127 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0006	0.6	0.003	25.3
	Vapour (75 th perc.)	8 × 10 ⁻⁵	0.08	1 × 10 ⁻⁸	0.0001
	Deposits (75 th perc.)	4 × 10 ⁻⁵	0.04	0.0001	1.2
	Re-entry (75 th perc.)	0.002	2.2	0.01	99.3
	Sum (mean)	0.002	2.2	0.009	94.2
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0001	0.1	0.0005	4.7
	Vapour (75 th perc.)	3 × 10 ⁻⁵	0.03	3 × 10 ⁻⁹	3 × 10 ⁻⁵
	Deposits (75 th perc.)	1 × 10 ⁻⁵	0.01	5 × 10 ⁻⁵	0.5
	Re-entry (75 th perc.)	0.001	1.2	0.006	55.2
	Sum (mean)	0.001	1.1	0.005	46.9

- * Exposure only relevant for in-use dilution during application
** A conversion of 100% is assumed. Based on a molecular weight of 344.26 g/mol for Prothioconazole and 312.19 g/mol for Prothioconazole-desthio a factor of 0.907 was applied.

Resident exposure for children is estimated at 0.003 and 0.008 mg/kg bw/d equal to approximately 3 and 4% of the AOEL for Boscalid and Prothioconazole, respectively.

Total mean exposure towards Prothioconazole-desthio is predicted to be 0.009 mg/kg bw/d for children and 0.005 mg/kg bw/d for an adult, equal approximately 95% or 47% of the AOEL, respectively.

Thus, no risk for residents and bystanders is anticipated for use of GPF515/ FGE03.

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 Boscalid or Prothioconazole and the degradation product Prothioconazole-desthio will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

The product is a mixture of two active substances.

6.6.5.1 Exposure assessment of Boscalid and Prothioconazole in GPF515/ FGE03

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.

Table 6.6-11: Risk assessment from combined exposure (longer term exposure)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – tractor mounted, (potential exposure) (no drift reduction)	Boscalid	0.029
	Prothioconazole	0.031
	Cumulative risk operators (HI)	0.06
Workers – inspection/irrigation (potential exposure)	Boscalid	0.17
	Prothioconazole	0.22
	Cumulative risk workers (HI)	0.4
Resident – child (2-3 m, no drift reduction)	Boscalid	
	Drift	0.021
	Vapour	0.0008
	Deposits	0.003
	Re-entry	0.022
	Sum of all pathways	0.032
	Prothioconazole	
	Drift	0.027
	Vapour	4×10^{-7}

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Deposits	0.003
	Re-entry	0.028
	Sum of all pathways	0.04
	Cumulative risk resident – child (HI)	
	Drift	0.05
	Vapour	0.0008
	Deposits	0.007
	Re-entry	0.05
	Sum of all pathways	0.07
Resident – adult (2-3 m, no drift reduction)	Boscalid	
	Drift	0.005
	Vapour	0.0003
	Deposits	0.0009
	Re-entry	0.012
	Sum of all pathways	0.013
	Prothioconazole	
	Drift	0.006
	Vapour	1×10^{-7}
	Deposits	0.001
	Re-entry	0.016
	Sum of all pathways	0.016
	Cumulative risk resident – adult (HI)	
	Drift	0.01
	Vapour	0.0003
	Deposits	0.002
	Re-entry	0.03
	Sum of all pathways	0.03

The Hazard Index is < 1. Thus, combined exposure to all active substances in GPF515/ FGE03 is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

However, for Prothioconazole-containing products, its degradation product Prothioconazole-desthio has also to be evaluated as regards combined exposure. In contrast to Boscalid and Prothioconazole exposure, risk mitigation measures are required.

Table 6.6-12: Risk assessment from combined exposure (longer term exposure) - desthio

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – tractor mounted, (potential exposure)	Boscalid	0.019
	Prothioconazole-desthio	0.303
	Cumulative risk operators (HI)	0.322
Workers – inspection/irrigation (workwear)	Boscalid	0.018
	Prothioconazole-desthio	0.824
	Cumulative risk workers (HI)	0.8

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Resident – child (10 m, 50% drift reduction)	Boscalid	
	Drift	0.006
	Vapour	0.0008
	Deposits	0.0004
	Re-entry	0.022
	Sum of all pathways	0.022
	Prothioconazole-desthio	
	Drift	0.0253
	Vapour	0.0001
	Deposits	0.012
	Re-entry	0.993
	Sum of all pathways	0.942
	Cumulative risk resident – child (HI)	
	Drift	0.3
	Vapour	0.0008
	Deposits	0.01
	Re-entry	1
	Sum of all pathways	1
Resident – adult (10 m, 50% drift reduction)	Boscalid	
	Drift	0.001
	Vapour	0.0003
	Deposits	0.0001
	Re-entry	0.012
	Sum of all pathways	0.011
	Prothioconazole-desthio	
	Drift	0.047
	Vapour	3×10^{-5}
	Deposits	0.005
	Re-entry	0.552
	Sum of all pathways	0.469
	Cumulative risk resident – adult (HI)	
	Drift	0.05
	Vapour	0.0003
	Deposits	0.005
	Re-entry	0.6
	Sum of all pathways	0.5

The Hazard Index for combined resident exposure towards Boscalid and Prothioconazole-desthio is not exceeding 1.

As displayed by the EFSA online calculator, yellow colour-coding indicates a “Safe use with drift reduction and/or increased buffer strip”. Thus, further refinement of the assessment is not 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 7.3/01	Nagane, R.M.	2023	Boscalid 350 g/kg + Prothioconazole 200 g/kg: <i>In vitro</i> dermal absorption of Boscalid using human split-thickness skin in a flow through diffusion system. Report No. 617-1-06-33517 (study no. UPL/2023/0324) Jai Research Foundation, Valvada - 396105, Dist. Valsad, Gujarat, India GLP Unpublished	N	UPL Europe
KCP 7.3/02	Desai, K.R.	2024	Boscalid 350 g/kg + Prothioconazole 200 g/kg: <i>In vitro</i> dermal absorption of Prothioconazole using human split-thickness skin in a flow through diffusion system. Report No. 617-1-06-34204 (study no. UPL/2023/0584) Jai Research Foundation, Valvada - 396105, Dist. Valsad, Gujarat, India GLP Unpublished	N	UPL Europe
KCP 7.3/03	Desai, K.R.	2023	Boscalid 350 g/kg + Prothioconazole 200 g/kg: <i>In vitro</i> dermal absorption of Prothioconazole-desthio using human split-thickness skin in a flow through diffusion system. Report No. 617-1-06-34201 study no. UPL/2023/0585) Jai Research Foundation, Valvada - 396105, Dist. Valsad, Gujarat, India GLP Unpublished	N	UPL Europe

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

Not relevant.

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

No bridging of data for other formulations was necessary.

Comments of zRMS:	Agree, the toxicological profile was tested on the same product as the one requested for registration. No further comments regarding this point.
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The acute toxicological profile of FGG01 / LOZZARE PRO was assessed according to the principles laid down in Regulation (EC) No 1272/2008.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).
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The acute oral toxicity of GPF515 / FGE03 was assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid, Prothioconazole and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details please refer to Part C.

The plant protection product GPF515 / FGE03 does not contain any component classified for acute oral toxicity, thus, it's reasonable to assume that the oral LD₅₀ of the formulation will be higher than 2000 mg/kg bw and no classification is warranted according to Regulation (EC) No. 1272/2008.

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

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).
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The acute dermal toxicity of GPF515 / FGE03 was assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid, Prothioconazole and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details please refer to Part C.

The plant protection product GPF515 / FGE03 does not contain any component classified for acute dermal toxicity, thus, it's reasonable to assume that the dermal LD₅₀ of the formulation will be higher than 2000 mg/kg bw and no classification is warranted according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C). Content of component classified as "May cause respiratory irritation" does not trigger classification of the mixture.
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The acute inhalation toxicity of GPF515 / FGE03 was assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid, Prothioconazole and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details on the calculation, please refer to Part C.

The plant protection product GPF515 / FGE03 does not contain any component classified for acute inhalation toxicity, thus, it's reasonable to assume that the inhalation LC₅₀ of the formulation will be higher than the trigger value of 5 mg/L for dusts and mists and no classification is warranted according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C). ~~Content of component classified as “Causes skin irritation” trigger classification of the mixture H315~~ Content of component classified as “Causes skin irritation” does not trigger classification of the mixture.
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The skin irritating properties of GPF515 / FGE03 were assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid, Prothioconazole and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details on the calculation, please refer to Part C.

~~The plant protection product GPF515 / FGE03 does not contain any component classified for skin corrosion or irritation, thus, it's reasonable to assume that the formulation is not irritating to skin and no classification is warranted according to Regulation (EC) No. 1272/2008.~~

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C). ~~Content of component classified as “Causes serious eye damage” trigger classification of the mixture H318~~ Content of component classified as “Causes serious eye damage” does not trigger classification of the mixture.
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The eye irritating properties of GPF515 / FGE03 were assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid, Prothioconazole and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details on the calculation, please refer to Part C.

~~The plant protection product GPF515 / FGE03 does not contain any component classified for eye corrosion or irritation, thus, it's reasonable to assume that the formulation is not irritating to eyes and no classification is warranted according to Regulation (EC) No. 1272/2008.~~

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).
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The skin sensitising properties of GPF515 / FGE03 were assessed according to the rules laid down in Regulation (EC) No 1272/2008.

It is considered scientifically acceptable to use the calculation method for classification of GPF515 / FGE03 because the toxicological profiles of Boscalid and the co-formulants are well characterized.

Due to the confidential nature of the formulation, for details on the calculation, please refer to Part C.

The plant protection product GPF515 / FGE03 does not contain any component classified for skin sensitisation, thus, it's reasonable to assume that the formulation is not sensitising to skin and no classification is warranted according to Regulation (EC) No. 1272/2008.

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

Not required. No use in combination with other plant protection products is intended.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

A 2.10.1 Study 1 – Boscalid in GPF515/ FGE03

Dermal absorption, in vitro using human skin

Comments of zRMS:	Study Nagane R.M. (2023) 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 intended product to be used for risk assessment were determined at 0.11% , 1.5% and 3.1% for the formulation concentrate and spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet. Study accepted.
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Reference KCP 7.3/01

Report Nagane R.M. (2023)
Boscalid 350 g/kg + Prothioconazole 200 g/kg WG: *In vitro* dermal absorption of Boscalid using human split-thickness skin in a flow through diffusion system.
Report no.: 617-1-06-33517

Guideline(s) Yes (OECD 428)

Deviations None

GLP Yes
Acceptability Yes
Duplication Not applicable
(if vertebrate study)

Materials and methods

Test material	Name (Lot/Batch No.)	Boscalid (batch no. 12745JGD012-3)
	Test preparation	spiking
	Specific activity	1821 MBq/mmol
	Radiochemical purity	99.5%
Product	Name (Lot/Batch No.)	Boscalid 350 g/kg + Prothioconazole 200 g/kg WG (batch no. BDPT/WG/220819/550/19)
	Company code	GPF515/FGE03
	Concentration a.s.	Boscalid: 351.3 g/kg Prothioconazole: 201.4 g/kg
	Formulation type	WG
Blank product	Name (Lot/Batch No.)	GPF515 Semi-blank with Prothioconazole (batch no. BDPT/WG/220905/BLK-1)
	Concentration a.s.	Boscalid: 0 g/kg Prothioconazole: 322.4 g/kg

Test system		
Diffusion cell	Cell type	dynamic
	(if dynamic) Flow rate	1.6 mL/h
	Exposed skin area	0.64 cm ²
	Cover	open
Membrane	Skin type	dermatomed epidermis
	Skin thickness range	200 - 400 µm
	Skin donors age	27 - 48
	Skin donors sex	Female
	Location	abdomen
	Source	ex vivo
	Integrity test	Permeability coefficient
Receptor	Receptor medium	Dulbecco's phosphate-buffered saline, pH 7.4, 6% PEG plus antibiotics
	Solubility in receptor medium	70 µg/mL
Sample Time	Exposure time	8 h
	Observation time	24 h
Sampling	Sample intervals	1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h
Washing		post exposure (8 h) / post observation (24 h)
Final Procedure	Tape stripping	yes
	TS1-2 analysed separately	yes
Remarks:None		

Tested doses	Concentrate	Spray dilution 1	Spray dilution 2
Target concentration [mg/ml]	175	3.5	0.61
Area dose [µg/cm ²]	1750	35	6.1
Total dose [µg/cell]	3200	3200	3200
Specific activity [kBq/ml]	5800	5800	3230
No. of donors	4	4	4
No of cells used/valid cells	8/8	8/8	8/8

Results and discussions

In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the study was evaluated using the Excel calculation sheet provided by BfR (efs24873-sup-0001-supinfo_1) as summarized below.

Table A 1: In-vitro dermal penetration of Boscalid formulated as GPF515/ FGE03 through human skin - Recovery data

Dose group	High dose		Mid dose		Low dose	
	(Formulation concentrate)		(Spray dilution 1:100)		(Spray dilution 1:574 1:571)	
Target concentration [mg/mL]	175 (g/kg)		3.5		6.1	
Target dose [$\mu\text{g}/\text{cm}^2$]	1750		35		6.1	
Mean actual applied dose [$\mu\text{g}/\text{cm}^2$]	1760.9		34.9		6.1	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose						
Skin washing after 8 h	100.96	0.76	96.48	2.37	97.29	2.08
Skin washing after 24 h	0.18	0.29	1.95	0.82	0.88	0.51
Total skin washing after 24 h (sum 8 + 24 h)	101.14	0.81	98.43	1.90	98.16	2.08
Donor chamber wash	0.05	0.13	0.58	0.55	0.35	0.28
Dose associated to skin						
Tape strips: 1 st sample, strips 1 + 2	0.01	0.01	0.13	0.09	0.08	0.05
Tape strips: 2 nd sample; strips 3 - 15	0.01	0.01	0.15	0.08	0.14	0.05
Skin preparation	0.03	0.01	0.64	0.34	0.58	0.29
Absorbed dose						
Receptor fluid	0.05	0.02	0.44	0.09	1.70	0.60
Receptor chamber wash	0.01	0.01	0.03	0.01	0.05	0.02
Total recovery¹	101.30	0.86	100.39	1.65	101.05	1.66
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]	No [65.84% $\pm$ 1.75]		No [60.88% $\pm$ 5.37]		No [73.20% $\pm$ 5.25]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) ²	0.09	0.03	1.25	0.34	2.46	0.76
If yes: Absorption estimates = absorbed dose + skin preparation	N/A	N/A	N/A	N/A	N/A	N/A
Measured absorption estimate normalised ³	0.09 $\pm$ 0.03		1.25 $\pm$ 0.34		2.46 $\pm$ 0.76	
Relevant absorption estimate ⁴	0.113		1.532		3.104	
Absorption estimates used for risk assessment⁵	0.11		1.5		3.1	

¹ Values may not calculate exactly due to rounding of figures

² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) 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 (see Table 7.6.2-1) Finally, 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, one standard deviation was added to the mean% dermal penetration in cases where the standard deviation was $\geq$ 25% of the mean value.

⁵ Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

Remarks

No further remarks are considered necessary. No recovery below 95% was determined.
No cells were excluded.

Conclusion/endpoint:

The dermal penetration of Boscalid formulated as GPF515/ FGE03 through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating the skin within 24 hours given as the sum of receptor fluid, receptor compartment wash, skin preparation and *stratum corneum* (as less than 75% of the absorption occurred in the first half of the study) was determined to be 0.09 $\pm$ 0.03% for the formulation concentrate, 1.24 $\pm$ 0.34% for spray dilution 1 (1:100) and 2.47 $\pm$ 0.76% for spray dilution 2 (1:574

1:571) respectively, according to the report.

The dermal penetration estimates to be used for risk assessment were set at **0.11%**, **1.5%** and **3.1%** for the formulation concentrate and spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet.

A 2.10.2 Study 2 – Prothioconazole in GPF515/ FGE03

Dermal absorption, in vitro using human skin

Comments of zRMS:	Study Desai K.R. (2024) 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 intended product to be used for risk assessment were determined at 0.77%, 2.9% and 14% for the formulation concentrate and spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet. Study accepted.
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Reference	KCP 7.3/02
Report	Desai K.R. (2024) Boscalid 350 g/kg + Prothioconazole 200 g/kg WG: <i>In vitro</i> dermal absorption of Prothioconazole using human split-thickness skin in a flow through diffusion system. Report no.: 617-1-06-34204
Guideline(s)	Yes (OECD 428)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	Not applicable

Materials and methods

Test material	Name (Lot/Batch No.)	Prothioconazole (batch no. 23BLY065)
	Test preparation	spiking
	Specific activity	740 MBq/mmol
	Radiochemical purity	>97%
Product	Name (Lot/Batch No.)	Boscalid 500 g/kg + Prothioconazole 200 g/kg WG (batch no. BDPT/WG/220819/550/19)
	Company code	GPF515/FGE03
	Concentration a.s.	Boscalid: 358.3 g/kg Prothioconazole: 199.9 g/kg
	Formulation type	WG
Blank product	Name (Lot/Batch No.)	GPF515 Semi-blank with Boscalid (batch no. BDPT/WG/220905/BLK-2)
	Concentration a.s.	Boscalid: 450.6 g/kg Prothioconazole: 0 g/kg

Test system		
Diffusion cell	Cell type	dynamic
	(if dynamic) Flow rate	1.6 mL/h
	Exposed skin area	0.64 cm ²
	Cover	open
Membrane	Skin type	dermatomed epidermis
	Skin thickness range	200 - 400 µm
	Skin donors age	33 - 50
	Skin donors sex	Female
	Location	abdomen

	Source	ex vivo
	Integrity test	Permeability coefficient
Receptor	Receptor medium	Dulbecco's phosphate-buffered saline, pH 7.4, 6% PEG) plus antibiotics
	Solubility in receptor medium	40 µg/mL
Sample Time	Exposure time	8 h
	Observation time	24 h
Sampling	Sample intervals	1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h
Washing		post exposure (8 h) / post observation (24 h)
Final Procedure	Tape stripping	yes
	TS1-2 analysed separately	yes
Remarks: None		

Tested doses	Concentrate	Spray dilution 1	Spray dilution 2
Target concentration [mg/ml]	100	2.0	0.35
Area dose [µg/cm²]	1025	20.1	3.5
Total dose [µg/cell]	3200	3200	3200
Specific activity [kBq/ml]	5800	4310	250
No. of donors	4	4	4
No of cells used/valid cells	7/8	8/8	8/8

Results and discussions

In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the study was evaluated using the Excel calculation sheet provided by BfR (efs24873-sup-0001-supinfo_1) as summarized below.

Table A 2: In-vitro dermal penetration of Prothioconazole formulated as GPF515/ FGE03 through human skin - Recovery data

Dose group	High dose		Mid dose		Low dose	
	(Formulation concentrate)		(Spray dilution 1:100)		(Spray dilution 1:571)	
Target concentration [mg/mL]	100 (g/kg)		2.0		0.35	
Target dose [µg/cm²]	1000		20		3.5	
Mean actual applied dose [µg/cm²]	1025		20.1		3.5	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose						
Skin washing after 8 h	95.54	1.38	95.79	1.76	84.34	3.04
Skin washing after 24 h	0.53	0.36	1.01	0.58	2.64	0.66
Total skin washing after 24 h (sum 8 + 24 h)	96.07	1.17	96.80	1.77	86.97	2.81
Donor chamber wash	0.74	0.59	0.16	0.13	0.42	0.29
Dose associated to skin						
Tape strips: 1 st sample, strips 1 + 2	0.25	0.07	0.28	0.15	1.13	0.24
Tape strips: 2 nd sample; strips 3 - 15	0.25	0.08	0.55	0.13	2.72	0.48
Skin preparation	0.16	0.13	0.57	0.19	2.86	1.04
Absorbed dose						
Receptor fluid	0.16	0.05	1.26	0.38	5.57	2.25
Receptor chamber wash	0.01	0.00	0.05	0.03	0.16	0.06
Total recovery¹	97.64	0.70	99.67	1.77	99.83	1.84
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at t _{0.5}]	No [60.45% ± 4.59]		No [66.62% ± 6.82]		No [66.67% ± 4.05]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) ²	0.09	0.03	1.25	0.34	2.46	0.76

If yes: Absorption estimates = absorbed dose + skin preparation	N/A	N/A	N/A	N/A	N/A	N/A
Measured absorption estimate normalised ³	0.58 ± 0.21		2.43 ± 0.54		11.30 ± 2.65	
Relevant absorption estimate ⁴	0.774		2.881		13.535	
Absorption estimates used for risk assessment⁵	0.77		2.9		14	

¹ Values may not calculate exactly due to rounding of figures

² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) 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 (see Table 7.6.2-1) Finally, 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, one standard deviation was added to the mean% dermal penetration in cases where the standard deviation was ≥ 25% of the mean value.

⁵ Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

Remarks

Results of the absorption of Prothioconazole in receptor fluid for replicate H1 showed spuriously high values after 8h skin wash due to the skin being damaged or slightly displaced during the 8 h skin washing procedure. A box plot statistical analysis for cumulative absorption also showed H1 as an outlier. Therefore, data of H1 replicate was rejected as outlier and mean ± SD for seven replicates (n=7) were considered for test preparation I.

Conclusion/endpoint:

The dermal penetration of Prothioconazole formulated as GPF515/ FGE03 through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating the skin within 24 hours given as the sum of receptor fluid, receptor compartment wash, skin preparation plus *stratum corneum* was determined to be 0.58 ± 0.21% for the formulation concentrate, 2.43 ± 0.54% for spray dilution 1 (1:100) and 11.3 ± 2.66% for spray dilution 2 (1:574 1:571), respectively, according to the report.

The dermal penetration estimates to be used for risk assessment were set at **0.77%**, **2.9%** and **14%** for the formulation concentrate and spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet.

A 2.10.3 Study 3 – Prothioconazole-desthio in GPF515/ FGE03

Dermal absorption, in vitro using human skin

Comments of zRMS:	Study Desai K.R. (2023) 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 intended product to be used for risk assessment were determined at at 7.6% and 27% for spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet. Study accepted.
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Reference	KCP 7.3/03
Report	Desai K.R. (2023) Boscalid 350 g/kg + Prothioconazole 200 g/kg WG: <i>In vitro</i> dermal absorption of Prothioconazole-desthio using human split-thickness skin in a flow through diffusion system. Report no.: 617-1-06-34205
Guideline(s)	Yes (OECD 428)
Deviations	None

GLP Yes
Acceptability Yes
Duplication Not applicable
(if vertebrate study)

Materials and methods

Test material	Name (Lot/Batch No.)	Prothioconazole-desthio (batch no. 12427SXD002-1)
	Test preparation	spiking
	Specific activity	1978 MBq/mmol
	Radiochemical purity	99.6%
Product	Name (Lot/Batch No.)	Boscalid 350 g/kg + Prothioconazole 200 g/kg WG (batch no. BDPT/WG/220819/550/19)
	Company code	GPF515/FGE03
	Concentration a.s.	Boscalid: 351.3 g/kg Prothioconazole: 201.4 g/kg
	Formulation type	WG
Blank product	Name (Lot/Batch No.)	GPF515 Semi-blank with Boscalid (batch no. BDPT/WG/220905/BLK-2)
	Concentration a.s.	Boscalid: 450.6 g/kg Prothioconazole: 0 g/kg

Test system		
Diffusion cell	Cell type	dynamic
	(if dynamic) Flow rate	1.6 mL/h
	Exposed skin area	0.64 cm ²
	Cover	open
Membrane	Skin type	dermatomed epidermis
	Skin thickness range	200 - 400 µm
	Skin donors age	32 - 48
	Skin donors sex	Female
	Location	abdomen
	Source	ex vivo
Receptor	Integrity test	Permeability coefficient
	Receptor medium	Dulbecco's phosphate-buffered saline, pH 7.4, 6% PEG) plus antibiotics
	Solubility in receptor medium	4 µg/mL
Sample Time	Exposure time	8 h
	Observation time	24 h
Sampling	Sample intervals	1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h
Washing		post exposure (8 h) / post observation (24 h)
Final Procedure	Tape stripping	yes
	TS1-2 analysed separately	yes
Remarks:None		

Tested doses	Concentrate	Spray dilution 1	Spray dilution 2
Target concentration [mg/ml]	n.a.*	2.0	0.35
Area dose [µg/cm ²]	n.a.	19.9	3.46
Total dose [µg/cell]	n.a.	3200	3200
Specific activity [kBq/ml]	n.a.	5800	2210
No. of donors	n.a.	4	4
No of cells used/valid cells	n.a.	8/8	8/8

* Prothioconazole-desthio is the main degradation product of Prothioconazole. As a conservative assumption, 100% conversion to Prothioconazole-desthio upon dilution are assumed. Desthio-PTC is not present in the concentrate.

Results and discussions

In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the study was evaluated using the Excel calculation sheet provided by BfR (efs24873-sup-0001-supinfo_1) as summarized below.

Table A 3: In-vitro dermal penetration of Prothioconazole-desthio formulated as GPF515/FGE03 through human skin - Recovery data

Dose group	High dose		Mid dose		Low dose	
	(Formulation concentrate)		(Spray dilution 1:100)		(Spray dilution 1:572)	
Target concentration [mg/mL]	N/A		2.0		0.35	
Target dose [$\mu\text{g}/\text{cm}^2$]	N/A		20		3.5	
Mean actual applied dose [$\mu\text{g}/\text{cm}^2$]	N/A		19.9		3.46	
	Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose						
Skin washing after 8 h	N/A	N/A	96.48	2.37	97.29	2.08
Skin washing after 24 h	N/A	N/A	1.95	0.82	0.88	0.51
Total skin washing after 24 h (sum 8 + 24 h)	N/A	N/A	92.42	1.94	76.26	5.57
Donor chamber wash	N/A	N/A	0.28	0.44	0.28	0.09
Dose associated to skin						
Tape strips: 1 st sample, strips 1 + 2	N/A	N/A	0.01	0.00	0.10	0.06
Tape strips: 2 nd sample; strips 3 - 15	N/A	N/A	0.03	0.01	0.26	0.15
Skin preparation	N/A	N/A	0.35	0.06	1.44	0.28
Absorbed dose						
Receptor fluid	N/A	N/A	5.80	1.49	20.62	5.48
Receptor chamber wash	N/A	N/A	0.16	0.05	0.39	0.25
Total recovery¹	N/A	N/A	99.04	1.40	99.35	0.88
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]	N/A		Yes [94.24% $\pm$ 1.73]		Yes [91.76% $\pm$ 2.33]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) ²	N/A	N/A	N/A	N/A	N/A	N/A
If yes: Absorption estimates = absorbed dose + skin preparation	N/A	N/A	N/A	N/A	N/A	N/A
Measured absorption estimate normalised ³	N/A		6.31 $\pm$ 1.56		22.45 $\pm$ 5.72	
Relevant absorption estimate ⁴	N/A		7.619		27.258	
Absorption estimates used for risk assessment⁵	N/A		7.6		27	

¹ Values may not calculate exactly due to rounding of figures

² In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) 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 (see Table 7.6.2-1) Finally, 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, one standard deviation was added to the mean% dermal penetration in cases where the standard deviation was $\geq$ 25% of the mean value.

⁵ Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

Remarks

No further remarks are considered necessary. No recovery below 95% was determined. No cells were excluded.

Conclusion/endpoint:

The dermal penetration of Prothioconazole-desthio formulated as GPF515/ FGE03 through human dermated skin was determined *in vitro*. The amount of applied dose penetrating the skin within 24 hours given as the sum of receptor fluid, receptor compartment wash and skin preparation (without *stratum corneum*, as more than 75% of the absorption occurred in the first half of the study) was determined to be $6.31 \pm 1.56\%$ for spray dilution 1 (1:100) and $22.45 \pm 5.72\%$ for spray dilution 2 (ca 1:574 1:571), respectively, according to the report.

The dermal penetration estimates to be used for risk assessment were set at **7.6%** and **27%** for spray dilutions 1 and 2 based on the EFSA guidance criteria and the BfR calculation sheet.

Please find attached the respective excel file:

Tox_Attachment B.6-1 - BfR _dermal absorption Boscalid

Tox_Attachment B.6-2 - BfR _dermal absorption Prothioconazole

Tox_Attachment B.6-3 - BfR _dermal absorption Prothioconazole-desthio

A 2.11 Other/Special Studies

No further studies were deemed necessary.

The relevant impurity/degradation product Prothioconazole-desthio is addressed sufficiently in the DAR on Prothioconazole and the risk assessments for operators, worker, residents and bystanders presented in this dossier.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

For details calculations see attached zip file and output file as provided by the EFSA online calculator tool.

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

For details calculations see attached zip file and output file as provided by the EFSA online calculator tool.

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

For details calculations see attached zip file and output file as provided by the EFSA online calculator tool.

A 3.4 Combined exposure calculations for Boscalid and Prothioconazole

For details calculations see attached zip file and output file as provided by the EFSA online calculator tool.

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

Not relevant.

Appendix 5 EFSA calculator output files

Please refer to the attached files:

Zip files as provided by EFSA online calculator

- Tox_Attachment B.6-4_FGE03_Boscalid_PTC_20241022_opex1.0.2 including the calculations for Boscalid and Prothioconazole
- Tox_Attachment B.6-5 - FGE03_Boscalid_desthio_20241104_opex1.0.2 including the calculations for Boscalid and Prothioconazole-desthio

Report output files as provided by EFSA online calculator

- Tox_Attachment B.6-6 FGE03_Boscalid_PTC_20241022 including the calculations for Boscalid and Prothioconazole
- Tox_Attachment B.6-7 FGE03_Boscalid_desthio_2024104 including the calculations for Boscalid and Prothioconazole-desthio