REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GF-3308

Product name(s): not yet defined

Chemical active substance:

Fenpicoxamid (XDE-777), 50 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Corteva Agriscience

Submission date: May 2021

MS Finalisation date: February 2022 (initial Core Assessment)
August 2022 (final Core Assessment)

Version history

When	What
May 2021	New submission of GF-3308 in the Central Zone.
February 2022	Initial assessment by the zRMS The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.
August 2022	Final report (Core Assessment updated following the commenting period). Additional information/assessments included by the zRMS in the report in response to comments received from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~.

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Reviewer comments:

This part of dossier summarizes data related to the toxicological assessment and exposure data for the plant protection product GF-3308/Questar and has been submitted to support registration according art. art. 33 of 1107/2009 in Poland. Product was not a representative formulation reviewed during the Annex I inclusion/renewal of active substance(s). ~~and has not been previously evaluated in any EU countries according to the Uniform Principles.~~ The application is made to fulfil the requirements of Article 29 of Regulation (EC) No 1107/2009 for the authorization of the product GF-3308. This is a new product submission in the Central zone.

For the current product registration, applicant provided relevant data on the plant protection product GF3308/Questar regarding toxicological assessment based two different approaches.

As first approach acute toxicity was evaluated based on calculation method (ATEmix) as well as the use of *in vitro* studies assessing dermal and ocular irritation (refer Table 6.3-1 & 6.3-2).

A second approach using "read across" from data on a similar formulations (GF-3521, GF-3309 each one in comparison with GF-3308) has also been submitted by the applicant (detailed comparison between GF-3521, GF-3309 and GF-3308 is provided in dRR Part C).

ZRMS consider these results as reliable data to conclude hazard assessment and registration of the GF-3308/Questar according art 33 of 1107/2009.

NDE assessment provided for operator, workers and B&R resulting from use of GF-3308/Questar (*an emulsion concentrate (EC) containing 50 g/L of fenpicoxamid active substance for use as a fungicide in cereals: wheat, rye, triticale. The product is intended for use by professional users only*, refer dRR part B0) considering critical use(s), identify safe use of the product GF-3308/Questar (for details sections 6.6.2.1; 6.6.3.1, 6.6.4.1 to this dRR).

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on GF-3308 *

Product name and code	GF-3308
Formulation type	EC
Active substance(s) (incl. content)	Fenpicoxamid; 50 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	Yes. Details given in Part B0

* Information on the detailed composition of GF-3308 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-3308 according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin irritation Cat 2 Eye irritation Cat 1 STOT single exp Cat 3 Chronic aquatic Cat 1
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS05; GHS07: GHS09
Signal word	Danger
Hazard statement(s)	H315 Cause skin irritation H318 Causes serious eye damage H335 May cause respiratory irritation H410 Very toxic to aquatic life with long lasting effects.
Precautionary statement(s)	P280 Wear protective gloves/clothing/eye/face protection P302 + 352 IF ON SKIN: Wash with plenty of water P305 + 351 + 338 IF IN EYES: Rinse cautiously with water for several minutes ~~P314 Get medical advice/attention if you feel unwell~~ P312 Call a POISON CENTRE/doctor/…if you feel unwell. P501 Dispose of contents/container in accordance with applicable regulations
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for GF3308

	Result	**PPE / Risk mitigation measures**
Operators	Acceptable	Gloves during mixing/loading
Workers	Acceptable	Working clothing
Residents	Acceptable	None
Bystanders	Acceptable	None

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.**	**F, Fn, Fpn**	**Application**		**Application rate**		**PHI****	**Remarks:**	**Acceptability of exposure assessment**

	growth stage of crop)	G, Gn, Gpn or I **	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		(e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Operator	Worker	Residents	Bystander
1-3, 7-9, 13	Winter cereals (BBCH 30-69)	F	Spraying, LCTM	- a) 1 b) 1	a) 0.1	100-300	F	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874	(1)	(2)		
4-6, 10-12, 14	Spring cereals (BBCH 30-69)	F	Spraying, LCTM	- a) 1 b) 1	a) 0.1	100-300	F	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874	(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

**** F: PHI is defined by the application stage at last treatment (time elapsing between last treatment and harvest of the crop).

(1) PPE: Gloves for M/L/A (additional information reflecting cMS comments refer point 6.6.2.1)

(2) no PPE: Worker wearing workwear (coveralls or long sleeved jacket and trousers made of cotton (>300g/m^2) or cotton/polyester (>200g/m^2)) i.e. arms, body and legs covered.

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:

None.

6.2 Toxicological Information on Active Substance(s)

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

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

	Active substance 1
Common Name	Fenpicoxamid

CAS-No.	517875-34-2
	Active substance 1
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 Very toxic to aquatic life with long lasting effects P273 Avoid release to the environment. P501 Dispose of contents/container in accordance with applicable regulations.
Additional C&L proposal	Not Applicable
Agreed EU endpoints	
AOEL systemic	0.05 mg/kg bw/d (corrected for 12% oral absorption)
AAOEL systemic	0.2 mg/kg bw/day (as ARfD but with corrected for 12% oral absorption). The use of minor body weight & feed consumption changes in rabbits for setting an ARfD is not approriate and therefore it is the applicants view that an AAOEL is not required for this assessment.
Reference	EFSA, 2018. Conclusion on the peer review of the pesticide risk assessment of the active substance fenpicoxamid (XDE-777). EFSA Journal 2018;16(1):5146 ~~EFSA Conclusion~~
Conditions to take into account/critical areas of concern with regard to toxicology	
According to EFSA Conclusion for Fenpicoxamid	None

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for GF-3308 is given in the following two tables. No *in vivo* toxicology studies were conducted using GF-3308. Acute toxicity was evaluated as per the CLP 1272/2008 calculation method as well as the use of *in vitro* studies assessing dermal and ocular irritation as summarised in Table 6.3-1 & 6.3-2.

A second approach using “read across” from data on a similar formulation has also been included. The formulation GF-3521 has the same coformulants and active ingredient fenpicoxamid, all at levels similar to those found in GF-3308. A major difference between the two formulations is the presence of a second active ingredient propiconazole in GF-3521. Detailed comparison between GF-3521 and GF-3308 is provided in dRR Part C.
Read across is also presented from data on GF-3309, a formulation similar to GF-3308. The formulation GF-3309 has the same coformulants and active ingredient fenpicoxamid, all at levels similar to those found in GF-3308. A major difference between the two formulations is the presence of a second active ingredient pyraclostrobin in GF-3309. Detailed comparison between GF-3309 and GF-3308 is provided in dRR Part C.

Full summaries of studies on the product GF-3308 as well as those conducted on GF-3521 and GF-3309 that have not been previously considered within an EU peer review process are described in detail in Appendix 2. Detailed assessments using the CLP calculation method are described in Section C of the dossier.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for GF-3308

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference

LD_{50} oral, rat (CLP Calculation)	7194 mg/kg bw	Yes	None	dRR Part C
LD_{50} dermal, rat (CLP calculation)	11364 mg/kg bw	Yes	None	dRR Part C
LC_{50} inhalation, rat (CLP calculation)	13.32 mg/L air (mist) 113.64 (vapour)	Yes	None	dRR Part C
Skin irritation, ~~Epiderm tissue model (OECD 439)~~# (CLP calculation)*	Irritant	Yes	H315	~~Settivari and Sosinski, 2016a~~ dRR Part C
Eye irritation, ~~EpiOcular model (OECD 492)~~# (CLP calculation) **	Irritant	Yes	H318	~~Settivari and Sosinski, 2016b~~ dRR Part C
Skin sensitisation (Contains no classified substances)	Non-sensitising	Yes	None	dRR Part C
Supplementary studies for combinations of plant protection products	No data – not required	--	--	--

* Considering all classified substances in this hazard category and using the criteria given in 1272/2008 as amended: the result exceeds 10% and skin irritation Cat 2, H315 classification is triggered (refer Part C Classification calculation for GF-3308 p.33).
** Considering all classified substances in this hazard category and using the criteria given in Table 3.3.3. of 1272/2008 as amended the result exceeds ≥ 3% and eye irritation Cat 1, H318 classification is triggered (refer Part C Classification calculation for GF3308 p.33).
#ZRMS detailed information regarding acceptability of the studies please refer Point A 2.5 and A 2.6

Calculation in detail is available in Part C.

Table 6.3-2: Additional toxicological information relevant for classification/labelling of GF-3308

	Substance (concentration in product)	**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 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
Further toxicological information	No data – not required			

Reviewer comments:

Regarding data discussed in the Part C, in the ZRMS opinion direct read-across approach from the hazard data available on GF-3521 and GF-3309 to the registered formulation GF-3308 does not comply fully with the current SANCO/12638/2011 20 November 2012 rev. 2 guidance (differences in co-formulant rates in GF-3308) also considering major difference between the two formulations GF-3521, vs. GF-3308 is the inherence of a second active ingredient propiconazole (GF-3521) and pyraclostrobin (GF-3309) thus for hazard characterization ZRMS decided take into account information obtained from prediction based on composition (ATEmix).
Thus, summarized below read-across assessment has not been considered by the ZRMS in the hazard classification.

Table 6.3-3: Summary of evaluation of the studies on acute toxicity for GF-3521

Type of test, species, model system (Guideline)	Result		Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat	2000>LD_{50}<5000 mg/kg bw		None	xxx, 2017a
LD_{50} dermal, rat	LD_{50} > 5000 mg/kg bw		None	xxx, 2017b
LC_{50} inhalation, rat	LD_{50} > 5.48 mg/L		None	xxx, 2017c
Skin irritation, rabbit (OECD 404)	Mild Irritant		None	xxx, 2017d
Eye irritation, rabbit (OECD 405)	Irritant		Cat 2	xxx, 2017e
Skin sensitisation (Contains no classified substances)	Sensitising (based on properties of propiconazole)		Cat 1B	xxx, 2017f
Supplementary studies for combinations of plant protection products	No data – not required			

Table 6.3-3: Summary of evaluation of the studies on acute toxicity for GF-3309

Type of test, species, model system (Guideline)	Result		Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 423)	300 < LD_{50} < 2000 mg/kg bw		Cat 4	xxx, 2018a
LD_{50} dermal, rat (OECD 402)	LD_{50} > 2000 mg/kg bw		None	xxx, 2018b
LC_{50} inhalation, rat (OECD 436)	5 < LD_{50} < 12.5 mg/L		None	xxx, 2018c
Skin irritation, Rabbit (OECD 404)	Not Irritant		None	xxx, 2018d
Eye irritation, Rabbit (OECD 405)	Irritant		Cat 2	xxx, 2018e
Skin sensitisation, Mouse (OECD 429)	Non Sensitising		None	xxxxxxxxxxxxxxxxxxxxxxxxx, 2018f
Supplementary studies for combinations of plant protection products	No data – not required			

A comparison of the classification outcomes between the calculation method and those from the *in vivo* studies used for read-across purposes demonstrate a broadly similar output for acute oral, dermal and inhalation endpoints. With regards to classification for skin and eye irritation, the *in vitro* studies give rise to a more conservative classification for GF-3308, in comparison to using read across data. For skin sensitisation, GF-3521 was found to be a skin sensitiser in the LLNA study. However, the positive result was solely based on the properties of propiconazole within the formulation as no other components within GF-3521 are sensitisers. This is confirmed by the negative result obtained with GF-3309 which is a mixture

of fenpicoxamid and pyroclostrobin, both known as non-skin sensitizers. Therefore, when accounting for the fact that GF-3308 does not contain any components, which are sensitisers the read across approach is consistent with the calculation method.

Reviewer comments:

regarding toxicological potential of the product based on toxicity predicted from composition, ZRMS supports this approach and agree with proposed hazard classification for the product GF-3308.
Information and ATEmix calculations in Part C of the dRR are appropriate and sufficient to conclude.

- Skin irritation Cat 2 - H315
- Eye irritation Cat 1 - H318
- STOT single exp Cat 3 - H335

Based on both the calculation and read across methods outlined above (see p.8) it can be concluded that GF-3308 would have low acute oral, dermal and inhalation toxicity. It is likely that GF-3308 would be irritating to both the skin and eyes and may cause respiratory irritation but would not be a dermal sensitizer. Therefore proposed classification regarding toxicology is:

- Skin irritation Cat 2 - H315
- Eye irritation Cat 1 - H318
- STOT single exp Cat 3 - H335

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-3308 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GF-3308

	Fenpicoxamid	
	Value	**Reference**
Concentrate	70%	Default value for an EC formulation which contains active substance at 50g/L* (EFSA, 2017)
Dilution	70%	Default value for an EC formulation (EFSA, 2017)

* According to the corrigendum of guidance document on dermal absorption 2017 (SANTE/2018/10591, 24 Oct. 2018): https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_tox_dermal-absorp-2018-paff.pdf

6.5.1 Justification for proposed values - Fenpicoxamid

No data on dermal absorption for fenpicoxamid in GF-3308 is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for Fenpicoxamid

	Value	**Justification for value**	**Acceptability of justification**

version

Concentrate	70 %	Default value for an undiluted EC formulation as stated in the EFSA guidance document on dermal absorption (EFSA, 2017)	~~According to the corrigendum of EFSA guidnace on dermal absorption (SANTE/2018/10591 rev.1): "A "dilution" when the active substance is present in the plant protection product at a concentration lower than or equal to 50 g/L (or 50g/Kg or 5%)."~~ ~~In the formulation GF-3308, the fenpicoxamid is present at 50g/L~~ ~~Thus, the default value for the product concentrated is 70%.~~ Justification accepted. Endpoint can be used for current product
Dilution	70 %	Default value for a diluted EC formulation as stated in the EFSA guidance	~~Text~~ Justification accepted. Endpoint can be used for current product

		document on dermal absorption (EFSA, 2017)	

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

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

Product name and code	GF-3308
Formulation type	EC
Category	Fungicide
Active substance(s) (incl. content)	**Fenpicoxamid** 50 g/L
AOEL systemic	0.05 mg/kg bw/d
Inhalation absorption	100%
Oral absorption	12%
Dermal absorption	Concentrate: 70% Dilution: 70% (Default)

The relevant dermal absorption value that has been used for all assessments is 70% (default value)) for product and concentrate.

The highest spray dilution associated with tractor mounted spray applications to winter and spring cereals will give a spray concentration of 0.33 g/L for fenpicoxamid (*i.e.* 100g in 300 L).

6.6.1 Selection of critical use(s) and justification

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

Justification

The presented risk assessments are based on the highest supported application rates and therefore, represent the worst-case scenario.

6.6.2 Operator exposure (KCP 7.2.1)

Operator exposure estimations carried out using the EFSA Model indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended use and with the operator wearing appropriate workwear and PPE (gloves) for both mixing/loading and application.

Using the EFSA Model, the estimated exposure with PPE (gloves) was 14% of the AOEL for fenpicoxamid (43% of the AAOEL).

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of GF-3308 according to the critical use(s) is presented in

Table 6.6-2. The outcome of the estimation is presented in tables below. Detailed calculations are in Appendix 3.

Table 6.6-3: Estimated operator exposure

		Fenpicoxamid			
Model data	**Level of PPE**	**Longer term systemic exposure (mg/kg/day)**	**% of systemic AOEL**	**Acute systemic exposure (mg/kg/day)**	**% of systemic AAOEL**
Tractor mounted boom spray application outdoors to low crops					
Maximum application rate 0.1 kg fenpicoxamid/ha					
EFSA Model Body weight: 60 kg	no PPE*	0.2089	418	0.8407	420
	PPE**	0.0070	14	0.0852	43

* no PPE: Operator wearing 'workwear' defined as coveralls or long sleeved jacket and trousers made of cotton (>300g/m2) or cotton/polyester (>200g/m2).
** PPE: Gloves for M/L/A

Reviewer comment: reflecting cMS comment zRMS PL clarify that safe use can be demonstrated even when the operator doesn't wear gloves during application (AOEL for work wear + gloves during M/L is 29 % or 63 % of the AAOEL respectively). However, in order to avoid the constant manipulation of the gloves (putting on and taking off), zRMS suggests the use of gloves during all activities.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Winter cereals and spring cereals (max. 2 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-3: Estimated operator exposure

		Fenpicoxamid			
Model data	**Level of PPE**	**Longer term systemic exposure (mg/kg/day)**	**% of systemic AOEL**	**Acute systemic exposure (mg/kg/day)**	**% of systemic AAOEL**
Tractor mounted boom spray application outdoors to low crops					
Maximum application rate 0.1 kg fenpicoxamid/ha					
EFSA Model Body weight: 60 kg	no PPE*	0.2089	418	0.8407	420
	PPE**	0.0070	14	0.0852	43

* no PPE: Operator wearing 'workwear' defined as coveralls or long sleeved jacket and trousers made of cotton (>300g/m^2) or cotton/polyester (>200g/m^2). ** PPE: Gloves for M/L/A

6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and consideration of the above mentioned

personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.3 Worker exposure (KCP 7.2.3)

Worker exposure estimations carried out using the EFSA Model indicated that the acceptable exposure level will not be exceeded under conditions of intended use and with the worker wearing appropriate workwear. Using the EFSA Model, the estimated exposures without PPE were ≤34% (AOEL) for fenpicoxamid.

6.6.3.1 Estimation of worker exposure

Table 6.6 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GF-3308 according to the critical use(s). Outcome of the estimation is presented in
Table 6.6-5. Detailed calculations are in Appendix 3.

Table 6.6: Exposure models for intended uses

Critical use(s)	Winter cereals and spring cereals (max. 2 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-5: Estimated worker exposure (acute exposure)

		Fenpicoxamid	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Application rate: 0.1 kg a.s./ha Work rate: 2 hours/day(1) TC: 1400 cm^2/person/h(2) Body weight: 60 kg	No PPE(3)	0.0098	20
	PPE(4)	N/A	N/A

(1) 2 h/day for inspection or irrigation activities
(2) EFSA Guidance document, Table 13 [EFSA Journal 2014; 12(10):3874]. TC: Transfer coefficient
(3) no PPE: Worker wearing workwear (coveralls or long sleeved jacket and trousers made of cotton (>300g/m^2) or cotton/polyester (>200g/m^2)) i.e. arms, body and legs covered.
(4) no TC available for this assessment. N/A = not applicable.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required.

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

Resident exposure estimations carried out using the EFSA Model indicated that the acceptable exposure level will not be exceeded under conditions of intended use. Using the EFSA Model, the highest estimated all pathways exposure for residents was 43% of the AOEL for fenpicoxamid.

For fenpicoxamid the highest predicted bystander exposure using the EFSA Model was 21% of the AAOEL for children (spray drift, 95th percentile).

6.6.4.1 Estimation of resident and bystander exposure

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 6.6-7 shows the exposure model(s) used for estimation of resident and bystander exposure to fenpicoxamid. The outcome of the estimation is presented in
Table 6.6-4 (resident exposure) and
Table 6.6- (bystander exposure). Detailed calculations are in Appendix 3.

The EFSA Model is used to assess exposure to residents and bystanders. Therefore, all relevant exposure scenarios are included in the presented assessments.

Table 6.6-7: Exposure models for intended uses

Critical use(s)	Winter cereals and spring cereals (max. 2 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-8: Estimated resident exposure

		Fenpicoxamid	
Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3(m) Drift reduction technology: no DFR: 3 µg/cm²/kg a.s./ha Interval between treatments: 14 days			
Number of applications and application rate		1 x 0.1 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75th perc.)	0.0188	37.58
	Vapour (75th perc.)	0.0011	2.14
	Deposits (75th perc.)	0.0010	2.06
	Re-entry (75th perc.)	0.0118	23.63
	Sum (mean)	0.0216	43.18
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0045	9.00
	Vapour (75th perc.)	0.0002	0.46
	Deposits (75th perc.)	0.0005	0.95
	Re-entry (75th perc.)	0.0066	13.13

	Sum (mean)	0.0079	15.90

Table 6.6-4: Estimated bystander exposure

		Fenpicoxamid	
Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AAOEL**
Tractor mounted boom spray application outdoors to low crops Buffer zone: 2-3 (m) Drift reduction technology: no DFR: 3 µg/cm^2/kg a.s./ha			
Application rate		0.1 kg a.s./ha	
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.0426	21.29
	Vapour (95th perc.)	0.0011	0.54
	Deposits (95th perc.)	0.0031	1.56
	Re-entry (95th perc.)	0.0118	5.91
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0116	5.79
	Vapour (95th perc.)	0.0002	0.12
	Deposits (95th perc.)	0.0014	0.72
	Re-entry (95th perc.)	0.0066	3.28

6.6.4.2 Measurement of resident and/or bystander exposure

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for fenpicoxamid will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

Not relevant. The product contains only one active substance.

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	xxx	2017a	Acute Oral Toxicity Study of GF-3521 in Rats Company Report No: 161065 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP 7.1.1/2	xxx	2018a	Acute Oral Toxicity Study of GF-3309 in Rats Company Report No: 180201 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP.7.1.2/1	xxx	2017b	Acute Dermal Toxicity Study of GF-3521 in Rats Company Report No: 161066 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP.7.1.2/2	xxx	2018b	Acute Dermal Toxicity Study of GF-3309 in Rats Company Report No: 180202 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP 7.1.3/1	xxx	2017c	Acute Inhalation Toxicity Study of GF-3521 in Rats Company Report No: 161067 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience

KCP.7.1.3/2	xxx	2018c	Acute Inhalation Toxicity Study of GF-3309 in Rats Company Report No: 180206 Source: xxx GLP Unpublished	Y	Dow AgroSciences/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**
KCP 7.1.4/1	Settivari, R. S., and Sosinski, L. K.	2016a	GF-3308: Evaluation of the Skin Irritation Potential Using the In Vitro EpiDerm Tissue Model Company Report No: 160427 Source Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan, USA non GLP Unpublished	N	Dow AgroSciences/Corteva Agriscience
KCP 7.1.4/2	xxx	2017d	Acute Dermal Irritation Study of GF-3521 in Rabbits Company Report No: 161062 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP.7.1.4/3	xxx	2018d	Acute Dermal Irritation Study of GF-3309 in Rabbits Company Report No: 180203 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP 7.1.5/1	Settivari, R. S., and Sosinski, L. K.	2016b	GF-3308: Evaluation of the Eye Irritation Potential Using the *In Vitro* EpiOcular Tissue Model Company Report No: 160426 Source: Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan, USA non GLP Unpublished	N	Dow AgroSciences/Corteva Agriscience

KCP 7.1.5/2	xxx	2017e	Acute Eye Irritation Study of GF-3521 in Rabbits Company Report No: 161063 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP.7.1.5/3	xxx	2018e	Acute Eye Irritation Study of GF-3309 in Rabbits Company Report No: 180204 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience
KCP 7.1.6/1	xxx	2017f	Skin Sensitisation Study of GF-3521 by Local Lymph Node Assay in Mice Company Report No: 161064	Y	Dow AgroSciences/Corteva
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**
			Source: xxx GLP Unpublished		Agriscience
KCP.7.1.6/2	xxx	2018f	Skin Sensitisation Study of GF-3309 by Local Lymph Node Assay in Mice Company Report No: 180205 xxx GLP Unpublished	Y	Dow AgroSciences/Corteva Agriscience

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	xxx	2012 a	XDE-777: PROBE STUDY TO DETERMINE ABSORPTION, METABOLISM AND ELIMINATION IN F344NTac RATS, Crl:CD1(ICR) MICE AND NEW ZEALAND WHITE RABBITS (Revision) xxx DAS Report No.: 101038 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.1.1/2	xxx	2012	A PROBE STUDY TO INVESTIGATE THE METABOLISM AND EXCRETION OF 14C-LABELED XDE-777 IN BEAGLE DOGS FOLLOWING A SINGLE ORAL (GAVAGE) ADMINISTRATION xxx DAS Report No.: 111004 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.1.1/3	xxx	2012b	XDE-777: TISSUE DISTRIBUTION IN F344DuCrl RATS xxxx DAS Report No.: 111150 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 5.1.1/4	xxx	2013	ELIMINATION OF RADIOACTIVITY IN BILE, URINE, AND FECES FOLLOWING ORAL ADMINISTRATION OF [14C]-LABELED XDE-777 TO RATS xxxx DAS Report No.: 130007 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.1.1/5	xxx	2013	XDE-777: PHARMACOKINETICS AND METABOLISM IN F344DuCrl RATS xxx DAS Report No.: 111149 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience

CA 5.1.1/6	Zhang F McClymont EL Fiting JA Erskine TC Clark AJ	2014	XDE-777: *In Vitro* 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	Dow AgroSciences/Corteva Agriscience
CA 5.2.1/1	xxx	2011 a	Acute Oral Toxicity Up And Down Procedure In Ratsx xxx DAS Report No.: 101555 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.2.2/1	xxx	2011 b	Acute Dermal Toxicity Study in Rats xxx DAS Report No.: 101664 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.2.3/1	xxx	2012	XR-777: ACUTE DUST AEROSOL INHALATION TOXICITY STUDY IN F344DuCrl RATS xxx DAS Report No.: 101136 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 5.2.4/1	xxx	2011 c	Primary Skin Irritation Study In Rabbits xxx DAS Report No.: 101665 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience

CA 5.2.5/1	xxx	2011 d	Primary Eye Irritation Study in Rabbits xxx DAS Report No.: 101666 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.2.6/1	xxx	2012	XR-777: LOCAL LYMPH NODE ASSAY IN CBAJ MICE xxx DAS Report No.: 101154 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 Harlan Cytotest Cell Research GmbH DAS Report No.: 150039 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/Corteva Agriscience
CA 5.3.1/1	xxx	2010	XR-777: PALATABILITY PROBE STUDY IN F344DuCrl RATS xxxx DAS Report No.: 100041 GLP/GEP (Y/N): No Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.1/2	xxx	2012a	XR-777: 28-DAY DIETARY TOXICITY STUDY IN F344DuCrl RATS xxxx DAS Report No.: 101053 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.1/3	xxx	2010	XR-777: PALATABILITY PROBE STUDY IN Crl:CD1(ICR) MICEx xxx DAS Report No.: 100043	Yes	Dow AgroSciences/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): No Published (Y/N): No		
CA 5.3.1/4	xxx	2012	XR-777: 28-DAY DIETARY TOXICITY STUDY IN Crl:CD1(ICR) MICE xxx DAS Report No.: 101052 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.1/5	xxx	2012	XDE-777: A PRELIMINARY PALATABILITY STUDY IN BEAGLE DOGS xxxx DAS Report No.: 110033 GLP/GEP (Y/N): No Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.1/6	xxx	2013a	XDE-777: A 28-DAY DIETARY TOXICITY STUDY IN BEAGLE DOGSx xxx. DAS Report No.: 111034 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.2/1	xxx	2012 b	XR-777: 90 DAY DIETARY TOXICITY STUDY IN F344DuCrl RATS xxxx DAS Report No.: 101110 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.2/2	xxx	2014	XR777: 90-DAY DIETARY TOXICITY STUDY WITH A 28-DAY RECOVERY IN Crl:CD1(ICR) MICE (Revision) xxx DAS Report No.: 101103 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.3.2/3	xxx	2013 b	XDE-777: A 90-DAY DIETARY TOXICITY STUDY IN BEAGLE DOGS xxx. DAS Report No.: 111035 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 5.3.2/4	xxx	2014	XDE-777: A One-Year Dietary Toxicity Study in Beagle Dog xxx DAS Report No.: 121002 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 BioReliance DAS Report No.: 100088 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/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 Toxicology & Environmental Research and Consulting, The Dow Chemical Company DAS Report No.: 101069 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/Corteva Agriscience
CA 5.4.1/3	Schisler MR	2011 b	EVALUATION OF XR-777 IN THE CHINESE HAMSTER OVARY CELLHYPOXANTHINE-GUANINEPHOSPHORIBOSYL TRANSFERASE (CHOHGPRT) FORWARD MUTATION ASSAY Toxicology & Environmental Research and Consulting, The Dow Chemical Company DAS Report No.: 101089 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/Corteva Agriscience
CA 5.4.2/1	xxx	2011 c	EVALUATION OF XR-777 IN THE MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST xxx DAS Report No.: 101061 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience

CA 5.4.2/2	xxx	2014	XDE-777: In Vivo Unscheduled DNA Synthesis (UDS) Test in Mouse Liver Cells xxx DAS Report No.: 140628 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.5/1	xxx	2013	XR-777: 18-MONTH DIETARY ONCOGENICITY STUDY IN Crl:CD1(ICR) MICE	Yes	Dow

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**
			xxx DAS Report No.: 111068 GLP/GEP (Y/N): Yes Published (Y/N): No		AgroSciences/Corteva Agriscience
CA 5.5/2	xxx	2014	XDE-777: Two-Year Dietary Chronic Toxicity/Oncogenicity Study in F344/DuCrl Rats xxx DAS Report No.: 111064 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.6.1/1	xxx	2012 a	XR-777: DIETARY REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST IN Crl:CD(SD) RATS xxx DAS Report No.: 101200 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.6.1/2	xxx	2013 a	XDE-777: TWO GENERATION DIETARY REPRODUCTION TOXICITY STUDY IN Crl:CD(SD) RATS xxx DAS Report No.: 111186 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience

CA 5.6.2/1	xxx	2012 b	XR-777: DIETARY DEVELOPMENTAL TOXICITY PROBE STUDY IN Crl:CD(SD) RATS xxx DAS Report No.: 101099 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.6.2/2	xxx	2012 c	XDE-777: DIETARY DEVELOPMENTAL TOXICITY STUDY IN Crl:CD(SD) RATS xxx DAS Report No.: 111184 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/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 5.6.2/3	xxx	2012 d	XDE-777: DIETARY DEVELOPMENTAL TOXICITY PROBE STUDY IN NEW ZEALAND WHITE RAB-BITS xxx DAS Report No.: 121001 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.6.2/4	xxx	2013 b	XDE-777: DIETARY DEVELOPMENTAL TOXICITY STUDY IN NEW ZEALAND WHITE RABBITS xxx DAS Report No.: 121070 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.8.1/1	Patel NN	2012	BACTERIAL REVERSE MUTATION TEST OF X642188 USING SALMONELLA TYPHIMURIUM JAI RESEARCH FOUNDATION DAS Report No.: 120873 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/Corteva Agriscience

CA 5.8.1/2	xxx	2013	ACUTE ORAL TOXICITY STUDY OF X642188 IN RATS xxx DAS Report No.: 120874 GLP/GEP (Y/N): Yes Published (Y/N): No	Yes	Dow AgroSciences/Corteva Agriscience
CA 5.8.2/3	Scherzer MK Passage JK	2014	XDE-777: Solubility in New Zealand White Rabbit Plasma Toxicology & Environmental Research and Consulting, The Dow Chemical Company DAS Report No.: 140630 GLP/GEP (Y/N): Yes Published (Y/N): No	No	Dow AgroSciences/Corteva Agriscience
K-CP 7.1.1/01	xxx	2012a	Acute Oral Toxicity Study of GF-2925 in Rats xxx DAS Report No.: 120725 GLP/GEP (Y/N): Y Published (Y/N): N	Y	Dow AgroSciences/Corteva Agriscience
K-CP 7.2.1/01	xxx	2012b	Acute Dermal Toxicity Study of GF-2925 in Rats xxx DAS Report No.: 120726	Y	Dow AgroSciences/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): Y Published (Y/N): N		
K-CP 7.1.3/01	xxx	2016	ACUTE INHALATION TOXICITY STUDY OF GF-2925 IN RATS JAi RESEARCH FOUNDATION DAS Report No.: 160249 GLP/GEP (Y/N): Yes Published (Y/N): No	Y	Dow AgroSciences/Corteva Agriscience
K-CP 7.1.4/01	xxx	2012c	Acute Dermal Irritation Study of GF-2925 in Rabbits xxx DAS Report No.: 120727 GLP/GEP (Y/N): Y Published (Y/N): N	Y	Dow AgroSciences/Corteva Agriscience

K-CP 7.1.5/01	xxx	2012d	Acute Eye Irritation Study of GF-2925 in Rabbits xxx DAS Report No.: 120728 GLP/GEP (Y/N): Y Published (Y/N): N	Y	Dow AgroSciences/Corteva Agriscience
K-CP 7.1.6/01	xxx	2012e	Skin Sensitisation Study of GF-2925 by Local Lymph Node Assay in Mice xxx DAS Report No.: 120729 GLP/GEP (Y/N): Y Published (Y/N): N	Y	Dow AgroSciences/Corteva Agriscience
K-CP 7.3/01	Maas WJM	2013	In Vitro Dermal Absorption of XDE-777, Formulated in GF-2925 and Two Dilutions, Through Human SplitThickness Skin Using Flow-Through Diffusion Cells TNO Triskelion BV DAS Report No.: 120518 GLP/GEP (Y/N): Y Published (Y/N): N	N	Dow AgroSciences/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
-	-	-	-	-	-

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

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

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Acute oral, dermal and inhalation toxicity studies along with skin sensitisation was not performed with ~~GF-3008~~ GF-3308 A toxicity estimate for each of these end-points was calculated using the approach defined in the Regulation EC 1272/2008. However, *in vitro* skin and eye irritation studies were performed and detailed below.

A second approach using "read across" from data on two similar formulations has also been included. The formulations GF-3521and GF-3309 have the same coformulants and active ingredient fenpicoxamid, all at levels similar to those found in GF-3308. A difference between the formulations is the presence of a second active ingredient propiconazole in GF-3521 and pyraclostrobin for GF-3309. Detailed comparison between GF-3521/GF-3309 and GF-3308 is provided in dRR Part C.
In vivo acute toxicology data on GF-3521 and GF-3309 are presented to support the current application. These studies have been generated to support application of GF-3521 and GF-3309 in another geography where these data are requested to grant approval.

Comments of zRMS:	Regarding data discussed in the Part C, in the ZRMS opinion direct read-across approach from the hazard data available on GF-3521 and GF-3309 to the registered formulation GF-3308 does not comply fully with the current SANCO/12638/2011 20 November 2012 rev. 2 guidance (differences in co-formulant rates in GF-3308) also considering key difference between the two formulations GF-3521, GF-3309 vs. GF-3308 is the inherence of a second active substance propiconazole (GF-3521) and pyraclostrobin (GF-3309) **thus for hazard characterization ZRMS decided take into account information obtained from prediction based on composition (ATEmix).** **Summarized below read-across assessment has not been considered by the ZRMS in the hazard classification.**

A 2.2 Acute oral toxicity (KCP 7.1.1)

A 2.2.1 Calculation approach (Regulation EC 1272/2008)

Comments of zRMS:	Acute oral toxicity assessment based on product composition is relevant and sufficient for hazard evaluation. Calculation is accepted (for details see Part C).

An acute oral toxicity study with GF-3008 was not performed. Acute toxicity estimate via the oral route was calculated using the approach defined in the Regulation EC 1272/2008. Based on the acute toxicity of the individual components, the estimated oral LD50 of GF-3008 is 7194 mg/kg bw. Composition and calculation details are provided in dRR Part C.

Conclusion

The oral LD_{50} of GF-3008 is estimated to be 7194 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008

A 2.2.2 Read across approach using data on GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference KCP 7.1.1/1

Report	xxx.; 2017; Acute Oral Toxicity Study of GF-3521 in Rats; xxx; Lab Study No. 409-1-01-15429; DAS Study No. 161064 ; 11 March 2017; Unpublished
Guideline(s)	Yes: OECD 423 (2001), OPPTS 870.1100 (2002), EC B.1 (2008), JMAFF 2-1-1 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber–brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	8-10 weeks Weight (g): Minimum 144.6, maximum 169.7
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	2-3 rats/cage
Feed and water:	Feed: Teklad certified Global High Fibre Rat and Mice Feed manufactured by Envigo, U.S.A. *ad libitum* with the exception of overnight fasting and three hours post-dosing Water: UV sterilized water filtered through Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 20 to 23°C Humidity: 57 to 66% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	6 to 10 days

Study Design

In-life dates

Start: 12 November 2016 End: 22 December 2016

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/Kg body weight)	Females
5000	3
2000	6

Following an overnight fast, rats were given a single dose of GF-3521 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.

One female rat (set I) was given a single dose of 5000 mg GF-3521/kg body weight. As no mortality was observed, another two rats were given same dose of 5000 mg GF-3521/kg body weight. As two rats were found dead, three female rats (set II) were administered with the lower dose of 2000 mg GF3521/kg body weight. As no mortality was observed at this dose level, a third set of three female rats (set III) was administered with same dose of 2000 mg GF-3521/kg body weight. Absence of mortality was confirmed at this dose level and, in turn, further testing was not required

Animals were 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 - Female Rats (# affected /total)	Time range of deaths (hours or days)
5000	2/3	1 day after dosing
2000	0/6	N/A

N/A: not applicable

Two rats were found dead treated with 5000 mg GF-3521/kg body weight following dosing. No mortality was observed in rats treated with 2000 mg GF-3521/kg body weight.

Clinical Observations

The clinical sign of lethargy was observed on day 1 in the rats treated at the dose level of 5000 mg/kg body weight. No signs of toxicity were observed in rats treated at the dose level of 2000 mg/kg body weight.

Body Weight

All surviving rats treated with GF-3521 at the dose level of 5000 and 2000 mg/kg body weight showed no effect on body weight.

Necropsy Observations

External

External examination of found dead and terminally sacrificed animals did not reveal any abnormality.

Internal Internal examination of found dead animals revealed liver congestion (Animal N° 3) and autolysis (Animal N° 2) whereas terminally sacrificed animals did not reveal any lesion. Lesions observed in the found dead rats could be correlated with the test item used in the study.

CONCLUSION

Two mortalities were observed in the rats treated at the dose level of 5000 mg GF-3521/kg body weight. No mortality was observed in the six rats treated with 2000 mg GF-3521/kg body weight.

The acute oral LD_{50} of GF-3521 in Wistar rats was found between 2000 and 5000 mg/kg body weight.

A 2.2.3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.1/02
Report	xxx 2018; Acute Oral Toxicity Study of GF-3309 in Rats; xxx; Lab Study No. 401-1-01-19441; DAS Study No. 180201; 17 August 2018; Unpublished
Guideline(s)	Yes: OECD 423 (2001), OPPTS 870.1100 (2002), EC B.1 (2008), JMAFF 2-1-1 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)
Vehicle:	Not applicable

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	8 to 10 weeks Weight (g): Minimum 171.4, Maximum 203.5
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	1 to 3 rats/cage
Feed and water:	Feed: Teklad certified Global High Fiber Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* with the exception of overnight fasting and three hours post dosing Water: UV sterilized water filtered through reverse osmosis water filtration system *ad libitum*

Environmental conditions: Temperature: 20 to 23 °C
Humidity: 49 to 66% relative humidity
Air changes: Minimum 15 air changes/hour
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 to 13 days

Study Design

In-life dates

Start: 10 April 2018 End: 14 May 2018

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/kg body weight)	Females
2000	3
300	6

Following an overnight fast, rats were given a single dose of GF-3309 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 - Female Rats (# affected /total)	Time range of deaths (hours or days)
2000	2/3	day 0 to day 2
300	0/6	N/A

N/A: not applicable

Two mortalities were observed in the rats treated with 2000 mg GF-3309/kg body weight while no mortality was observed at 300 mg GF-3309/kg body weight.

Clinical Observations

Clinical sign like lethargy was observed in rats (rat N° 1 and 3) treated at the dose level of 2000 mg/kg body weight while no signs of toxicity were observed in any of the rats treated at the dose level of 300 mg/kg body weight, throughout the 14-day observation period.

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

External examination of terminally sacrificed and found dead animals did not reveal any abnormalities.

Internal

Internal examination of found dead rats (rat N° 1 and 3) revealed liver: reddish discolouration whereas terminally sacrificed rat did not reveal any abnormalities.

CONCLUSION

Two mortalities were observed in the rats treated with 2000 mg GF-3309/kg body weight while no mortality was observed at 300 mg GF-3309/kg body weight. The acute oral LD_{50} of GF-3309 in female Wistar rats was found to be between 300 and 2000 mg/kg body weight. According to the test guideline, cut-off LD_{50} would be 1000 mg/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Rat	Wistar	F	Oral	Gavage (undiluted)	LD_{50} = between 300 and 2000 mg/kg body weight (LD_{50} cut-off value =1000 mg/kg body weight)

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Category 4

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

A 2.3.1 Calculation approach (Regulation EC 1272/2008

Comments of zRMS:	Acute dermal toxicity assessment based on product composition is relevant and sufficient for hazard evaluation. Calculation is accepted (for details see Part C).

An acute dermal toxicity study with GF-3008 was not performed. Acute toxicity estimate via the dermal route was calculated using the approach defined in the Regulation EC 1272/2008. Based on the acute toxicity of the individual components, the estimated dermal LD_{50} of GF-3008 is 11364 mg/kg bw. Composition and calculation details are provided in dRR Part C.

Conclusion

The dermal LD_{50} of GF-3008 is estimated to be 11364 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.3.2 Read across approach using data on GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding readacross approach point A 2.1

Reference KCP 7.1.2/1

Report	xxx.; 2017; Acute Dermal Toxicity Study of GF-3521 in Rats; xxx; Lab Study No. 4091-01-15429; DAS Study No. 161064 ; 16 March 2017; Unpublished
Guideline(s)	Yes: OECD 402 (1987), OPPTS 870.1200 (1998), EC B.3 (2008), JMAFF 2-1-2 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber–brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	8-11 weeks Weight (g): Male: Minimum 265.0, maximum 294.3; Female: Minimum 221.9, maximum 248.3
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	2 to 3 rats/cage except on the day of test item application, in which the rats were housed in individual cages following test item application up to patch removal
Feed and water:	Feed: Teklad certified Global High Fibre Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 20 to 23°C Humidity: 57 to 66% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	6 days

Study Design

In-life dates

Start: 12 November 2016 End: 02 December 2016

Animal assignment and treatment

Animal assignment is shown in Table 1

Table 1: Animal assignment

Dose (mg/Kg body weight)	Males	Females	Combined
5000	5	5	10

A calculated dose volume (1.08 to 1.43 mL) of GF-3521 was applied over the clipped area (approximately 7 × 5 cm area, corresponding to 10% of the body surface) of the rats and observed for a period of 14 days. 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 h 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 (24 hours), the residual test item was removed using cotton soaked in 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)	Number with evident toxicity (# affected /total)		
	Male	Female	Combined		Male	Female	Combined
5000	0/5	0/5	0/10	N/A	0/5	0/5	0/10

N/A: not applicable

Clinical Observations

No treatment related clinical signs were observed in any of the rats treated with 5000 mg GF-3521/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 with GF-3521/kg body weight.

Necropsy

External

External examination of terminally sacrificed male and female rats did not reveal any abnormalities of pathological significance Internal

Visceral examination of male and female rats sacrificed at termination did not reveal any lesions.

In the absence of any pathological lesion in terminally sacrificed animals, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

CONCLUSION

No mortality, adverse clinical observations, effects on body weight, macroscopic external or internal abnormalities at necropsy were observed in any of the animals treated with 5000 mg GF-3521/kg body weight.
The acute dermal LD_{50} of GF-3521 in Wistar male and female rats was found to be greater than 5000 mg/kg body weight

A 2.3.3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.2/02
Report	xxx. Acute Dermal Toxicity Study of GF-3309 in Rats. xxx Laboratory report number: 403-1-01-19442; Dow AgroSciences study number: 180202; August 18, 2018. Unpublished.
Guideline(s)	Yes: OECD 402 (2017)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)
Vehicle:	Not applicable

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	11 to 13 weeks Weight (g): Female: Minimum 245.0, Maximum 261.7
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	Three rats/cage except from test item application until patch removal, when rats were housed individually.
Feed and water:	Feed: Teklad certified Global High Fiber Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through reverse osmosis water filtration system *ad libitum*

Environmental conditions: Temperature: 20 to 23°C
Humidity: 49 to 66% relative humidity
Air changes: Minimum 15 air changes/hour
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 to 13 days

Study Design

In-life dates

Start: 10 April 2018 End: 07 May 2018

Animal assignment and treatment

Animal assignment is shown in Table 1

Table 1: Animal assignment

Dose (mg/kg body weight)	Females
2000	3

Before treatment, the pH of the test item was measured at JRF and found to be 5.32 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment.

A calculated dose volume (0.48 to 0.51 mL) of GF-3309 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 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 - Female Rats (# affected /total)	Time range of deaths (hours or days)
2000	0/3	N/A

N/A: not applicable

No mortality was observed in rats treated with 2000 mg GF-3309/kg body weight.

Clinical Observations

No treatment related clinical signs were observed in any of the rats treated with 2000 mg GF-3309/kg body weight.

No erythema and oedema were observed at 24, 48 and 72 hours post patch removal in all three rats.

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 with 2000 mg GF-3309/kg body weight.

Necropsy

External

External examination of terminally sacrificed female rats did not reveal any abnormalities of pathological significance. Internal

Visceral examination of female rats sacrificed at termination did not reveal any lesions.

In the absence of any pathological lesion in terminally sacrificed animals, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study.

CONCLUSION

No mortality, adverse clinical observations, effects on body weight and macroscopic external or internal abnormalities at necropsy were observed in any of the animals treated with 2000 mg GF-3309/kg body weight.

Based on the study results, the acute dermal median lethal dose (LD_{50} value) of GF-3309 in female Wistar rats was found to be greater than 2000 mg/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Rat	Wistar	F	Dermal	Topical (24-hour semi-occlusive exposure)	LD_{50} > 2000 mg/kg body weight

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Unclassified

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

A 2.4.1 Calculation approach (Regulation EC 1272/2008)

Comments of zRMS:	Acute inhalation toxicity assessment based on product composition is relevant and sufficient for hazard evaluation. Calculation is accepted (for details see Part C).

An acute inhalation toxicity study with GF-3008 was not performed. Acute toxicity estimate via the inhalation route was calculated using the approach defined in the Regulation EC 1272/2008. Based on the acute toxicity of the individual components, the estimated inhalation LC_{50} of GF-3008 is 13.32 mg/L for mist and 113.64 mg/L for vapour. Composition and calculation details are provided in dRR Part C

Conclusion

The inhalation LC_{50} of GF-3008 is estimated to be 13.32 (mist) or 113.64 mg/kg bw (vapour) in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4.2 Read across approach using data on GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.3/1
Report	xxx.; 2017; Acute Inhalation Toxicity Study of GF-3521 in Rats; xxx Lab Study No. 409-1-0115429; DAS Study No. 161064 ; 15 March 2017; Unpublished

Guideline(s)	Yes: OECD 436 (2009)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber–brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	8 to 10 weeks Weight (g): Male: Minimum: 262.1, Maximum: 275.2, Female: Minimum: 202.6, Maximum: 212.3
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	3 rats/cage
Feed and water:	Feed: Teklad certified Global High Fibre Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 19 to 23°C Humidity: 49 to 66% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	7 days

Study Design

In-life dates

Start: 14 December 2016 End: 04 January 2017

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/L air)	Males	Females	Combined
5.48	3	3	6

Rats were exposed to the test item by nose only exposure for 4 hours.

Animals were observed daily and weighed on test days 1, 3, 7 and 14. Survivors were sacrificed and a necropsy was performed in all animals.

RESULTS AND DISCUSSION

Concentration Details in the Inhalation Chamber

The time-weighted average (TWA) exposure concentration of GF-3521 in the air for rats was 5.48 mg/L. The mass median aerodynamic diameter (MMAD) of GF-3521 aerosols was determined to be 2.94 µm with an average geometric standard deviation (GSD) of 1.61

Mortality

No mortality was observed in rats exposed for 4 hours to an aerosol concentration of 5.48 mg GF3521/L air (TWA).

Table 2: Dose, mortality/animals treated

Time-Weighted Average (TWA) Concentration (mg/L air)	Mortality (# affected/total)			Time range of deaths (hours)	Number with evident toxicity (# affected/total)		
	Male	Female	Combined		Male	Female	Combined
5.48	0/3	0/3	0/6	NA	0/3	0/3	0/6

N/A: Not applicable

Clinical Observations

No sign of toxicity was observed in any of the rats exposed to aerosol concentration of 5.48 mg GF3521/L air (TWA).

Body Weight

A slight decrease in body weight was observed following dosing on days 1 and 3 in all animals treated at 5.48 mg/L air. Recovery occurred by day 7.

Necropsy Observations

External

External examination of terminally sacrificed rats did not reveal any abnormality Internal

Visceral examination of terminally sacrificed rats did not reveal any abnormality.

In the absence of any pathological lesion in terminally sacrificed rats, it is concluded that the test item did not produce any treatment related effect at the dose level used in the present study

CONCLUSION

No mortality was observed in rats following nose only inhalation exposure to aerosol concentration of 5.48 mg GF-3521/L air (TWA).

Under the conditions of this study, the 4 hour acute inhalation (LC_{50}) of GF-3521 in male and female Wistar rats was found to be greater than the time-weighted average (TWA) exposure concentration of 5.48 mg GF-3521/L air.

A 2.4.3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.4/02
Report	xxx 2018; Acute Inhalation Toxicity Study of GF-3309 in Rats; xxx; Lab Study No. 405-1-01-19443; DAS Study No. 180206; 20 August 2018; Unpublished
Guideline(s)	Yes: OECD 436 (2009)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)

Test System

Species:	Rat (*Rattus norvegicus*)
Strain:	Wistar (RCCHan:WIST)
Age and weight at dosing:	10 to 11 weeks Weight (g): Male: Minimum 293.8, Maximum 302.1; Female: Minimum 194.1, Maximum 198.7
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	1-3 rats/cage
Feed and water:	Feed: Teklad certified Global High Fiber Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through reverse osmosis water filtration system *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:	7 days

Study Design

<u>In-life dates</u>

Start: 28 April 2018 End: 22 May 2018

<u>Animal assignment and treatment</u>

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/L air)	Males	Females	Combined
5.45	3	3	6

The rats were exposed for 4 h (nose only) followed by a 14 day post-exposure observation period during which animals were observed daily. Body weights were recorded prior to exposure on day 0 and on days 1, 3, 7 and 14 after exposure and at death. Survivors were sacrificed and a necropsy was performed in all animals.

RESULTS AND DISCUSSION Concentration Details in the Inhalation Chamber

The time-weighted average (TWA) GF-3309 aerosol concentration in the exposure chamber was 5.45 mg/L air. The average mass median aerodynamic diameter (MMAD) of aerosolized GF-3309 was determined to be 3.27 µm with an average geometric standard deviation (GSD) of 1.55.

Mortality

Mortality data are presented in the following table.

Table 2: Dose, mortality/animals treated

Time-Weighted Average (TWA) Concentration (mg/L air)	Mortality (# affected/total)			Time range of deaths (hours)	Number with evident toxicity (# affected/total)		
	Male	Female	Combined		Male	Female	Combined
5.45	2/3	0/3	2/6	N/A	3/3	3/3	6/6

N/A: Not applicable

Two out of six rats (2 males) were found dead after exposure to a time-weighted average concentration of 5.45 mg GF-3309/L air (TWA). One animal was found dead during the exposure time (hour 4); the other at day 2 post-exposure.

Clinical Observations

All animals showed abdominal breathing during and after the 4-hour exposure. The 5 (2 male and 3 female) rats who survived the exposure demonstrated lethargy 2 hours later. The 4 (1 male and 3 female) surviving rats reverted to normal by day 2 post-exposure..

Body Weight

The surviving male rat showed a decrease in body weight on days 1 (~12%) and 3 (~8%) and exceeded initial (day 0) body weight by days 7 and 14. The three female rats showed a decrease in mean body weight on days 1 (~12%) and 3 (~6%) and exceeded their initial (day 0) body weight by days 7 and 14.

Necropsy Observations

External

External examination of found dead and terminally sacrificed rats did not reveal any abnormality of pathological significance.

Internal

Visceral examination of found dead (male) rats revealed lesions such as lungs: reddish discolouration (Animal N° 2 to 3) and liver: reddish discolouration (Animal N° 3) whereas the terminally sacrificed animals did not reveal any lesion.

Lesion observed in the found dead animals could be correlated with the test item used in the present study.

CONCLUSION

Two (males) out of six rats were found dead following nose-only inhalation exposure to an aerosol concentration of 5.45 mg GF-3309/L air (TWA).

The 4-hour acute inhalation median lethal concentration (LC_{50}) of GF-3309 in Wistar rats (male and female combined) was found to be between 5 and 12.5 mg/L air. According to the test guideline, cut-off LC_{50} would be 12.5 mg/L.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Rat	Wistar	M & F	Inhalation	Nose only (4-hour)	LC_{50} = between 5 and 12.5 mg/L air (cut-off value 12.5 mg/L)

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Category 5

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Considering information available in GD OECD 439 revision 14 June 2021 INITIAL CONSIDERATIONS AND LIMITATIONS Subsection 8: p.2 (..) data indicates a lack of applicability of the RhE based *in vitro* skin irritation test for agrochemical formulations (47). (..) See also: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). *Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations*. Regul. Toxicol. Pharmacol 89, 125-130. Thus, taking into account mentioned above information ZRMS decided to conclude assessment in this hazard category for the GF-3308 based on composition and using the criteria given in 1272/2008. Based on the skin irritation of the individual components, estimation trigger classification H315. Composition and calculation details are provided in dRR Part C is relevant and sufficient for hazard evaluation.

A 2.5.1 Study 1 (GF-3308)

Reference	KCP 7.1.4/01
Report	Settivari, R. S., Sosinski, L. K.; 2016; GF-3308: Evaluation of the Skin Irritation Potential Using the *In Vitro* EpiDerm Tissue Model; Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan, USA; Lab Study No. 160058; DAS Study No. 160427; 26 September 2016; Unpublished
Guideline(s)	Yes: OECD 439
Deviations	None

GLP	No
Acceptability	NO
Duplication (if vertebrate study)	N/A

Materials and methods

Test Item(s)

Test item (Common name):	GF- 3308
Purity:	4.8 % w/w XDE-777
Description (physical state):	Information not included in the study report
Lot/batch no.:	E3240-85-1 (TSN311166)
Vehicle and/or positive control:	Not applicable

Test System

Test cells:	3-D Normal Human Epidermal Keratinocytes (NHEK)
Source:	MatTek Corporation (Ashland, Massachusetts)
Media:	MatTek Corporation
Reagents:	MatTek Corporation

Study Design

Cell culture procedures

The EpiDerm System (EPI-200) consists of normal, human-derived epidermal kerotinocytes which have been cultured to form a multilayered, highly differentiated model of the human epidermis. It consists of organized basal, spinous and granular layers, and a multilayered stratum corneum containing intercellular lamellar lipid layers arranged in patterns analogous to those found *in vivo*. The EpiDerm tissues are cultured
on polycarbonate membranes of cell culture inserts (MILLICELLs, 10 mm diameter, 0.6 cm² surface) and shipped as kits, containing 24 tissues mounted on agarose.

Preliminary assay

NA

Definitive assays

The test is based on the principle that chemicals with irritant potential can cause cytotoxic response to the *stratum corneum* and the rate of cytotoxicity is proportional to irritation potency. In the assay, the EpiDerm tissue model was incubated with the test chemical for 60 minutes, followed by 42-hour incubation (recovery) under standard cell culture conditions. Following the post-treatment incubation period, cell viability was assessed using the MTT (3-[4,5- dimethylthiazol-2-yl] -2,5 – diphenyltetrazolium bromide) assay
(Mosmann, 1983). Relative cell viability was calculated for each tissue as % of the mean of the negative control-treated tissues. A test chemical was interpreted as a potential skin irritant or non-irritant (GHS No label), when the cell viability was ≤ or > 50%, respectively (OECD 439, 2013).

Evaluation of Test Results

Data Analysis
Skin irritation potential of the test chemical was determined based on relative cell viability (corrected to negative control values), following exposure and post-exposure incubations. The mean OD_{570} value of the blank wells was calculated. Individual blank corrected OD_{570} values for each test chemical or control tissue were determined by subtracting the mean OD_{570} value of the blank wells from their individual OD_{570} values.
The mean of the corrected OD_{570} values for the negative control was calculated.

Corrected Individual Tissue OD_{570} = individual tissue OD_{570} – mean blank OD_{570}

For each individual tissue, % viability relative to negative control was calculated by taking the ratio of Corrected Individual OD_{570} of Test Chemical (or Control) and Corrected mean OD_{570} of Negative Control. The individual relative viabilities were tabulated for each tissue and the mean and standard deviations for viability values were calculated for the test chemical and control.

Acceptability criteria
The results for negative and positive controls met assay acceptance criteria, suggesting appropriate conduct of the study.
The corrected mean OD_{570} value of the negative control tissues (exposed for 60 minutes) was 2.707 (*i.e.* ≥ 1.00; criteria set by the tissue manufacturer).
The relative mean viability of positive control (5% SDS) was 5.5% (*i.e.* < 20% compared to negative control).

Results and discussions Preliminary Assay

Not applicable

Definitive Assays

The mean relative tissue viability for EpiDerm tissues treated with GF-3308 and positive control (5% SDS) were 4.2% and 2.7%, respectively.

Table A1: Epiderm – results

Test article		1 Hr Treatment plus 42 Hr Recovery			Mean Viability %	Classification prediction
		Replicate 1	Replicate 2	Replicate 3		
Test material	GF-3307	4.3	4.3	4.0	4.2	Irritant
Negative control	DPBS	109.6	101.1	89.6	100.0	Non-irritant
Positive control	5% SDS	3.1	2.6	2.6	2.7	Irritant

Conclusion

Under the experimental conditions, GF-3308 is a skin irritant. Thus, classification is required according to Regulation (EC) No. 1272/2008.

A 2.5.2 Study 2 Read across approach using data on GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.4/02
Report	Xxx 2017; Acute Dermal Irritation Study of GF-3521 in Rabbits xxx; Lab Study No. 406-1-01-15427; DAS Study No. 161062 ; 15 March 2017; Unpublished
Guideline(s)	Yes: OECD 404 (2015), OPPTS 870.2500 (1998), EC B.4 (2008), JMAFF 2-1-4 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber–brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Strain:	New Zealand White
Age and weight at dosing:	11 to 12 weeks old Weight (kg): Minimum 1.914, maximum 1.949
Source:	Animal breeding Facility, Jai Research Foundation
Housing:	Individually
Feed and water:	Feed: Teklad certified Global High Fibre Rabbit Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 19 to 22°C Humidity: 64 to 65% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	6 to 8 days

Study Design

<u>In-life dates</u>

Start: 22 November 2016 End: 07 December 2016

Animal assignment and treatment

The pH of GF-3521 was found to be 4.67 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment. .

A total of 3 rabbits 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.

A volume of 0.5 mL GF-3521 was applied evenly to one of the clipped sites of each rabbit and on the other clipped site of each rabbit remained untreated. The latter served as the control site. The treated and the control sites were covered with gauze patches of approximately 6 cm^2 (gauze rolled) which were not more than 8-ply and were secured at the margins by non-irritating tape (Medi tape 330 hypoallergenic 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 no. 404) at 1, 24, 48, 72 hours and on day 7 post patch removal. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION

Dermal Irritation

At 1 h post patch removal, the treated skin site revealed very slight erythema (barely perceptible) (score of 1) and very slight oedema (barely perceptible) (score of 1) in all rabbits.

At 24 h, 48 h and 72 h post patch removal, the treated skin site revealed well-defined erythema (score of 2) and very slight oedema (barely perceptible) (score of 1) in all three rabbits.

On day 7 post patch removal, treated skin site of all the three rabbits recovered completely and appeared normal. .

Individual animal irritation scores are presented in Table 1.

Table 5: Doses, scoring/animals treated

Rabbit no.	Site of treatment	Site of control	Observations after patch removal											
			Erythema						Oedema					
			Hours				Days		Hours				Days	
			1	24	48	72	7	14	1	24	48	72	7	14
1	Left	Right	1	2	2	2	0	N/A	1	1	1	1	0	N/A
2	Right	Left	1	2	2	2	0	N/A	1	1	1	1	0	N/A
3	Right	Left	1	2	2	2	0	N/A	1	1	1	1	0	N/A

Key: N/A: not applicable/available

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 recorded and all animals gained body weight throughout the study.

CONCLUSION

The mean dermal irritation scores at 24, 48 and 72 h post patch removal, for the 3 rabbits respectively, were: 2.00, 2.00, 2.00 for erythema; and 1.00, 1.00, 1.00 for oedema.

Recovery was completed in all rabbits by day 7 post patch removal.

A 2.5.3 Study 3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.4/03
Report	xxx 2018; Acute Dermal Irritation Study of GF-3309 in Rabbits; xxx; Lab Study No. 406-1-01-19444; DAS Study No. 180203; 18 August 2018; Unpublished
Guideline(s)	Yes: OECD 404 (2015), OPPTS 870.2500 (1998), EC B.4 (2008), JMAFF 2-1-4 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Strain:	New Zealand White
Age and weight at dosing:	3.5 to 4.5 months Weight (kg): Minimum 1.871, maximum 2.245
Source:	Sainath Agencies, Hyderabad, India
Housing:	Individually
Feed and water:	Feed: Teklad certified Global High Fibre Rabbit Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Reverse Osmosis water filtration system *ad libitum*

Environmental conditions:	Temperature: 19 to 22 °C Humidity: 64 to 65% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	6 to 8 days

Study Design

In-life dates

Start: 11 April 2018 End: 22 April 2018

Animal assignment and treatment

Before treatment, the pH of the test item was measured at JRF and found to be 5.32 (1% solution of test item at room temperature), which is considered acceptable for treatment.

A total of 3 rabbits (3 males) 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.

A volume of 0.5 mL of GF-3309 (undiluted) was applied evenly to one of the clipped sites of each rabbit and the other clipped site of each rabbit remained untreated. The latter served as the control site. The treated and the control sites were covered with gauze patches of approximately 6 cm^2 (gauze rolled) which were 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 no. 404) at 1, 24, 48, 72 hours post patch removal. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION Dermal Irritation

At 1 hour post patch removal, the treated skin site revealed very slight erythema (score of 1) in all the three rabbits.

At 24 hours post patch removal, the treated skin site of all the three rabbits recovered completely and appeared normal until the end of the 72 hours observation period.

The control skin sites of all rabbits were normal with no erythema and no oedema observed throughout the experimental period.

Individual animal irritation scores are presented in Table 1.

Table 6: Doses, scoring/animals treated

Rabbit no.	Site of treatment	Site of control	Observations after patch removal			
			Erythema		Oedema	
			Hours	Days	Hours	Days

			1	24	48	72	7	14	1	24	48	72	7	14
1	Right	Left	1	0	0	0	N/A	N/A	0	0	0	0	N/A	N/A
2	Right	Left	1	0	0	0	N/A	N/A	0	0	0	0	N/A	N/A
3	Right	Left	1	0	0	0	N/A	N/A	0	0	0	0	N/A	N/A

Key: N/A: not applicable/available

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
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 preventing grading of erythema beyond area of exposure)
Maximum possible: 4

Systemic toxicity

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

CONCLUSION

In conclusion, based on these study results, GF-3309 caused a minimal dermal reaction in all the three animals, fully reversible by 24 hours post patch removal. No systemic effects were observed.

The individual animal average dermal irritation scores observed at 24, 48 and 72 hours post GF-3309 application were, for each rabbit respectively: 0.00, 0.00, 0.00 for erythema; 0.00, 0.00, 0.00 for oedema.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Rabbit	NZW	M	Dermal	Topical (4 hour, semi-occlusive)	Mean Erythema Scores: 0.00, 0.00, 0.00. Mean Oedema Scores: 0.00, 0.00, 0.00. Recovery completed by 24 hours.

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Unclassified

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Considering two aspects of the following assessment, first GD OECD 492 18 June 2019 describes an *in vitro* procedure allowing the identification of chemicals (substances and mixtures) not requiring classification and labelling for eye irritation or serious eye damage in accordance with UN GHS and second indications of irritating effect from *in vivo* studies which allow classification of the product GF-3308, ZRMS in this particular case (eye corrosion/irritation) decided to take into account for hazard assessment predictions for eye corrosion/irritation based on composition of the product. This approach is supported by following paper: Kolle S.N., van Cott A., van Ravenzwaay B. and Landsiedel R. (2017): *Lacking applicability of in vitro eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS*. Regulatory Toxicology and Pharmacology 85 (2017) 33-47. Based on the eye irritation of the individual components, estimation trigger classification H318. Composition and calculation details are provided in dRR Part C is relevant and sufficient for hazard evaluation.

A 2.6.1 Study 1 (GF-3308)

Reference	KCP 7.1.5/01
Report	Settivari, R. S., Sosinski, L. K.; 2016; GF-3308: Evaluation of the Eye Irritation Potential Using the *In Vitro* EpiOcular Tissue Model; Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan, USA; Lab Study No. 160059; DAS Study No. 160426; 28 September 2016; Unpublished
Guideline(s)	Yes: OECD 492
Deviations	None
GLP	No
Acceptability	No
Duplication (if vertebrate study)	N/A

Materials and methods

Test Item(s)

Test item (Common name):	GF-3308
Purity:	4.8 % w/w XDE-777
Description (physical state):	Information not included in the study report
Lot/batch no.:	E3240-85-1 (TSN311166)
Vehicle and/or positive control:	Not applicable

Test System

Test cells:	Normal Human Epidermal Keratinocytes (NHEK)
Source:	MatTek Corporation (Ashland, Massachusetts)
Media:	MatTek Corporation
Reagents:	MatTek Corporation

Study Design

Cell culture procedures

The EpiOcular model (OCL-200) uses Normal Human Epidermal Keratinocytes (NHEK) from a single donor as the cell source. The cells are cultured on polycarbonate membranes of cell culture inserts (MILLICELLs, 10 mm diameter, 0.6 cm² surface), in serum-free medium to form a multi-layered (5-8 cell layers), highly differentiated stratified, squamous epithelia that closely mimics human eye (corneal) epithelium at biochemical and physiological levels. The EpiOcular tissue is mitotically and metabolically active and releases many of the pro-inflammatory agents (cytokines) that are important in ocular irritation and inflammation.

Preliminary assay

NA

Definitive assays

The EpiOcular model estimates the potential ocular irritation of a test substance by measuring cytotoxicity following topical exposure (Freeman *et al*., 2010) (MatTek Corporation, Ashland, MA). This assay assumes that *in vitro* cytotoxicity is directly proportional to *in vivo* damage that a test substance would inflict upon exposure to the eye (cornea) (Jackson *et al*., 2006). This assumption is based in part on Maurer *et al*. (2002) proposed hypothesis, which suggests that the level of ocular irritation is related to the extent of initial injury, regardless of the processes leading to tissue damage.
The test consisted of topical application of the test material to the EpiOcular tissue for 30±2 min. followed by thorough washing with DPBS and incubating with cell culture medium. The EpiOcular tissues were then evaluated for viability using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay (Berridge *et al.*, 1996). Relative cell viability was calculated for each tissue as % of the mean of the negative control-treated tissues. Eye irritation potential of the test substance was classified into UN GHS Cat 1/2 or UN GHS Cat NC based on cell viability as described below.

Evaluation of Test Results

Data Analysis

The mean OD_{570} values of the blank wells were calculated. Individual blank-corrected OD_{570} values for each test chemical or control tissue were determined by subtracting the mean OD_{570} value of the blank wells from their individual OD_{570} values. The mean of the corrected OD_{570} values for the negative control were calculated.
Corrected Individual Tissue OD_{570} = Individual Tissue OD_{570} – mean Blank OD_{570} The following % of Control calculations were made for each individual tissue:

% viability = (Corrected Individual OD_{570} of Test Chemical (or Control) / Corrected mean OD_{570} of Negative Control) x 100

The individual % of Control viability values were tabulated for each individual tissue. Mean (and standard deviation) viability values were calculated for each test chemical and control.

Acceptability criteria

The results for negative and positive controls met assay acceptance criteria, suggesting appropriate conduct of the study. The corrected mean OD_{570} value of the negative control tissues (exposed for 30 minutes) was 2.227 (*i.e.*, □ 1.00; criteria set by the tissue manufacturer). The percent cell viability of the positive control (8.1%) showed a mean tissue viability <50%, relative to the negative control.

Results and discussions

Table A 2: Percent Cell Viability of GF-3308 in EpiOcular Eye Irritation Model

Test Material	% Viability	Irritancy Classification
GF-3308	4.1	UN GHS Category 1/2
Negative Control	100.0	UN GHS No Category (NC)
Positive Control	8.1	UN GHS Category 1/2

Conclusion

Under the experimental conditions, GF-3308 is an eye irritant. Thus, classification is required according to Regulation (EC) No. 1272/2008.

A 2.6.2 Study 2 Read across approach using data on GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.5/02
Report	xxx.; 2017; Acute Eye Irritation Study of GF-3521 in Rabbits; xxx; Lab Study No. 409-1-0115429; DAS Study No. 161064 ; 16 March 2017; Unpublished
Guideline(s)	Yes: OECD 405 (2012), OPPTS 870.2400 (1998), EC B.5 (2008), JMAFF 2-1-5 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber-brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Not applicable

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Strain:	New Zealand White
Age and weight at dosing:	14 to 17 weeks Weight (kg): Minimum 2.320, maximum 2.390
Source:	Animal Breeding Facility, Jai Research Foundation

Housing:	Individually
Feed and water:	Feed: Teklad certified Global High Fiber Rabbit Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Kent Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 19 to 22°C Humidity: 64 to 65% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	7 to 9 days

Study Design

In-life dates

Start: 22 November 2016 End: 08 December 2016

Animal assignment and treatment

The pH of GF-3521 was found to be 4.67 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment.

A total of 3 rabbits (3 males) 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.

On day 0, approximately 60 minutes prior to GF-3521 application, buprenorphine 0.01 mg/kg body weight was administered by subcutaneous injection (SC). Approximately 5 minutes prior to GF-3521 application, one to two drops of 0.5% proparacaine hydrochloride was applied to each eye.

A volume of 0.1 mL of GF-3521 (undiluted) 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 to remove residual test item at 24 h post application.

After 8 to 8.5 h of application, buprenorphine 0.01 mg/kg body weight SC and meloxicam 0.5 mg/kg body weight SC were administered to provide a continued therapeutic level of systemic analgesia. Initial 8-hour post GF-3521 application, buprenorphine 0.01 mg/kg body weight SC was administered every 12 (± 30 minutes) hours, in conjunction with meloxicam 0.5 mg/kg body weight SC every 24 (± 30 minutes) hours, until the ocular lesions resolved.

Irritation was scored by the method of Draize (as described in OECD Test Guideline no. 405) at 1, 24, 48, 72 hours and day 7. Fluorescein staining was used to assess the corneal epithelium damage at 24, 48, 72 h and on day 7 post GF-3521 application in all animals. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION Eye Irritation

At 1 h post GF-3521 application, the treated eye of all the rabbits revealed conjunctival redness (score of 1) and conjunctival chemosis (score of 1).

At 24 h post GF-3521 application, the treated eye revealed corneal opacity (score of 1) in rabbits 2 and 3; and conjunctival redness (score of 2) in all the rabbits.

At 48 and 72 h post GF-3521 application, the treated eye of all the rabbits revealed corneal opacity (score of 1), conjunctival redness (score of 2); and conjunctival chemosis (score of 1).

Examination with fluorescein dye and cobalt blue filter post GF-3521 application revealed corneal epithelium damage (10 to 40% of surface involvement) at 24, 48 and 72 h in all three rabbits.

Individual animal irritation scores are presented in Table 1.

Table 7: 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
Conjuctivae (redness)	1	2	2	2	0	N/A	N/A	1	2	2	2	0	N/A	N/A	1	2	2	2	0	N/A	N/A
Conjuctivae (chemosis)	1	1	1	1	0	N/A	N/A	1	1	1	1	0	N/A	N/A	1	1	1	1	0	N/A	N/A
Cornea (degree of opacity)	0	0	1	1	0	N/A	N/A	0	1	1	1	0	N/A	N/A	0	1	1	1	0	N/A	N/A
Iris inflammation	0	0	0	0	0	N/A	N/A	0	0	0	0	0	N/A	N/A	0	0	0	0	0	N/A	N/A

Key: N/A: not applicable/available

Conjunctivae - Redness (refers to palpebral and bulbar conjunctivae; excluding cornea and
0: No ulceration or opacity
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 iris)

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: Nacrous 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 were recorded and all animals gained body weight throughout the study.

CONCLUSION

The three individual animal average eye irritation scores (mean of scores observed at 24, 48 and 72 h post GF-3521 application) were: 2.00, 2.00, 2.00 for conjunctival redness; 1.00, 1.00, 1.00 for conjunctival chemosis; 0.67, 1.00, 1.00 for corneal opacity; and 0.00, 0.00, 0.00 for iris inflammation.

Recovery was completed in all animals by day 7.

A 2.6.3 Study 3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.5/03
Report	xxx; 2018; Acute Eye Irritation Study of GF-3309 in Rabbits; xxx; Lab Study No. 407-1-01-19445; DAS Study No. 180204; 18 August 2018; Unpublished
Guideline(s)	Yes: OECD 405 (2012), OPPTS 870.2400 (1998), EC B.5 (2008), JMAFF 21-5 (2000)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)
Vehicle:	Not applicable

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Strain:	New Zealand White (NZW)
Age and weight at dosing:	3.5 to 4.5 months Weight (kg): Minimum 2.060, Maximum 2.171
Source:	Sainath Agencies, Hyderabad, India
Housing:	Individually
Feed and water:	Feed: Teklad certified Global High Fiber Rabbit Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through reverse osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 19 to 22 °C Humidity: 64 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: 11 April 2018 End: 04 May 2018

Animal assignment and treatment

The pH of GF-3309 was found to be 5.32 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment.

A total of 3 rabbits (3 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.

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.

A volume of 0.1 mL of GF-3309 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.

Approximately 8 hours (± 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 (± 30 minutes), in conjunction with meloxicam 0.5 mg/kg body weight every 24 hours (± 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-3309 instillation. Fluorescein staining was used to assess the corneal epithelium damage at 24, 48 and 72 hours and on days 7 and 14 after the test item instillation in all animals. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION Eye Irritation

At 1 hour post GF-3309 instillation, the treated eye of all the rabbits revealed conjunctival redness [some blood vessels definitely hyperaemic (injected); score of 1] and conjunctival chemosis [some swelling above normal (includes nictitating membranes); score of 1].

At 24, 48 and 72 h post GF-3309 application, the treated eye of all the rabbits revealed conjunctival redness [diffuse, crimson colour, individual vessels not easily discernible; score of 2], conjunctival chemosis [obvious swelling with partial eversion of lids; score of 2] and discharge [any amount different from normal (does not include small amounts observed in inner canthus of normal animals); score of 1].

On day 7 post GF-3309 application, the treated eye of all the rabbits revealed conjunctival redness [diffuse, crimson colour, individual vessels not easily discernible; score of 2], conjunctival chemosis [some swelling above normal (includes nictitating membranes); score of 1 in rabbit N° 1 to obvious swelling with partial eversion of lids; score of 2 in rabbit N° 2 and 3] and discharge [any amount

different from normal (does not include small amounts observed in inner canthus of normal animals); score of 1].

On day 14 post GF-3309 instillation the treated eye of all rabbits appeared normal.

No corneal opacity and iritis reactions were observed in any of the rabbits throughout the experimental period.

Examination with fluorescein dye and cobalt blue filter was carried out post GF-3309 application in all rabbits. Rabbit N° 1 revealed 40%, 40%, 35%, 30% and 0%; rabbit N° 2 revealed 40%, 30%, 30%, 25% and 0%; rabbit N° 3 revealed 45%, 35%, 30%, 20% and 0%, corneal epithelium damage at 24, 48 and 72 h and on days 7 and 14, respectively.

Individual animal irritation scores are presented in Table 1.

Table 8: Grades for ocular lesions (eye treated with the test item)

Rabbit no.	1							2							3						
Site of application	Right							Right							Right						
Reaction post application	Hours				Days			Hours				Days			Hours				Days		
	1	24	48	72	7	14	21	1	24	48	72	7	14	21	1	24	48	72	7	14	21
Conjuctivae (redness)	1	2	2	2	2	0	N/A	1	2	2	2	2	0	N/A	1	2	2	2	2	0	N/A
Conjuctivae (chemosis)	1	2	2	2	1	0	N/A	1	2	2	2	2	0	N/A	1	2	2	2	2	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
0: No ulceration or opacity
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 iris)

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: Nacrous 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 were recorded and all animals gained body weight throughout the study.

CONCLUSION

GF-3309 caused conjunctival redness (scores of 1 and 2) and conjunctival chemosis (scores of 1 and 2) at 1, 24, 48 and 72 hours and on day 7 post instillation, in all rabbits, which resolved by day 14.

Examination with fluorescein dye and cobalt blue filter performed post application revealed corneal epithelium damage (20 to 45% of surface involvement) at 24, 48 and 72 h and on day 7 in all the three rabbits which resolved by day 14.

The three individual average eye irritation scores (mean of scores observed at 24, 48 and 72 hours post GF3309 application) were, for each rabbit respectively: 0.00, 0.00, 0.00 for corneal opacity, 0.00, 0.00, 0.00 for iris inflammation, 2.00, 2.00, 2.00 for conjunctival redness, 2.00, 2.00, 2.00 for conjunctival chemosis.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Rabbit	NZW	F	Eye	Instillation - washing at 24 h post instillation	Mean Redness Scores: 2.00, 2.00, 2.00 Mean Chemosis Scores: 2.00, 2.00, 2.00 Mean Corneal Scores: 0.00, 0.00, 0.00 Mean Iris Scores: 0.00, 0.00, 0.00 Recovery completed by 14 days

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Category 2/2A

A 2.7 Skin sensitisation (KCP 7.1.6)

A 2.7.1 Calculation approach (Regulation EC 1272/2008)

Comments of zRMS:	Skin sensitization assessment based on product composition is relevant and sufficient for hazard evaluation. Calculation is accepted (for details see Part C).

A skin sensitisation study with GF-3008 was not performed. Skin sensitisation potential of GF-3008 was estimated using the approach defined in the Regulation EC 1272/2008. As none of the components in GF3008 are classified for skin sensitisation, estimation of skin sensitisation potential of GF-3008 is not applicable. Composition and calculation details are provided in dRR Part C.

Conclusion

Estimation of the skin sensitisation potential of GF-3008 is not applicable as none of the components in GF-3008 are classified for skin sensitisation. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.7.2 Read across approach using data from GF-3521

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3521 to the formulation of interest GF-3308, study has not been taken into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP 7.1.6/1
Report	xxx.; 2017; Skin Sensitisation Study of GF-3521 by Local Lymph Node Assay in Mice; xxxx; Lab Study No. 409-1-01-15429; DAS Study No. 161064 ; 15 March 2017; Unpublished

Guideline(s)	Yes: OECD 429 (2010), OPPTS 870.2600 (2003), EC B.42 (2008)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication	No

(if vertebrate study)

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3521
Purity:	4.9 wt% XDE-777 AI (50 g/L); 8.0 wt% Propiconazole AI (82 g/L)
Description (physical state):	Amber–brown liquid
Lot/batch no.:	201500340-15-1 (TSN312215)
Compound stability:	Not applicable
Vehicle and/or positive control:	Vehicle: 1% Pluronic®L-92 Surfactant; Positive control: HCA (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 18.7, maximum 26.1
Source:	Animal Breeding Facility, Jai Research Foundation
Housing:	Animals were group-housed during acclimatisation. On the days of test item application (days 0, 1 and 2), the animals were housed in individual cages. From day 3 the animals were group-housed 5 mice/cage. On day 5 post administration of the radiolabelled material, the animals were transferred to the metabolic cages.
Feed and water:	Feed: Teklad certified Global High Fibre Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through Kent Reverse Osmosis water filtration system *ad libitum*
Environmental conditions:	Temperature: 20 to 23°C Humidity: 57 to 66% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 h dark/12 h light
Acclimation period:	7 days

Study Design

In-life dates

Start: 30 November 2016 End: 21 December 2016

Preliminary test and dose selection

In a preliminary test, 4 groups of mice comprising 2 females per group were treated with GF-3521, applied at 5%, 25%, 50% and 100% (v/v) in 1% solution of Pluronic® L-92 for three consecutive days (days 0, 1 and 2). 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 at the site of application at the dose concentrations of 5%, 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92 while very slight erythema was observed at 100% GF-3521 in 1% solution of Pluronic® L-92. Ear thickness increase was below 25% on days 2 and 5 at the dose concentration of 5%, 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92 while ear thickness increase of more than 25% was observed at 100% (undiluted) on day 5. Therefore, dose concentrations of 5%, 25% and 50% (v/v) GF-3521 in 1% solution of 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-3521 at concentrations of 5%, 25% and 50% (v/v) in 1% solution of Pluronic® L-92. Female mice from the vehicle control and positive control groups were maintained in similar conditions with treatment of 1% solution of Pluronic® L-92 and 25% (v/v) of HCA in 1% solution of Pluronic® 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) 250 µL of sterile phosphate buffered saline (PBS) containing approximately (20±1) µCi of tritiated methyl thymidine. On day 5, five hours (5 h) post injection of ^{3}H-methyl thymidine, 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 ^{3}H-methyl thymidine 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 meet 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 clinical signs were observed in any of the mice from the control, positive control and groups treated at 5%, 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92.

No erythema was observed at the site of application of control group and at the dose levels of 5%, 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92. Very slight erythema was observed in the group treated with 25% (v/v) HCA in 1% solution of Pluronic® L-92 (during days 1 to 4) in all mice (5/5 mouse)).

Body Weight

The mean body weight of positive control as well as GF-3521 treated mice was comparable to that of the control group.

Group Mean DPM

Proliferative responses in the draining lymph nodes were monitored by measuring the incorporation of ^{3}Hmethyl thymidine. These analyses revealed group mean DPM mouse values of 841.60, 1281.20, 3796.20, 5660.60 and 9652.80 for the vehicle control (1% L-92), 5%, 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92 and positive control (25% v/v HCA in 1% solution of Pluronic® L-92), respectively.

A statistically significant increase in DPM was observed at 25% and 50% (v/v) GF-3521 in 1% solution of Pluronic® L-92 and 25% (v/v) HCA in 1% solution of Pluronic® L-92 when compared to control group values.

Stimulation Index (SI Value) and EC_3 Value

Stimulation Index (SI) values calculated for groups treated with GF-3521 were found to be 1.52, 4.51 and 6.73 at the dose concentrations of 5%, 25% and 50% (v/v) in 1% solution of Pluronic® L-92, respectively and 11.47 for 25% (v/v) HCA in 1% solution of Pluronic® L-92 positive control group.

Individual and group mean values are reported in Table 1.

Table 9: 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	1336	841.60 ± 422.02	(1)
	2	1133		
	3	246		
	4	818		
	5	675		
GF-3521 5% v/v in vehicle	6	1319	1281.20 ± 391.31	1.52
	7	1258		
	8	1147		
	9	800		
	10	1882		
GF-3521 25% v/v in vehicle	11	4393	3796.20 ± 999.48↑↑	4.51
	12	4833		
	13	2850		
	14	2606		
	15	4299		
GF-3521 50% v/v in vehicle	16	4750	5660.60 ± 1716.00↑↑	6.73
	17	5935		
	18	8548		
	19	4496		
	20	4574		
HCA (Positive control) 25% v/v in 1% Pluronic® L-92	21	11546	9652.80 ± 2793.28↑↑	11.47
	22	7708		
	23	10402		
	24	5910		
	25	12698		

↑↑= Significantly higher than control (p □ 0.01)

CONCLUSION

The SI obtained for GF-3521 at 25% and 50% (v/v) in 1% solution of Pluronic® L-92 concentration showed a greater than threefold increase over the control value with an EC_3 value found to be 14.90%. Therefore, GF-3521 is a dermal sensitiser.

A 2.7.3 Study 3 Read across approach using data on GF-3309

Comments of zRMS:	From the scientific point of view study is valid however due to the differences in composition of GF-3309 to the formulation of interest GF-3308, study has not been taken

	into the consideration. See our detailed comment regarding read-across approach point A 2.1

Reference	KCP.7.1.6/2
Report	xxx.: 2018; Skin Sensitisation Study of GF-3309 by Local Lymph Node Assay in Mice; xxx; Lab Study No. 409-1-01-19446; DAS Study No. 180205; 18 August 2018; Unpublished
Guideline(s)	Yes: OECD 429 (2010), OPPTS 870.2600 (2003), EC B.4 (2008),
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

.

MATERIALS AND METHODS Test Item(s)

Test item (Common name):	GF-3309
Purity:	6.2 wt% (63 g/L) Pyraclostrobin; 4.9 wt% (50 g/L) Fenpicoxamid
Description (physical state):	Amber to brown liquid
Lot/batch no.:	ENBK-166226-023-1 (TSN314593)

Vehicle/Control Item(s)

Vehicle/Negative control:	1% Pluronic® L92
Positive control:	α-hexylcinnamaldehyde, 25% v/v in 1% Pluronic® L92

Test System

Species:	Mouse *(Mus musculus)*
Strain:	CBA/J
Age and weight at dosing:	10 to 12 weeks Weight (g): Minimum 19.3, Maximum 23.4
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 High Fiber Rat/Mice Feed manufactured by Envigo, U.S.A. *ad libitum* Water: UV sterilized water filtered through reverse osmosis water filtration system *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: 10 April 2018 End: 23 May 2018

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, 4 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 µL/ear) with GF-3309 at concentrations of 10%, 25%, 50% (v/v) in 1% Pluronic® L92 and 100% GF-3309 (undiluted).

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, an increase of >25% in ear thickness was observed at 25%, 50% (v/v) in 1% Pluronic® L92 and 100% GF-3309 (undiluted) while an increase of <25% in ear thickness was observed at 10% (v/v) in 1% Pluronic® L92. Erythema was observed at 25% and 50% (v/v) in 1% Pluronic® L92 and 100% GF-3309 (undiluted). Therefore, dose concentrations of 2.5%, 5.0% and 10% (v/v) in 1% Pluronic® L92 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-3309 at concentrations of 2.5%, 5.0% and 10% (v/v) in 1% Pluronic® L92. Female mice from the vehicle control and positive control groups were maintained in similar conditions with treatment of 1% Pluronic® L92 and 25% (v/v) of HCA in 1% Pluronic® L92, 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 (^{3}H-TdR). On day 5, 5 hours post injection of ^{3}H-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 ^{3}H-TdR into the auricular (local) lymph nodes draining the site of chemical application was measured to assess the lymph node proliferative response.

RESULTS AND DISCUSSION

Clinical Observations and Irritation

No signs of toxicity were observed in any of the mice from all groups, including controls.

No erythema was observed at the site of application at the dose levels of 2.5%, 5.0% and 10% (v/v) in 1% Pluronic® L92. In all mice treated with 25% (v/v) HCA, a local reaction consisting of erythema (score of 1) was observed from days 1 to 5. **Body Weight**

No effect on body weight was observed in mice treated with GF-3309, positive control and vehicle control.

Group Mean DPM

Proliferative responses in the draining lymph nodes were monitored by measuring the incorporation of ^{3}Hmethyl thymidine. These analyses revealed group mean DPM mouse values of 1637.60, 1608.80, 2508.40, 4342.80 and 9063.00 for the vehicle control (1% L92), 2.5%, 5.0% and 10.0% (v/v) in 1% Pluronic® L92 treated groups, and positive control (25% v/v HCA), respectively.

Stimulation Index (SI Value) and EC_3 Value

Stimulation Index (SI) values calculated for groups treated with GF-3309 were found to be 0.98, 1.53 and 2.65 at the dose concentrations of 2.5%, 5.0% and 10.0% (v/v) in 1% Pluronic® L92, respectively, and 5.53 for 25% (v/v) HCA positive control group.

The SI obtained for GF-3309 showed a less than threefold increase over the control value at all the tested concentrations. Therefore, EC_3 value cannot be calculated.
Individual and group mean values are reported in Table 1.

Table 10: 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® L92)	1	1375	1637.60 ± 476.95	(1)
	2	2166		
	3	2028		
	4	1621		
	5	998		
2.5% (v/v) in 1% Pluronic® L92	6	967	1608.80 ± 564.87	0.98
	7	1863		
	8	2262		
	9	1065		
	10	1887		
5.0% (v/v) in 1% Pluronic® L92	11	793	2508.40 ± 1068.67	1.53
	12	3032		
	13	3666		
	14	2452		
	15	2599		
10.0% (v/v) in 1% Pluronic® L92	16	4911	4342.80 ± 627.75	2.65
	17	4647		
	18	4727		
	19	3380		
	20	4049		
HCA (Positive control) 25% (v/v) in 1% Pluronic® L92	21	5721	9063.00 ± 3545.45	5.53
	22	5885		
	23	8270		
	24	13626		
	25	11813		

CONCLUSION

The SI obtained for GF-3309 at all tested concentrations showed a less than threefold increase over the control value. Therefore, GF-3309 did not demonstrate dermal sensitisation potential in the local lymph node assay.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3309	Mouse	CBA/J	F	Dermal	Topical - Local lymph node assay	Dermal non sensitiser SI = 0.98, 1.53 and 2.65 at 2.5%, 5.0% and 10% (v/v), respectively.

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 7, GHS 2017)	Unclassified

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 2.9.1 Material safety data sheet for each co-formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

No specific dermal absorption study was performed with GF-3008. Accordingly, as per EFSA GD on dermal absorption, default values were used for fenpicoxamid.

A 2.11 Other/Special Studies

No further studies were conducted on GF-3308.

version

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for fenpicoxamid

Table A 1: Input parameters considered for the estimation of operator exposure

Substance	Fenpicoxamid Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1 kg a.s. /ha	Spray dilution = 1 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted		Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product Dermal for in use diluation = 70 Oral = 12 = 70		Inhalation = 100	
RVNAS	0.05 mg/kg bw/day	RVAAS	0.2 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg	DT50 a.s./ha	30 days	

Table A 2: Estimation of operator exposure towards active substance (no PPE) according to EFSA guidance

Operator Model		Mixing, loading and application AOEM			
Potential	Longer term systemic exposure mg/kg bw/day exposure		0.3415	% of RVNAS	683.00%
	Acute systemic exposure mg/kg bw/day		2.1979	% of RVAAS	1098.97%
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure options	Longer term systemic exposure mg/kg bw/day (including PPE above)		0.2089	% of RVNAS	417.89%
	Acute systemic exposure mg/kg bw/day		0.8407	% of RVAAS	420.33%

Table A 3: Estimation of operator exposure towards active substance (PPE) according to EFSA guidance

Operator Model		Mixing, loading and application AOEM			
Potential	Longer term systemic exposure mg/kg bw/day exposure		0.3415	% of RVNAS	683.00%
	Acute systemic exposure mg/kg bw/day		2.1979	% of RVAAS	1098.97%
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure options	Longer term systemic exposure mg/kg bw/day (including PPE above)		0.0070	% of RVNAS	14.02%
	Acute systemic exposure mg/kg bw/day		0.0852	% of RVAAS	42.62%

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for fenpicoxamid

Table A 4: Input parameters considered for the estimation of worker exposure

Crop type	Cereals	
Indoor or outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Worker's task	Inspection, irrigation	
Main body parts in contact with foliage	Hand and body	
Application rate of active substance	0.1 kg a.s./ha	*i_AppRate*
Number of applications	1	*i_AppNo*
Interval between multiple applications	365 days	*i_AppInt*
Half-life of active substance	30 days	*d_HalflifeAS*
Multiple application factor	1.0	*d_MAF*
Dermal absorption of the product	70.00%	*i_AbsorpProduct*
Dermal absorption of the in-use dilution	70.00%	*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3 µg a.s./cm^2	*d_DFR*
Working hours	2 hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500 cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400 cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10^(-3)	*d_InhalTcSort*

Table A 5: Estimation of worker exposure towards fenpicoxamid according to EFSA guidance

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	5.2500000	0.5880000	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0875000	0.0098000		
% of RVNAS	175.00%	19.60%		

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for fenpicoxamid

Table A 6: Input parameters considered for the estimation of longer term resident exposure

Croptype	Cereals		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Formulation type	entrates, emulsifiable concentrate, etc.		
Buffer strip	2-3	m	
Application rate of the product	0.1	kg a.s./ha	
Concentration of active substance (in-use dilution for liquid applications)	1	g a.s./l	
Dermal absorption of product	70.00%		
Dermal absorption of in-use dilution	70.00%		
Oral absorption	12.00%		
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm²	*i_AppEquip*
			i_FormVal
Vapour pressure of in-use dilution	low volatile substances having a vapour		*i_Buffer*
		Pa	
Concentration in air	pressure of <5*10-3Pa		*i_AppRate*
Resident dermal spray drift exposure 75th percentile - adult	0.001	mg/m³	*d_ConcAS*
Resident dermal spray drift exposure 75th percentile - child	0.47	ml spray dilution/person	*i_AbsorpProduct*
Resident inhal. spray drift exposure 75th percentile - adult	0.327	ml spray dilution/person	*i_AbsorpInuse*
Resident inhal. spray drift exposure 75th percentile - child	0.00010	ml spray dilution/person	*i_AbsorpOralInuse*
Resident dermal spray drift exposure mean - adult	0.00022	ml spray dilution/person	*d_DFR*
Resident dermal spray drift exposure mean - child	0.22318	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.18	ml spray dilution/person	*i_Volat d_AirCon*
Resident inhal. spray drift exposure mean - child	0.00009	ml spray dilution/person	
Exposure duration dermal	0.00017	ml spray dilution/person	*d_ReExpDur*
Exposure duration inhalation	2	hours	
Exposure duration entry into treated crops	24	hours	*d_ReExpDurInhal*
Light clothing adjustment factor	0.25	hours	
Breathing rate adult	18.0%		
Breathing rate child (1-3 year old)	0.23	m³/day/kg	*d_ExpDurTreatCrop*
Drift percentage on surface (75th percentile)	1.07	m³/day/kg	
Drift percentage on surface (mean)	5.60%		*d_ClothAF*
Turf transferable residues percentage	4.10%		
Transfer coeff. of surface deposits-adult	5.00%		*d_BreathRAd*
Transfer coeff. of surface deposits-child (1-3 year old)	7300	cm²/hour	
Saliva extraction percentage	2600	cm²/hour	*d_BreathRCh*
Surface area of hands mouthed	50.00%		
Frequency of hand to mouth activity	20	cm²	
Ingestion rate for mouthing of grass per day	9.5	events/hour	*d_Turf*
Dislodgeable residues percentage transferability for object to mouth	25	cm²	*d_ReTCAd*
Transfer coefficient for entry into treated crops (75th percentile) - adu	20.00%		*d_ReTCCh*
Transfer coefficient for entry into treated crops (75th percentile) - chi	7500	cm²/h	*d_SalExt*
Transfer coefficient for entry into treated crops (mean) - adult	2250	cm²/h	*d_AreaHM*
Transfer coefficient for entry into treated crops (mean) - child	5980	cm²/h	*d_ReFreqHM*
	1794	cm²/h	*d_MouthGrass*
			d_DRP
			d_TcEntryAd
			d_TcEntryCh
			d_TcEntryAd
			d_TcEntryCh

Table A 7: Estimation of resident exposure towards fenpicoxamid (EFSA Model)

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.1879180	0.0107000	0.0102894	0.1181250	0.2159083
Total systemic exposure per kg body weight	0.0187918	0.0010700	0.0010289	0.0118125	0.0215908
(mg/kg bw/day) % of RVNAS	37.58%	2.14%	2.06%	23.63%	43.18%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.2698800	0.0138000	0.0286160	0.3937500	0.4768963
Total systemic exposure per kg body weight	0.0044980	0.0002300	0.0004769	0.0065625	0.0079483
(mg/kg bw/day) % of RVNAS	9.00%	0.46%	0.95%	13.13%	15.90%

version

Table A 8:

Croptype	Cereals		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		*i_AppEquip*
Formulation type	oluble concentrates, emulsifiable concentrate, etc.		
Application rate of the product	0.1	kg a.s./ha	*i_AppRate*
Buffer strip	2-3	m	*i_Buffer*
Concentration of active substance (in-use dilution for liquid applications)	1	g a.s./l	*d_ConcAS*
Dermal absorption of product	70.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	70.00%		*i_AbsorpInuse*
Oral absorption	12.00%		*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm^2	*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa	*i_Volat*
Concentration in air	0.001	mg/m^3	*d_AirCon*
Bystander dermal spray drift exposure - adult	1.21	ml spray dilution/person	
Bystander dermal spray drift exposure - child	0.74	ml spray dilution/person	
Bystander inhal. spray drift exposure - adult	0.00050	ml spray dilution/person	
Bystander inhal. spray drift exposure - child	0.00112	ml spray dilution/person	
Exposure duration	2	hours	*d_ByExpDur*
Exposure duration entry into treated crops	0.25	hours	*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%		*d_ClothAF*
Breathing rate adult	0.23	m^3/kg bw/day	*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/kg bw/day	*d_BreathRCh*
Drift percentage on surface (90th percentile)	8.50%		
Turf transferable residues percentage	5.00%		*d_Turf*
Transfer coeff. of surface deposits-adult	14500	cm^2/hour	*d_ByTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	5200	cm^2/hour	*d_ByTCCh*
Saliva extraction percentage	50.00%		*d_SalExt*
Surface area of hands mouthed	20	cm^2	*d_AreaHM*
Frequency of hand to mouth activity	20	events/hour	*d_ByFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2	*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%		*d_DRP*
Transfer coefficient for entry into treated crops - ad	7500	cm^2/h	*d_TcEntryAd*
Transfer coefficient for entry into treated crops - ch	2250	cm^2/h	*d_TcEntryCh*

Input parameters considered for the estimation of acute bystander exposure

Table A 9: Estimation of acute bystander exposure towards fenpicoxamid (EFSA Model)

1.1 1-3 year old child

	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.4258800	0.0107000	0.0311950	0.1181250
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0425880	0.0010700	0.0031195	0.0118125
% of RVAAS	21.29%	0.54%	1.56%	5.91%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.6950400	0.0138000	0.0862750	0.3937500
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0115840	0.0002300	0.0014379	0.0065625
% of RVAAS	5.79%	0.12%	0.72%	3.28%

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.