

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GF-3307 (S7K-3-3)

Product name(s): QUEEN

Chemical active substance(s):

Fenpicoxamid (XDE-777), 50 g/L

Prothioconazole, 100 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(extension of use)

Applicant: Corteva Agriscience

Submission date: March 2025

MS Finalization date: July 2025 (initial Core Assessment)

December 2025 (final Core Assessment)

Version history

When	What
March 2025	Submission of GF-3307 (S7K-3-3) Sugar beet/Fodder beet Extension of Use in the Central Zone.
July 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.
December 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.

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Reviewer general comment:

This section of the dossier provides a summary of the toxicological profile and exposure data for the plant protection product QUEEN / GF-3307 (S7K-3-3). It has been submitted to support the proposed label extension for use on sugar beet and fodder beet (see Part A, Section 2.6 for further details).

The product GF-3307 (S7K-3-3) is an emulsion concentrate (EC) formulation containing fenpicoxamid (50 g/L) and prothioconazole (100 g/L). It is currently authorised as a fungicide for use in cereals. Evaluation of this product was previously carried out in accordance with the Uniform Principles by the Member State: Poland (zRMS:PL), and it was registered under authorisation number R-140/2023.

The proposed extension of use does not impact the previously assessed toxicological studies or the established endpoints. Consequently, it does not alter the toxicological classification of the product. A repeated toxicological assessment is therefore not required in the current process. For a detailed toxicological evaluation, please refer to the Registration Report (RR) Part B, Section 6: Mammalian Toxicology (Product code: GF-3307, dated January 2023). However, due to scientific progress, a brief review of the previous RR in relation to the product's registration confirmed that all studies remain valid and are consistent with the current OECD guidelines.

For the purposes of ongoing registration of the product Queen (extension of use), the applicant has provided a new NDE (Non-Dietary Exposure) assessment using the latest version of the EFSA online exposure model (version 1.0.1). Additionally, a revised dermal absorption value for the prothioconazole was submitted (study Maas, W.J.M., 2023, Study ID 220958), in line with the proposed application rate (refer to Section B0 GAP). The updated NDE assessment confirmed the safe use of the proposed product for the intended new application on sugar beet and fodder beet and did not indicate any exceedance of the AOEL (Acceptable Operator Exposure Level) for exposed individuals.

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.

ENDOCRINE DISRUPTION PROPERTIES - prothioconazole.

1) With regard to T modality, the data set was considered complete, and a pattern of T-mediated adversity was not identified.

The minor effects observed in thyroid hormones (THs) below the maximum tolerated dose (MTD), in the absence of any histopathological change in the thyroid follicular cell, were not considered sufficient evidence of adversity and the overall weight-of-evidence (WoE) indicates that prothioconazole is not affecting the T modality.

2) With regard to EAS modality, the data set was considered complete, and a pattern of EAS-mediated adversity was not observed.

Therefore, based on the available and sufficient data set, it was concluded that the ED criteria are not met for the EAST modalities (Scenario 1a of the EFSA/ECHA, 2018, ED Guidance).

Refer EFSA Journal. 2025;23:e9593. Peer review of the pesticide risk assessment of the active substance prothioconazole.

6 Mammalian Toxicology (KCP 7)

This document reviews the toxicology studies and risk calculations for the plant protection product G-3307 (S7K-3-3), a formulation containing fenpicoxamid (XDE-777) (50 g as/L) and prothioconazole (100 g as/L) for the use on sugar beet/fodder beet.

6.1 Summary

Table 6.1-1: Information on GF-3307 *



Product name and code	QUEEN / GF-3307 (S7K-3-3)
Formulation type	Emulsion concentrate [EC]
Active substance(s) (incl. content)	Fenpicoxamid, 50 g/L Prothioconazole, 100 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	Formulation GF-3307 has already been evaluated for uses on cereals with PL zRMS for CZ.

* Information on the detailed composition of GF-3307 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 GF-3307 according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Eye irritation Cat 2 – H319 Acute inhalation tox Cat 4* STOT SE Cat 3 – H335 Chronic aquatic Cat 1 – H410**
Hazard pictograms or Code(s) for hazard pictogram(s)	 GHS07  GHS09**
Signal word	Warning
Hazard statement(s)	H319 Causes serious eye irritation. H332 Harmful if inhaled* H335 May cause respiratory irritation. H335 May cause respiratory irritation. H410 Very toxic to aquatic life with long lasting effects**
Precautionary statement(s)	P261 Avoid breathing mist/vapours/spray P280 Wear protective gloves/ clothing /eye/face protection P304+P340 IF INHALED: Remove person to fresh air and keep comfortable for breathing* P305+P351+P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P312 Call a POISON CENTRE/doctor/...if you feel unwell. P391 Collect spillage. P501 Dispose of contents/container in accordance with applicable regulations
Additional labelling phrases	To avoid risks to human and the environment, comply with the instructions for use. [EUH401]

***zRMS Reviewer comment:** Due to the fact that the applicant did not provide alternative inhalation toxicity study, zRMS PL adjusted the CLP classification to remain consistent with the previously accepted hazard classification. Refer Registration Report (RR) Part B, Section 6: Mammalian Toxicology (Product code: GF-3307, dated January 2023)

(December 2025) zRMS has analyzed the available information and based on this data, considers the following that no deaths were observed in the study and therefore the classification indicated in the RR B6 is not warranted. The adjusted classification is: STOT SE Cat 3; H335, triggered by CLP concentration limits (refer Part C).

** Hazard statement H410 concerns the classification of environmental hazards and has therefore been deleted from part B6

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for GF-3307

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Normal workwear ^(a) Required based on hazard classification: protective gloves/ clothing / eye/face protection
Workers	Acceptable	Normal workwear ^(a) and gloves for the tasks of manual reaching/picking and removal of bolting sugar beets
Residents	Acceptable	None
Bystanders	Acceptable	None

a) Risk assessments were conducted assuming the wearing of normal workwear (arms, body and legs covered). Normal workwear is not considered to be PPE *per se*. As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton ($\geq 300 \text{ g/m}^2$) or of cotton and polyester with at least 65% polyester ($\geq 245 \text{ g/m}^2$)”.

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

Table 6.1-3 are applied.

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 ****	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
1-2	Sugar beet Fodder beet (BBCH 39-49)	F	Spraying, LCTM	a) 1 b) 2 (21-day interval)	a) 0.075 fenpicoxamid + b) 0.15 prothioconazole	150 - 300	21	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 EFSA online OPEX calculator https://r4eu.efsa.europa.eu/app/opex		1)		
										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

1) Inspection, irrigation

2) Normal workwear and gloves for the tasks of manual reaching/picking and removal of bolting sugar beets

Note: Estimated worker exposure – prothioconazole-desthio. The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.

Explanation for column 10 “Acceptability of exposure assessment”

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

Data gaps

Noticed data gaps are: none.

6.2 Toxicological Information on Active Substance(s)

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

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

	Fenpicoxamid	Prothioconazole	Prothioconazole-desthio
Common Name	Fenpicoxamid	Prothioconazole	Prothioconazole-desthio
CAS-No.	517875-34-2	178928-70-6	
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: None Code(s) for hazard pictogram(s):GHS09 Signal word: Warning Hazard statement(s): H410, Precautionary statement(s): P273, P501	Hazard classes (s), categories: None Code(s) for hazard pictogram(s):GHS09 Signal word: Warning Hazard statement(s): H400, H410 Precautionary statement(s): None	Not applicable
Additional C&L proposal	Not applicable	Not applicable	Not applicable
Agreed EU endpoints			
AOEL systemic	0.05 mg/kg bw/d (with a 100-fold assessment factor and corrected for 12% oral absorption)	0.2 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)	0.01 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)
AAOEL systemic	0.2 mg/kg bw/day (as ARfD (100-fold safety factor) and corrected for 12% oral absorption). Note that the use of minor body weight & feed consumption changes in rabbits for setting an ARfD is not appropriate and therefore it is the applicant's view that an AAOEL is not required for this assessment. Nevertheless, the agreed EU end-points as defined in EFSA Journal 2018;16(1):5146 have been used in the exposure assessments.	Not assigned at EU level	Not assigned at EU level
Reference	EFSA Journal 2018;16(1):5146 Fenpicoxamid Final Review Report SANTE/10319/2018 Rev. 2	EFSA Scientific Report (2007) 106, 1-98 Prothioconazole Review Report SANCO/3923/07 - final	EFSA Scientific Report (2007) 106, 1-98
Proposed EU endpoints			
AOEL systemic	Not applicable	0.036 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)	0.01 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)
AAOEL systemic	Not applicable	0.2 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)	0.01 mg/kg bw/day (with a 100-fold assessment factor) (no correction for oral absorption required)
Reference	Not applicable	EFSA Journal 2025:9593	EFSA Journal 2025:9593
Conditions to take into account/critical areas of concern with regard to toxicology			

	Fenpicoxamid	Prothioconazole	Prothioconazole-desthio
According to Review Report/EFSA Conclusion	None	The operator safety in spray applications. Conditions of use should include adequate protective measures.	

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for GF-3307 (S7K-3-3) is given in the following two tables. *In vivo* toxicology studies have been conducted using GF-3307 (S7K-3-3). 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 GF-3307

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral, rat (OECD 423)	2000 – 5000 mg/kg bw	Yes	None	██████████ 2021, 211324
LD ₅₀ dermal, rat (OECD 402)	>2000 mg/kg bw	Yes	None	██████████ 2021, 211323
LC ₅₀ inhalation, rat (OECD 436)	>2.9 mg/L air	Yes	Category 4 H332 – Harmful if inhaled None	██████████ 211432
Skin irritation, Dermal, Rabbit (OECD 404)	Non irritant	Yes	None	██████████ 2021, 211322
Eye irritation, Eye, Rabbit (OECD 405)	Irritant	Yes	Category 2 H319 Causes serious eye irritation	██████████ 2021, 211321
Skin sensitisation	Dermal non sensitiser	Yes	None	██████████ 2021, 211320
Supplementary studies for combinations of plant protection products	No data – not required	Yes	--	--

Table 6.3-2: Additional toxicological information relevant for classification/labelling of GF-3307 (S7K-3-3)

	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)	Fenpicoxamid (50 g/L)	None	Fenpicoxamid: EFSA Journal 2018;16(1):5146	Hazard statement(s): Not applicable
Toxicological properties of active substance(s) (relevant for classification of product)	Prothioconazole	None	SANCO/3923 /07 - final 10 December 2007	Hazard statement(s): Not applicable
Toxicological properties of non-active substance(s) (relevant for classification of product)	See part C, point 1.3.2	See part C, point 1.3.2	See part C, point 1.3.2	See part C, point 1.3.2

	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)
Further toxicological information	No data – not required			

Based on the results from the *in vivo* acute toxicity studies outlined above, it can be concluded that GF-3307 (S7K-3-3) has low concern for acute oral, dermal and inhalation toxicity and is not a skin irritant or dermal sensitizer. Based on the results from the acute eye irritation study in the rabbit, there was evidence of eye irritation which resolved by day 14 in all rabbits. Therefore, proposed classification regarding acute toxicity endpoints is:

- Eye irritation: Cat 2 – H319
- **STOT SE Cat 3 – H335**
- ~~Acute inhalation toxicity: Cat 4 – H332~~

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 GF-3307 (S7K-3-3) are presented in the following table.

Table 6.5-1: Dermal absorption rates for the active substances fenpicoxamid and prothioconazole in GF-3307 (S7K-3-3) and the metabolite prothioconazole-desthio

	Fenpicoxamid		Prothioconazole		Prothioconazole-desthio	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	0.33%	Study ID: 200109 GF-3307: In Vitro Percutaneous Absorption of Fenpicoxamid in Human Skin (Whitfield, C, 2021)	0.68%	New data reported in Appendix 2 (A2.10) (Maas, W.J.M., 2023, Study ID 220958)	Not needed	See for 6.5.3 explanation
Dilution	12% (for 1:250 dilution)	Study ID: 200109 GF-3307: In Vitro Percutaneous Absorption of Fenpicoxamid in Human Skin (Whitfield, C, 2021)	14% (for 1:250 dilution)	New data reported in Appendix 2 (A2.10) (Maas, W.J.M., 2023, Study ID 220958)	14% (for 1:250 dilution)	Study ID: 200102 GF-3307: In Vitro Percutaneous Absorption of Prothioconazole-desthio in Human Skin (Whitfield, C, 2020)

6.5.1 Justification for proposed values – Fenpicoxamid

Proposed dermal absorption rates for fenpicoxamid are based on a dermal absorption study conducted with formulation GF-3307 (S7K-3-3). The study results are summarised in the following table. A full summary of this study on the dermal absorption of fenpicoxamid in GF-3307 (S7K-3-3) is described in detail in Appendix 2.

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

Test	Concentrate	Spray dilution (1:250)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
<i>In vitro</i> (human)	0.33% ^(a)	12% ^(a)	GF-3307	Yes	Not required – study formulation is identical to the current product	Justification accepted. Endpoint can be used for current product	Whitfield, C., 2021, Study ID 200109

(a): value calculated from experimental study data in accordance with EFSA Guidance on Dermal Absorption (2017)

6.5.2 Justification for proposed values - Prothioconazole

Proposed dermal absorption rates for prothioconazole are based on a dermal absorption study conducted with formulation GF-3307 (S7K-3-3). The study results are summarised in the following table. A full summary of this study on the dermal absorption of prothioconazole in GF-3307 (S7K-3-3) which 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

Test	Concentrate	Spray dilution (1:250)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
<i>In vitro</i> (human)	0.68% ^(a)	14% ^(a)	GF-3307	Yes	Not required – study formulation is identical to the current product	Justification accepted. Endpoint can be used for current product	New data Maas, W.J.M., 2023, Study ID 220958

* indicates that a study was reviewed at EU level

(a): value calculated from experimental study data in accordance with EFSA Guidance on Dermal Absorption (2017)

6.5.3 Justification for proposed values – Prothioconazole-desthio

The metabolite, prothioconazole-desthio is not part of the formulation of GF-3307 (S7K-3-3) *per se*. However, it has been found that **prothioconazole can convert to prothioconazole-desthio in diluted solutions** during the drying process on clothing, skin or certain plant surfaces. Although prothioconazole-desthio is not an active substance and not a component of the formulation *per se*, **non-dietary risk assessments are always performed for prothioconazole-desthio** due to its toxicological properties.

Formation of prothioconazole-desthio is not expected to occur in the product concentrate and operator exposure to prothioconazole-desthio during mixing and loading procedures of the concentrate is not expected. Therefore, a dermal absorption rate for prothioconazole-desthio in the concentrate is not needed and the default absorption value is set as 0 in the exposure assessments to remove this aspect for the operator mixing and loading procedures.

Proposed dermal absorption rates for prothioconazole-desthio in the dilution are based on a dermal absorption study conducted with formulation GF-3307 (S7K-3-3). The study results are summarised in the following table. A full summary of this study on the dermal absorption of prothioconazole in GF-3307 (S7K-3-3) is described in detail in Appendix 2.

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

Test	Concentrate	Spray dilution (1:250)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
<i>In vitro</i> (human)	Not tested	14% ^(a)	GF-3307	Yes	Not required – study formulation is identical to the current product	Justification accepted. Endpoint can be used for current product	Whitfield, C., 2020, Study ID 200102

* indicates that a study was reviewed at EU level

(a): value calculated from experimental study data in accordance with EFSA Guidance on Dermal Absorption (2017)

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

At the time of product submission (March 2025), the renewal of the active substance prothioconazole was ongoing. In August 2025, EFSA published the peer review conclusions (EFSA Journal. 2025;23:e9593), in which a lower AOEL value was proposed for prothioconazole and new AAOEL values were proposed for both prothioconazole and prothioconazole-desthio. These values are not yet formally adopted in the European Union. However, at the request of the zRMS (PL) (December 2025), updated exposure assessments are provided below considering the new AAOEL values. The updated assessments are presented in yellow highlight colour and are indicated with 'New'.

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

Product name and code	GF-3307 (S7K-3-3)		
Formulation type	EC		
Category	Fungicide		
Active substance(s) (incl. content)	Fenpicoxamid 50 g/L	Prothioconazole 100 g/L	Prothioconazole-desthio (PTZ-desthio) ^(a)
Current AOEL systemic	0.05 mg/kg bw/day	0.2 mg/kg bw/day	0.01 mg/kg bw/day
Current AAOEL systemic	0.2 mg/kg bw/day	Not assigned at EU level	Not assigned at EU level
New AOEL systemic	N/A	0.036 mg/kg bw/day	0.01 mg/kg bw/day
New AAOEL systemic	N/A	0.2 mg/kg bw/day	0.01 mg/kg bw/day
Inhalation absorption	100%	100%	100%
Oral absorption	12%	100%	100%
Dermal absorption	Concentrate (50 g a.s./L): 0.33% Dilution (0.2 g a.s./L): 12% (Whitfield, C., 2021, Study ID 200109, see 6.5)	Concentrate (100 g a.s./L): 0.68% Dilution (0.4 g a.s./L): 14% (Maas, W.J.M., 2023, Study ID 220958, see 6.5)	Concentrate (0 g a.s./L): N/A ^(b) Dilution (0.363 g a.s./L): 14% (Maas, W.J.M., 2023, Study ID 220958, see 6.5)

- (a) The metabolite, prothioconazole-desthio is not part of the formulation of GF-3307 *per se*. However, it has been found that **prothioconazole can convert to prothioconazole-desthio in diluted solutions** during the drying process on clothing, skin or certain plant surfaces. Although prothioconazole-desthio is not an active substance and not a component of the formulation *per se*, **non-dietary risk assessments are always performed for prothioconazole-desthio** due to its toxicological properties.
- (b) Formation of prothioconazole-desthio is not expected to occur in the product concentrate and operator exposure to prothioconazole-desthio during mixing and loading procedures of the concentrate is not expected. Therefore, a dermal absorption rate for prothioconazole-desthio in the concentrate is not needed and has been set as 0 in the exposure assessments to remove this aspect for the operator mixing and loading procedure assessments.

6.6.2 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 critical GAP used for the exposure assessments is based on the highest supported application rate and the lowest water volume and represents the worst-case exposure scenarios.

For the assessment of prothioconazole-desthio in diluted solutions, a worst-case assessment has been performed assuming 100% conversion of prothioconazole to prothioconazole-desthio. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.

6.6.3 Operator exposure (KCP 7.2.1)

Comments of zRMS:	<p>The NDE (Non-Dietary Exposure) calculation performed by the Applicant using the EFSA online model OPEX (version 1.0.1 and 1.1.3) is considered acceptable. The zRMS Reviewer agrees with the conclusions presented.</p> <p>The risk to operators is deemed acceptable under the conditions of the proposed uses and taking into account the following risk mitigation measures, namely the wearing of workwear covering the arms, body, and legs during mixing, loading, and application (M, L, A).</p> <p>Note: Risk assessments were conducted on the assumption that standard workwear—covering the arms, body, and legs—is worn. Standard workwear is not classified as personal protective equipment (PPE) per se. As defined by EFSA (2022), “normal workwear consists of coveralls or a long-sleeved shirt and trousers made of cotton ($\geq 300 \text{ g/m}^2$), or cotton-polyester fabric containing at least 65% polyester ($\geq 245 \text{ g/m}^2$).”</p>
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Conclusion: Operator exposure estimations conducted using the EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex_v1.0.1) indicated that the acceptable operator exposure level (AOEL) and acute acceptable operator exposure level (AAOEL, where relevant) will not be exceeded under conditions of intended use and with the operator wearing normal work wear and no specialised PPE for mixing/loading and application procedures. Assuming normal workwear and no specialised PPE, the maximum predicted exposures were 4.7% of the AOEL and 8.2% of the AAOEL for fenpicoxamid, 3.1% of the AOEL for prothioconazole and 26% of the AOEL for prothioconazole-desthio. Estimations of exposure to prothioconazole-desthio were for a worst-case scenario of 100% conversion of prothioconazole to prothioconazole-desthio once the product was diluted with water.

New: Operator exposure estimations conducted using the EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex_v1.1.3) and considering the new (A)AOELs (EFSA, 2025) indicated that the AOELs and AAOELs will not be exceeded under conditions of intended use with 50% drift reduction technology, and with the operator wearing normal work wear and no specialised PPE for mixing/loading and application procedures. With these conditions, the maximum predicted exposures were 3.3%, 13.1% and 11.7% of the AOELs and 3.6%, 9.7% and 57.4% of the AAOELs for fenpicoxamid, prothioconazole and prothioconazole-desthio, respectively. Risk assessments have been performed for both the parent (prothioconazole) and metabolite (prothioconazole-desthio) with the exposure estimates for prothioconazole-desthio assuming a worst-case scenario of 100% conversion of prothioconazole to prothioconazole-desthio once the product was diluted with water.

Assessments for prothioconazole are provided for information only. This is because only prothioconazole or its metabolite, prothioconazole-desthio can be present at a time if 100% conversion is assumed. Due to its toxicological properties, the assessment for 100% conversion to prothioconazole-desthio results in the

more critical assessment.

6.6.3.1 Estimation of operator exposure

A summary of the exposure model used for estimation of operator exposure to the active substances during application of GF-3307 (S7K-3-3) according to the critical use is presented in Błąd! Nie można odnaleźć źródła odwołania.. The outcomes of the estimations are presented in Table 6.6-3 (acute exposure - fenpicoxamid) and Table 6.6-4, Table 6.6-5 and

Table 6.6-6 (short term exposure – fenpicoxamid, prothioconazole and prothioconazole-desmethio, respectively). Detailed calculations are presented in Appendix 3. For the acute exposure, no estimations are presented for prothioconazole or prothioconazole-desmethio because no AAOEL values are assigned at EU level.

First tier estimates of exposure are presented which assume the operator is wearing normal workwear (arms, body and legs covered) as defined in EFSA, 2022. These estimates indicate that the acceptable operator exposure level (AOEL) and acute acceptable operator exposure level (AAOEL, where relevant) will not be exceeded for the conditions of intended use and with the operator wearing normal work wear and no specialised PPE for mixing/loading and application procedures. Thus, specific PPE is not required according to the presented risk assessments. However, taking into account the hazard classification of the product (Table 6.1-2), protective gloves/protective clothing/eye protection/face protection are required. Exposure estimates for various PPE/RPE scenarios are available in the embedded EFSA OPEX risk assessment file given in Appendix 3.

New: Updated estimations are provided below considering the lower AOEL for prothioconazole and new AAOELs for prothioconazole and prothioconazole-desmethio (EFSA, 2025). Using these values, estimated exposures were above the new AAOEL for prothioconazole-desmethio for the previously assessed scenario of the operator wearing normal work wear and no specialised PPE for mixing/loading and application procedures. Therefore, further PPE and risk mitigation measures were evaluated for the intended uses and are presented in Błąd! Nie można odnaleźć źródła odwołania. and New Table 6.6-2, for short term and acute exposure, respectively. These estimates indicate that the AOELs and AAOELs will not be exceeded for the conditions of intended use with the use of 50% drift reduction technologies during application and the operator wearing normal work wear and no specialised PPE for mixing/loading and application procedures. Detailed calculations are in Appendix 5.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Sugar beet (max. 1.5 L product/ha, min. 150 L water/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 EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.0.1) New: EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.1.3)

Table 6.6-3: Estimated operator exposure (acute) - fenpicoxamid

		Fenpicoxamid	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables			
Application rate:		0.075 kg a.s./ha	
Spray application (AOEM; 95 th percentile) Body weight: 60 kg	Normal work wear for M/L & A ^(a) No PPE	0.02	8.2

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton ($\geq 300 \text{ g/m}^2$) or of cotton and polyester with at least 65% polyester ($\geq 245 \text{ g/m}^2$)”.

Table 6.6-4: Estimated operator exposure (short-term) - fenpicoxamid

		Fenpicoxamid	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables			
Application rate:		0.075 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Normal work wear for M/L & A ^(a) No PPE	0.002	4.7

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”.

Table 6.6-5: Estimated operator exposure (short-term) - prothioconazole

Estimated operator exposure (short term) - prothioconazole			
		Prothioconazole	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables			
Application rate:		0.150 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Normal work wear for M/L & A ^(a) No PPE	0.006	3.1

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”.

Table 6.6-6: Estimated operator exposure (short-term) – prothioconazole-desthio

Prothioconazole-desthio ^(b)			
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables			
Application rate:		0.136 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Normal work wear for M/L & A ^(a) No PPE	0.003	26

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”.
- b) Formation of prothioconazole-desthio is not expected to occur in the product concentrate and operator exposure to prothioconazole-desthio during mixing and loading procedures of the concentrate is not expected. The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.

		Fenpicoxamid		Prothioconazole		Prothioconazole-desthiob (b)	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL	Total absorbed dose (mg/kg/day)	% of New systemic AAOEL (c)	Total absorbed dose (mg/kg/day)	% of New systemic AAOEL (c)
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables							
Application rate:		0.075 kg a.s./ha		0.150 kg a.s./ha		0.136 kg a.s./ha	
Spray application (AOEM; 95 th percentile) Body weight: 60 kg	Normal work wear for M/L & A (a) No PPE	0.02	8.2	0.04	18.7	0.02	224
	Normal work wear for M/L & A (a) + gloves and FP2, P2 and similar for M/L & A	0.008	4.1	0.01	5.5	0.01	100.1
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables; drift reduction: 50%							
Application rate:		0.075 kg a.s./ha		0.150 kg a.s./ha		0.136 kg a.s./ha	
Spray application (AOEM; 95 th percentile) Body weight: 60 kg	Normal work wear for M/L & A (a) No PPE	0.007	3.6	0.02	9.7	0.006	57.4

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton ($\geq 300 \text{ g/m}^2$) or of cotton and polyester with at least 65% polyester ($\geq 245 \text{ g/m}^2$)”.
- b) Formation of prothioconazole-desthio is not expected to occur in the product concentrate and operator exposure to prothioconazole-desthio during mixing and loading procedures of the concentrate is not expected. The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.
- c) Assessment considers the new AAOLs for prothioconazole and prothioconazole-desthio in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

		Fenpicoxamid		Prothioconazole		Prothioconazole-desmethio (b)	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of New systemic AOEL (c)	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables							
Application rate:		0.075 kg a.s./ha		0.150 kg a.s./ha		0.136 kg a.s./ha	
Spray application (AOEM; 75 th percentile) Body weight: 60 kg	Normal work wear for M/L & A (a) No PPE	0.002	4.7	0.006	17.4	0.003	26.0
	Normal work wear for M/L & A (a) + gloves and FP2, P2 and similar for M/L & A	0.0002	0.5	0.0005	1.3	0.0004	3.8
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables; drift reduction: 50%							

Application rate:		0.075 kg a.s./ha		0.150 kg a.s./ha		0.136 kg a.s./ha	
Spray application (AOEM; 75th percentile) Body weight: 60 kg	Normal work wear for M/L & A ^(a) No PPE	0.002	3.3	0.005	13.1	0.001	11.7

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”.
- b) Formation of prothioconazole-desthio is not expected to occur in the product concentrate and operator exposure to prothioconazole-desthio during mixing and loading procedures of the concentrate is not expected. The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.
- c) Assessment considers the lower AOEL for prothioconazole in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

6.6.3.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) and acute acceptable operator exposure level (AAOEL, where relevant) will not be exceeded under conditions of intended uses, **with the use of 50% drift reduction technologies during application**, a study to provide measurements of operator exposure was not necessary and was therefore not performed..

6.6.4 Worker exposure (KCP 7.2.3)

Comments of zRMS:	NDE calculation (EFSA on-line model OPEX ver. 1.0.1 and 1.1.3) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. Exposure for workers (entry into a previously treated area or handling a crop according to the critical uses) is acceptable under conditions of intended uses considering below mentioned risk mitigation measures such as Work wear, (arms, body and legs covered) but no PPE is used for Inspection, irrigation. In case of for manual reaching, picking and removing bolting sugar beet tasks additionally gloves are required.
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Conclusion: Worker exposure estimations conducted using the EFSA online OPEX calculator (<https://r4eu.efsa.europa.eu/app/opex v 1.0.1>) indicated that the acceptable exposure level (AOEL) will not be exceeded under conditions of intended use and with the worker wearing normal workwear and gloves for manual reaching, picking and removing bolting sugar beet tasks (gloves not required for inspection, irrigation tasks). The maximum predicted exposures were 6.8, 3.9 and 71.6% of the AOEL for fenpicoxamid, prothioconazole and prothioconazole-desthio, respectively, assuming normal workwear and gloves for manual reaching, picking activities. Estimations of exposure to prothioconazole-desthio were for a worst-case scenario of 100% conversion of prothioconazole to prothioconazole-desthio.

New: Worker exposure estimations conducted using the EFSA online OPEX calculator (<https://r4eu.efsa.europa.eu/app/opex v1.1.3>) and considering the new AOEL for prothioconazole (EFSA, 2025) indicated that the AOELs will not be exceeded under conditions of intended use and with the worker wearing normal workwear and gloves for manual reaching, picking and removing bolting sugar beet tasks (gloves not required for inspection, irrigation tasks). The maximum predicted exposures were 6.8%, 21.9% and 71.6% of the AOELs for fenpicoxamid, prothioconazole and prothioconazole-desthio, respectively, assuming normal workwear and gloves for manual reaching, picking activities. Estimations of exposure to prothioconazole-desthio were for a worst-case scenario of 100% conversion of prothioconazole to prothioconazole-desthio.

Assessments for prothioconazole are provided for information only. This is because only prothioconazole

or its metabolite, prothioconazole-desthio can be present at a time if 100% conversion is assumed. Due to its toxicological properties, the assessment for 100% conversion to prothioconazole-desthio results in the more critical assessment.

6.6.4.1 Estimation of worker exposure

Table 6.6-7 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GF-3307 (S7K-3-3) according to the critical use. Outcomes of the estimations are presented in Table 6.6-8,

Table 6.6-9 and Table 6.6-10 for fenpicoxamid, prothioconazole and prothioconazole-desthio, respectively. Detailed calculations are in Appendix 3.

Results presented in Table 6.6-8,

Table 6.6-9 and Table 6.6-10 are the estimates of exposure with (i) the worker wearing normal workwear (arms, body and legs covered) as defined in EFSA, 2022 and (ii) with the worker wearing normal workwear and PPE, gloves.

New: Updated estimations are provided below in

Table 6.6-9 considering the lower AOEL for prothioconazole (EFSA, 2025). An updated assessment was not needed for prothioconazole-desthio because a change in the current EU-agreed AOEL was not proposed (EFSA, 2025). The estimates indicate that no additional PPE/RMM are needed, the AOELs will not be exceeded for the conditions of intended use and with the worker wearing normal workwear and gloves for manual reaching, picking and removing bolting sugar beet tasks (gloves not required for inspection, irrigation tasks). Detailed calculations are in Appendix 5.

Table 6.6-7: Exposure models for intended uses

Critical use	Sugar beet (max. 2 x 1.5 L product/ha, min. 150 L water/ha, 21-day retreatment interval)
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 EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.0.1) New: EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.1.3)

Table 6.6-8: Estimated worker exposure - fenpicoxamid

		Fenpicoxamid	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Inspection, irrigation Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha Work rate: 2 hours/day DT ₅₀ : 30 days Dermal absorption: 12%			
Number of applications and application rate		2 x 0.075 kg a.s./ha	
Body weight: 60 kg	Normal workwear ^(a) TC: 1400 cm ² /h	0.002	4.1
	Normal workwear ^(a) and gloves TC: 1250 cm ² /h	0.002	3.6
Reaching, picking Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha Work rate: 8 hours/day DT ₅₀ : 30 days Dermal absorption: 12%			
Number of applications and application rate		2 x 0.075 kg a.s./ha	
Body weight: 60 kg	Work wear ^(a) TC: 2500 cm ² /h	0.01	29.2
	Normal workwear ^(a) and gloves TC: 580 cm ² /h	0.003	6.8

		Fenpicoxamid	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Removing bolting sugar beets Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha <div> Work rate: 8 hours/day DT₅₀: 30 days Dermal absorption: 12% </div>			
Number of applications and application rate		2 x 0.075 kg a.s./ha	
Body weight: 60 kg	Normal workwear ^(a) TC: 4400 cm ² /h	0.03	51.3
	Normal workwear ^(a) and gloves TC: 430 cm ² /h	0.003	5.0

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”

Table 6.6-9: Estimated worker exposure – prothioconazole

		Prothioconazole		
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	% of new systemic AOEL ^(b)
Inspection, irrigation Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha <div> Work rate: 2 hours/day DT₅₀: 30 days Dermal absorption: 14% </div>				
Number of applications and application rate		2 x 0.15 kg a.s./ha		
Body weight: 60 kg	Normal workwear ^(a) TC: 1400 cm ² /h	0.005	2.4	13.2
	Normal workwear ^(a) and gloves TC: 1250 cm ² /h	0.004	2.1	11.8
Reaching, picking Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha <div> Work rate: 8 hours/day DT₅₀: 30 days Dermal absorption: 14% </div>				
Number of applications and application rate		2 x 0.15 kg a.s./ha		
Body weight: 60 kg	Work wear ^(a) TC: 2500 cm ² /h	0.03	17.0	94.5
	Normal workwear ^(a) and gloves TC: 580 cm ² /h	0.008	3.9	21.9
Removing bolting sugar beets Outdoor Retreatment interval: 21 days DFR: 3 µg/cm ² /kg a.s./ha <div> Work rate: 8 hours/day DT₅₀: 30 days Dermal absorption: 14% </div>				
Number of applications and application rate		2 x 0.15 kg a.s./ha		
Body weight: 60 kg	Normal workwear ^(a) TC: 4400 cm ² /h	0.06	29.9	166
	Normal workwear ^(a) and gloves TC: 430 cm ² /h	0.006	2.9	16.3

		Prothioconazole		
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	% of new systemic AOEL (b)
a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m ²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m ²)”				
b) Assessment considers the lower AOEL for prothioconazole in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.				

Table 6.6-10: Estimated worker exposure – prothioconazole-desthio

		Prothioconazole-desthio	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Inspection, irrigation Outdoor Retreatment interval: 21 days DFR: 3 µg/cm²/kg a.s./ha Work rate: 2 hours/day DT ₅₀ : 30 days Dermal absorption: 14%			
Number of applications and application rate		2 x 0.136 kg a.s./ha ^(b)	
Body weight: 60 kg	Normal workwear ^(a) TC: 1400 cm²/h	0.004	43.2
	Normal workwear ^(a) and gloves TC: 1250 cm²/h	0.004	38.6
Reaching, picking Outdoor Retreatment interval: 21 days DFR: 3 µg/cm²/kg a.s./ha Work rate: 8 hours/day DT ₅₀ : 30 days Dermal absorption: 14%			
Number of applications and application rate		2 x 0.136 kg a.s./ha ^(b)	
Body weight: 60 kg	Work wear ^(a) TC: 2500 cm²/h	0.03	309
	Normal workwear ^(a) and gloves TC: 580 cm²/h	0.007	71.6
Removing bolting sugar beets Outdoor Retreatment interval: 21 days DFR: 3 µg/cm²/kg a.s./ha Work rate: 8 hours/day DT ₅₀ : 30 days Dermal absorption: 14%			
Application rate		2 x 0.136 kg a.s./ha ^(b)	
Body weight: 60 kg	Normal workwear ^(a) TC: 4400 cm²/h	0.05	543
	Normal workwear ^(a) and gloves TC: 430 cm²/h	0.005	53.1

- a) Normal work wear (arms, body and legs covered). As defined in EFSA, 2022, “normal workwear consists of coveralls or long-sleeved shirt and trousers that are made of cotton (≥ 300 g/m²) or of cotton and polyester with at least 65% polyester (≥ 245 g/m²)”
- b) The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

Not required.

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded for fenpicoxamid, prothioconazole and prothioconazole-desthio 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.

6.6.5 Resident and bystander exposure (KCP 7.2.2)

6.6.5.1 Estimation of resident and bystander exposure

Comments of zRMS:	NDE calculation (EFSA on-line model OPEX ver. 1.0.1 and 1.1.3) performed by the Applicant is acceptable and zRMS Reviewer agrees to the conclusions. B&R long term exposure for fenpicoxamid, prothioconazole and prothioconazole-desthio also acute acceptable operator exposure level (AAOEL) for fenpicoxamid will not be exceeded under conditions of intended uses.
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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 6.6-11 shows the exposure model used for estimation of resident and bystander exposure to fenpicoxamid, prothioconazole and prothioconazole-desthio according to the critical use. Outcomes of the estimations are presented in Table 6.6-12, Table 6.6-13 and Table 6.6-14 (resident exposure for fenpicoxamid, prothioconazole and prothioconazole-desthio, respectively) and Table 6.6-15 (bystander (acute) exposure for fenpicoxamid). No acute estimations are presented for prothioconazole or prothioconazole-desthio because no AAOEL values are assigned at EU level. Detailed calculations are in Appendix 3.

New: Updated estimations are provided below considering the new AAOELs (EFSA, 2025). This includes estimation of resident exposure considering the lower AOEL for prothioconazole (**Błąd! Nie można odnaleźć źródła odwołania.**) and estimations of bystander exposure considering the new AAOELs for prothioconazole and prothioconazole-desthio (New Table 6.6- and New Table 6.6-, respectively). Estimations of exposure to prothioconazole-desthio were for a worst-case scenario of 100% conversion of prothioconazole to prothioconazole-desthio once the product was diluted with water. These estimates indicate that the AOELs and AAOELs will not be exceeded for the conditions of intended use for residents and bystanders. The presented estimations of resident and bystander exposure are for the intended uses with no drift reduction technology. Detailed calculations, including the scenario for drift reduction technology are in Appendix 5.

Assessments for prothioconazole are provided for information only. This is because only prothioconazole or its metabolite, prothioconazole-desthio can be present at a time if 100% conversion is assumed. Due to its toxicological properties, the assessment for 100% conversion to prothioconazole-desthio results in the more critical assessment.

Table 6.6-11: Exposure models for intended uses

Critical use(s)	Sugar beet (max. 2 x 1.5 L product/ha, min. 150 L water/ha, 21-day retreatment interval)
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 EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.0.1) New: EFSA online OPEX calculator (https://r4eu.efsa.europa.eu/app/opex v 1.1.3)

Table 6.6-12: Estimated resident exposure - fenpicoxamid

		Fenpicoxamid	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 12%			
Number of applications and application rate		2 x 0.075 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.002	3.3
	Vapour (75 th perc.)	0.0008	1.6
	Deposits (75 th perc.)	0.0002	0.4
	Re-entry (75 th perc.)	0.002	4.9
	Sum (mean)	0.004	7.6
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0004	0.8
	Vapour (75 th perc.)	0.0003	0.5
	Deposits (75 th perc.)	0.0001	0.2
	Re-entry (75 th perc.)	0.001	2.7
	Sum (mean)	0.002	3.2

Table 6.6-13: Estimated resident exposure – prothioconazole

		Prothioconazole		
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	% of new systemic AOEL ^(a)
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 14%				
Number of applications and application rate		2 x 0.15 kg a.s./ha		
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.004	1.9	10.6
	Vapour (75 th perc.)	0.0008	0.4	2.2
	Deposits (75 th perc.)	0.0007	0.3	1.9
	Re-entry (75 th perc.)	0.006	2.9	15.9
	Sum (mean)	0.008	4.0	22.1
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0009	0.5	2.5
	Vapour (75 th perc.)	0.0003	0.1	0.8
	Deposits (75 th perc.)	0.0002	0.1	0.6
	Re-entry (75 th perc.)	0.003	1.6	8.9
	Sum (mean)	0.003	1.7	9.5

a) Assessment considers the lower AOEL for prothioconazole in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

Table 6.6-14: Estimated resident exposure – prothioconazole-desthio

		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL ^(b)
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 14%			
Number of applications and application rate		2 x 0.136 kg a.s./ha ^(a)	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.003	34.5
	Vapour (75 th perc.)	0.0008	8.0
	Deposits (75 th perc.)	0.0006	6.3
	Re-entry (75 th perc.)	0.005	52.1
	Sum (mean)	0.007	73.0
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0008	8.2
	Vapour (75 th perc.)	0.0003	2.7
	Deposits (75 th perc.)	0.0002	2.1
	Re-entry (75 th perc.)	0.003	28.9
	Sum (mean)	0.003	31.1

- a) The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.
- b) **New assessment not required because a change in the current EU-agreed AOEL was not proposed (EFSA, 2025).**

New Table 6.6-15: Estimated bystander exposure (acute exposure) – prothioconazole – new assessment

		Prothioconazole	
Model data		Total absorbed dose (mg/kg bw/day)	% of new systemic AAOEL ^(a)
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 12%			
Number of applications and application rate		2 x 0.15 kg a.s./ha	
Bystander child Body weight: 10 kg	Drift (95 th perc.)	0.009	4.3
	Vapour (95 th perc.)	0.0008	0.4
	Deposits (95 th perc.)	0.002	1.0
	Re-entry (95 th perc.)	0.006	2.9
Bystander adult Body weight: 60 kg	Drift (95 th perc.)	0.002	1.2
	Vapour (95 th perc.)	0.0003	0.1
	Deposits (95 th perc.)	0.0007	0.3
	Re-entry (95 th perc.)	0.003	1.6

- a) Assessment considers the new AAOEL for prothioconazole in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

New Table 6.6-16: Estimated bystander exposure (acute exposure) – prothioconazole-desthio – new assessment

		Prothioconazole-desthio	
Model data		Total absorbed dose (mg/kg bw/day)	% of new systemic AAOEL ^(b)
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 12%			
Number of applications and application rate		2 x 0.136 kg a.s./ha ^(b)	
Bystander child Body weight: 10 kg	Drift (95 th perc.)	0.008	78.3
	Vapour (95 th perc.)	0.0008	8.0
	Deposits (95 th perc.)	0.002	18.3
	Re-entry (95 th perc.)	0.005	52.1
Bystander adult Body weight: 60 kg	Drift (95 th perc.)	0.002	21.1
	Vapour (95 th perc.)	0.0003	2.7
	Deposits (95 th perc.)	0.0006	6.3
	Re-entry (95 th perc.)	0.003	28.9

- a) The assessment assumes worst case scenario of 100% conversion from prothioconazole to prothioconazole-desthio once the product was diluted with water. To convert the maximum application rate of prothioconazole (150 g a.s./ha) to prothioconazole-desthio, a conversion factor of 0.907 was applied based on the molecular weights of prothioconazole (344.26 g/mol) and prothioconazole-desthio (312.2 g/mol) to give 136 g a.s./ha of prothioconazole-desthio.
- b) Assessment considers the new AAOEL for prothioconazole-desthio in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

Table 6.6-17: Estimated bystander exposure (acute exposure) - fenpicoxamid

		Fenpicoxamid	
Model data		Total absorbed dose (mg/kg bw/day)	% of systemic AAOEL
Vehicle-mounted, downward spraying, normal cultivation, outdoor, low vegetables Season: not relevant Buffer zone: 2-3 m Drift reduction technology: no Retreatment interval: 21 days DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha Dermal absorption: 12%			
Number of applications and application rate		2 x 0.075 kg a.s./ha	
Bystander child Body weight: 10 kg	Drift (95 th perc.)	0.004	1.9
	Vapour (95 th perc.)	0.0008	0.4
	Deposits (95 th perc.)	0.0007	0.3
	Re-entry (95 th perc.)	0.002	1.2
Bystander adult Body weight: 60 kg	Drift (95 th perc.)	0.001	0.5
	Vapour (95 th perc.)	0.0003	0.1
	Deposits (95 th perc.)	0.0003	0.1
	Re-entry (95 th perc.)	0.001	0.7

6.6.5.2 Measurement of resident and/or bystander exposure

Since the resident and bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for fenpicoxamid, prothioconazole and prothioconazole-desthio, and acute

acceptable operator exposure level (AAOEL) for fenpicoxamid, **prothioconazole and prothioconazole-desthio** will not be exceeded under conditions of intended uses, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.6 Combined exposure

GF-3307 (S7K-3-3) is a mixture of two active substances, fenpicoxamid and prothioconazole, so combined exposure risk assessment is requested.

From a scientific point of view, it is regarded necessary to take into account potential combination effects. However, the evaluation of cumulative or synergistic effects as requested by Art. 4 (3b) of Regulation (EC) No. 1107/2009 should only be performed when harmonised “scientific methods accepted by the Authority to assess such effects are available.”

6.6.6.1 Exposure assessment of fenpicoxamid, prothioconazole and prothioconazole-desthio in GF-3307 (S7K-3-3)

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 a percentage of the systemic AOEL from e.g., Table 6.6-4, converted to decimal values. The Hazard Index (HI) is the sum of the individual HQs.

A cumulative assessment for acute exposures is not required as only fenpicoxamid currently has an AAOEL assigned at EU level.

GF-3307 (S7K-3-3) is a mixture of two active substances, fenpicoxamid and prothioconazole. However, it has been found that **prothioconazole can convert to prothioconazole-desthio in diluted solutions** during the drying process on clothing, skin or certain plant surfaces. Therefore, exposure to diluted solutions of GF-3307 (S7K-3-3) will be a mixture of fenpicoxamid, prothioconazole (parent) and prothioconazole-desthio (metabolite). Although prothioconazole-desthio is not an active substance and not a component of the formulation *per se*, **non-dietary risk assessments are always performed for prothioconazole-desthio** due to its toxicological properties. To ensure the risk assessments are suitably conservative, risk assessments have been performed for both the parent (prothioconazole) and metabolite (prothioconazole-desthio), with the exposure estimates for prothioconazole-desthio assuming 100% conversion from prothioconazole to prothioconazole-desthio. However, for the combined risk assessment, it is not appropriate to combine the risk assessments for prothioconazole and prothioconazole-desthio because only one chemical can be present at a time if 100% conversion is assumed. In all cases, the worst-case exposure (highest HQ) for each exposure population was from prothioconazole-desthio. Therefore, the combined risk assessment has been performed taking into consideration fenpicoxamid and prothioconazole-desthio.

New: Updated cumulative assessments are provided below considering the lower AOEL for prothioconazole and the new AAOELs for prothioconazole and prothioconazole-desthio reported by EFSA (EFSA Journal. 2025;23:e9593). These AAOELs are not yet formally adopted in the European Union.

Table 6.6-15: Risk assessment from combined exposure (longer term exposure)

Application scenario	Active Substance	Estimated exposure / AOEL (HQ)
Operators (vehicle-mounted, downward spray to low vegetables) Normal workwear	Fenpicoxamid	0.047
	Prothioconazole-desthio	0.26
	Cumulative risk operators (HI)	0.307
New ^(a) Operators (vehicle-mounted, downward spray to low vegetables) Normal workwear 50% drift reduction technology	Fenpicoxamid	0.033
	New Prothioconazole ^(a)	0.131 ^(a)
	Cumulative risk operators (HI)	0.164
Workers (inspection/irrigation) Normal workwear	Fenpicoxamid	0.041
	Prothioconazole-desthio	0.432
	Cumulative risk workers (HI)	0.473
Workers (reaching, picking) Normal workwear + Gloves	Fenpicoxamid	0.068
	Prothioconazole-desthio	0.716
	Cumulative risk workers (HI)	0.784
Workers (removing bolting sugar beets) Normal workwear + Gloves	Fenpicoxamid	0.050
	Prothioconazole-desthio	0.531
	Cumulative risk workers (HI)	0.581
Resident - child No drift-reduction technology	Fenpicoxamid	
	Drift	0.033
	Vapour	0.016
	Deposits	0.004
	Re-entry	0.049
	Sum of all pathways	0.076
	Prothioconazole-desthio	
	Drift	0.345
	Vapour	0.080
	Deposits	0.063
	Re-entry	0.521
	Sum of all pathways	0.730
	Cumulative risk resident – child (HI)	
	Drift	0.378
	Vapour	0.096
	Deposits	0.067
	Re-entry	0.570
	Sum of all pathways	0.806

Application scenario	Active Substance	Estimated exposure / AOEL (HQ)
Resident – adult No drift-reduction technology	Fenpicoxamid	
	Drift	0.008
	Vapour	0.005
	Deposits	0.002
	Re-entry	0.027
	Sum of all pathways	0.032
	Prothioconazole-desthio	
	Drift	0.082
	Vapour	0.027
	Deposits	0.021
	Re-entry	0.289
	Sum of all pathways	0.311
	Cumulative risk resident – adult (HI)	
	Drift	0.090
	Vapour	0.032
	Deposits	0.023
	Re-entry	0.316
	Sum of all pathways	0.343

- a) Assessment considers the lower AOEL for prothioconazole in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

New Table 6.6-19: Risk assessment from combined exposure (acute exposure) – new assessment

Application scenario	Active Substance	Estimated exposure / new AAOEL (HQ)
New ^(a) Operators (vehicle-mounted, downward spray to low vegetables) Normal workwear 50% drift reduction technology	Fenpicoxamid	0.036
	New Prothioconazole-desthio ^(a)	0.574
	Cumulative risk operators (HI)	0.610
New ^(a) Bystander – child No drift-reduction technology	Fenpicoxamid	
	Drift	0.019
	Vapour	0.004
	Deposits	0.003
	Re-entry	0.012
	New Prothioconazole-desthio ^(a)	
	Drift	0.783
	Vapour	0.080
	Deposits	0.183
	Re-entry	0.521
	Cumulative risk resident – child (HI)	
	Drift	0.802
	Vapour	0.084
	Deposits	0.186
	Re-entry	0.533
New ^(a) Resident – adult No drift-reduction technology	Fenpicoxamid	
	Drift	0.005
	Vapour	0.001
	Deposits	0.001
	Re-entry	0.007
	New Prothioconazole-desthio ^(a)	
	Drift	0.211
	Vapour	0.027
	Deposits	0.063
	Re-entry	0.289
	Cumulative risk resident – adult (HI)	
	Drift	0.216
	Vapour	0.028
	Deposits	0.064
	Re-entry	0.296

a) Assessment considers the new AAOELs for prothioconazole and prothioconazole-desthio in EFSA Journal. 2025;23:e9593 - not yet formally adopted in the European Union.

The Hazard Index is < 1 . Thus, combined exposure to all active substances in GF-3307 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 7.1.1/1	██████	2021a	Acute Oral Toxicity Study of GF-3307 in Rats Company Report No: 211324 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP.7.1.2/1	██████	2021b	Acute Dermal Toxicity Study of GF-3307 in Rats Company Report No: 211323 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP 7.1.3/1	██████	2021	GF-3307: Inhalation Median Lethal Concentration (LC50) Study in Rats Company Report No: 211432 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP 7.1.4/1	██████	2021c	Acute Dermal Irritation Study of GF-3307 in Rabbits Company Report No: 211322 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP 7.1.5/1	██████	2021d	Acute Eye Irritation Study of GF-3307 in Rabbits Company Report No: 211321 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP 7.1.6/1	██████	2021e	Skin Sensitisation Study of GF-3307 by Local Lymph Node Assay in Mice Company Report No: 211320 ██████ GLP Unpublished	Y	Corteva Agriscience
KCP 7.3/1	Whitfield, C.	2020	GF-3307: In Vitro Percutaneous Absorption of Prothioconazole-desthio in Human Skin	N	Corteva Agriscience

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
			Company Report No: 200102 Source: Dow AgroSciences LLC GLP Unpublished		
KCP 7.3/2	Whitfield, C.	2021	GF-3307: In Vitro Percutaneous Absorption of Fenpicoxamid in Human Skin Company Report No: 200109 Source: Dow AgroSciences LLC GLP Unpublished	N	Corteva Agriscience
KCP 7.3/3	Maas, W.J.M	2023	GF-3307: In Vitro Percutaneous Absorption of Prothioconazole in Human Skin Company Report No: 220958 Source: Charles River Laboratories GLP Unpublished	N	Corteva Agriscience
KCA 6.10/01	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 Company Report No. M 455270-01-1 Source: Bayer Crop Science GLP Unpublished	N	BCS*
KCA 6.10/02	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 Company Report No. M 507834-01-1 Source: Bayer Crop Science GLP Unpublished	N	BCS*

*Letter of Access is provided in Part A for Bayer CropScience data

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
CA 5.1.1/1	██████	2012a	XDE-777: PROBE STUDY TO DETERMINE ABSORPTION, METABOLISM AND ELIMINATION IN F344NTac RATS, CrI:CD1(ICR) MICE AND NEW ZEALAND WHITE RABBITS (Revision) DAS Report No.: 101038 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.1.1/2	██████	2012	A PROBE STUDY TO INVESTIGATE THE METABOLISM AND EXCRETION OF 14C-LABELED XDE-777 IN BEAGLE DOGS FOLLOWING A SINGLE ORAL (GAVAGE) ADMINISTRATION DAS Report No.: 111004 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.1.1/3	██████	2012b	XDE-777: TISSUE DISTRIBUTION IN F344DuCrI RATS DAS Report No.: 111150 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.1.1/4	██████	2013	ELIMINATION OF RADIOACTIVITY IN BILE, URINE, AND FECES FOLLOWING ORAL ADMINISTRATION OF [14C]-LABELED XDE-777 TO RATS DAS Report No.: 130007 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.1.1/5	██████	2013	XDE-777: PHARMACOKINETICS AND METABOLISM IN F344DuCrI RATS DAS Report No.: 111149 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.1.1/6	Zhang F McClymont EL Fiting JA Erskine TC Clark AJ	2014	XDE-777: <i>In Vitro</i> Comparative Metabolism Study Toxicology & Environmental Research and Consulting, The Dow Chemical Company DAS Report No.: 130798 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience

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
CA 5.2.1/1	████	2011 a	Acute Oral Toxicity Up And Down Procedure In Rats DAS Report No.: 101555 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.2/1	████	2011 b	Acute Dermal Toxicity Study in Rats DAS Report No.: 101664 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.3/1	████	2012	XR-777: ACUTE DUST AEROSOL INHALATION TOXICITY STUDY IN F344DuCrI RATS DAS Report No.: 101136 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.4/1	████	2011 c	Primary Skin Irritation Study In Rabbits DAS Report No.: 101665 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.5/1	████	2011 d	Primary Eye Irritation Study in Rabbits DAS Report No.: 101666 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.6/1	████	2012	XR-777: LOCAL LYMPH NODE ASSAY IN CBAJ MICE DAS Report No.: 101154 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.2.7/1	Roth M	2015	XDE-777: Cytotoxicity Assay in vitro with Balb/c 3T3 Cells: Neutral Red (NR) Test during Simultaneous Irradiation with Artificial Sunlight DAS Report No.: 150039 Harlan Cytotest Cell Research GmbH	No	Corteva Agriscience

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			GLP/GEP (Y/N): Yes Published (Y/N): No		
CA 5.3.1/1	██████	2010	XR-777: PALATABILITY PROBE STUDY IN F344DuCrI RATS DAS Report No.: 100041 ██████ GLP/GEP (Y/N): No Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.1/2	██████	2012a	XR-777: 28-DAY DIETARY TOXICITY STUDY IN F344DuCrI RATS DAS Report No.: 101053 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.1/3	██████	2010	XR-777: PALATABILITY PROBE STUDY IN CrI:CD1(ICR) MICE DAS Report No.: 100043 ██████ GLP/GEP (Y/N): No Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.1/4	██████	2012	XR-777: 28-DAY DIETARY TOXICITY STUDY IN CrI:CD1(ICR) MICE DAS Report No.: 101052 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.1/5	██████	2012	XDE-777: A PRELIMINARY PALATABILITY STUDY IN BEAGLE DOGS DAS Report No.: 110033 ██████ GLP/GEP (Y/N): No Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.1/6	██████	2013a	XDE-777: A 28-DAY DIETARY TOXICITY STUDY IN BEAGLE DOGS DAS Report No.: 111034 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience

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
CA 5.3.2/1	██████	2012 b	XR-777: 90 DAY DIETARY TOXICITY STUDY IN F344DuCrI RATS DAS Report No.: 101110 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.2/2	██████	2014	XR777: 90-DAY DIETARY TOXICITY STUDY WITH A 28-DAY RECOVERY IN CrI:CD1(ICR) MICE (Revision) DAS Report No.: 101103 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.2/3	██████	2013 b	XDE-777: A 90-DAY DIETARY TOXICITY STUDY IN BEAGLE DOGS DAS Report No.: 111035 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.3.2/4	██████	2014	XDE-777: A One-Year Dietary Toxicity Study in Beagle Dog DAS Report No.: 121002 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.4.1/1	Dakoulas EW Divi K	2010	Salmonella - Escherichia coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with XR-777 DAS Report No.: 100088 BioReliance GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience
CA 5.4.1/2	Schisler MR	2011 a	EVALUATION OF XR-777 IN AN IN VITRO CHROMOSOMAL ABERRATION ASSAY UTILIZING RAT LYMPHOCYTES DAS Report No.: 101069 Toxicology & Environmental Research and Consulting, The Dow Chemical Company GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience

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
CA 5.4.1/3	Schisler MR	2011 b	EVALUATION OF XR-777 IN THE CHINESE HAMSTER OVARY CELLHYPOXANTHINE-GUANINE-PHOSPHORIBOSYL TRANSFERASE (CHOHGPRT) FORWARD MUTATION ASSAY DAS Report No.: 101089 Toxicology & Environmental Research and Consulting, The Dow Chemical Company GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience
CA 5.4.2/1	████	2011 c	EVALUATION OF XR-777 IN THE MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST DAS Report No.: 101061 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.4.2/2	████	2014	XDE-777: In Vivo Unscheduled DNA Synthesis (UDS) Test in Mouse Liver Cells DAS Report No.: 140628 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.5/1	████	2013	XR-777: 18-MONTH DIETARY ONCOGENICITY STUDY IN CrI:CD1(ICR) MICE DAS Report No.: 111068 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.5/2	████	2014	XDE-777: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in F344/DuCrI Rats DAS Report No.: 111064 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.6.1/1	████	2012 a	XR-777: DIETARY REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN CrI:CD(SD) RATS DAS Report No.: 101200 ████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.6.1/2	████	2013a	XDE-777: TWO GENERATION DIETARY REPRODUCTION TOXICITY STUDY IN CrI:CD(SD) RATS DAS Report No.: 111186 ████	Yes	Corteva Agriscience

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			GLP/GEP (Y/N): Yes Published (Y/N): No		
CA 5.6.2/1	██████	2012b	XR-777: DIETARY DEVELOPMENTAL TOXICITY PROBE STUDY IN Crl:CD(SD) RATS DAS Report No.: 101099 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.6.2/2	██████	2012c	XDE-777: DIETARY DEVELOPMENTAL TOXICITY STUDY IN Crl:CD(SD) RATS DAS Report No.: 111184 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.6.2/3	██████	2012d	XDE-777: DIETARY DEVELOPMENTAL TOXICITY PROBE STUDY IN NEW ZEALAND WHITE RABBITS DAS Report No.: 121001 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.6.2/4	██████	2013b	XDE-777: DIETARY DEVELOPMENTAL TOXICITY STUDY IN NEW ZEALAND WHITE RABBITS DAS Report No.: 121070 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience
CA 5.8.1/1	Patel NN	2012	BACTERIAL REVERSE MUTATION TEST OF X642188 USING SALMONELLA TYPHIMURIUM DAS Report No.: 120873 JAI RESEARCH FOUNDATION GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience
CA 5.8.1/2	██████	2013	ACUTE ORAL TOXICITY STUDY OF X642188 IN RATS DAS Report No.: 120874 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Corteva Agriscience

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
CA 5.8.2/3	Scherzer MK Passage JK	2014	XDE-777: Solubility in New Zealand White Rabbit Plasma DAS Report No.: 140630 Toxicology & Environmental Research and Consulting, The Dow Chemical Company GLP/GEP (Y/N): Yes Published (Y/N): No	No	Corteva Agriscience
K-CP 7.1.1/01	██████	2012a	Acute Oral Toxicity Study of GF-2925 in Rats DAS Report No.: 120725 ██████ GLP/GEP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience
K-CP 7.2.1/01	██████	2012b	Acute Dermal Toxicity Study of GF-2925 in Rats DAS Report No.: 120726 ██████ GLP/GEP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience
K-CP 7.1.3/01	██████	2016	ACUTE INHALATION TOXICITY STUDY OF GF-2925 IN RATS DAS Report No.: 160249 ██████ GLP/GEP (Y/N): Yes Published (Y/N): No	Y	Corteva Agriscience
K-CP 7.1.4/01	██████	2012c	Acute Dermal Irritation Study of GF-2925 in Rabbits DAS Report No.: 120727 ██████ GLP/GEP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience
K-CP 7.1.5/01	██████	2012d	Acute Eye Irritation Study of GF-2925 in Rabbits DAS Report No.: 120728 ██████ GLP/GEP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience
K-CP 7.1.6/01	██████	2012e	Skin Sensitisation Study of GF-2925 by Local Lymph Node Assay in Mice DAS Report No.: 120729 ██████ GLP/GEP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience

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
K-CP 7.3/01	Maas WJM	2013	In Vitro Dermal Absorption of XDE-777, Formulated in GF-2925 and Two Dilutions, Through Human Split-Thickness Skin Using Flow-Through Diffusion Cells DAS Report No.: 120518 TNO Triskelion BV GLP/GEP (Y/N): Y Published (Y/N): N	N	Corteva Agriscience

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
KCA 6.10/01	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 Company Report No. M-455270-01-1 Source: Bayer Crop Science GLP Unpublished	N	BCS*
KCA 6.10/02	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 Company Report No. M-507834-01-1 Source: Bayer Crop Science GLP Unpublished	N	BCS*

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

zRMS Reviewer General comment: The proposed extension of use does not impact the previously assessed toxicological studies or the established endpoints. Consequently, it does not alter the toxicological classification of the product. A repeated toxicological assessment is therefore not required in the current process. For a detailed toxicological evaluation, please refer to the Registration Report (RR) Part B, Section 6: Mammalian Toxicology (Product code: GF-3307, dated January 2023). However, due to scientific progress, a brief review of the previous RR in relation to the product's registration confirmed that all studies remain valid and are consistent with the updated OECD guidelines.

A 2.1 Statement on bridging possibilities

Acute oral, dermal and inhalation toxicity studies along with skin sensitisation have been performed with GF-3307. Therefore no bridging is required

Comments of zRMS:	<i>In vivo</i> studies submitted by the applicant to support registration of the product GF-3307 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:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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REFERENCE

KCP 7.1.1/1

CITATION

██████; 2021; Acute Oral Toxicity Study of GF-3307 in Rats; ██████; Lab Study No. 401-1-01-28631; Sponsor Study No. 211324 ; 15 November 2021; Published: No

COMPLIANCE

Guideline(s):	OECD 423 (2001), OPPTS 870.1100 (2002), EC B.1 (2008), JMAFF 2-1-1 (2000)
US EPA Guideline(s):	OPPTS 870.1100 (2002)
Guideline Deviations:	None
Dates of work:	18 August 2021 to 11 September 2021
GLP status:	Yes
Number of pages in final report:	46

MATERIALS AND METHODS

Test item(s)

Test item (Common name): GF-3307

Purity: 4.7 wt% (49 g/L) Fenpicoxamid
9.7 wt% (101 g/L) Prothioconazole
Description (physical state): Orange liquid
Lot/batch no.: MAR19CE01Q (TSN400550)
Vehicle: N/A

Test System

Species: Rat (*Rattus norvegicus*)
Strain: Wistar (RCCHan:WIST)
Age and weight at dosing: 10 to 12 weeks
Weight (g): Minimum 176.2, Maximum 207.3
Source: Animal Breeding Facility, Jai Research Foundation, India
Housing: 1 to 3 rats/cage
Feed and water: Feed: Teklad certified Global 14% Protein Rodent Maintenance Diet (sterilizable) manufactured by Envigo, USA. *ad libitum* with the exception of overnight fasting and three hours post dosing
Water: UV sterilized water *ad libitum*
Environmental conditions: Temperature: 20 to 23°C
Humidity: 56 to 66% relative humidity
Air changes: Minimum 15 air changes/hour
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 to 10 days

Study Design

In-life dates

Start: 18 August 2021 End: 11 September 2021

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1:Animal assignment

Dose (mg/kg body weight)	No. of Animals
5000	1
2000	6

Following an overnight fast, rats were given a single oral dose of GF-3307 by gavage. The test item was a liquid end-use product and was tested undiluted (at a constant concentration) and dose volume was adjusted according to the dose and body weight to permit constant dose administration.

Animals were then observed daily and weighed weekly for 14 days. Survivors were sacrificed and a necropsy was performed in all animals.

RESULTS AND DISCUSSION

Mortality

Mortality data are presented in the table below:

Table 2: Dose, mortality/animals treated

Dose (mg/kg body weight)	Mortality (# affected /total)	Time range of deaths (hours or days)
5000	1/1	Day 1
2000	0/6	N/A

N/A: not applicable

One animal found died following treatment at 5000 mg GF-3307/kg body weight. No mortality was observed following treatment at 2000 mg GF-3307/kg body weight.

Clinical Observations

Clinical sign of lethargy, abdominal breathing and dyspnoea were observed in the one rat treated with 5000 mg GF-3307/kg body weight. No signs of toxicity were observed in rats treated with the dose level of 2000 mg GF-3307/kg body weight.

Body Weight

Changes in body weight were considered within the expected range for this strain and age of animals and not influenced by the treatment.

Necropsy Observations

External

An external examination of the terminally sacrificed female rats and found dead rat did not reveal any gross lesion of pathological significance.

Internal

Internal examination of found dead rat revealed red discoloration of lungs (rat N° 1), whereas other terminally sacrificed rats did not reveal any abnormality.

CONCLUSION

Mortality was observed in the one rat treated with 5000 mg GF-3307/kg body weight. No mortality was observed in rats treated with 2000 mg GF-3307/kg body weight. The acute oral LD50 of GF-3307 in female Wistar rats was found to be between 2000 and 5000 mg/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rat	Wistar (RccHan:WIST)	F	Oral	Gavage (undiluted)	LD50 = 2000 - 5000 mg/kg body weight

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Category 5
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A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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REFERENCE

KCP 7.1.2/1

CITATION

██████; 2021; Acute Dermal Toxicity Study of GF-3307 in Rats; ██████; Lab Study No. 403-1-01-28632; Sponsor Study No. 211323 ; 11 November 2021; Published: No

COMPLIANCE

Guideline(s): OECD 402 (2017)
US EPA Guideline(s): N/A
Guideline Deviations: None
Dates of work: 05 August 2021 to 06 September 2021
GLP status: Yes
Number of pages in final report: 45

MATERIALS AND METHODS

Test item(s)

Test item (Common name): GF-3307
Purity: 4.7 wt% (49 g/L) Fenpicoxamid
9.7 wt% (101 g/L) Prothioconazole
Description (physical state): Orange liquid
Lot/batch no.: MAR19CE01Q (TSN400550)
Vehicle: Reverse osmosis (RO) water (only for rat N° 1 dosed at 200 mg/kg body weight)

Test System

Species: Rat (*Rattus norvegicus*)
Strain: Wistar (RccHan:WIST)
Age and weight at dosing: 13 to 17 weeks
Weight (g): Female: Minimum 227.5, Maximum 254.4
Source: Animal Breeding Facility, Jai Research Foundation
Housing: Group-housed during acclimatization; individually caged during the 24-hour exposure period; 1 to 3 rats/cage after patch removal
Feed and water: Feed: Teklad Certified Global 14% Protein Rodent Maintenance Diet (sterilizable) manufactured by Envigo, USA. *ad libitum*
Water: UV sterilized water *ad libitum*

Environmental conditions: Temperature: 19 to 23°C
 Humidity: 56 to 66% relative humidity
 Air changes: Minimum 15 air changes/hour
 Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 to 18 days

Study Design

In-life dates

Start: 05 August 2021 End: 06 September 2021

Animal assignment and treatment

Animal assignment is shown in Table 1

Table 1: Animal assignment

Dose (mg/kg body weight)	Number of Animals
200*	1
200	1
1000	1
2000	3

* = diluted in the ratio of 1:10 in RO water

A calculated dose volume/amount (0.05 to 0.50 mL/mg) of GF-3307 was applied over the clipped area (approximately 7 × 5 cm area, corresponding to 10% of the body surface) of the rats. The test item was held in contact with the skin using porous gauze dressing (not more than 8 ply) and a non-irritating tape (Medi tape 330 hypo-allergenic surgical tape) throughout the 24-hour exposure period to prevent any loss of the test item and also to ensure that the rats did not lick or ingest it. At the end of the exposure period, the residual test item was removed using cotton soaked in RO water.

Animals were then observed daily and weighed weekly for 14 days. Survivors were sacrificed and a necropsy was performed in all animals.

RESULTS AND DISCUSSION

Mortality

Mortality data are presented in the table below:

Table 2: Dose, mortality/animals treated

Dose (mg/kg body weight)	Mortality (# affected /total)	Time range of deaths (hours or days)
200*	0/1	N/A
200	0/1	N/A
1000	0/1	N/A
2000	0/3	N/A

N/A: not applicable, * = diluted in the ratio of 1:10 in RO water

No mortality occurred following treatment at 200, 1000, and 2000 mg GF-3307/kg body weight.

Clinical Observations

No clinical signs were observed in any rat treated with 200 (1:10 dilution), 200, 1000, and 2000 mg GF-3307/kg body weight.

No erythema or oedema was observed in any rat at 24, 48, and 72 hours post patch removal.

Body Weight

All rats treated with GF-3307 at 200 (1:10 dilution), 200, 1000, and 2000 mg/kg body weight showed no effect on body weight. All rats gained weight during the course of the study.

Necropsy

External

An external examination of the terminally sacrificed animals did not reveal any gross abnormality of pathological significance.

Internal

The visceral examination of animals sacrificed at the termination did not reveal any gross lesion.

CONCLUSION

No mortality, clinical observation, effect on body weight and macroscopic external or internal gross abnormality at necropsy were observed in any rat treated with 200 (1:10 dilution), 200, 1000, and 2000 mg GF-3307/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rat	Wistar RccHan:WIST	F	Dermal	Topical (24-hour semi-occlusive exposure)	LD50 = >2000 mg/kg body weight

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Unclassified
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A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	During previous registration process (Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023) it was concluded that the maximum attainable exposure atmosphere concentration was limited by the Lower
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<p>Explosive Limit (LEL) of benzyl acetate, a co-formulant. Maintaining an exposure chamber atmospheric concentration that does not exceed 50% of the Lower Explosive Limit (LEL) for any tested component is critical for occupational safety of the workers performing the exposure, and to minimize risk of adverse events that could compromise animal welfare. This strategy is also consistent with the OECD guidance and OECD test guidelines that were followed during the conduct of the study. In the Limit Test section of OECD Guidance Document No. 39 on Acute Inhalation Toxicity Testing, page 37 section 50, the following is stated: “In the case of potentially explosive test articles, care should be taken to avoid conditions favorable for an explosion. For safety reasons it is generally advisable to not exceed 50% of the published Lower Explosive Limit (LEL).” Additionally, from the Test Guideline OECD 436, Acute Inhalation Toxicity – Acute Toxic Class Method, page 3 section 13 it is stated: “Care should be taken not to generate explosive atmospheres.”</p> <p>Benzyl acetate comprises approximately 40% of the total GF-3307 liquid formulation and has an LEL of 0.9% (9000 ppm). The vapor pressure of benzyl acetate warranted concentration quantification in both the aerosol and vapor phases of the exposure chamber atmosphere. In attempt to avoid exceeding 50% of the benzyl acetate LEL (4500 ppm) in the exposure chamber atmosphere, the delivery rate of the GF-3307 liquid formulation to the nebulizer used to produce the exposure atmosphere was calculated based on the percentage of benzyl acetate in the liquid formulation. This resulted during exposure, with rats exposed to a total GF-3307 atmospheric chamber concentration of 2.9 ± 0.16 mg/L (mean \pm standard deviation). The means and standard deviations for aerosol (gravimetric) and vapor (Gas Chromatography) concentrations were 1.8 ± 0.13 mg/L and 1.1 ± 0.044, respectively.</p> <p>However concentration of the aerosol failed to reach the upper limit for classification with acute inhalation toxicity cat. 4 (5 mg/L), considering a co-formulant properties to maintain a chamber concentration of components below the Lower Explosive Level, a design concentration of >2.0 mg/L was selected for this study. In the event no deaths occur among animals exposed to a mean concentration of 2.0 mg/L or greater, the LC₅₀ is considered equal to or greater than 2.0 mg/L, and no further testing is pursued.</p> <p>No mortality occurred following exposure to a total mean concentration of 2.9 mg GF-3307/L air.</p> <p><u>Clinical Observations:</u> Rats displayed normal startle response throughout the exposure. One female rat was lethargic immediately after the exposure and continued to display lethargy the next day. There were no other toxicologically significant clinical signs observed in any rats during the remainder of the recovery period.</p> <p><u>Body Weight:</u> On the day after the exposure, 1 male rat displayed a bodyweight loss 21 grams and 2 females lost 8.2 and 10 grams. After test day 2, all rats displayed weight gains throughout the remainder of the recovery period.</p> <p><u>Necropsy Observations:</u> No gross lesions were present in the rats at necropsy.</p>						
Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)					None	
Test-item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rat	Crj:CD(SD)	M/F	Inhalation	Nose only(4-hour)	LC50 >2.9 mg/L air
GHS-classification						
Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)					Category 4	

REFERENCE

KCP 7.1.3/1

CITATION

██████; 2021; F-3307: Inhalation Median Lethal Concentration (LC50) Study in Rats; ██████; Lab Study No. 22455-721; Sponsor Study No. 211432 ; 10 November 2021; Published: No

COMPLIANCE

Guideline(s): OPPTS 870.1300 (1998); OECD 436 (2009); EC B.2 (2014);
JMAFF 12 Nousan 8147 and 13 Seisan 1739 (2000 and 2001)
US EPA Guideline(s): OPPTS 870.1300 (1998)
Guideline Deviations: None
Dates of work: 24 August 2021 to 7 September 2021
GLP status: Yes
Number of pages in final report: 64

MATERIALS AND METHODS

Test item(s)

Test item (Common name): GF-3307
Purity: 4.7 wt% (49 g/L) fenpicoxamid,
9.7 wt% (101 g/L) prothioconazole
Description (physical state): Transparent amber liquid
Lot/batch no.: MAR19CE01Q (TSN400550)
Vehicle: Air

Test System

Species: Rat (*Rattus norvegicus*)
Strain: Crl:CD(SD)
Age and weight at dosing: ~8 weeks
Weight (g): Male: Minimum 260, Maximum 270; Female:
Minimum 151, Maximum 181
Source: Charles River Laboratories International, Inc., Raleigh, North
Carolina, U.S.A
Housing: Except during exposure and during the restrainer acclimation period,
animals were housed individually in solid-bottom caging with bedding and
appropriate species-specific enrichment.
Feed and water: Feed: PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002
ad libitum (except during exposure)
Water: ad libitum (except during exposure)
Environmental conditions: Temperature: 20 to 25°C
Humidity: 30 to 70% relative humidity
Air changes: Not reported
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 days

Study Design

In-life dates

Start: 24 August 2021 End: 07 September 2021

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/L air)	Males	Females	Combined
2.9	3	3	6

The rats were exposed for 4 h (nose only) followed by a 14 day post-exposure observation period during which body weight and clinical observations were recorded. Survivors were sacrificed and a necropsy was performed in all animals.

Each animal was weighed and observed prior to exposure. Animals were observed 3 times during the exposure. After the exposure, animals were individually observed for clinical signs before they were returned to their cages. Animals were weighed and observed on the day of the exposure (test day 1), and on test days 2, 3, 4, 8 and 15. Rats were checked daily for mortality or signs of illness, injury, and abnormal behaviour.

Atmosphere Generation

The chamber atmosphere was generated by aerosolization of the test substance in air with a Spraying Systems Company® nebulizer. The test substance mixture was metered into the nebulizer using a Harvard Apparatus model 22 Infusion pump. High-pressure air, metered into the nebulizer by a Brooks model 5850E mass flow controller (MFC), carried the resulting atmosphere into the exposure chamber. Chamber concentrations of the aerosol test substance mixture were controlled by varying the Infusion pump's feed rate to the nebulizer.

Chamber Construction and Design

The exposure chamber was constructed of glass (cylindrical) with a nominal internal volume of 14 L. A polymethylmethacrylate baffle inside the chamber promoted uniform chamber distribution of the test atmosphere.

Chamber Distribution of Test Substance

Prior to the start of the exposure, the distribution of the test substance aerosol was determined in the exposure chamber using gravimetric chamber samples. Air samples were collected from 3 separate locations in the faceplate and at the sampling port of the exposure chamber 4 times. An overall average of the 7 samples taken was determined and individual samples from the faceplate compared to the overall average. All samples taken from the faceplate were within 10% of the overall mean of the chamber samples collected.

RESULTS AND DISCUSSION

Concentration Details in the Inhalation Chamber

All aerosol (gravimetric) samples taken from the faceplate demonstrated differences that were less than 10% from the overall mean aerosol concentration. The test substance atmosphere was considered to be homogeneously distributed in the breathing zone of the animals and the use of the sampling port for air sampling was considered adequate.

During the exposure, rats were exposed to a total atmospheric chamber concentration of 2.9 ± 0.16 mg/L GF-3307 (mean \pm standard deviation). The means and standard deviations for aerosol (gravimetric)

concentration and vapor (Gas Chromatography) were 1.8 ± 0.13 mg/L and 1.1 ± 0.044 , respectively. Two samples were taken to determine mass median aerodynamic diameters (MMADs) during the exposures. The MMADs were 2.6 and 2.5 μm and geometric standard deviations were both 2.3.

The chamber concentrations and aerosol size were considered adequate for the conduct of this study.

Mortality

Mortality data are presented in the following table.

Table 2: Dose, mortality/animals treated

Concentration (mg/L air)	Mortality (# affected/total)			Time range of deaths (hours)	Number with evident toxicity (# affected/total)		
	Male	Female	Combined		Male	Female	Combined
2.9	0/3	0/3	0/6	N/A	0/3	1/3	1/6

N/A: Not applicable

No mortality occurred following exposure to a total mean concentration of 2.9 mg GF-3307/L air.

Clinical Observations

Rats displayed normal startle response throughout the exposure. One female rat was lethargic immediately after the exposure and continued to display lethargy the next day. There were no other toxicologically significant clinical signs observed in any rats during the remainder of the recovery period.

Body Weight

On the day after the exposure, 1 male rat displayed a bodyweight loss 21 grams and 2 females lost 8.2 and 10 grams. After test day 2, all rats displayed weight gains throughout the remainder of the recovery period.

Necropsy Observations

No gross lesions were present in the rats at necropsy.

CONCLUSION

Under the conditions of this study, the 4-hour inhalation median lethal concentration (LC50) for GF-3307 in male and female rats was greater than 2.9 mg/L.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rat	CrI:CD(SD)	M/F	Inhalation	Nose only(4-hour)	LC50 >2.9 mg/L air

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	None
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A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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REFERENCE

KCP 7.1.4/1

CITATION

██████; 2021; Acute Dermal Irritation Study of GF-3307 in Rabbits; ██████; Lab Study No. 406-1-01-28633; Sponsor Study No. 211322 ; 15 November 2021; Published: No

COMPLIANCE

Guideline(s):	OECD 404 (2015), OPPTS 870.2500 (1998), EC B.4 (2008), JMAFF 2-1-4 (2000)
US EPA Guideline(s):	OPPTS 870.2500
Guideline Deviations:	None
Dates of work:	19 August 2021 to 31 August 2021
GLP status:	Yes
Number of pages in final report:	39

MATERIALS AND METHODS

Test item(s)

Test item (Common name):	GF-3307
Purity:	4.7 wt% (49 g/L) Fenpicoxamid 9.7 wt% (101 g/L) Prothioconazole
Description (physical state):	Orange liquid
Lot/batch no.:	MAR19CE01Q (TSN400550)
Vehicle:	N/A

Test System

Species:	Rabbit (<i>Oryctolagus cuniculus</i>)
Strain:	New Zealand White (NZW)
Age and weight at dosing:	4 to 5 months Weight (kg): Minimum 2.0, Maximum 2.1
Source:	Vab Biosciences, Hyderabad, India
Housing:	Individual
Feed and water:	Feed: Teklad certified Global High Fiber Rabbit Feed manufactured by Envigo, U.S.A. ad libitum Water: UV sterilized water ad libitum
Environmental conditions:	Temperature: 18 to 23°C Humidity: 63 to 65% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	7 to 9 days

Test item(s)

Species:	Rabbit (<i>Oryctolagus cuniculus</i>)
Strain:	New Zealand White (NZW)
Age and weight at dosing:	4 to 5 months Weight (kg): Minimum 2.0, Maximum 2.1

Source:	Vab Biosciences, Hyderabad, India
Housing:	Individual
Feed and water:	Feed: Teklad certified Global High Fiber Rabbit Feed manufactured by Envigo, U.S.A. <i>ad libitum</i> Water: UV sterilized water <i>ad libitum</i>
Environmental conditions:	Temperature: 18 to 23°C Humidity: 63 to 65% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	7 to 9 days

Study Design

In-life dates

Start:	19 August 2021	End:	31 August 2021
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Animal assignment and treatment

The pH of GF-3307 was found to be 4.39 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment.

A total of 03 rabbits (females) were assigned to treatment. A sequential testing strategy was adopted. Initially one rabbit was tested. As severe effects were not observed in the first treated rabbit, two additional rabbits were subsequently treated in an identical manner.

A volume of 0.5 mL of GF-3307 (undiluted) was applied evenly to one of the clipped sites of each rabbit. The contralateral site remained untreated and served as control. The treated and the control sites were covered with gauze patches of approximately 6 cm² (gauze rolled) with semi-occlusive dressing (not more than 8-ply) and were secured at the margins by non-irritating tape (Medi tape 330 hypo-allergenic surgical tape) to ensure that the rabbits did not ingest the test item. At the end of the 4-hour exposure period (day 0), the residual test item was removed with cotton soaked in distilled water.

Irritation was scored by the method of Draize (as described in OECD Test Guideline 404) at 1, 24, 48, and 72 hours post patch removal. General health condition and body weight were monitored.

RESULTS AND DISCUSSION

Dermal Irritation

Individual animal irritation scores are presented in Table 1.

Table 16: *Doses, scoring/animals treated*

Rabbit No.	Treatment Site	Control Site	Observation (post patch removal)											
			Erythema						Oedema					
			Hour				Day		Hour				Day	
			1	24	48	72	7	14	1	24	48	72	7	14
1	Left	Right	1	2	1	0	N/A	N/A	1	1	1	0	N/A	N/A
2	Right	Left	1	2	1	0	N/A	N/A	1	1	1	0	N/A	N/A
3	Right	Left	1	2	1	0	N/A	N/A	1	1	1	0	N/A	N/A

Key: N/A: Not applicable

Erythema

0: No erythema

1: Very slight erythema (barely perceptible)

2: Well-defined erythema

3: Moderate to severe erythema

4: Severe erythema (beef redness) to eschar formation preventing grading of erythema

Maximum possible: 4

Oedema

0: No oedema

1: Very slight oedema (barely perceptible)

2: Slight oedema (edges of area well defined by raising)

3: Moderate oedema (raised approximately 1 mm)

4: Severe oedema (raised more than 1 mm and extending beyond area of exposure)

Maximum possible: 4

Systemic toxicity

No signs of toxicity were observed and all animals gained body weight throughout the study.

CONCLUSION

Based on these study results, GF-3307 caused a minimal dermal irritation in all rabbits, fully reversible by 72 hours. No systemic effect was observed. The individual rabbit mean dermal irritation score at 24, 48, and 72 h post patch removal was 1.00, 1.00, 1.00 for erythema, 0.67, 0.67, 0.67 for oedema for rabbit N° 1, 2 and 3 respectively.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rabbit	NZW	F	Dermal	Topical (4-hour, semi-occlusive)	Mean Erythema Score: 1.00, 1.00, 1.00 Mean Oedema Score: 0.67, 0.67, 0.67 Recovery completed by 72 hours

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Unclassified
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A 2.6 Eye Irritation (KCP 7.1.5)

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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REFERENCE

KCP 7.1.5/1

CITATION

█; 2021; Acute Eye Irritation Study of GF-3307 in Rabbits; █;

Lab Study No. 407-1-01-28634; Sponsor Study No. 211321 ; 15 November 2021; Published: No

COMPLIANCE

Guideline(s):

OECD 405, OPPTS 870.2400, EC B.5, JMAFF 2-1-5

US EPA Guideline(s): OPPTS 870.2400
Guideline Deviations: None
Dates of work: 20 August 2021 to 11 September 2021
GLP status: Yes
Number of pages in final report: 45

MATERIALS AND METHODS

Test item(s)

Test item (Common name): GF-3307
Purity: 4.7 wt% (49 g/L) Fenpicoxamid, 9.7 wt% (101 g/L) Prothioconazole
Description (physical state): Orange liquid
Lot/batch no.: MAR19CE01Q (TSN400550)
Vehicle: N/A

Test System

Species: Rabbit (*Oryctolagus cuniculus*)
Strain: New Zealand White (NZW)
Age and weight at dosing: 4 to 5 months
Weight (kg): Minimum 2.143, Maximum 2.285
Source: Vab Biosciences, Hyderabad, India
Housing: Individual
Feed and water: Feed: Teklad certified Global High Fiber Rabbit Feed manufactured by Envigo, U.S.A. *ad libitum*
Water: UV sterilized water *ad libitum*
Environmental conditions: Temperature: 18 to 22 °C
Humidity: 63 to 64% relative humidity
Air changes: Minimum 15 air changes/hour
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 to 8 days

Study Design

In-life dates

Start: 20 August 2021 End: 11 September 2021

Animal assignment and treatment

The pH of GF-3307 was found to be 4.39 (1% aqueous solution in distilled water at room temperature), which was considered acceptable for treatment.

A total of 03 rabbits (females) were assigned to treatment. A sequential testing strategy was adopted. Initially one rabbit was tested. Immediately after administration of the test item, assessments of any initial local pain reactions were made. As severe effects were not observed in the first treated rabbit, two additional rabbits were subsequently treated in an identical manner.

0.1 mL of GF-3307 was instilled in the conjunctival sac after gently pulling the lower lid away from the eyeball. Then the lids were gently held together for about one second in order to prevent loss of the test

item. The contralateral (untreated) eye served as the control. In all animals, both the eyes were gently washed with 0.9% normal saline at 24 hours post instillation.

On day 0, approximately 60 minutes prior to the test item instillation, buprenorphine 0.01 mg/kg body weight was administered by subcutaneous injection (SC). Approximately 5 minutes prior to the test item instillation, one or two drops of 0.5% proparacaine hydrochloride was applied to each eye.

Approximately 8 hours (\pm 30 minutes) post instillation, buprenorphine 0.01 mg/kg body weight (SC) and meloxicam 0.5 mg/kg body weight were administered both subcutaneously to provide a continued therapeutic level of systemic analgesia.

Subsequently, buprenorphine 0.01 mg/kg body weight was administered subcutaneously every 12 hours (\pm 30 minutes), in conjunction with meloxicam 0.5 mg/kg body weight every 24 hours (\pm 30 minutes), until the ocular lesions resolved.

Irritation was scored by the method of Draize (as described in OECD Test Guideline 405) at 1, 24, 48, and 72 hours and up to 14 days after GF-3307 instillation. Fluorescein staining was used to assess the corneal epithelium damage at 24 hours after the test item instillation in all animals. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION

Eye Irritation

At 1 h post-application, the treated eye of all rabbits revealed conjunctival redness (score of 1) and conjunctival chemosis (score of 1).

At 24, 48 and 72 h post-application, the treated eye of all rabbits revealed conjunctival redness (score of 2) and conjunctival chemosis (score of 1).

On day 7 post-application, the treated eye of all rabbits revealed conjunctival redness (injected) (score of 1) and conjunctival chemosis (score of 1).

On day 14 post-application, the treated eye of all rabbits recovered completely and appeared normal.

No corneal opacity, iritis, or discharge was observed in any rabbit throughout the experimental period. An examination with fluorescein dye and cobalt blue filter carried out at 24 h post-application revealed no disruption of corneal epithelium in any rabbit.

Individual animal irritation scores are presented in Table 1.

Table 17: *Grades for ocular lesions (eye treated with the test item)*

Rabbit no.	1							2							3						
Site of application	Right							Right							Right						
Reaction post application	Hour				Day			Hour				Day			Hour				Day		
	1	24	48	72	7	14	21	1	24	48	72	7	14	21	1	24	48	72	7	14	21
Conjunctivae (redness)	1	2	2	2	1	0	N/A	1	2	2	2	1	0	N/A	1	2	2	2	1	0	N/A
Conjunctivae (chemosis)	1	1	1	1	1	0	N/A	1	1	1	1	1	0	N/A	1	1	1	1	1	0	N/A
Cornea (degree of opacity)	0	0	0	0	0	0	N/A	0	0	0	0	0	0	N/A	0	0	0	0	0	0	N/A
Iris inflammation	0	0	0	0	0	0	N/A	0	0	0	0	0	0	N/A	0	0	0	0	0	0	N/A

Key: N/A: Not applicable

Conjunctivae - Redness (refers to palpebral and bulbar conjunctivae; excluding cornea and iris)

0: Normal

1: Some blood vessels hyperaemic (injected)

2: Diffuse, crimson colour; individual vessels not easily discernible

3: Diffuse beefy red

Maximum possible: 3

Chemosis – Swelling (refers to lids and/or nictating membranes)

0: Normal

1: Some swelling above normal

2: Obvious swelling, with partial eversion of lids

3: Swelling, with lids about half closed

4: Swelling, with lids more than half closed

Maximum possible: 4

Opacity: degree of density

0: No ulceration or opacity

1: Scattered or diffuse areas of opacity (other than slight dulling of normal lustre); details of iris clearly visible

2: Easily discernible translucent area; details of iris slightly obscured

3: Necrotic area; no details of iris visible; size of pupil barely discernible

4: Opaque cornea; iris not discernible through the opacity

Maximum possible: 4

Iris

0: Normal

1: Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia; or injection; iris reactive to light (a sluggish reaction is considered to be an effect)

2: Hemorrhage, gross destruction, or no reaction to light

Maximum possible: 2

Systemic toxicity

No signs of toxicity was observed and all animals gained body weight throughout the study.

CONCLUSION

GF-3307 caused conjunctival redness (scores of 1 or 2) and conjunctival chemosis (score of 1) at 1, 24, 48 and 72 h and on day 7, which resolved by day 14 in all rabbits.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Rabbit	NZW	F	Eye	Instillation (washing at 24 hours post instillation)	Mean Redness Score: 2.00, 2.00, 2.00 Mean Chemosis Score: 1.00, 1.00, 1.00 Mean Corneal Score: 0.00, 0.00, 0.00 Mean Iris Score: 0.00, 0.00, 0.00 Recovery completed by 14 days

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Category 2/2A
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A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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REFERENCE

KCP 7.1.6/1

CITATION

██████; 2021; Skin Sensitisation Study of GF-3307 by Local Lymph Node Assay in Mice; ██████
Lab Study No. 409-1-01-28635; Sponsor Study No. 211320 ; 15 November 2021; Published: No

COMPLIANCE

Guideline(s):	OECD 429 (2010), OPPTS 870.2600 (2003), EC B.42 (2012)
US EPA Guideline(s):	OPPTS 870.2600
Guideline Deviations:	None
Dates of work:	18 August 2021 to 04 September 2021
GLP status:	Yes
Number of pages in final report:	66

MATERIALS AND METHODS

Test item(s)

Test item (common name):	GF-3307
Purity:	4.7 wt% (49 g/L) Fenpicoxamid 9.7 wt% (101 g/L) Prothioconazole
Description (physical state):	Orange liquid
Lot/batch no.:	MAR19CE01Q (TSN400550)

Vehicle/Control Item(s)

Vehicle/Negative control: 1% Pluronic® L-92 in water (1% L-92)
Positive control: α -hexylcinnamaldehyde, 25% v/v in 1% Pluronic® L-92

Test System

Species: Mouse (*Mus musculus*)
Strain: CBA/J
Age and weight at dosing: 9 to 10 weeks
Weight (g): Minimum 17.5, Maximum 23.9
Source: Animal Breeding Facility, Jai Research Foundation
Housing: Group-housed during acclimatisation; individually caged on the days of test item application (days 0, 1 and 2); 5 mice/cage from day 3; 5 mice/cage in metabolic cages from day 5 (post injection of radiolabelled material)
Feed and water: Feed: Teklad Certified Global 14% Protein Rodent Maintenance Diet (sterilizable) manufactured by Envigo, USA. *ad libitum*
Water: UV sterilized water *ad libitum*
Environmental conditions: Temperature: 20 to 23°C
Humidity: 57 to 66% relative humidity
Air changes: Minimum 15 air changes/hour
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 7 days

Study Design

In-life dates

Start: 18 August 2021 End: 05 September 2021

Formulation procedure

Procedure: The Test Item and the Positive Control Item were freshly dissolved/suspended in the vehicle. An adjustment was not made for the purity of the Test or Positive Control Item.
Stability in the vehicle: Unknown
Formulation analysis: Concentration/homogeneity check not performed
Concentrations used: see description below

Preliminary test and dose selection

In a preliminary test, 6 groups of female mice comprising 2 females per group were treated topically for three consecutive days (days 0, 1 and 2) on the dorsal surface of both ears (25 μ L/ear) with GF-3307 at concentrations of 5%, 10%, 25%, 50%, 75% (v/v) and 100% (undiluted) in 1% Pluronic® L-92.

Individual clinical observations (including systemic clinical signs and scoring of irritation) were recorded daily during the experiment. Ear thickness was measured on days 0, 2 and 5. Body weight was recorded on days 0 and 5.

In the preliminary assay, no erythema was observed, and an increase of less than 25% in ear thickness was observed at tested concentrations up to 50% in 1% Pluronic® L-92 whereas an increase of greater than 25% in ear thickness was observed at concentrations 75% in 1% Pluronic® L-92 and 100% (undiluted), erythema (score of 1) was also observed at concentration 100% (undiluted). Therefore, dose concentrations of 10%, 25% and 50% (v/v) in 1% Pluronic® L-92 were evaluated in the main study of LLNA.

Animal assignment and treatment

In the main assay, 3 groups of female mice comprising 5 females per group were treated topically for three consecutive days (days 0, 1 and 2) on the dorsal surface of both ears (25 µL/ear) with GF-3307 at concentrations of 10%, 25% and 50% (v/v) in 1% Pluronic® L-92. Female mice from the vehicle control and positive control groups were maintained in similar conditions with treatment of 1% Pluronic® L-92 and 25% (v/v) of HCA in L-92, respectively.

Individual clinical observations (including systemic clinical signs and scoring of irritation) were recorded daily during the experiment. Body weight was recorded on days 0 and 5. On day 5 of treatment, all mice from each group were injected intravenously (tail vein) with 250 µL of sterile phosphate buffered saline (PBS) containing approximately (20±1) µCi of tritiated methyl thymidine (3H-TdR). On day 5, 5 hours - post injection of 3H-TdR, the animals were euthanized and the draining auricular (local) lymph node from both ears of each animal was excised and collected into PBS. Single cell suspensions of lymph node cells from individual animals were prepared. The uptake of 3H-TdR into the auricular (local) lymph nodes draining the site of chemical application was measured to assess the lymph node proliferative response.

Statistics

All the parameters characterised by continuous data such as body weight and radioactive disintegrations per minute (DPM) were subjected to Bartlett's test to assess the homogeneity of variance before conducting Analysis of Variance (ANOVA). To compare vehicle and positive control data, Student's t-test was performed to calculate significance.

RESULTS AND DISCUSSION

Clinical Observations and Irritation

No erythema was observed at the site of application at 10%, 25% and 50% (v/v) GF-3307 in 1% Pluronic® L-92. A local reaction consisting of very slight erythema (score of 1) was observed in all mice treated with 25% (v/v) HCA from day 1 to 4.

Body Weight

No effect on the body weight was observed in mice treated with GF-3307, positive control, and vehicle control.

Group Mean DPM

Proliferative responses in the draining lymph nodes were monitored by measuring the incorporation of 3H-methyl thymidine. These analyses revealed the group mean DPM/mouse value of 689.60, 756.40, 1121.40, and 1729.80, for the vehicle control (1% Pluronic® L-92), 10%, 25% and 50% (v/v) in 1% Pluronic® L-92 treated groups, and 3947.60 for positive control (25% v/v HCA), respectively.

Stimulation Index (SI Value) and EC₃ Value

Stimulation Index (SI) values calculated for groups treated with GF-3307 were found to be 1.10, 1.63, and 2.51 at 10%, 25% and 50% (v/v) in 1% Pluronic® L-92, respectively, and 5.72 for 25% (v/v) HCA positive control group.

A correlation was observed between the dose and the proliferative response in groups treated with GF-3307 when compared to the control. The SI obtained for GF-3307 at the tested concentrations showed a less than threefold increase over the control value. Therefore, GF-3307 did not demonstrate dermal sensitisation potential in the local lymph node assay.

The SI value of 5.72 obtained for the concurrent positive control α -Hexylcinnamaldehyde, showed a greater than three-fold increase compared to the vehicle control value, indicating a clear positive response for this known weak sensitiser. This response was within the historical control data range of the laboratory, which confirmed the reliability of this test procedure.

The SI obtained for GF-3307 showed a less than threefold increase over the control value at all tested concentrations. Therefore, an EC₃ value was not calculated.

Individual and group mean values are reported in Table 1.

Table 18: Dose concentration, group mean DPM value and Stimulation Index

Test Material/ Dose concentration	Animal #	Individual Animal DPM	Group Mean +/- SE (DPM)	Stimulation Index (SI)*
Vehicle (1% Pluronic® L-92)	1	817	689 ± 119.43	1
	2	630		
	3	753		
	4	735		
	5	513		
GF-3307 10% (v/v) in vehicle]	6	909	756.40 ± 209.87	1.10
	7	867		
	8	686		
	9	418		
	10	902		
GF-3307 25% (v/v) in vehicle	11	1486	1121.40 ± 283.23	1.63
	12	1091		
	13	1117		
	14	699		
	15	1214		
GF-3307 50% (v/v) in vehicle	16	1296	1729.80 ± 509.38	2.51
	17	1133		
	18	2080		
	19	1806		
	20	2334		
HCA (Positive control) 25% (v/v) in vehicle	21	2799	3947.60 ± 1287.77	5.72
	22	3007		
	23	3285		
	24	5004		
	25	5643		

CONCLUSION

The SI obtained for GF-3307 at all tested concentrations showed a less than three-fold increase over the control value. Therefore, GF-3307 did not demonstrate dermal sensitisation potential in the local lymph node assay.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3307	Mouse	CBA/J	F	Dermal	Topical - Local lymph node assay	Dermal non sensitiser SI = 1.10, 1.63 and 2.51 at 10%, 25% and 50% (v/v) respectively.

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev 8, GHS 2019)	Not classified as a skin sensitiser
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A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

No supplementary studies were conducted.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.10 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 2.11 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 2.12 Studies on dermal absorption (KCP 7.3)

Default dermal absorption values as detailed in the EFSA guidance document on dermal absorption (EFSA, 2017) were used for prothioconazole.

Prothioconazole-desthio is not part of the formulation. Rather it is a metabolite of prothioconazole which is formed at different rates during the drying process of aqueous diluted solutions of the active substance on surfaces. One specific *in vitro* dermal absorption study was performed with GF-3307 assessing the absorption of PTZ-desthio through human skin.

A 2.12.1 Prothioconazole-desthio, dermal absorption study using in vitro human skin

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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Reference	KCP 7.3/1
Report	Whitfield, C.; 2020; GF-3307: In Vitro Percutaneous Absorption of Prothioconazole-desthio in Human Skin; Haskell R&D Center, E.I. du Pont de Nemours and Company, Member of the Corteva Agriscience Group of Companies, Newark, Delaware, U.S.A.; Lab Study No. 22368-1377; DAS Study No. 200102 ; 20 March 2020; Unpublished
Guideline(s)	Yes: OECD 428 (2004)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item #1

Test item (Common name):	Prothioconazole-desthio (active ingredient)
Purity:	99.6%
Description (physical state):	Solid
Lot/batch no.:	1107201601 (TSN312897)

Test item #2

Radiolabelled test item (Common name):	[¹⁴ C]Prothioconazole-desthio
Radiochemical purity:	100%
Specific activity	33.5 mCi/mmol, 107.3 µCi/mg
Description (physical state):	Solid
Lot/batch no.:	DE3-171310-100

Test item #3

Test item (Common name):	Fenpicoxamid (ancillary active ingredient)
Purity:	82.8 wt%
Description (physical state):	Solid
Lot/batch no.:	XDE-777-01-02 (TSN303159)

Study Design

The study was designed to examine the *in vitro* dermal absorption of [¹⁴C]prothioconazole-desthio formulated as GF-3307 (assuming that all prothioconazole in the diluted formulation formed prothioconazole-desthio) in 24 hours through human skin following an 8-hour dermal exposure to a single, finite application. The test preparation was tested at target concentrations: 0.363 g L⁻¹ (aqueous spray dilution; 1:250). The spray dilution reflects the concentration recommended for use in the field (*i.e.*, in-use spray dilution). The study design is summarised below.

Table 19: In vitro dermal absorption from GF-3307: study design

Test group	No. of replicates*	Species	Target concentration of Prothioconazole-desthio (g L ⁻¹)	Target dose of Prothioconazole-desthio (µg cm ⁻²)	Exposure duration	Serial sampling time points
A	8 ^a	Human	0.363	3.63	8 h	0-24 h

*2 replicates per donor.

^a One replicate excluded due to misapplication of dose.

Preparation of skin membranes

Human surgical skins were prepared in duplicate from four separate donors (n=8).

After thawing the frozen skin samples, the skin was dermatomed using a dermatome to a recorded thickness of *ca* 0.2-0.4 mm measured with a digimatic micrometer.

Integrity of the skin membranes

Skin was hydrated in 0.9% saline for approximately 15 minutes at room temperature. Following hydration, the skin was mounted onto the top of the receptor chamber, which was filled with 0.9% saline. The donor chamber was then clamped in place and filled with 0.9% saline. The skin was then allowed to equilibrate for approximately 30 minutes. Following equilibration, a resistance measurement of each skin membrane was taken using a Tinsley 6401 Databridge set in the resistance (R) and parallel equivalent (PAR) modes at an alternating current (AC) frequency of 1000 Hertz (1 kHz). Skin with a resistance of ≥ 17 k Ω was considered intact and retained for use on study. Skin not meeting these criteria was replaced, and electrical resistance confirmed following equilibration. This procedure was followed until 8 skin preparations represented by 4 individuals (2 replicates per donor) was achieved. Following the electrical resistance measurement, saline in the donor chamber was removed and discarded. The skin was rinsed with deionized water and dried with a lint-free wipe. Saline in the receptor chamber was removed and replaced with the receptor fluid.

Solubility in the receptor fluid

The solubility of Prothioconazole-desthio in the receptor fluid (≥ 108 µg mL⁻¹) was observed to be at least 10 fold higher than the maximum concentration achieved in the receptor fluid, ensuring the receptor fluid offered sink conditions to Prothioconazole-desthio and was not rate limiting to passive diffusion. The maximum penetration of Prothioconazole-desthio into the receptor fluid was 0.157 µg equivalents mL⁻¹ (Cell 5).

In addition, in the flow through cells used, the volume of the receptor fluid in the receptor chamber beneath the skin was *ca* 0.2 mL. At a flow rate of *ca* 1.5 mL h⁻¹, this volume was replenished continuously such that the rate of diffusion into the receptor fluid did not become a rate-limiting step in the experiment.

Study conduct and sample collection

The study was performed in flowthrough diffusion cells (PermeGear Inc., Riegelsville, Pennsylvania, USA). The prepared formulations were applied to each skin surface (0.64 cm²), via the donor chamber, at a rate of 10 µL cm⁻². The dose was distributed evenly over the exposure area using a glass rod. The donor chamber remained unoccluded for the duration of the study. The exposed area of each skin (0.64 cm²) remained in contact with the test item for a period of 8 h (normal working h day⁻¹) with a postexposure time of 16 h (*i.e.*, the total study duration was 24 h). Skin washing was performed at the end of both the contact (at 8 h) and postexposure (at 24 h) periods. Skins were then removed from the cells and tapestripped up to 15 times each to remove the *stratum corneum*. The tape stripped skin was then placed on an aluminum pan and heated in an oven at approximately 55°C for approximately one minute and 45 seconds. The epidermis was then peeled away from the dermis using a scalpel and/or forceps. Epidermis and dermis samples were collected in separate vials for analysis. The donor and receptor compartments were rinsed to collect any remaining test material.

In order to determine the recovery, the amount of Prothioconazole-desthio was measured by liquid scintillation counting in the following samples:

- a. test concentrations
- b. spreader device rinses
- c. receptor fluid samples collected as: 0-1 h, 1-2 h followed by 2-h intervals until 24 h after application
- d. skin washes at 8 h and 24 h, separately
- e. the *stratum corneum* (SC) (*ca* 15 tape strips, individually analyzed)
- f. the dermis and epidermis (without SC), separately
- g. receptor and donor compartments rinse, separately

RESULTS AND DISCUSSION

The absorbed dose of Prothioconazole-desthio from the GF-3307 spray dilution is calculated based on guidance from different regulatory bodies and presented below:

Table 20: Absorbed doses

Absorbed dose	Aqueous spray dilution (0.363 g L ⁻¹) (1:250)
Absorbed dose I ¹	9.68 ± 3.22
Absorbed dose II ²	10.36 ± 3.04
Absorbed dose III ³	11.53 ± 2.49

¹ Absorbed dose I is calculated from the amount recovered in receptor fluid, the receptor compartment wash, and the dermis.

² Absorbed dose II is calculated from the absorbed dose I, plus the epidermis (without *stratum corneum*). The absorbed dose II can be considered conservative.

³ Absorbed dose III is calculated from the absorbed dose II plus the *stratum corneum* (excluding tape strips 1 and 2). The absorbed dose III can be considered highly conservative.

The mean total recovery of [¹⁴C]prothioconazole-desthio for the aqueous spray dilution was 99.18 (±1.34)%.

For the aqueous spray dilution, absorption was 9.68 ± 3.22% (absorbed dose I = the amount recovered in receptor fluid, the receptor compartment wash and the dermis), or 10.36 ± 3.04% (absorbed dose II =

absorbed dose I plus epidermis without *stratum corneum*), or $11.53 \pm 2.49\%$ (absorbed dose III = the absorbed dose II plus the *stratum corneum* (excluding tape strips 1 and 2)) of the applied dose.

Dermal absorption and total recovery data for the test group is summarised in the following table.

Table 21: Total recoveries and dermal absorption of prothioconazole-desthio from GF-3307 aqueous spray dilution through human skin

A – Aqueous spray dilution (1:250)		
Total concentration [g L ⁻¹]	0.363	
Dose [µg.cm ⁻²]	3.63	
N	7	
Cumulative penetration into the receptor fluid	% of dose	µg equiv m ⁻²
after 12 h	--	0.0961 ± 0.0556
after 24 h	7.67 ± 3.39	0.247 ± 0.109
Maximal flux [µg equiv. cm ⁻² h ⁻¹]	0.0162 ± 0.0073	
Lag time [h]	6.2 ± 1.4	
Recovery of [¹⁴ C]Prothioconazole-desthio (% of dose, mean ± SD)		
Receptor fluid (0-24 h)	7.67 ± 3.39	
Receptor compartment wash	0.34 ± 0.11	
Dermis	1.66 ± 0.42	
Stratum corneum (SC) Total	2.42 ± 2.03	
Tape strips (1-2)	1.25 ± 1.08	
Tape strips (3 – 15)	1.17 ± 0.98	
Epidermis	0.69 ± 0.39	
Skin wash t = 8 h	79.89 ± 4.33	
Skin wash t = 24 h	6.34 ± 3.39	
Donor compartment wash	0.17 ± 0.11	
Total recovery	99.18 ± 1.34	

CONCLUSION

The percent dermal absorption values for prothioconazole-desthio are:

Total concentration [g L ⁻¹]	Aqueous spray dilution (0.363 g L ⁻¹) (1:250)
Absorbed dose I ¹	9.68 ± 3.22
Absorbed dose II ²	10.36 ± 3.04
Absorbed dose III ³	11.53 ± 2.49

¹ Absorbed dose I is calculated from the amount recovered in receptor fluid, the receptor compartment wash, and the dermis.

² Absorbed dose II is calculated from the absorbed dose I, plus the epidermis (without *stratum corneum*). The absorbed dose II can be considered conservative.

³ Absorbed dose III is calculated from the absorbed dose II plus the *stratum corneum* (excluding tape strips 1 and 2). The absorbed dose III can be considered highly conservative.

EFSA Calculator

Results and discussion				
	Concentrate		Dilution 1	
			(1:250)	
Target concentration [mg/mL]	0		0.363	
Target dose [$\mu\text{g}/\text{cm}^2$]	0		3.63	
Mean actual applied dose [$\mu\text{g}/\text{cm}^2$]			3.23	
Recovery [%]	Mean	SD	Mean	SD
<u>Dislodgeable dose</u>				
Skin wash after 8 and 24 hours	N/A	N/A	87.71	4.85
Donor chamber wash	N/A	N/A	0.19	0.12
<u>Skin associated dose</u>				
Tape strips 1-2	N/A	N/A	1.86	2.00
Tape strips 3-x	N/A	N/A	1.49	1.29
Skin preparation	N/A	N/A	2.79	1.45
<u>Absorbed dose</u>				
Receptor fluid	N/A	N/A	8.16	3.43
Receptor chamber wash	N/A	N/A	0.41	0.21
Total recovery	#DIV/0!	#DIV/0!	99.18	1.34
LLC of t _{0.5} absorption	#DIV/0!	N/A	28.75	7.62
Absorption complete?	#DIV/0!		No	
Measured absorption, if LLC of t _{0.5} ≤ 75%	#DIV/0!	#DIV/0!	12.85	4.38
Measured absorption, if LLC of t _{0.5} > 75%	#DIV/0!	#DIV/0!	N/A	N/A
Measured absorption corrected	#DIV/0!	#DIV/0!	11.53	2.49
Relevant absorption estimate	#DIV/0!		13.824	
Final estimate (rounded)	#DIV/0!		14	

A 2.12.2 Fenpicoxamid, dermal absorption study using in vitro human skin

Comments of zRMS:	The study was reviewed and approved for initial registration (please refer to the Registration Report (RR), Part B, Section 6: Mammalian Toxicology; Product code: GF-3307, dated January 2023). Since the study results remain valid, the zRMS PL did not conduct a second review.
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Reference	KCP 7.3/2
Report	Whitfield, C.; 2021; GF-3307: In Vitro Percutaneous Absorption of Fenpicoxamid in Human Skin; Haskell R&D Center, E.I. du Pont de Nemours and Company, Member of the Corteva Agriscience Group of Companies, Newark, Delaware, U.S.A.; Lab Study No. 22369-1377; DAS Study No. 200109 ; 29 January 2021; Unpublished
Guideline(s)	Yes: OECD 428 (2004)
Deviations	None
GLP	Yes
Acceptability	Yes

Duplication No
(if vertebrate study)

MATERIALS AND METHODS

Test item(s)

Test item (Common name): GF-3307 (Formulation)
Purity: 4.7 wt% (49 g/L) fenpicoxamid; 9.7 wt% (101 g/L) prothioconazole
Description (physical state): Liquid
Lot/batch no.: MAR19CE01Q (TSN400550)

Test item (Common name): Fenpicoxamid (Active Ingredient)
Purity: 82.8%
Description (physical state): Solid
Lot/batch no.: XDE-777-01-02 (TSN303159)

Test item (Common name): XDE-777-pyr-2-14C (Radiolabeled Active Ingredient)
Purity: 99.8% (Radiochemical Purity)
Description (physical state): Solid
Lot/batch no.: INV-175292-066 (INV403689)

Study Design

The study was designed to examine the *in vitro* dermal absorption of [¹⁴C]Fenpicoxamid formulated as GF-3307 formulation through human skin following an 8 hour dermal exposure to a single, finite application. The test preparation was tested at two target concentrations: 50 g.L⁻¹ (as concentrate) and 0.2 g.L⁻¹ (aqueous spray dilution; 1:250). The study design is summarised below.

Table 22: In vitro dermal absorption from GF-3307: study design

Test group	No. of replicates*	Species	Target concentration of Fenpicoxamid (g.L ⁻¹)	Target dose of Fenpicoxamid (µg.cm ⁻²)	Exposure duration	Serial sampling time points
A	8 ^a	Human	50	500	8 h	0-24 h
B	8	Human	0.2	2	8 h	0-24 h

*2 replicates were from each 4 donors.

^a One replicate excluded due to expected damage to skin at dosing.

Preparation of skin membranes

Human skin membranes were prepared in duplicate from four separate donors (n=8).

After thawing the frozen skin samples, the skin was dermatomed using a dermatome to a recorded thickness of *ca* 0.2-0.4 mm measured with a digimatic micrometer.

Integrity of the skin membranes

The integrity of each skin was assessed by measurement of electrical resistance prior to application of test substance. Skin was hydrated in 0.9% saline for approximately 15 minutes at room temperature. Following hydration, the skin was mounted onto the top of the receptor chamber, which was filled with 0.9% saline. The donor chamber was then clamped in place and filled with 0.9% saline. The skin was then allowed to equilibrate for approximately 30 minutes. Following equilibration, a resistance measurement of each skin membrane was taken using a Tinsley 6401 Databridge set in the resistance (R) and parallel equivalent (PAR) modes at an alternating current (AC) frequency of 1000 Hertz (1 kHz). Skin with a resistance of $\geq 17 \text{ k}\Omega$ was considered intact and retained for use on study. Skin not meeting these criteria was replaced, and electrical resistance confirmed following equilibration. This procedure was followed until 8 skin preparations represented by 4 individuals (2 replicates per donor) per dose concentration was achieved. Following the electrical resistance measurement, saline in the donor chamber was removed and discarded. The skin was rinsed with deionized water and dried with a lint-free wipe. Saline in the receptor chamber was removed and replaced with the receptor fluid.

Solubility in the receptor fluid

The solubility of fenpicoxamid in the receptor fluid ($\geq 31.7 \text{ }\mu\text{g.mL}^{-1}$) was observed to be at least 10-fold higher than the maximum concentration achieved in the receptor fluid, ensuring the receptor fluid offered sink conditions to fenpicoxamid and was not rate limiting to passive diffusion. The maximum penetration of fenpicoxamid into the receptor fluid was $0.00264 \text{ }\mu\text{g equivalents.mL}^{-1}$ (Cell 3, Group A).

In addition, in the flow through cells used, the volume of the receptor fluid in the receptor chamber beneath the skin was ca 0.7 mL. At a flow rate of ca 1.5 mL.h^{-1} , this volume was replenished continuously such that the rate of diffusion into the receptor fluid did not become a rate limiting step in the experiment.

Study conduct and sample collection

The study was performed in flow-through diffusion cells (PermeGear Inc., Hellertown, Pennsylvania, USA). The prepared formulations were applied to each skin surface (0.64 cm^2), via the donor chamber, at a rate of $10 \text{ }\mu\text{L.cm}^{-2}$. The dose was distributed evenly over the exposure area using a glass rod. The donor chamber remained unoccluded for the duration of the study. The exposed area of each skin (0.64 cm^2) remained in contact with the test item for a period of 8 h (normal working h.day^{-1}) with a post-exposure time of 16 h (*i.e.*, the total study duration was 24 h). Skin washing was performed at the end of both the contact (at 8 h) and post-exposure (at 24 h) periods. Skins were then removed from the cells and tape-stripped up to 15 times each to remove the *stratum corneum*. The tape stripped skin was then placed on an aluminum pan and heated in an oven at approximately 55°C for approximately one minute and 45 seconds. The epidermis was then peeled away from the dermis using a scalpel and/or forceps. Epidermis and dermis samples were collected in separate vials for analysis. The donor and receptor compartments were rinsed to collect any remaining test material.

In order to determine the recovery, the amount of fenpicoxamid was measured by liquid scintillation counting in the following samples:

- a. test concentrations
- b. spreader device rinses
- c. receptor fluid samples collected as: 0-1 h, 1-2 h followed by 2-h intervals until 24 h after application
- d. skin washes at 8 h and 24 h, separately
- e. the *stratum corneum* (SC) (ca 15 tape strips, individually analyzed)

- f. the dermis and epidermis (without SC), separately
- g. receptor and donor compartments rinse, separately

RESULTS AND DISCUSSION

The absorbed dose of fenpicoxamid from the GF-3307 undiluted concentrate and its aqueous spray dilution are calculated based on guidance from different regulatory bodies and are presented below:

Table 23: Absorbed doses

Absorbed dose	Concentrate (50 g.L ⁻¹) (undiluted)	Aqueous spray dilution (0.2 g.L ⁻¹) (1:250)
Absorbed dose I ¹	0.022 ± 0.005	0.40 ± 0.12
Absorbed dose II ²	0.10 ± 0.07	3.35 ± 2.33
Absorbed dose III ³	0.21 ± 0.13	8.14 ± 4.16

¹ Absorbed dose I = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, and dermis

² Absorbed dose II = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis, and epidermis (without *stratum corneum*).

³ Absorbed dose III = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis, epidermis, and *stratum corneum* (excluding the first 2 tape strips).

The mean total recovery of [¹⁴C]Fenpicoxamid in human skin was 99.03 ± 1.78% (concentrate) and 101.04 ± 3.02% (aqueous spray dilution).

For the concentrate, absorption was 0.022 ± 0.005% (absorbed dose I), or 0.10 ± 0.07% (absorbed dose II) or 0.21 ± 0.13% (absorbed dose III) of the applied dose.

For the aqueous spray dilution, absorption was 0.40 ± 0.12% (absorbed dose I), or 3.35 ± 2.33% (absorbed dose II) or 8.14 ± 4.16% (absorbed dose III) of the applied dose.

Dermal absorption and total recovery data for each test group is summarised in the following table.

Table 24: Total recoveries and dermal absorption of [¹⁴C]Fenpicoxamid from GF-3307 and its aqueous spray dilution through human skin

		A – Concentrate (undiluted)		B – Aqueous spray dilution (1:250)	
Total concentration [g.L ⁻¹]	50		0.2		
Dose [μg.cm ⁻²]	500		2		
N	7 ^a		8		
Cumulative penetration into the receptor fluid	% of dose	μg equiv. cm ⁻² h ⁻¹	% of dose	μg equiv. cm ⁻² h ⁻¹	
after 12 h	--	0.0259±0.0067	--	0.00158±0.00132	
after 24 h	0.0097±0.0018	0.0481±0.0086	0.18±0.10	0.00300±0.00177	
Maximal flux [μg equiv. cm ⁻² h ⁻¹]	0.00335±0.00181		0.00018±0.00016		
Lag time [h]	2.8±2.7		2.1±2.1		
Recovery of [¹⁴ C]Fenpicoxamid (% of dose, mean ± SD)					
Receptor fluid (0-24 h)	0.0097±0.0018		0.18±0.10		
Receptor compartment wash	0.0016±0.0005		0.048±0.013		
Dermis	0.011±0.007		0.16±0.05		
Stratum corneum (SC) Total	0.33±0.15		10.70±3.38		
Tape strips (1-2)	0.23±0.12		5.91±3.39		
Tape strips (3 – 15)	0.12±0.09		4.79±1.90		
Epidermis	0.081±0.068		2.96±2.28		
Skin wash t = 8 h	98.11±1.83		78.17±5.35		
Skin wash t = 24 h	0.45±0.08		8.21±2.96		
Donor compartment wash	0.045±0.033		0.61±0.29		
Total recovery	99.03±1.78		101.04±3.02		

a One replicate excluded due to expected damage to skin at dosing.

CONCLUSION

The percent dermal absorption values for fenpicoxamid are:

Absorbed dose	Concentrate (50 g.L ⁻¹) (undiluted)	Aqueous spray dilution (0.2 g.L ⁻¹) (1:250)
Absorbed dose I ¹	0.022 ± 0.005	0.40 ± 0.12
Absorbed dose II ²	0.10 ± 0.07	3.35 ± 2.33
Absorbed dose III ³	0.21 ± 0.13	8.14 ± 4.16

¹ Absorbed dose I = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, and dermis

² Absorbed dose II = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis, and epidermis (without *stratum corneum*).

³ Absorbed dose III = Percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis, epidermis, and *stratum corneum* (excluding the first 2 tape strips).

EFSA Calculator

There was one replicate out of 8 in the in vitro dermal absorption study with the concentrate that was excluded in the study report since there was damage to the skin while dosing. This explanation is included on the summary page of the Excel spreadsheet, column E row 11. In calculations in the report, the replicate was excluded but in the spreadsheet the replicate could not be excluded. If the replicate is excluded then the spreadsheet value would match the report value.

It appears that even though the replicate is excluded in the calculator, the calculation for the receptor fluid continues to include that replicate. If you select the receptor fluid values for the 7 valid replicates, the average is 0.0097. When all 8 replicates are included the average is the 0.73 and this is the value that the EFSA calculator reports.

E	F	G	H	I	J	K	L	M	N	O	P
Tested doses							Results and discussion				
								Concentrate		Dilution 1	
										(1.250)	
Target concentration [mg/mL]	50	0.2					Target concentration [mg/mL]	50		0.2	
Surface area dose [$\mu\text{g}/\text{cm}^2$]	500	2					Target dose [$\mu\text{g}/\text{cm}^2$]	500		2	
Total dose [$\mu\text{g}/\text{cell}$]	320	1.28					Mean actual applied dose [$\mu\text{g}/\text{cm}^2$]	499		1.63	
Specific activity [kBq/mL]	3220	265.6					Recovery [%]	Mean	SD	Mean	SD
No. of donors	5	4					Dislodgeable dose				
No. of replicates used/valid replicates*	8/7	8/8					Skin wash after 8 and 24 hours	97.54	3.34	85.84	2.72
* One replicate was excluded due to damage to the skin at dosing.							Donor chamber wash	0.04	0.03	0.61	0.29
							Skin associated dose				
							Tape strips 1-2	0.21	0.11	5.91	3.39
							Tape strips 3-x	0.12	0.08	4.79	1.90
							Skin preparation	0.09	0.07	3.12	2.32
							Absorbed dose				
							Receptor fluid	0.73	2.05	0.18	0.10
							Receptor chamber wash	0.03	0.08	0.05	0.01
							Total recovery	99.03	1.78	100.50	3.11
							LLC of t _{0.5} absorption	49.11	4.15	40.33	9.23
							Absorption complete?	No		No	
							Measured absorption, if LLC of t _{0.5} ≤ 75%	0.96	2.12	8.14	4.16
							Measured absorption, if LLC of t _{0.5} > 75%	N/A	N/A	N/A	N/A
							Measured absorption corrected	0.21	0.13	8.14	4.16
							Relevant absorption estimate	0.330		11.640	
							Final estimate (rounded)	0.33		12	
							Remarks				
							Add your remarks here.				

A 2.12.3 ~~Fenpicoxamid~~, Prothioconazole dermal absorption study using *in vitro* human skin

Comments of zRMS:	<p>Dermal absorption study on prothioconazole has been conducted according to the OECD TG 428 revision 2004. For testing human split thickness skin has been used. There were no deviations from the TG.</p> <p>Highest spray dilution according to the GAP (refer dRR B0) which is corresponding to 0.4 g prothioconazol/L (1:250) was tested, then the in-use dilution is covered by the dilution tested in the study, and no pro-rata correction is required. DA for the in use-dilution was found to be 14%.</p> <p>Results of the DA study and conclusions are adequate for risk assessment (NDE) Study accepted.</p>
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REFERENCE

KCP 7.3/3

CITATION

Maas, W. J. M.; 2023; GF-3307: *In Vitro* Percutaneous Absorption of Prothioconazole in Human Skin; Charles River Laboratories Den Bosch BV, Hambakenwetering 7, Hertogenbosch, The Netherlands ; Lab Study No. 20391368; Sponsor Study No. 220958 ; 04 July 2023; Published: No

COMPLIANCE

Guideline(s):	OECD 428 (2004); OECD Environmental Health and Safety Publication Series on Testing and Assessment Number 28 (2004); Guidance on Dermal Absorption; Guidance on Dermal Absorption (EFSA Journal, 2017
US EPA Guideline(s):	None
Guideline Deviations:	None
Dates of work:	12 September 2022 to 10 March 2023
GLP status:	Yes
Number of pages in final report:	131

MATERIALS AND METHODS

Test item(s)

Test item (common name):	Prothioconazole
Purity:	98.9%
Description (physical state):	White crystalline powder
Lot/batch no.:	NK61EX0988 TSN316434
Test item (common name):	Fenpicoxamid
Purity:	77.5 wt%
Description (physical state):	Orange lumps
Lot/batch no.:	XDE-777-01-02 TSN303159
Test item (common name):	Prothioconazole-triazole-3,5-14C
Purity:	99.8%

Description (physical state): Solution in acetonitrile
Lot/batch no.: 236419_Prothioc_BX1_DEC22 NA

Test item (common name): GF-3307
Purity: 4.8 wt% (50 g.L-1) Fenpicoxamid; 9.6 wt% (101 g.L-1) Prothioconazole

Description (physical state): Brown liquid
Lot/batch no.: OCT21CE005 & S7K-3-3-19 NA

Study Design

The study was designed to examine the *in vitro* dermal absorption of [¹⁴C]prothioconazole, formulated as GF-3307 in 24 hours through human skin following an 8-hour dermal exposure to a single, finite application. The test preparation was tested at two target concentrations: 100 g/L (as concentrate), and 0.4 g/L (as spray dilution; 1:250). The concentrate represents the maximum concentration possible when handling the undiluted formulation (*e.g.*, during mixing and loading), while the spray dilution reflects the concentration recommended for use in the field (*i.e.*, in-use spray dilution). The objective of the study was to elucidate the extent of dermal absorption of the compound-related radioactivity. The study design is summarised below.

Table 25: In vitro dermal absorption from GF-3307: study design

Test group	No. of replicates*	Species	Target concentration of Prothioconazole (g/L)	Target dose of Prothioconazole (µg/cm ²)	Exposure duration	Serial sampling time points
A	8	Human	100	1000	8 h	0-24 h
B	8	Human	0.4	4.0	8 h	0-24 h

Preparation of skin membranes

Human skin membranes were prepared in duplicate from at least four separate donors (n=8). Two experiments were performed with the concentrate formulation. In both experiments, 8 samples of human split-thickness skin membranes obtained from 4 different donors were dosed topically with the undiluted concentrate.

The skin was removed from the freezer and allowed to thaw to room temperature. The skin was cut to a thickness of *ca.* 200-400 µm using an electric dermatome. The thickness of the skin was confirmed using a micrometer.

Integrity of the skin membranes

The skin integrity was tested by permeation of tritiated water. Tritiated water (250 µL/cm², 25.3 kBq/mL in Exp. 1 and 26.4 kBq/mL in Exp. 2) was applied to the skin and the donor compartment of the flow-through cells occluded. The absorption of tritiated water was assessed over 1 h by collecting a single 1 h fraction of receptor fluid. At the end of the 1 h period, residual tritiated water remaining at the donor compartment was removed with a pipette and the skin was dried with two cotton swabs. Subsequently the skin was washed with 500 µL water and dried with one cotton swab, this washing procedure was repeated once. The receptor fluid samples were analyzed by LSC. Tritiated water absorption (% applied dose) was

calculated from the LSC data for each skin sample. Any skin sample exhibiting absorption >1.6% of the applied dose, was excluded from subsequent absorption measurements.

Solubility in the receptor fluid

The receptor fluid chosen for use in this study was saline (0.9% NaCl) containing bovine serum albumin (5%, w/v), sodium azide (0.01%, w/v), streptomycin (0.1 mg/mL) and penicillin G (100 units/mL). The pH was checked and adjusted to pH 7.4. For the assessment of the skin barrier integrity, saline (0.9%, w/v) NaCl in water) was used.

In order to confirm adequate solubility of prothioconazole in the receptor fluid, prothioconazole technical (10 mg/mL, dissolved in ACN) and [¹⁴C]prothioconazole, (dissolved in ACN), were added to a brown 3 mL glass vial (*ca.* 5 mg total amount of test item). After mixing, the solvent was evaporated. Subsequently, 500 µL ACN was added and after 2 minutes of sonication, the radioactive concentration was determined by taking three 10 µL samples and analyzing them using liquid scintillation counting (LSC). From the same solution, 50 µL samples (in triplicate) were transferred to glass 16×100 vials and the solvent was evaporated. Subsequently, 5 mL of receptor fluid was added to a final concentration of *ca.* 100 µg/mL. The solution was gently mixed for *ca.* 1 h at 32°C and subsequently centrifuged at 2000×g for 5 minutes. From the supernatant, three samples from the top, the middle, and the bottom of the vial were analyzed by LSC to determine the amount of radioactivity.

The solubility of prothioconazole in the receptor fluid was 19.3 ± 13.2 µg/mL. The maximum absorption rate (flux) into the receptor fluid was 0.031 µg equiv./cm²/h (Cell 10, test preparation 1, Exp.2), which corresponds to $(0.031 \text{ µg equiv.} \times 0.64)/(1 \text{ h} \times 1.5 \text{ mL/h}) = 0.013$ µg/mL. Therefore, the solubility of the test material in the receptor fluid was demonstrated to be adequate and not rate-limiting to the absorption process.

Furthermore, in the flow-through cells used, the volume of the receptor fluid in the receptor chamber beneath the skin was *ca.* 0.25 mL. At a flow rate of *ca.* 1.5 mL/h, this volume was replenished continuously (6 times per h) such that the rate of diffusion into the receptor fluid did not become a rate-limiting step (i.e. sink conditions were maintained).

Study conduct and sample collection

The study was performed in flow through diffusion cells (McGregor/Toner cells, CRL, Edinburgh, Scotland). The prepared formulations were applied to each skin surface (6.4 µL), via the donor chamber, at a rate of 10 µL/cm². The dose was applied evenly over the exposure area using a positive displacement pipette. The donor chamber remained unoccluded for the duration of the study. The exposed area of each skin (0.64 cm²) remained in contact with the test item for a period of 8 h (normal working h/day) with a post exposure time of 16 h (i.e., the total study duration was 24 h). Skin washing was performed at the end of both the contact (at 8 h) and post exposure (at 24 h) periods. The stratum corneum was removed with a maximum of 20 successive tape strips. The skin sample was rotated 90° after each tape strip. Rotation was stopped if the epidermis/dermis junction became fragile or if the epidermis was removed. The skin under the cell flange (unexposed skin) was cut away from the exposed skin. The exposed skin was separated in epidermis and dermis by scraping. The exposed (epidermis and dermis, separately) and non-exposed skin samples were digested individually in Solvable® (2 mL). All skin samples were placed in an incubator set to *ca.* 60°C to aid solubilization overnight. Stannous chloride solution (0.2 g/mL in ethanol; 150 µL) and scintillation cocktail was added and total radioactivity was analyzed by LSC. The donor and receptor compartments were extracted and cleaned, respectively, to collect any remaining test item.

In order to determine the recovery, the amount of [^{14}C]prothioconazole was measured by liquid scintillation counting in the following samples:

- test concentrations
- receptor fluid samples collected as: 0-1 h, 1-2 h followed by 2-h intervals until 24 h after application
- residues remaining in the *stratum corneum* (SC) (ca 20 tape strips, individually analysed)
- residues remaining in dermis and epidermis (without SC), separately
- receptor and donor compartments rinse, separately
- skin membrane washes at 8 h and 24 h, separately
- unexposed skin

RESULTS AND DISCUSSION

The absorbed dose of prothioconazole from the GF-3307 formulation and its spray dilution are calculated based on guidance from different regulatory bodies and are presented below:

Table 26: Absorbed doses

Absorbed dose	Concentrate (100 g/L) (undiluted)	Spray dilution (0.4 g/L) (1:250)
Absorbed dose I ¹	0.11 ± 0.06	2.95 ± 1.53
Absorbed dose II ²	0.15 ± 0.08	5.09 ± 1.94
Absorbed dose III ³	0.42 ± 0.33	11.3 ± 2.90

¹ Absorbed dose I is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, and dermis.

² Absorbed dose II is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis and epidermis (without stratum corneum).

³ Absorbed dose III is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis and epidermis, and stratum corneum (excluding the first 2 tape strips).

The mean total recovery of prothioconazole in human skin was 99.7 ± 4.8% (concentrate), and 97.6 ± 2.2% (spray dilution).

For the concentrate, absorption was 0.11 ± 0.06% (absorbed dose I), or 0.15 ± 0.08% (absorbed dose II), or 0.42 ± 0.33% (absorbed dose III) of the applied dose.

For the spray dilution, absorption was 2.95 ± 1.53% (absorbed dose I), or 5.09 ± 1.94% (absorbed dose II), or 11.3 ± 2.9% (absorbed dose III) of the applied dose.

Dermal absorption and total recovery data for each test group is summarised in the following table.

Table 27: Total recoveries and dermal absorption of [^{14}C]Prothioconazole from GF-3307 and its spray dilution through human skin

	A – Concentrate (undiluted)		B – Spray dilution	
Target total concentration [g/L]	100		0.40	
Target dose [μg/cm²]	1000		4.0	
N	9 ^a		8	
Cumulative penetration into the receptor fluid	% of dose	ng/cm²	% of dose	ng/cm²
after 12 h	0.018 ± 0.005	177 ± 50	1.50 ± 0.49	64.8 ± 21.2
after 24 h	0.034 ± 0.010	334 ± 99	1.95 ± 0.54	84.4 ± 23.0
Maximal flux [ng/cm²/h]	26.8 ± 2.4		12.6 ± 4.5	
Lag time [h]	-		-	
Recovery of [¹⁴ C]Prothioconazole (% of dose, mean ± SD)				
Receptor fluid (0-24 h)	0.034 ± 0.010		1.95 ± 0.54	
Dislodgeable Dose 8 h	98.2 ± 4.8		79.0 ± 6.2	
Dislodgeable Dose 24 h	0.34 ± 0.19		4.11 ± 2.54	
Total Dislodgeable Dose	99.0 ± 4.8		84.5 ± 4.1	
Receptor compartment wash	0.008 ± 0.006		0.054 ± 0.015	
Dermis	0.073 ± 0.053		0.94 ± 1.28	
Tape strip total	0.53 ±0.60		7.78 ± 3.24	
Tape strips (1-2)	0.26 ± 0.31		1.53 ± 1.28	
Tape strips (3 – last)	0.27 ± 0.30		6.25 ± 2.17	
Unexposed skin	0.078 ± 0.073		0.20 ± 0.19	
Epidermis	0.040 ± 0.032		2.14 ± 0.64	
Donor chamber wash	0.45 ± 0.38		1.40 ± 1.38	
Total recovery	99.7 ± 4.8		97.6 ± 2.2	

a Two experiments were performed; four cells in Exp. 1 and two cells in Exp. 2 were excluded from the calculations related to a (very) high recovery in the unexposed skin, probably due to leakage from the donor compartment which also resulted in a low overall mass balance. In addition, one cell in Exp. 2 was excluded from the calculations since it was reported damaged prior to the 24 h wash and showed a notably higher absorption (outlier based on Dixon's Q-test at 95% confidence level). As a result, in total 9 evaluable membranes remained. Mean results are calculated across experiment 1 and 2.

CONCLUSION

The percent dermal absorption values for prothioconazole are:

Total concentration [g/L]	Concentrate (100 g/L) (undiluted)	Spray dilution (0.4 g/L) (1:250)
Absorbed dose I ¹	0.11 ± 0.06	2.95 ± 1.53
Absorbed dose II ²	0.15 ± 0.08	5.09 ± 1.94
Absorbed dose III ³	0.42 ± 0.33	11.3 ± 2.90

¹ Absorbed dose I is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, and dermis.

² Absorbed dose II is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis and epidermis (without stratum corneum).

³ Absorbed dose III is calculated from the percentage of applied dose detected in the receptor fluid, receptor chamber wash, dermis and epidermis, and stratum corneum (excluding the first 2 tape strips).

A 2.13 Other/Special Studies

No further studies were conducted on GF-3307.

Appendix 3 Exposure calculations

Exposure calculations performed according to EFSA online OPEX calculator
(<https://r4eu.efsa.europa.eu/app/opex v 1.0.1>):



GF-3307_20240312_
14h02_opex1.0.1.zip



GF-3307_20240312.
docx

Information on product and active substance(s)

Product name	GF-3307
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Product category	Other
Name of active substance	Fenpicoxamid
Concentration of active substance [g a.s./l or kg]	50
AOEL [mg/kg bw/day]	0.05
AAOEL [mg/kg bw]	0.2
Inhalation absorption [%]	100
Oral absorption [%]	12
Dermal absorption [%] (concentrate)	0.33
Dermal absorption [%] (dilution) 0.2 [g a.s./l or kg]	12
Name of active substance	Prothioconazole
Concentration of active substance [g a.s./l or kg]	100
AOEL [mg/kg bw/day]	0.2
AAOEL [mg/kg bw]	
Inhalation absorption [%]	100
Oral absorption [%]	100
Dermal absorption [%] (concentrate)	0.68
Dermal absorption [%] (dilution) 0.4 [g a.s./l or kg]	14
Name of active substance	Prothioconazole-desthio
Concentration of active substance [g a.s./l or kg]	90.7
AOEL [mg/kg bw/day]	0.01
AAOEL [mg/kg bw]	
Inhalation absorption [%]	100
Oral absorption [%]	100
Dermal absorption [%] (concentrate)	0
Dermal absorption [%] (dilution) 0.363 [g a.s./l or kg]	14

Assessed uses

Use	Crops	Max. application rate of the product [l or kg/ha]	Unit	Max. no. of applications	Interval between multiple applications [days]	Min. volume water [l/ha]	Max. volume water [l/ha]	Indoor/outdoor	Application method	Type of cultivation	Application technique	Buffer strip [m]	Drift reduction [%]
Use 1	Low vegetables	1.5	l/ha	2	21	150	300	Outdoor	Downward spraying	Normal	Vehicle-mounted	2-3	0

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

Use 1: Low vegetables

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

Summary data - short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
Fenpicoxamid	Number of applications and application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %		
	M/L: Workwear App: Workwear	0.002	4.7
Prothioconazole	Number of applications and application rate: 2 x 0.15 kg a.s./ha Dermal absorption (concentrate): 0.68 % Dermal absorption (in-use dilution): 14 %		
	M/L: Workwear App: Workwear	0.006	3.1
Prothioconazole-desthio	Number of applications and application rate: 2 x 0.13605 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 14 %		
	M/L: Workwear App: Workwear	0.003	26

Summary data - acute exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw]	% of systemic AAOEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/95th percentile Crop density: Normal			
Fenpicoxamid	Number of applications and application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %		
	M/L: Workwear App: Workwear	0.02	8.2

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

Use 1: Low vegetables; Reaching, picking

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Reaching, picking (all except Brassica) / Outdoor Work rate: 8 hours/day Interval: 21 days Body weight: 60 kg TC (potential): 5800 cm ² /h TC (workwear (arms, body and legs covered)): 2500 cm ² /h TC (workwear (arms, body and legs covered) and gloves): 580 cm ² /h TC (gloves): NA cm ² /h			
Fenpicoxamid Number of applications & application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.03	67.7	0
Workwear	0.01	29.2	0
Workwear and gloves	0.003	6.8	0
Hands covered, no workwear			
Prothioconazole Number of applications & application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.08	39.5	0
Workwear	0.03	17	0
Workwear and gloves	0.008	3.9	0
Hands covered, no workwear			
Prothioconazole-desthio Number of applications & application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.07	716	86
Workwear	0.03	309	49
Workwear and gloves	0.007	71.6	0
Hands covered, no workwear			

Use 1: Low vegetables; Inspection, irrigation

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation (All) / Outdoor Work rate: 2 hours/day Interval: 21 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			
Fenpicoxamid Number of applications & application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			
Potential	0.02	36.5	0
Workwear	0.002	4.1	0
Workwear and gloves	0.002	3.6	0
Hands covered, no workwear			
Prothioconazole Number of applications & application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days			

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Potential	0.04	21.3	0
Workwear	0.005	2.4	0
Workwear and gloves	0.004	2.1	0
Hands covered, no workwear			
Prothioconazole-desthio <div> Number of applications & application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days </div>			
Potential	0.04	386	59
Workwear	0.004	43.2	0
Workwear and gloves	0.004	38.6	0
Hands covered, no workwear			

Use 1: Low vegetables; Removing bolting sugar beets

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
removing bolting sugar beets / Outdoor Work rate: 8 hours/day Interval: 21 days Body weight: 60 kg TC (potential): 18600 cm²/h TC (workwear (arms, body and legs covered)): 4400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 430 cm²/h TC (gloves): 14300 cm²/h			
Fenpicoxamid <div> Number of applications & application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days </div>			
Potential	0.1	217	34
Workwear	0.03	51.3	0
Workwear and gloves	0.003	5	0
Hands covered, no workwear	0.08	167	23
Prothioconazole <div> Number of applications & application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days </div>			
Potential	0.3	127	11
Workwear	0.06	29.9	0
Workwear and gloves	0.006	2.9	0
Hands covered, no workwear	0.2	97.3	0
Prothioconazole-desthio <div> Number of applications & application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days </div>			
Potential	0.2	2296	136
Workwear	0.05	543	74
Workwear and gloves	0.005	53.1	0
Hands covered, no workwear	0.2	1765	125

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

Resident - Use 1 : Low vegetables

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: 21 days Minimum volume of water: 150 l			
Number of applications and application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Fenpicoxamid			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.002	3.3
	Vapour (75th perc.)	0.0008	1.6
	Deposits (75th perc.)	0.0002	0.4
	Re-entry (75th perc.)	0.002	4.9
	Sum (mean)	0.004	7.6
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0004	0.8
	Vapour (75th perc.)	0.0003	0.5
	Deposits (75th perc.)	0.0001	0.2
	Re-entry (75th perc.)	0.001	2.7
	Sum (mean)	0.002	3.2
Number of applications and application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.004	1.9
	Vapour (75th perc.)	0.0008	0.4
	Deposits (75th perc.)	0.0007	0.3
	Re-entry (75th perc.)	0.006	2.9
	Sum (mean)	0.008	4
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0009	0.5
	Vapour (75th perc.)	0.0003	0.1
	Deposits (75th perc.)	0.0002	0.1
	Re-entry (75th perc.)	0.003	1.6
	Sum (mean)	0.003	1.7
Number of applications and application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Prothioconazole-desthio			
Resident child Body weight: 10 kg	Drift (75th perc.)	0.003	34.5
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.0006	6.3
	Re-entry (75th perc.)	0.005	52.1
	Sum (mean)	0.007	73
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0008	8.2
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0002	2.1
	Re-entry (75th perc.)	0.003	28.9
	Sum (mean)	0.003	31.1

Bystander - Use 1 : Low vegetables

Scenario 1 : Outdoor, season not relevant

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AAOEL
Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: 21 days Minimum volume of water: 150 l			
Number of applications and application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Fenpicoxamid	Drift (95th perc.)	0.004	1.9
	Vapour (95th perc.)	0.0008	0.4
	Deposits (95th perc.)	0.0007	0.3
	Re-entry (95th perc.)	0.002	1.2
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.001	0.5
	Vapour (95th perc.)	0.0003	0.1
	Deposits (95th perc.)	0.0003	0.1
	Re-entry (95th perc.)	0.001	0.7

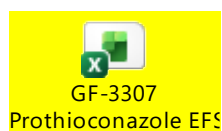
A 3.4 Combined exposure calculations for fenpicoxamid and prothioconazole

No further calculations are needed. All details are provided in chapter 6.2.3 .

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)

Not applicable.

The DA calculation data (BfR Excel table) can be found in the attached document and summarised in the table below.



	Concentrate		Dilution 1	
Target concentration [mg/mL]	100		0.4	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 hours	84.37	24.46	83.14	5.12
Donor chamber wash	7.77	11.79	1.60	1.35
Skin associated dose				
Tape strips 1-2	0.87	1.58	1.53	1.28
Tape strips 3-x	1.02	1.57	6.25	2.17
Skin preparation	1.30	2.29	3.08	1.78
Absorbed dose				
Receptor fluid	0.11	0.22	1.95	0.53
Receptor chamber wash	0.54	1.22	0.05	0.02
Total recovery	99.71	4.76	97.61	2.19
LLC of t 0.5 absorption	49.85	2.98	71.84	4.25
Absorption complete?	No		No	
Measured absorption, if LLC of t 0.5 ≤ 75%	2.96	4.33	11.34	2.87
Measured absorption, if LLC of t 0.5 > 75%	N/A	N/A	N/A	N/A
Measured absorption corrected	0.42	0.33	11.34	2.87
Relevant absorption estimate	0.676		13.747	
Final estimate (rounded)	0.68		14	

Appendix 5 New: Exposure calculations

New: In August 2025, EFSA published the peer review conclusions (EFSA Journal. 2025;23:e9593), in which a lower AOEL value was proposed for prothioconazole and new AAOEL values were proposed for both prothioconazole and prothioconazole-desthio. These values are not yet formally adopted in the European Union. However, at the request of the zRMS (PL) (December 2025), updated exposure assessments are provided considering the new (A)AOEL values.

Exposure calculations performed according to EFSA online OPEX calculator
<https://r4eu.efsa.europa.eu/app/opex> v 1.1.3:

Information on product and active substance(s)

Product name	GF-3307 (S7K-3-3)
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Product category	Other
Name of active substance	Fenpicoxamid
Concentration of active substance in product [g a.s./l or kg]	50
AOEL [mg/kg bw per day]	0.05
AAOEL [mg/kg bw]	0.2
Inhalation absorption [%]	100
Oral absorption [%]	12
Dermal absorption [%] (concentrate)	0.33
Dermal absorption [%] (dilution) 0.2 [g a.s./l or kg]	12
Name of active substance	Prothioconazole
Concentration of active substance in product [g a.s./l or kg]	100
AOEL [mg/kg bw per day]	0.036
AAOEL [mg/kg bw]	0.2
Inhalation absorption [%]	100
Oral absorption [%]	100
Dermal absorption [%] (concentrate)	0.68
Dermal absorption [%] (dilution) 0.4 [g a.s./l or kg]	14
Name of active substance	Prothioconazole-desthio
Concentration of active substance in product [g a.s./l or kg]	90.7
AOEL [mg/kg bw per day]	0.01
AAOEL [mg/kg bw]	0.01
Inhalation absorption [%]	100
Oral absorption [%]	100
Dermal absorption [%] (concentrate)	0
Dermal absorption [%] (dilution) 0.363 [g a.s./l or kg]	14

Assessed uses

Use	Crops	Max. application rate of the product [l or kg/ha]	Unit	Max. no. of applications	Interval between multiple applications [days]	Min. volume water [l/ha]	Max. volume water [l/ha]	Indoor/outdoor	Application method	Type of cultivation	Application technique	Buffer strip [m]	Drift reduction [%]
Use 1	Low vegetables	1.5	l/ha	2	21	150	300	Outdoor	Downward spraying	normal	Vehicle-mounted	2-3	0
Use 1	Low vegetables	1.5	l/ha	2	21	150	300	Outdoor	Downward spraying	normal	Vehicle-mounted	2-3	50

A 5.1 New Operator exposure calculations (KCP 7.2.1.1)

Use 1: Low vegetables

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

Summary data - short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0% Crop density: Normal			
Fenpicoxamid	Application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %		
	M/L: Workwear App: Workwear	0.002	4.7
	M/L: Potential exposure App: Potential exposure	0.003	6.9
Prothioconazole	Application rate: 2 x 0.15 kg a.s./ha Dermal absorption (concentrate): 0.68 % Dermal absorption (in-use dilution): 14 %		
	M/L: Workwear App: Workwear	0.006	17.4
	M/L: Potential exposure App: Potential exposure	0.01	26.4
Prothioconazole-desthio	Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 14 %		
	M/L: Workwear App: Workwear	0.003	26
	M/L: Potential exposure App: Potential exposure	0.004	38.9

Summary data - acute exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw]	% of systemic AAEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0% Crop density: Normal			

Model data	Level of PPE	Total absorbed dose [mg/kg bw]	% of systemic AAOEL
Application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %			
Fenpicoxamid	M/L: Workwear App: Workwear	0.02	8.2
	M/L: Potential exposure App: Potential exposure	0.02	12.5
Application rate: 2 x 0.15 kg a.s./ha Dermal absorption (concentrate): 0.68 % Dermal absorption (in-use dilution): 14 %			
Prothioconazole	M/L: Workwear App: Workwear	0.04	18.7
	M/L: Potential exposure App: Potential exposure	0.06	31.1
Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 14 %			
Prothioconazole-desthio	M/L: Workwear App: Workwear	0.02	No safe use (224)
	M/L: Workwear + Protected hands + FP2, P2 and similar App: Workwear + Protected hands + FP2, P2 and similar	0.01	No safe use (100.1)

Use 1: Low vegetables – drift reduction (50%)

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

Summary data - short term exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 50% Crop density: Normal			
Application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %			
Fenpicoxamid	M/L: Workwear App: Workwear	0.002	3.3
	M/L: Potential exposure App: Potential exposure	0.002	4.6
Application rate: 2 x 0.15 kg a.s./ha Dermal absorption (concentrate): 0.68 % Dermal absorption (in-use dilution): 14 %			
Prothioconazole	M/L: Workwear App: Workwear	0.005	13.1
	M/L: Potential exposure App: Potential exposure	0.007	18.7
Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 14 %			
Prothioconazole-desthio	M/L: Workwear App: Workwear	0.001	11.7

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
	M/L: Potential exposure App: Potential exposure	0.001	13.7

Summary data - acute exposure

Model data	Level of PPE	Total absorbed dose [mg/kg bw]	% of systemic AAEL
Low vegetables/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 50% Crop density: Normal			
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption (concentrate): 0.33 % Dermal absorption (in-use dilution): 12 %	
	M/L: Workwear App: Workwear	0.007	3.6
	M/L: Potential exposure App: Potential exposure	0.01	6.3
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption (concentrate): 0.68 % Dermal absorption (in-use dilution): 14 %	
	M/L: Workwear App: Workwear	0.02	9.7
	M/L: Potential exposure App: Potential exposure	0.04	18.6
Prothioconazole-desthio		Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption (concentrate): 0 % Dermal absorption (in-use dilution): 14 %	
	M/L: Workwear App: Workwear	0.006	57.4
	M/L: Potential exposure App: Potential exposure	0.006	59.4

A 5.2 Worker exposure calculations (KCP 7.2.3.1)

Use 1: Low vegetables; Reaching, picking

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Reaching, picking (all except Brassica); Outdoor Work rate: 8 hours/day ; Interval: 21 days ; Body weight: 60 kg TC (potential): 5800 cm²/h TC (workwear (arms, body and legs covered)): 2500 cm²/h TC (workwear (arms, body and legs covered) and gloves): 580 cm²/h TC (gloves): NA cm²/h			
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.03	67.7	0
Workwear	0.01	29.2	0
Workwear and gloves	0.003	6.8	0
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.08	219	34
Workwear	0.03	94.5	0
Workwear and gloves	0.008	21.9	0
Prothioconazole-desthio		Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.07	716	86
Workwear	0.03	309	49
Workwear and gloves	0.007	71.6	0

Use 1: Low vegetables; Inspection, irrigation

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Inspection, irrigation (all); Outdoor Work rate: 2 hours/day ; Interval: 21 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			
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.02	36.5	0
Workwear	0.002	4.1	0
Workwear and gloves	0.002	3.6	0
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.04	118	8
Workwear	0.005	13.2	0

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Workwear and gloves	0.004	11.8	0
Prothioconazole-desthio Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.04	386	59
Workwear	0.004	43.2	0
Workwear and gloves	0.004	38.6	0

Use 1: Low vegetables; Removing bolting sugar beets

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
Removing bolting sugar beets; Outdoor Work rate: 8 hours/day ; Interval: 21 days ; Body weight: 60 kg TC (potential): 18600 cm²/h TC (workwear (arms, body and legs covered)): 4400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 430 cm²/h TC (gloves): 14300 cm²/h			
Fenpicoxamid Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.1	217	34
Workwear	0.03	51.3	0
Workwear and gloves	0.003	5	0
Hands covered, no workwear	0.08	167	23
Prothioconazole Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.3	703	85
Workwear	0.06	166	23
Workwear and gloves	0.006	16.3	0
Hands covered, no workwear	0.2	541	74
Prothioconazole-desthio Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days			
Potential	0.2	2296	136
Workwear	0.05	543	74
Workwear and gloves	0.005	53.1	0
Hands covered, no workwear	0.2	1765	125

A 5.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

Resident - Use 1 : Low vegetables

Scenario 1 : Outdoor, season not relevant, drift reduction 0 [%] buffer strip 2-3 [m]

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Outdoor; Season:Not relevant; Buffer zone:2-3m; Drift reduction:0%; Interval between treatments:21 days; Minimum volume of water: 150 l			

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Fenpicoxamid			Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
	Drift (75th perc.)	0.002	3.3
	Vapour (75th perc.)	0.0008	1.6
	Deposits (75th perc.)	0.0002	0.4
	Re-entry (75th perc.)	0.002	4.9
	Sum (mean)	0.004	7.6
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0004	0.8
	Vapour (75th perc.)	0.0003	0.5
	Deposits (75th perc.)	0.0001	0.2
	Re-entry (75th perc.)	0.001	2.7
	Sum (mean)	0.002	3.2
	Resident adult Body weight: 60 kg		
Drift (75th perc.)		0.004	10.6
Vapour (75th perc.)		0.0008	2.2
Deposits (75th perc.)		0.0007	1.9
Re-entry (75th perc.)		0.006	15.9
Sum (mean)		0.008	22.1
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0009	2.5
	Vapour (75th perc.)	0.0003	0.8
	Deposits (75th perc.)	0.0002	0.6
	Re-entry (75th perc.)	0.003	8.9
	Sum (mean)	0.003	9.5
	Resident adult Body weight: 60 kg		
Drift (75th perc.)		0.003	34.5
Vapour (75th perc.)		0.0008	8
Deposits (75th perc.)		0.0006	6.3
Re-entry (75th perc.)		0.005	52.1
Sum (mean)		0.007	73
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0008	8.2
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0002	2.1
	Re-entry (75th perc.)	0.003	28.9
	Sum (mean)	0.003	31.1
	Resident adult Body weight: 60 kg		
Drift (75th perc.)			
Vapour (75th perc.)			
Deposits (75th perc.)			
Re-entry (75th perc.)			
Sum (mean)			

Resident - Use 1 : Low vegetables – drift reduction (50%)

Scenario 1 : Outdoor, season not relevant, drift reduction 50 [%] buffer strip 2-3 [m]

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Outdoor; Season:Not relevant; Buffer zone:2-3m; Drift reduction:50%; Interval between treatments:21 days; Minimum volume of water: 150 l			
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0008	1.6
	Vapour (75th perc.)	0.0008	1.6
	Deposits (75th perc.)	0.0001	0.2
	Re-entry (75th perc.)	0.002	4.9
	Sum (mean)	0.003	6.6
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0002	0.4
	Vapour (75th perc.)	0.0003	0.5
	Deposits (75th perc.)	5e-05	0.1
	Re-entry (75th perc.)	0.001	2.7
	Sum (mean)	0.001	3
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.002	5.3
	Vapour (75th perc.)	0.0008	2.2
	Deposits (75th perc.)	0.0003	1
	Re-entry (75th perc.)	0.006	15.9
	Sum (mean)	0.007	18.5
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0005	1.3
	Vapour (75th perc.)	0.0003	0.8
	Deposits (75th perc.)	0.0001	0.3
	Re-entry (75th perc.)	0.003	8.9
	Sum (mean)	0.003	8.6
Prothioconazole-desthio		Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.002	17.3
	Vapour (75th perc.)	0.0008	8
	Deposits (75th perc.)	0.0003	3.1
	Re-entry (75th perc.)	0.005	52.1
	Sum (mean)	0.006	61.2
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0004	4.1
	Vapour (75th perc.)	0.0003	2.7
	Deposits (75th perc.)	0.0001	1.1
	Re-entry (75th perc.)	0.003	28.9
	Sum (mean)	0.003	28.5

Bystander - Use 1 : Low vegetables

Scenario 1 : Outdoor, season not relevant, drift reduction 0 [%] buffer strip 2-3 [m]

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Outdoor; Season:Not relevant; Buffer zone:2-3m; Drift reduction:0%; Interval between treatments:21 days; Minimum volume of water: 150 l			
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.004	1.9
	Vapour (95th perc.)	0.0008	0.4
	Deposits (95th perc.)	0.0007	0.3
	Re-entry (95th perc.)	0.002	1.2
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.001	0.5
	Vapour (95th perc.)	0.0003	0.1
	Deposits (95th perc.)	0.0003	0.1
	Re-entry (95th perc.)	0.001	0.7
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.009	4.3
	Vapour (95th perc.)	0.0008	0.4
	Deposits (95th perc.)	0.002	1
	Re-entry (95th perc.)	0.006	2.9
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.002	1.2
	Vapour (95th perc.)	0.0003	0.1
	Deposits (95th perc.)	0.0007	0.3
	Re-entry (95th perc.)	0.003	1.6
Prothioconazole-desthio		Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.008	78.3
	Vapour (95th perc.)	0.0008	8
	Deposits (95th perc.)	0.002	18.3
	Re-entry (95th perc.)	0.005	52.1
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.002	21.1
	Vapour (95th perc.)	0.0003	2.7
	Deposits (95th perc.)	0.0006	6.3
	Re-entry (95th perc.)	0.003	28.9

Bystander - Use 1 : Low vegetables – drift reduction (50%)

Scenario 1 : Outdoor, season not relevant, drift reduction 50 [%] buffer strip 2-3 [m]

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Outdoor; Season:Not relevant; Buffer zone:2-3m; Drift reduction:50%; Interval between treatments:21 days; Minimum volume of water: 150 l			

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Fenpicoxamid		Application rate: 2 x 0.075 kg a.s./ha Dermal absorption: 12 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.002	0.9
	Vapour (95th perc.)	0.0008	0.4
	Deposits (95th perc.)	0.0003	0.2
	Re-entry (95th perc.)	0.002	1.2
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0005	0.2
	Vapour (95th perc.)	0.0003	0.1
	Deposits (95th perc.)	0.0001	0.07
	Re-entry (95th perc.)	0.001	0.7
Prothioconazole		Application rate: 2 x 0.15 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.004	2.2
	Vapour (95th perc.)	0.0008	0.4
	Deposits (95th perc.)	0.001	0.5
	Re-entry (95th perc.)	0.006	2.9
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.001	0.6
	Vapour (95th perc.)	0.0003	0.1
	Deposits (95th perc.)	0.0003	0.2
	Re-entry (95th perc.)	0.003	1.6
Prothioconazole-desthio		Application rate: 2 x 0.13605 kg a.s./ha Dermal absorption: 14 % DFR: 3 µg/cm ² foliage per kg a.s./ha DT50: 30 days	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.004	39.1
	Vapour (95th perc.)	0.0008	8
	Deposits (95th perc.)	0.0009	9.2
	Re-entry (95th perc.)	0.005	52.1
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.001	10.5
	Vapour (95th perc.)	0.0003	2.7
	Deposits (95th perc.)	0.0003	3.2
	Re-entry (95th perc.)	0.003	28.9

A 5.4 Combined exposure calculations for fenpicoxamid and prothioconazole

No further calculations are needed. All details are provided in chapter 6.2.3.

The HIs presented in the EFSA online OPEX calculator have not been relied upon. This is because the calculator will automatically combine total exposure of fenpicoxamid, prothioconazole and prothioconazole-desthio, which is not appropriate for the exposure estimates based on the scenario of 100% conversion of prothioconazole to prothioconazole desthio. Therefore, please see chapter 6.2.3 for details.