

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

GF-4021

Product name: LaDiva

Chemical active substances:

Halauxifen-methyl 10 g a.s./L (9.594 g a.e./L)

Picloram 48 g a.s./L

Aminopyralid 32 g a.s./L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(new submission of the product)

Applicant: Dow AgroSciences

Submission date: November 2020

MS Finalisation date: September 2021 (initial Core Assessment)

December 2022 (final Core Assessment)

Version history

When	What
November 2020	Initial dRR Part B6, new submission of GF-4021 to the Central Zone.
September 2021	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 .
December 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 .

Table of Contents

6	Mammalian Toxicology (KCP 7).....	5
6.1	Summary.....	5
6.2	Toxicological Information on Active Substance(s).....	8
6.3	Toxicological Evaluation of Plant Protection Product	9
6.4	Toxicological Evaluation of Groundwater Metabolites	11
6.5	Dermal Absorption (KCP 7.3).....	11
6.5.1	Justification for proposed values – Halauxifen-methyl	11
6.5.2	Justification for proposed values – Picloram.....	12
6.5.3	Justification for proposed values – Aminopyralid.....	12
6.6	Exposure Assessment of Plant Protection Product (KCP 7.2)	12
6.6.1	Selection of critical use(s) and justification.....	13
6.6.2	Operator exposure (KCP 7.2.1)	13
6.6.2.1	Estimation of operator exposure.....	13
6.6.2.2	Measurement of operator exposure	14
6.6.3	Worker exposure (KCP 7.2.3)	14
6.6.3.1	Estimation of worker exposure.....	14
6.6.3.2	Refinement of generic DFR value (KCP 7.2).....	15
6.6.3.3	Measurement of worker exposure	15
6.6.4	Resident and bystander exposure (KCP 7.2.2)	15
6.6.4.1	Estimation of resident and bystander exposure	15
6.6.4.2	Measurement of resident and/or bystander exposure	16
6.6.5	Combined exposure	16
6.6.5.1	Exposure assessment halauxifen-methyl, picloram, and aminopyralid in GF-4021	16
Appendix 1	Lists of data considered in support of the evaluation.....	19
Appendix 2	Detailed evaluation of the studies relied upon	22
A 2.1	Statement on bridging possibilities.....	22
A 2.2	Acute oral toxicity (KCP 7.1.1).....	22
A 2.3	Acute percutaneous (dermal) toxicity (KCP 7.1.2)	25
A 2.4	Acute inhalation toxicity (KCP 7.1.3)	27
A 2.5	Skin irritation (KCP 7.1.4)	30
A 2.6	Eye irritation (KCP 7.1.5).....	33
A 2.7	Skin sensitisation (KCP 7.1.6).....	40
A 2.8	Supplementary studies for combinations of plant protection products (KCP 7.1.7)	44
A 2.9	Data on co-formulants (KCP 7.4).....	44
A 2.10	Studies on dermal absorption (KCP 7.3)	44
A 2.11	Other/Special Studies	44
Appendix 3	Exposure calculations.....	45
A 3.1	Operator exposure calculations (KCP 7.2.1.1)	45
A 3.2	Worker exposure calculations (KCP 7.2.3.1)	48
A 3.3	Resident and bystander exposure calculations (KCP 7.2.2.1)	50
A 3.4	Combined exposure calculations for halauxifen-methyl, picloram, and aminopyralid.....	52

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).....	53
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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-4021’/LaDiva 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/active substances renewal and has not previously been evaluated in any EU countries according to the Uniform Principles.

For the current product registration, applicant provided relevant data on the plant protection product ‘GF-4021’/LaDiva regarding toxicological potential of the product, based on *in vivo* and *in vitro* tests. ZRMS accepted already existing *in vivo* studies for the purposes of hazard classification and do not request for the new *in vivo* data. Considering 3R rules and stepwise approach applicant were performed two *in vitro* studies (irritating potential for eye (..... 2020, No 200696 OECD TG 437 and No 190394 OECD TG 492) leading to positive results (causes serious eye damage) that were sufficient for a final assessment, thus both studies has been considered as appropriate for hazard classification and were accepted by the ZRMS. Product classification has been agreed by the ZRMS taking into account both *in vivo* and *in vitro* studies.

Regarding *in vivo* studies Reviewer points out that since there are *in vivo* tests already exist the information gained on animal studies are more than just a classification. Existing animal studies allow to identify of effects following a single exposure to the plant protection product can be established. The data is sufficient to indicate the time course and characteristics of the effect with full details of behavioral changes and possible gross pathological findings at post-mortem. These studies are valid for hazard classification and toxicological risk assessment.

NDE assessment and Combined exposure calculations provided for operator, workers and B&R resulting from use of ‘GF-4021’/LaDiva (*EC formulation containing 10g/L (9.594g ae/L) g/kg of halauxifen-methyl, 48g/kg picloram and 32g/L aminopyralid for use as a herbicide in winter oil seed rape; refer dRR part B0*) considering critical use(s), identify safe use of the product ‘GF-4021’/LaDiva.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on GF-4021/LaDiva *

Product name and code	GF-4021/LaDiva
Formulation type	Emulsifiable concentrate [Code: EC]
Active substance(s) (incl. content)	Halauxifen-methyl, 10 g a.s./L (9.594 g a.e./L); Picloram, 37.5 g a.s./L, Aminopyralid 187.5 g a.s./L
Function	Herbicide
Product already evaluated as the ‘representative formulation’ during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

* Information on the detailed composition of GF-4021/LaDiva 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-4021/LaDiva according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin irritation Cat 2; Eye irritation Cat 1; STOT SE Cat 3
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS05, GHS07
Signal word	Danger
Hazard statement(s)	H315: Causes skin irritation. H318: Causes serious eye damage H335: May cause respiratory irritation.
Precautionary statement(s)	P261: Avoid breathing mist/vapours/spray. P280: Wear protective gloves/ protective clothing /eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of water. P304 + P340: IF INHALED: Remove person to fresh air and keep comfortable for breathing. P305 + P351 + P338 + P310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor. 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 GF-4021/LaDiva

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves required during mixing/loading/application and safety glasses when handling concentrated product due to product classification Gloves and safety glasses required when handling concentrated product during mixing and loading due to product classification
Workers	Acceptable	None
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. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind (incl. application technique ***	Max. number (min. interval between applications) a) per use b) per crop/season	Max. application rate kg as/ha a) halauxifen-methyl b) picloram c) aminopyralid	Water L/ha min / max			Operator	Worker	Residents	Bystander
1	Winter oil seed rape (BBCH 12 – 19)	F	Broadcast Foliar Spray, LCTM	a) 1 b) 1	a) 0.0025 (0.0024 ae) b) 0.012 c) 0.008	100 - 300	N/A	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				

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

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

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

Explanation for column 10 “Acceptability of exposure assessment”

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





Data gaps

Noticed data gaps are: no data gaps have been noticed.

6.2 Toxicological Information on Active Substance(s)

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

Table 6.2-1: Information on active substances

	Halauxifen-methyl	Picloram	Aminopyralid
Common Name	Halauxifen-methyl	Picloram	Aminopyralid
CAS-No.	943831-98-9	1918-02-1	150114-71-9
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	<p>Hazard classes, categories: Chronic aquatic Cat 1</p> <p>Codes for hazard pictograms:</p>  <p>GHS09</p> <p>Signal word: Warning</p> <p>Hazard statements: H410: Very toxic to aquatic life with long lasting effects.</p> <p>Precautionary statements: P273: Avoid release to the environment. P501: Dispose of contents/container in accordance with applicable regulations.</p> <p>EU specific statements: EUH401: To avoid risks to human health and the environment, comply with the instructions for use.</p>	<p>Hazard classes, categories: Chronic aquatic Cat 1</p> <p>Codes for hazard pictograms:</p>  <p>GHS09</p> <p>Signal word: Warning</p> <p>Hazard statements: H410: Very toxic to aquatic life with long lasting effects.</p> <p>Precautionary statements: P273: Avoid release to the environment. P305/351/338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.</p> <p>P501: Dispose of contents/container in accordance with applicable regulations.</p> <p>EU specific statements: EUH401: To avoid risks to human health and the environment, comply with the instructions for use.</p>	<p>Not classified (no harmonised classification)</p> <p>Hazard classes, categories: Eye irritation Cat 1 Chronic aquatic Cat 1</p> <p>Codes for hazard pictograms:</p>   <p>GHS05 GHS09</p> <p>Signal word: Danger</p> <p>Hazard statements: H318: Causes serious eye damage H410: Very toxic to aquatic life with long lasting effects.</p> <p>Precautionary statements: P273: Avoid release to the environment. P280: Wear protective gloves/protective clothing/eye protection/face protection. P305/351/338/310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor. P391: Collect spillage. P501: Dispose of contents/container in accordance with applicable regulations.</p> <p>EU specific statements: EUH401: To avoid risks to human health and the environment, comply with the instructions for use.</p>
Additional C&L proposal	No need for the proposal for additional C&L as sufficient harmonized classification is available	No need for the proposal for additional C&L as sufficient harmonized classification is available	Peer review of aminopyralid (EFSA 2013) proposed H318 and STOT-SE (nervous system) (category 2 or 4)

	Halauxifen-methyl	Picloram	Aminopyralid
Agreed EU endpoints			
AOEL systemic	0.058 mg/kg bw/d	0.3 mg/kg bw/d	0.26 mg/kg bw/d (correction for oral absorption not required)
Reference	EFSA Journal 2014;12(12):3913 [Rabbit developmental study (....., 2012; Study ID: 111137)]	EFSA Journal 2009; 7(12):1390 [Rabbit developmental study supported by 1 year dog study (..... 1992; Study ID: K-049877-015;, 1988; Study ID: K-038323-040)]	EFSA Journal 2013;11(9): 3352 [Rabbit Developmental Study; 2002; Study ID: 0011047]
Conditions to take into account/critical areas of concern with regard to toxicology			
Review Report/EFSA Conclusion for active substance	None	None	None

6.3 Toxicological Evaluation of Plant Protection Product

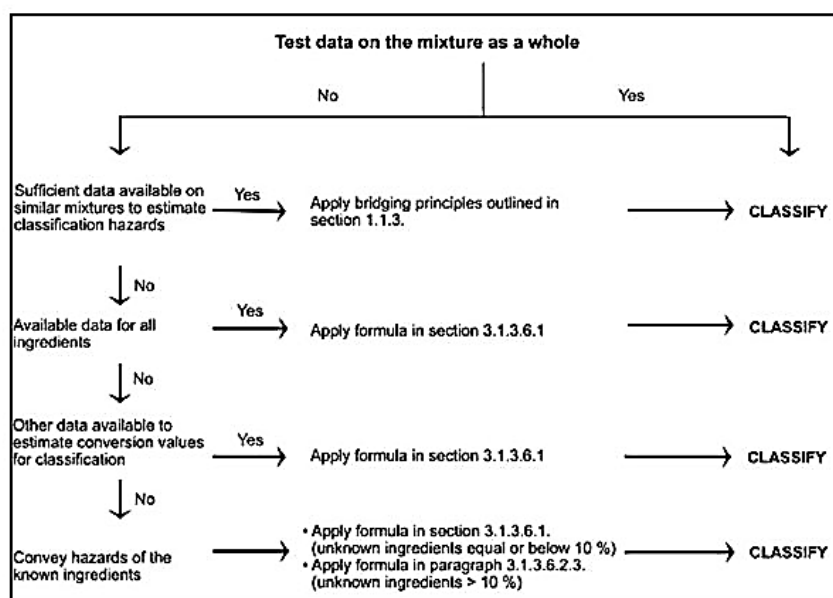
In accordance with Article 33.3.c the applicant confirms that no vertebrate studies were performed for the purpose of providing data on formulation GF-4021/LaDiva in the EU. Acute *in vivo* studies are presented in this dossier which were not conducted to meet the requirements for assessment of acute mammalian toxicity under Regulation (EC) No. 1107/2009. Rather they were conducted to meet the requirements for registering GF-4021 in several non-EU countries where there is no accepted alternative approach to the *in vivo* testing of the formulations.

Therefore, the application aligns fully with the criteria laid down in Regulation (EC) Article 62 and the supporting Regulation (EC) 283/213 5.5.1 as these articles state that no vertebrate testing should be performed where alternative methods exist as explained the studies were not performed for the purpose of the EU submission.

In accordance with CLP Regulation (EC) No. 1272/2008 it is stated that where test data is available on a given formulation this given data must be submitted and used to determine the classification. Please see below the excerpt of the regulation.

Figure 3.1.1

Tiered approach to classification of mixtures for acute toxicity



Reference- Regulation (EC) 1272/2008 section 3.1.3 Figure 3.1.1

A summary of the toxicological evaluation for GF-4021/LaDiva is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for GF-4021/LaDiva

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral, rat (OECD 423)	> 2000 mg/kg bw	Yes	None2020.
LD ₅₀ dermal, rat (OECD 402)	> 2000 mg/kg bw	Yes	None No.: 190373; 2020.
LC ₅₀ inhalation, rat (OECD 436)	5.91 mg GF-4021/L air	Yes	Hazard statement (Triggered by concentration limits, not study result): STOT SE Cat 3: H335: May cause respiratory irritation. No.: 190377; 2020
Skin irritation, rabbit (OECD 404)	Irritant (moderate to severe dermal reaction fully reversible by day 14).	Yes	Hazard statement: Skin irritation Cat 2. H315: Causes skin irritation. Report No.: 190381; 2020
Eye irritation, <i>in-vitro</i> (OECD TG 437)	Irritant (Predicted to be a severe eye irritant)	Yes	Hazard statement (Triggered by a combination of <i>in-vitro</i> studies): Eye irritation Cat 1; H318: Causes serious eye damage DAS Report No.: 200696; 2020
Eye irritation, <i>in-vitro</i> (OECD TG 492)	Irritant (Considered to have potential for eye irritation or serious eye damage)	Yes	Hazard statement (Triggered by a combination of <i>in-vitro</i> studies): Eye irritation Cat 1; H318: Causes serious eye damage DAS Report No.: 190394; 2020
Skin sensitisation, mouse (OECD 429/LLNA)	Non-sensitising	Yes	None; DAS Report No.: 190544; 2020.
Supplementary studies for combinations of plant protection products	No data – not required	-	-	-

Table 6.3-2: Additional toxicological information relevant for classification/labelling of GF-4021/LaDiva

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Halauxifen-methyl 10 g a.s. (9.594 g a.e.)/L; Aminopyralid 32 g a.s./L; Picloram 48 g a.s./L.	Hazard statements: Halauxifen-methyl: Not classified. Aminopyralid: H318: Causes serious eye damage. Picloram: Not classified.	Reg. 1272/2008 / MSDS** / Halauxifen-methyl: EFSA Journal 2014;12(12):3913. Aminopyralid: EFSA Journal 2013;11(9):3352.	Hazard statements: Skin irritation Cat 2 H315: Causes skin irritation. Eye irritation Cat 1 H318: Causes serious eye damage. STOT SE Cat 3 H335: May cause respiratory irritation.

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
			Picloram: EFSA Journal 2009;7(12): 1390.	
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	No data – not required	No data – not required	No data – not required

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

** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

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

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in GF-4021/LaDiva are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GF-4021/LaDiva

	Halauxifen-methyl		Picloram		Aminopyralid	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	70%	Default value for an EC formulation with active substance concentration ≤50 g/L (EFSA dermal absorption guidance, 2017; SANTE/2018/ 10591 rev 1)	70%	Default value for an EC formulation with active substance concentration ≤50 g/L (EFSA dermal absorption guidance, 2017; SANTE/2018/ 10591 rev 1)	70%	Default value for an EC formulation with active substance concentration ≤50 g/L (EFSA dermal absorption guidance, 2017; SANTE/2018/ 10591 rev 1)
Dilution	70%	Default value for diluted EC formulation based on 2017 EFSA Guidance on Dermal Absorption	70%	Default value for diluted EC formulation based on 2017 EFSA Guidance on Dermal Absorption	70%	Default value for diluted EC formulation based on 2017 EFSA Guidance on Dermal Absorption

6.5.1 Justification for proposed values – Halauxifen-methyl

No data on dermal absorption for halauxifen-methyl in GF-4021/LaDiva is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, and SANTE/2018/10591 rev 1) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for halauxifen-methyl

	Value	Justification for value	Acceptability of justification
Concentrate	70%	Default value for a solution with an active substance concentration ≤50 g/L for EC formulation based on EFSA dermal absorption guidance (EFSA, 2017; SANTE/2018/10591 rev 1)	Proposed default dermal absorption value and justification are accepted
Dilution	70%	Default value for diluted EC WG formulation as stated in the EFSA guidance document on dermal absorption	Proposed default dermal absorption value and justification

	Value	Justification for value	Acceptability of justification
		(EFSA, 2017)	are accepted

6.5.2 Justification for proposed values – Picloram

No data on dermal absorption for halauxifen-methyl in GF-4021/LaDiva is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, and SANTE/2018/10591 rev 1) are presented in the following table.

Table 6.5-3: Default dermal absorption rates for picloram

	Value	Justification for value	Acceptability of justification
Concentrate	70%	Default value for a solution with an active substance concentration ≤ 50 g/L for EC formulation based on EFSA dermal absorption guidance (EFSA, 2017; SANTE/2018/10591 rev 1)	Proposed default dermal absorption value and justification are accepted
Dilution	70%	Default value for diluted EC WG formulation as stated in the EFSA guidance document on dermal absorption (EFSA, 2017)	Proposed default dermal absorption value and justification are accepted

6.5.3 Justification for proposed values – Aminopyralid

No data on dermal absorption for halauxifen-methyl in GF-4021/LaDiva is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873, and SANTE/2018/10591 rev 1) are presented in the following table.

Table 6.5-4: Default dermal absorption rates for aminopyralid

	Value	Justification for value	Acceptability of justification
Concentrate	70%	Default value for a solution with an active substance concentration ≤ 50 g/L for EC formulation based on EFSA dermal absorption guidance (EFSA, 2017; SANTE/2018/10591 rev 1)	Proposed default dermal absorption value and justification are accepted
Dilution	70%	Default value for diluted EC WG formulation as stated in the EFSA guidance document on dermal absorption (EFSA, 2017)	Proposed default dermal absorption value and justification are accepted

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-4021		
Formulation type	EC		
Category	Herbicide		
Active substance(s) (incl. content)	Halauxifen-methyl 10 g as/L; 9.594 g ae/L	Picloram 48 g/L	Aminopyralid 32 g/L
AOEL systemic	0.058 mg/kg bw/d	0.3 mg/kg bw/d	0.26 mg/kg bw/d
Inhalation absorption	100%	100%	100%
Oral absorption	100%	100%	100%
Dermal absorption (EFSA Defaults) ^{a,b}	Concentrate: 70% Dilution: 70%	Concentrate: 70% Dilution: 70%	Concentrate: 70% Dilution: 70%

^a EFSA Journal 2017; 15(6):4873

^b SANTE/ 2018/ 10591 rev 1

6.6.1 Selection of critical use(s) and justification

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

Justification

The presented critical GAP is based on the supported crops, the associated maximum application rate, and the lowest water volume. This approach, from a human health risk assessment perspective, represents the worst-case exposure scenarios and, therefore, considered to be the most appropriate way of assessing the supported uses of GF-4021.

6.6.2 Operator exposure (KCP 7.2.1)

No unacceptable risk for operators from the supported uses of GF-4021 was identified based on exposure estimates from the EFSA Model under conditions of intended use with the operator wearing normal workwear with no additional PPE. However, safety glasses must be worn when handling the concentrated product, and gloves worn during mixing, loading, and application, due to GF-4021 being classified as a risk of causing severe skin burns and damage to eyes (H314). Thus, the predicted operator exposure to GF-4021 based on appropriate workwear and gloves worn for mixing, loading, and application is < 1% of the AOEL for each of the three active substances.

No unacceptable risk for operators from the supported uses of GF-4021 was identified based on exposure estimates from the EFSA Model under conditions of intended use with the operator wearing normal workwear with no additional PPE. However, gloves and safety glasses must be worn when handling the concentrated product during mixing and loading due to GF-4021 being classified as a risk of causing skin irritation (H315) and damage to eyes (H318). Thus, the predicted operator exposure to GF-4021 based on appropriate workwear and gloves worn for mixing and loading is < 1% of the AOEL for each of the three active substances.

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-4021/LaDiva according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical uses	Winter OSR (max. 0.25 L product/ha, Minimum Water Volume = 100 L/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 6.6-3: Estimated operator exposure (longer-term exposure)

Tractor mounted boom spray application outdoors to winter OSR Area Treated: 50 ha/day							
Model Information		Halauxifen-methyl		Picloram		Aminopyralid	
Application rate		0.0024 kg a.e./ha		0.012 kg a.s./ha		0.008 kg a.s./ha	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Spray application (AOEM);	Work wear (arms, body)	0.011	20%	0.040	13%	0.029	11%

75 th percentile) Body weight: 60 kg	and legs covered) M/L and A						
	Work wear (arms, body and legs covered) M/L and A + Gloves for Mixing and Loading	0.0004 0.0005	< 1%	0.0013 0.0020	< 1%	0.001 0.0014	< 1%

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)

No unacceptable risk for workers from the supported uses of GF-4021 was identified based on exposure estimates from the EFSA Model. The predicted worker exposure to halauxifen-methyl, picloram, and aminopyralid is < 1% of the AOEL for each of the three active substances, based on normal work wear and no additional PPE.

6.6.3.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GF-4021/LaDiva according to the critical use(s). Outcome of the estimation is presented in

Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-4: Exposure models for intended uses

Critical use	Winter OSR (max. 0.25 L product/ha, Minimum Water Volume = 100 L/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 (longer-term exposure)

Model Information		Halauxifen-methyl		Picloram		Aminopyralid	
Model data	Level of PPE	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Inspection and irrigation Outdoor Work rate: 2 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha							
Number of applications and application rate		1 × 0.0024 kg a.s./ha		1 × 0.012 kg a.s./ha		1 × 0.008 kg a.s./ha	
Potential exposure TC: 12,500 cm ² /person/h		0.0021	3.6%	0.0105	3.5%	0.0070	2.7%
Work wear (arms, body and legs covered) TC: 1,400 cm ² /person/h		0.0002	< 1%	0.0012	< 1%	0.0008	< 1%

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses, a refinement of the generic dislodgeable foliar residues (DFR) was not necessary.

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

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 6.6-6 shows the exposure model(s) used for estimation of resident and bystander exposure to halauxifen-methyl, picloram, and aminopyralid. The outcome of the estimation is presented in Table 6.6-7(longer term resident exposure). Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Winter OSR (max. 0.25 L product/ha, Minimum Water Volume = 100 L/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 6.6-7: Estimated resident exposure (longer term exposure)

Model data		Halauxifen-methyl		Picloram		Aminopyralid	
		Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL	Total absorbed dose (mg/kg bw/day)	% of systemic AOEL
Tractor mounted boom spray Buffer zone: 2-3(m) Drift reduction technology: No DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha							
Number of applications and application rate		1 × 0.0024 kg a.s./ha		1 × 0.012 kg a.s./ha		1 × 0.008 kg a.s./ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0005	0.8%	0.0023	0.8%	0.0015	0.6%
	Vapour (75 th perc.)	0.0011	2%	0.0011	0.4%	0.0011	0.4%
	Deposits (75 th perc.)	0.0000	0.05%	0.0001	0.04%	0.0001	0.03%
	Re-entry (75 th perc.)	0.0003	0.5%	0.0014	0.5%	0.0009	0.4%
	Sum (mean)	0.002	3%	0.004	1%	0.003	1%
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0001	0.2%	0.0005	0.2%	0.0004	0.1%
	Vapour (75 th perc.)	0.0002	0.4%	0.0002	0.08%	0.0002	0.09%
	Deposits (75 th perc.)	0.0000	0.02%	0.0001	0.02%	0.0000	0.01%
	Re-entry (75 th perc.)	0.0002	0.3%	0.0008	0.3%	0.0005	0.2%
	Sum (mean)	0.0004	0.7%	0.001	0.4%	0.0008	0.3%

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 halauxifen-methyl, picloram, and aminopyralid will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.5 Combined exposure

The product is a mixture of three active substances; halauxifen-methyl, picloram, and aminopyralid.

6.6.5.1 Exposure assessment halauxifen-methyl, picloram, and aminopyralid in GF-4021

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

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to

the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from Table 6.6-3 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-8: Risk assessment from combined exposure (longer-term exposure)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators – Tractor Mounted Boom Applications (normal workwear + gloves for Mixing and Loading)	Halauxifen-methyl	0.007 0.008
	Picloram	0.004 0.007
	Aminopyralid	0.004 0.005
	Cumulative risk operators (HI)	0.02
Workers – crop inspection/irrigation	Halauxifen-methyl	0.004
	Picloram	0.004
	Aminopyralid	0.003
	Cumulative risk workers (HI)	0.01
Resident – child	Halauxifen-methyl	
	Drift	0.008
	Vapour	0.02
	Deposits	0.0005
	Re-entry	0.005
	Sum (mean) of all pathways	0.03
	Picloram	
	Drift	0.008
	Vapour	0.004
	Deposits	0.0004
	Re-entry	0.005
	Sum (mean) of all pathways	0.01
	Aminopyralid	
	Drift	0.006
	Vapour	0.004
	Deposits	0.0003
	Re-entry	0.004
	Sum (mean) of all pathways	0.01
	Cumulative risk resident – child (HI)	
	Drift	0.02
	Vapour	0.03
	Deposits	0.001
	Re-entry	0.01
	Sum (mean) of all pathways	0.05
Resident - adult	Halauxifen-methyl	
	Drift	0.002
	Vapour	0.004

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Deposits	0.0002
	Re-entry	0.003
	Sum (mean) of all pathways	0.007
	Picloram	
	Drift	0.002
	Vapour	0.0008
	Deposits	0.0002
	Re-entry	0.003
	Sum (mean) of all pathways	0.004
	Aminopyralid	
	Drift	0.001
	Vapour	0.0009
	Deposits	0.0001
	Re-entry	0.002
	Sum (mean) of all pathways	0.003
	Cumulative risk resident – adult (HI)	
	Drift	0.005
	Vapour	0.006
	Deposits	0.0005
	Re-entry	0.008
	Sum of all pathways	0.01

The Hazard Index is < 1. Thus, combined exposure to all active substances in GF-4021/LaDiva is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Authors	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	2020	Acute Oral Toxicity Study of GF-4021 In Rats. DAS Report No.: 190369 GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCP 7.1.2	...	2020	Acute Dermal Toxicity Study of GF-4021 In Rats. DAS Report No.: 190373. ... GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCP 7.1.3	2020	Acute Inhalation Toxicity Study of GF-4021 In Rats. DAS Report No.: 190377. ... GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCP 7.1.4	...	2020	Acute Dermal Irritation Study of GF-4021 In Rabbits. DAS Report No.: 190381. ... GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCP 7.1.5/01	2020	GF-4021: Bovine Corneal Opacity And Permeability Assay. DAS Report No.: 200696. GLP (Y/N): Y Published (Y/N): N	N	Corteva Agriscience (Dow AgroSciences)
KCP 7.1.5/02	2020	GF-4021: EPIOCULAR™ Eye Irritation Test (EIT) For Identifying Chemical Not Requiring Classification And Labelling For Eye Irritation Or Serious Eye Damage. DAS Report No.: 190394.	N	Corteva Agriscience (Dow AgroSciences)

Data point	Authors	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			GLP (Y/N): Y Published (Y/N): N		
KCP 7.1.6	2020	Skin Sensitisation Study of GF-4021 By Local Lymph Node Assay In Mice. DAS Report No.: 190544. ... GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)

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

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCA 5.6.2 (IIA 5.6.2)	2002	XDE-750: Oral Gavage Developmental Toxicity Study in New Zealand White Rabbits. DAS Report No.: 011047. GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCA 5.3.2 (IIA 5.3.2)	1988	Picloram: 12-Month Dog Chronic Dietary Toxicity Study. DAS Report No.: K-038323-040. GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)
KCA 5.3.2 (IIA 5.3.2)	1992	Picloram Triisopropanolamine Salt: Oral Gavage Teratology Study In New Zealand White Rabbits. DAS Report No.: K-049877-015. GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCA 5.6.2 (KIIA 5.6.10)	2012	XDE-729 Methyl: Dietary Development Toxicity Study in Crl: CD(SD) Rats. DAS Report No.: 111137. GLP (Y/N): Y Published (Y/N): N	Y	Corteva Agriscience (Dow AgroSciences)

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

Comments of zRMS:	Accepted. Data package has been generated on the product applied for the current registration.
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Not applicable for the current dossier.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol. The OECD 423 procedure implements the 3R rules thus study is in line with the suggestions of point 5 of Regulation 284/2013. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference KCP 7.1.1/01

Report CITATION

.....; 2020; Acute Oral Toxicity Study of GF-4021 in Rats;; DAS Study No. 190369; 06 August 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 423 (2001), OPPTS 870.1100 (2002), EC B.1 (2008), JMAFF 2-1-1 (2000)
US EPA Guideline(s):	OPPTS 870.1100 (2002)
Deviations:	None
Dates of work:	22 May 2020 to 13 June 2020
GLP status:	Yes
Number of pages in final report:	41

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-4021
Purity:	3.3 wt% Aminopyralid (31 g/L), 1.08 wt% Halauxifen-methyl (10 g/L); 5.1 wt% Picloram (48 g/L)
Description (physical state):	Amber liquid
Lot/batch no.:	ENBK-170903-012 (TSN401447)
Vehicle:	Not applicable

Test System

Species:	Rat (<i>Rattus norvegicus</i>)
Strain:	Wistar (RccHan:WIST)

Age and weight at dosing:	10 to 11 weeks Weight (g): Minimum 184.3, Maximum 193.0
Source:	Animal Breeding Facility,
Housing:	3 rats/cage
Feed and water:	Feed: Teklad Certified Global 16% protein Rodent Diet (sterilizable) manufactured by Envigo, USA. <i>ad libitum</i> with the exception of overnight fasting and three hours post dosing Water: UV sterilized water filtered through reverse osmosis water filtration system <i>ad libitum</i>
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:	6 to 8 days

Study Design

In-life dates

Start: 22 May 2020 End: 13 June 2020

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/kg body weight)	Females
2000	6

Following an overnight fast, rats were given a single dose of GF-4021 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	0/6	N/A

N/A: not applicable

No mortality occurred following treatment at 2000 mg GF-4021/kg body weight.

Clinical Observations

No sign of toxicity was observed in any rat treated with 2000 GF-4021 mg/kg body weight.

Body Weight

All animals gained weight during the course of the study. Changes in body weight were considered within the expected range for this strain and age of rats and not influenced by the treatment.

Necropsy Observations

External

An external examination of terminally sacrificed female rats did not reveal any abnormality of pathological significance.

Internal

The visceral examination of female rats sacrificed at the termination did not reveal any gross abnormality of pathological significance.

In the absence of any pathological lesion in the terminally sacrificed rats, it is concluded that GF-4021 did not produce any treatment-related effect at the dose level used in the present study.

CONCLUSION

No mortality was observed in rat treated with 2000 mg GF-4021/kg body weight. The acute oral LD₅₀ of GF-4021 in female Wistar rats was found to be greater than 2000 mg/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Rat	Wistar (RccHan:WIST)	F	Oral	Gavage (undiluted)	LD ₅₀ > 2000 mg/kg body weight

zRMS: no classification is warranted for acute toxicity via oral exposure.

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

Comments of zRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 402 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference KCP 7.1.2/01

Report ~~CITATION~~

.....; 2020; Acute Dermal Toxicity Study of GF-4021 in Rats;; Lab Study No. 403-1-01-24694; DAS Study No. 190373; 08 August 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 402 (2017)
US EPA Guideline(s):	Not applicable
Deviations:	None
Dates of work:	22 May 2020 to 18 June 2020
GLP status:	Yes
Number of pages in final report:	43

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-4021
Purity:	3.3 wt% Aminopyralid (31 g/L), 1.08 wt% Halauxifen-methyl (10 g/L); 5.1 wt% Picloram (48 g/L)
Description (physical state):	Amber liquid
Lot/batch no.:	ENBK-170903-012 (TSN401447)
Vehicle:	Not applicable

Test System

Species:	Rat (<i>Rattus norvegicus</i>)
Strain:	Wistar (RccHan:WIST)
Age and weight at dosing:	11 to 13 weeks Weight (g): Female: Minimum 232.7, Maximum 237.5
Source:	Animal Breeding Facility,
Housing:	Group-housed during acclimatization; individually caged during the 24-hour exposure period
Feed and water:	Teklad Certified Global 16% protein Rodent Diet (sterilizable) manufactured by Envigo, USA. <i>ad libitum</i> Water: UV sterilized water filtered through reverse osmosis water filtration system <i>ad libitum</i>
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: 6 to 13 days

Study Design

In-life dates

Start: 22 May 2020 End: 18 June 2020

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 and found to be 5.93 (1% aqueous solution in distilled water at room temperature), which was considered acceptable for treatment.

A calculated dose volume (0.49 to 0.50 mL) of GF-4021 (undiluted) 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 occurred following treatment at 2000 mg GF-4021/kg body weight.

Clinical Observations

Clinical signs oedema, erythema, papule and scale were observed at the site of test item application in rats treated with 2000 mg GF-4021/kg body weight.

Scoring for oedema and erythema was recorded for 24, 48, and 72 h post patch removal.

At 24 h post patch removal, treated skin site of rat N° 2 and 3 revealed very slight erythema (barely perceptible) (score of 1) and very slight oedema (barely perceptible) (score of 1).

At 48 h post patch removal, treated skin site of rat N° 2 and 3 revealed well-defined erythema (score of 2) and slight oedema (edges of area well-defined by raising) (score of 2).

At 72 h post patch removal, treated skin site of rat N° 1 revealed very slight erythema (barely perceptible) (score of 1) and very slight oedema (barely perceptible) (score of 1) and treated skin site of rat N° 2 and 3

revealed well-defined erythema (score of 2) and slight oedema (edges of area well-defined by raising) (score of 2).

Body Weight

All animals gained weight during the course of the study. Changes in body weight were considered within the expected range for this strain and age of rats and not influenced by the treatment with 2000 mg GF-4021/kg body weight.

Necropsy

External

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

Internal

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

In the absence of any gross 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, effects on body weight, and macroscopic external or internal abnormality at necropsy was observed in any rat treated with 2000 mg GF-4021/kg body weight.

Based on study results, the acute dermal median lethal dose (LD₅₀ value) of GF-4021 in female Wistar rats was found to be greater than 2000 mg/kg body weight.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Rat	Wistar (RccHan:WIST)	F	Dermal	Topical (24-hour semi-occlusive exposure)	LD ₅₀ > 2000 mg/kg body weight

zRMS: no classification is warranted for acute toxicity via dermal exposure

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 436 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference KCP 7.1.3/01

Report CITATION

.....; 2020; Acute Inhalation Toxicity Study of GF-4021 in Rats;; Lab Study No. 405-1-01-24695; DAS Study No. 190377; 11 September 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 436 (2009)
US EPA Guideline(s):	None
Deviations:	None
Dates of work:	29 July 2020 to 24 August 2020
GLP status:	Yes

Number of pages in final report: 66

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-4021
Purity:	3.3 wt% Aminopyralid (31 g/L), 1.08 wt% Halauxifen-methyl (10 g/L); 5.1 wt% Picloram (48 g/L)
Description (physical state):	Amber liquid
Lot/batch no.:	ENBK-170903-012 (TSN401447)

Test System

Species:	Rat (<i>Rattus norvegicus</i>)
Strain:	Wistar (RccHan:WIST)
Age and weight at dosing:	9-11 weeks Weight (g): Male: Minimum 276.8, Maximum 298.5; Female (nulliparous and non-pregnant): Minimum 202.3, Maximum 211.9
Source:	Animal Breeding Facility,
Housing:	3 rats/cage
Feed and water:	Feed: Teklad Certified Global 14% Protein Rodent Maintenance Diet (sterilizable) manufactured by Envigo, USA. <i>ad libitum</i> , except during the 4-hour acclimation to the restraining tubes and the 4-hour exposure and 1-hour post exposure Water: UV sterilized water filtered through reverse osmosis water filtration system <i>ad libitum</i> , except during the 4-hour acclimation to the restraining tubes and the 4-hour exposure and 1-hour post exposure
Environmental conditions:	Temperature: 19 to 25 °C Humidity: 56 to 91% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	6 days

Study Design

In-life dates

Start: 29 July 2020 End: 24 August 2020

Animal assignment and treatment

Animal assignment is shown in Table 1.

Table 1: Animal assignment

Dose (mg/L air)	Males	Females	Combined
5.91	3	3	6

The rats were exposed for 4 h (nose only) followed by a 14-day post-exposure observation period during which body weight and clinical observations were recorded. Animals were observed daily

and body weights were recorded prior to exposure on day 0 and on day 1, 3, 7, and 14 after exposure and at death. After the 14-day recovery period, the animals 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-4021 aerosol concentration in the exposure chamber was 5.91 mg/L air. The average mass median aerodynamic diameter (MMAD) of aerosolized GF-4021 was 2.89 μm with a geometric standard deviation (GSD) of 1.60.

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
5.91	1/3	1/3	2/6	Day 1 to Day 2 (post exposure - day 0)	3/3	3/3	6/6

One male and one female rats were found dead following exposed to aerosol concentration of 5.91 mg GF-4021/L air (TWA).

Clinical Observations

Lethargy, abdominal breathing, and gasping were observed in all rats exposed to a time-weighted average concentration 5.91 mg GF-4021/L air (TWA).

Body Weight

A decrease in the mean body weight was observed in both sexes on day 1, 3, 7, and 14 when compared to day 0 mean body weight. An increase in mean body weight was observed in both sexes on day 14 when compared to day 7 mean body weight indicating recovery.

Necropsy Observations

External

An external gross examination of the found dead and all terminally sacrificed rats did not reveal any abnormalities.

Internal

An internal gross examination of one male rat that found dead (rat N° 1) revealed reddish discolouration of lungs and liver) whereas, the other found dead female rat and all terminally sacrificed rats did not reveal any gross abnormalities.

CONCLUSION

Two mortalities were observed in rats following 4-hour nose-only inhalation exposure to an aerosol concentration of 5.91 mg GF-4021/L air (TWA). Under the conditions of this study, the 4-hour acute inhalation median lethal concentration (LC_{50}) of GF-4021 in male and female Wistar rats was found to be greater than the time-weighted average (TWA) exposure concentration of 5.91 mg GF-4021/L air.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Rat	Wistar (RccHan:WIST)	M/F	Inhalation	Nose only (4-hour)	$\text{LC}_{50} > 5.91 \text{ mg/L air}$

zRMS: no classification is warranted for acute toxicity via inhalation exposure

Note: hazard statement STOT SE Cat 3 H355 is triggered by concentration limits of relevant compound not study results.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Study has been reviewed for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 404 procedure is still valid and acceptable. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference KCP 7.1.4/01

Report ~~CITATION~~

..... 2020; Acute Dermal Irritation Study of GF-4021 in Rabbits;; Lab Study No. 406-1-01-24696; DAS Study No. 190381; 22 September 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 404 (2015), OPPTS 870.2500 (1998), EC B.4 (2008), JMAFF 2-1-4 (2000)
US EPA Guideline(s):	OPPTS 870.2500 (1998)
Deviations:	None
Dates of work:	14 July 2020 to 04 September 2020
GLP status:	Yes
Number of pages in final report:	43

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-4021
Purity:	3.3 wt% Aminopyralid (31 g/L), 1.08 wt% Halauxifen-methyl (10 g/L); 5.1 wt% Picloram (48 g/L)
Description (physical state):	Amber liquid
Lot/batch no.:	ENBK-170903-012 (TSN401447)
Vehicle:	Not applicable

Test System

Species:	Rabbit (<i>Oryctolagus cuniculus</i>)
Strain:	New Zealand White (NZW)
Age and weight at dosing:	16 to 21 weeks Weight (kg): Minimum 2.020, Maximum 2.705
Source:	Animal breeding Facility,
Housing:	Individually

Feed and water:	Feed Teklad Certified Global High fiber rabbit diet manufactured by Envigo, U.S.A. <i>ad libitum</i> Water: UV sterilized water filtered through reverse osmosis water filtration system <i>ad libitum</i>
Environmental conditions:	Temperature: 18 to 27 °C Humidity: 63 to 92% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	6 to 38 days

Study Design

In-life dates

Start:	14 July 2020	End:	04 September 2020
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Animal assignment and treatment

The pH of GF-4021 was found to be 5.93 (1% aqueous solution in distilled water at room temperature), which was 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 observed in the first treated rabbit, two additional rabbits were sequentially treated in an identical manner.

A volume of 0.5 mL of GF-4021 (undiluted) was applied evenly to one of the clipped sites of each rabbit and the contralateral site remained untreated. The latter served as the control site. The treated and the control sites were covered with gauze patches of approximately 6 cm² (gauze rolled) with semi-occlusive dressing (not more than 8-ply) and were secured in place by non-irritating tape (Medi tape 330 hypo-allergenic surgical tape) to ensure that the rabbits did not ingest the test item. At the end of the 4-hour exposure period (day 0), the residual test item was removed with cotton soaked in distilled water.

Irritation was scored by the method of Draize (as described in OECD Test Guideline 404) at 1, 24, 48, 72 hours and on day 7 and 14 post patch removal. General health condition and body weight were monitored.

RESULTS AND DISCUSSION

Dermal Irritation

Following the 4 h exposure period (day 0), skin of each rabbit was observed at 1, 24, 48 and 72 h and on day 7 and 14 post patch removal.

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

At 24 h post patch removal, the treated skin site revealed well defined erythema (score of 2) and slight oedema (score of 2) in all rabbits.

At 48 and 72 h post patch removal, the treated skin site revealed moderate to severe erythema (score of 3) and moderate oedema (score of 3) in all rabbits.

On day 7 post patch removal, very slight erythema (score of 1) in rabbit N° 1 and 2 to well defined erythema (score of 2) in rabbit N° 3 and slight oedema (score of 2) in all rabbits.

On day 14 post patch removal, treated skin site of all rabbits recovered completely and appeared normal.

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

Individual animal irritation scores are presented in Table 1.

Table 9: 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	3	3	1	0	0	2	3	3	2	0
2	Left	Right	1	2	3	3	1	0	0	2	3	3	2	0
3	Left	Right	1	2	3	3	2	0	0	2	3	3	2	0

Key:

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

CLINICAL OBSERVATIONS

Fissuring was observed at the treated site in two rabbits on day 2 and in another rabbit on day 3 post patch removal. Two rabbits recovered on day 12 and the other rabbit on day 13. No other signs of toxicity were recorded, and all animals gained body weight throughout the study.

CONCLUSION

In conclusion, based on these study results, GF-4021 caused a moderate to severe dermal reaction in all rabbits, fully reversible by day 14. No systemic effects were observed.

Individual rabbit average dermal irritation score observed at 24, 48 and 72 h post patch removal were 2.67, 2.67, 2.67 for erythema and 2.67, 2.67, 2.67 for oedema for Rabbit N° 1, 2 and 3 respectively.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Rabbit	NZW	F	Dermal	Topical (4-hour, semi-occlusive)	Mean Erythema Scores: 2.67, 2.67, 2.67 Mean Oedema Scores: 2.67, 2.67, 2.67 Complete recovery by 14 days

zRMS: classification is warranted for product for skin corrosion/irritation.

Skin irritation Cat 2; H315 Causes skin irritation

A 2.6 Eye irritation (KCP 7.1.5)

A 2.6.1 Rabbit Eye Irritation Study

In vitro studies were conducted for eye irritation and eye corrosion and are described in the sections below. Study 190394 indicates that GF-4021 did show the potential for ocular irritation. Study 200606 concludes that according to the prediction model presented in OECD TG 437, the test substance is predicted to be a severe eye irritant (GHS Category 1).

Conclusion

The *in vivo* rabbit eye irritation study was not conducted based on the results of the *in vitro* eye irritation and corrosion studies and the prediction of severe eye irritation.

Comments of zRMS:	Studies (....., 2020, No 200696 OECD TG 437 and No 190394 OECD TG 492) has been reviewed for compliance with the current requirements. There are no deviation from studies protocol. Both <i>in vitro</i> studies procedure fully implements the 3R rules (replacement) thus studies are in line with the suggestions of point 5 of Regulation 284/2013. Studies accepted. Prediction can be made regarding the classification of the test product GF-4021 according to the evaluation criteria. Therefore, an <i>in vivo</i> follow up study was not performed.
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A 2.6.2 Study 200696

Reference KCP 7.1.5/01

Report CITATION

.....; 2020; GF-4021: Bovine Corneal Opacity and Permeability Assay with Histology;; Lab Study No. 19AK30.350000; DAS Study No. 200696; 28 August 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 437 (2017)
US EPA Guideline(s):	None
Deviations:	None
Dates of work:	09 March 2020
GLP status:	Yes

Number of pages in final report: 32

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test item(s)

Test item (Common name):	GF-4021
Purity	3.3 wt% (31 g/L) of aminopyralid, 1.08 wt% (10 g/L) of halauxifen-methyl, 5.1 wt% (48 g/L) of picloram
Description (physical state)	Clear light yellow semi-viscous liquid
Lot/batch no:	ENBK-170903-012 (TSN 401447)

Vehicle:	Sterile, deionized water
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Control Items

Negative control:	Sterile, deionized water
Positive control:	100% ethanol (CAS: 64-17-5)

Test System

The test system (target tissue) is the isolated bovine cornea obtained as a by-product of freshly slaughtered animals. Bovine eyes were obtained from the abattoir of, MD.

Other reagents included:

Hanks' Balanced Salt Solution with Ca^{++} and Mg^{++} containing penicillin/streptomycin, sodium bicarbonate, and L-glutamine (HBSS)

Minimal Essential Medium (EMEM) without phenol red supplemented to contain 1% Fetal Bovine Serum (FBS) and 2 mM L-glutamine (Complete MEM without phenol red)

Minimal Essential Medium (EMEM) containing phenol red supplemented to contain 1% Fetal Bovine Serum (FBS) and 2 mM L-glutamine (Complete MEM with phenol red)

Sodium Fluorescein diluted in Delbucco's Phosphate Buffered Solution containing Ca^{++} and Mg^{++}

Sterile deionized water

Methods

Preparation of Corneas

All eyes were carefully examined for defects and those exhibiting defects were discarded. The tissue surrounding the eyeball was carefully pulled away and the cornea excised leaving a 2-3 mm rim of sclera. Isolated corneas were stored in a petri dish containing HBSS prior to mounting. Corneas were then mounted in the cornea holders with the endothelial side against the O-ring of the posterior chamber. The anterior chamber was positioned on top of the cornea and tightened with screws. The chambers of the cornea holder were filled with Complete MEM (without phenol red) with the posterior chamber being filled first. The corneas were incubated for a minimum of 1 hour at $32\pm 1^\circ\text{C}$.

Treatment of Corneas

At the end of the 1-hour incubation period, the medium was removed from both chambers and replaced with fresh Complete MEM (without phenol red). An initial opacity measurement was performed on each of the corneas using the OP-KIT opacitometer. The opacity of each cornea (including the negative control corneas) was read against an air-filled chamber and recorded.

Method A: The test material was tested neat (undiluted). Seven hundred fifty microliters of the test substance (test article, negative control, or positive control) was introduced into the anterior chamber. The holder was slightly rotated to ensure uniform distribution. The substance was incubated for 10 minutes. The test substance was then removed and the epithelium washed at least three times with Complete MEM (with phenol red). Once the media was free of the test substance, the corneas were given a final rinse with Complete MEM (without phenol red). The anterior chamber was then refilled with fresh Complete MEM (without phenol red) and an opacity measurement was performed. Corneas were incubated for approximately 2 hours at $32\pm 1^\circ\text{C}$. At the completion of the post-exposure incubation period, a second measure of opacity was performed.

Opacity Measurement

The difference in the light transmission between each treated or control cornea and an air-filled chamber was determined using an opacitometer. The numerical opacity value displayed on the opacitometer was recorded.

Permeability Determination

Method A: After the second opacity measurement was performed, the medium was removed from both chambers of the holder. The posterior chamber was refilled with fresh Complete MEM (without phenol red). One mL of a 4 mg/mL sodium fluorescein solution was added to the anterior chamber.

The corneas were then incubated in a horizontal position for approximately 90 minutes at $32\pm1^{\circ}\text{C}$. The medium from the posterior chamber was removed at the completion of the incubation period, and 360 μL were transferred to the appropriate wells of a labelled 96-well plate. Three hundred and sixty microliters of fresh Complete MEM (without phenol red) was added to the wells designated as blanks. The optical density at 490 nm (OD_{490}) was determined using a spectrophotometer.

Evaluation of Test Results

Data Analysis

The change in opacity for each cornea (including the negative control corneas) was calculated by subtracting the initial opacity reading from the final opacity reading. These values were corrected by subtracting from each the average change in opacity observed for the negative control corneas. The mean opacity value for each treatment was calculated by averaging the corrected opacity values of each cornea for a given treatment.

The mean OD_{490} was calculated for the blank wells. The mean blank OD_{490} was subtracted from the OD_{490} of each well (corrected OD_{490}).

Final corrected $\text{OD}_{490} = (\text{OD}_{490} - \text{mean blank } \text{OD}_{490}) - \text{Average corrected negative control } \text{OD}_{490}$

The mean OD_{490} for each treatment group was calculated by averaging the final corrected OD_{490} values of the treated corneas for that treatment condition.

An *in vitro* irritation score was calculated with the following formula:

In vitro score = Mean opacity value + (15 x Mean OD_{490} value)

Assay interpretation

The *in vitro* irritation score (IVIS) was used as follows per guidance in OECD 437.

Table 1: Prediction model outlined in OECD TG 437

In vitro Irritation Score (IVIS)	UN GHS
≤ 3	No Category
$> 3; \leq 55$	No prediction can be made
> 55	Category 1

Assay acceptance criteria

A test is considered acceptable if the positive control gives a value that falls within two standard deviations of the historical mean of the IVIS for the OP-KIT device.

RESULTS AND DISCUSSION

Observations

The In Vitro Score of the test substance was 81.4. According to the prediction model presented in OECD TG 437, the test substance is predicted to be a severe eye irritant (GHS Category 1).

The positive control IVIS was 50.4 and was within 2 standard deviation of the historical control mean.

Table 1: BCOP Summary Results

Treatment		Corrected Opacity		Corrected OD ₄₉₀ Value ¹		In vitro score (IVIS)	Classification prediction
		Individual Cornea	Mean ± SD ³	Individual Cornea	Mean ± SD ³		
Test item (n ⁴ =3)	GF-4021	37.3	44.7 ± 7.5	2.156	2.448 ± 0.288	81.4	Irritant
		44.3		2.457			
		52.3		2.731			
Negative control (n ⁴ =3)	Sterile distilled water	N/A	N/A	0.002	0.004	-0.3	Non-irritant
		N/A		0.006			
		N/A		0.003			
Positive control (n ⁴ =3)	100% ethanol/20% imidazole	29.3	31.7 ± 2.5	1.568	1.247 ± 0.301	50.4	Within acceptability criteria
		34.3		0.970			
		31.3		1.203			

N/A = Not Applicable

zRMS: classification is warranted for product for serious eye damage/irritation.
Eye irritation Cat 1, H318: Causes serious eye damage

A 2.6.3 Study 190394

Reference KCP 7.1.5/02

Report CITATION

..... 2020; GF-4021: EpiOcular™ Eye Irritation Test (EIT) for Identifying Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage;; Lab Study No. 19AK30.015091; DAS Study No. 190394 ; 27 April 2020; Unpublished

COMPLIANCE

Guideline(s): OECD 492
US EPA Guideline(s): Not available
Deviations: None
Dates of work: 20 January 2020 to 23 January 2020
GLP status: Yes
Number of pages in final report: 37

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name): GF-4021
Purity: 3.3 wt% (31 g/L) of aminopyralid
1.08 wt% (10 g/L) of halauxifen-methyl
5.1 wt% (48 g/L) of picloram
Description (physical state): Clear light yellow semi-viscous liquid
Lot/batch no.: ENBK-170903-012 (TSN401447)

Control Items

Negative control: Sterile deionized water

Positive control: Methyl acetate

Test System

The EpiOcular™ human cell construct consists of stratified human keratinocytes which have been cultured to form a multilayered (3-D), model of the corneal epithelium. Tissues and media for cells were provided by, U.S.A.).

Other reagents included MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) solution and an extraction solution, prepared in house.

Study Design

Preliminary assay

To confirm the lack of potential for the test item to directly reduce MTT, 50 µL of GF-4021 (undiluted) was incubated with 1 mL of the MTT solution in the dark at 37°C, for 1-3 hours. A test item would be considered an MTT reducer if MTT solution turn to blue/purple colour following incubation, compared to an equivalent amount of untreated MTT medium.

The test article was checked for its colorant properties (interfere with the photometric MTT measurement). Approximately 50 µL was added to 2.0 mL isopropanol in 6-well plates and placed on an orbital plate shaker for 2 to 3 hours at room temperature. Two x 200 µL aliquots of the isopropanol solutions and 2 blank samples of isopropanol were transferred to a 96-well plate, and the absorbance measured with a plate reader at the MTT measurement wavelength.

Cell culture procedures

Upon receipt, EpiOcular™ tissue were stored at 2-8°C until used. On the day of receipt, an appropriate volume of EpiOcular™ assay medium was warmed to approximately 37°C. one (1.0) milliliter of assay medium was aliquoted into the appropriate wells of labelled 6-well plates. The 6-well plates were labelled with the test substance or control codes and exposure times. Each tissue was inspected for air bubbles between the agarose gel and cell culture insert prior to opening the sealed package. Cultures with air bubbles under greater than 50% of the cell culture insert area were not used. Each 24-well shipping container was removed from its plastic bag and its surface disinfected by wiping with 70% ethanol-soaked tissue paper. The tissues were allowed to come to room temperature for at least 15 minutes prior to transfer to the 6-well plates. An appropriate number of tissues were transferred aseptically from the 24-well shipping containers into the 6-well plates. The EpiOcular™ tissues were incubated at standard culture conditions for 60 ± 5 minutes. After the incubation, the tissues were either be refed, or transferred to new plates containing fresh warmed media and incubated at standard culture conditions overnight (16 to 24 hours). Upon opening the bag, any unused tissues remaining on the shipping agar at the time of tissue transfer were briefly gassed with an atmosphere of 5% CO₂/95% air, and the bag was sealed and stored at 2 to 8°C for subsequent use.

Definitive assays

A suitable number of EpiOcular™ tissues (0.6 cm² epidermal surface) were incubated with 50 µL of the GF-4017 (undiluted; 2 replicates), positive control (methyl acetate; 2 replicates) or negative control (Sterile, deionized water; 2 replicates), for 30 ± 2 minutes. Tissues were rinsed with sterile CMF-DPBS followed by 120 ± 15-minute incubation in fresh medium under standard cell culture condition.

Tissues were transferred to a well containing 300 µL MTT solution and incubated for 3 ± 0.1 hours at standard cell culture conditions, and then incubated with extractant solution for 2 to 3 hours shaking at room temperature. The amount of formazan extracted from each individual tissue was measured spectrophotometrically (OD550) in microplates.

Evaluation of Test Results

Data Analysis

The absorbance raw data were transformed as follows:

- background correction: A 'mean blank OD550' value was calculated, averaging the OD550 of the blank wells and was subtracted from each individual OD550 values of wells treated with test or control items ('corrected individual tissue OD550');
- a 'mean corrected Negative control OD550' was obtained from relevant replicates;
- for each individual tissue treated with test or control items, the percentage (%) viability relative to the 'mean corrected Negative control OD550' was calculated;
- mean and standard deviations for relative viability values were calculated.

Assay interpretation

Ocular irritation potential of the test chemical was determined based on cell viability, relative to negative control values:

- mean relative tissue viability equal or less 60% → potential ocular irritant
- mean tissue viability higher than 60% → does not require labelling for ocular irritation

Assay acceptance criteria

Appropriate conduct of the study was assessed against the following criteria:

- negative control: The corrected mean OD550 value of the negative control tissues should be >0.8 and <2.5.
- positive control: The relative mean viability of positive control should be less than or equal to 50%, compared to negative control.

RESULTS AND DISCUSSION

Preliminary Assay

GF-4021 was not able to turn MTT solution to blue/purple colour, suggesting no reduction of MTT dye by direct contact. The test article was not considered to have probable photometric MTT interference.

Definitive Assays

Results are summarized in Table 1.

The mean relative tissue viability for EpiOcular™ tissues treated with GF-4021 was 5.15%, compared to the negative control.

The results for negative and positive controls met assay acceptance criteria, suggesting appropriate conduct of the study:

- the corrected mean OD550 value of the negative control tissues was 1.611;
- the relative mean viability of positive control was 21.37%.

Table 10: Summary of Individual and mean Percentage (%) relative viability

Treatment		Absorbance		Relative viability ¹		Classification prediction
		Individual Tissue ²	Mean \pm SD ³	Individual Tissue	Mean \pm SD ³	
Test item (n ⁴ =2)	GF-4021	0.083	0.083 \pm 0.00	5.15	5.15 \pm 0.00	Irritant
		0.083		5.15		
Negative control (n ⁴ =2)	Sterile, Deionized Water	1.475	1.611 \pm 0.193	91.54	100 \pm 11.96	No-Category
		1.747		108.46		
Positive control (n ⁴ =2)	Methyl Acetate	0.358	0.344 \pm 0.019	22.19	21.37 \pm 1.16	Irritant
		0.331		20.55		

¹ Compared to negative control mean value

² Corrected Individual Tissue OD550

³ SD: standard deviation

⁴ n = number of replicates

CONCLUSION

According to the EpiOcular™ Eye Irritation Test prediction model, GF-4021 did show the potential for ocular irritation.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Human	Not applicable	Not applicable	Ocular	EpiOcular - Topical	Mean relative tissue viability: 5.15%

**zRMS: classification is warranted for product for serious eye damage/irritation.
Eye irritation Cat 1, H318: Causes serious eye damage**

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Study has been evaluated and reviewed by the evaluators for compliance with the current guidelines, resulting from scientific progress. There is no deviation from studies protocol, the OECD 429 procedure is valid and acceptable. Study is in line with the suggestions of point 5 of Regulation 284/2013 and Annex VII to REACH REG (EC) No 1907/2006. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference KCP 7.1.6/01

Report CITATION

.....; 2020; Skin Sensitisation Study of GF-4021 by Local Lymph Node Assay in Mice;; Lab Study No. 409-1-01-24698; DAS Study No. 190544; 24 September 2020; Unpublished

COMPLIANCE

Guideline(s):	OECD 429 (2010), OPPTS 870.2600 (2003), EC B.42 (2012)
US EPA Guideline(s):	OPPTS 870.2600 (2003)
Deviations:	None
Dates of work:	31 July 2020 to 08 September 2020
GLP status:	Yes
Number of pages in final report:	67

Acceptability	Yes
Duplication (if vertebrate study)	No

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-4021
Purity:	3.3 wt% Aminopyralid (31 g/L), 1.08 wt% Halauxifen-methyl (10 g/L); 5.1 wt% Picloram (48 g/L)
Description (physical state):	Amber liquid
Lot/batch no.:	ENBK-170903-012 (TSN401447)

Vehicle/Control Item(s)

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

Test System

Species:	Mouse (<i>Mus musculus</i>)
Strain:	CBA/J
Age and weight at dosing:	9 to 10 weeks Weight (g): Minimum 17.8, Maximum 24.4
Source:	Animal Breeding Facility.....

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 radio-labelled material)
Feed and water:	Feed: Teklad Certified Global 14% Protein Rodent Maintenance Diet (sterilizable) manufactured by Envigo, USA <i>ad libitum</i> . Water: UV sterilized water filtered through reverse osmosis water filtration system <i>ad libitum</i>
Environmental conditions:	Temperature: 19 to 23 °C Humidity: 58 to 66% relative humidity Air changes: Minimum 15 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	6 days

Study Design

In-life dates

Start:	31 July 2020	End:	08 September 2020
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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-4021 at concentrations of 5% (v/v), 10% (v/v), 25% (v/v) and 50% (v/v) in 1% L-92.

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

In the preliminary assay, no erythema was observed at the site of application at the dose levels of 5% (v/v), 10% (v/v), 25% (v/v) GF-4021 in 1% L-92 and very slight erythema (score of 1) was observed at 50% (v/v) GF-4021 in 1% L-92. Ear thickness increases were below 25% at 5% (v/v) and 10% (v/v) GF-4021 in 1% L-92 while at 25% (v/v) and 50% (v/v) GF-4021 in 1% L-92, >25% increase in ear thickness was observed. Therefore, dose concentrations of 2.5%, 5.0% and 10.0% (v/v) in 1% 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-4021 at concentrations of 2.5%, 5.0% and 10.0% (v/v) in 1% L-92. Female mice from the vehicle control and positive control groups were maintained in similar conditions with treatment of 1% L-92 and 25% (v/v) of HCA in L-92, respectively.

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

from individual animals were prepared. The uptake of ^3H -TdR into the auricular (local) lymph nodes draining the site of chemical application was measured to assess the lymph node proliferative response.

RESULTS AND DISCUSSION

Clinical Observations and Irritation

No sign of toxicity was observed in any mouse from any group, including controls.

No erythema was observed at the site of application at 2.5%, 5.0% and 10.0 (v/v) in 1% L-92. In all mice treated with 25% (v/v) HCA, a local reaction consisting of very slight erythema (score of 1) was observed from day 1 to 4.

Body Weight

No effect on the body weight was observed in mice treated with GF-4021, positive control and vehicle control.

Group Mean DPM

Proliferative responses in the draining lymph nodes were monitored by measuring the incorporation of ^3H -methyl thymidine. These analyses revealed the group mean DPM/mouse value of 558.00, 829.60, 1026.60, 1140.80, and 2337.60 for the vehicle control (1% L-92), 2.5%, 5.0%, and 10.0 (v/v) in 1% Pluronic® L-92 treated groups, and the positive control (25% v/v HCA), respectively.

Stimulation Index (SI Value) and EC₃ Value

Stimulation Index (SI) values calculated for groups treated with GF-4021 were found to be 1.49, 1.84, and 2.04 at 2.5%, 5.0%, and 10.0 (v/v) in 1% Pluronic® L-92, respectively, and 4.19 for 25% (v/v) HCA positive control group.

The SI obtained for GF-4021 showed a less than threefold increase over the control value at all tested concentrations. Therefore, an EC₃ value was not calculated.

Individual and group mean values are reported in Table 1.

Table 11: 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% L-92)	1	415	558.00 ± 195.45	1
	2	346		
	3	566		
	4	848		
	5	615		
GF-4021 2.5% (v/v) in vehicle	6	1223	829.60 ± 342.88	1.49
	7	670		
	8	1114		
	9	377		
	10	764		
GF-4021 5.0% (v/v) in vehicle	11	1215	1026.60 ± 397.87	1.84
	12	965		
	13	555		
	14	804		
	15	1594		
GF-4021 10.0% (v/v) in vehicle	16	1618	1140.80 ± 402.58	2.04
	17	1313		
	18	897		
	19	1291		
	20	585		
HCA (Positive control) 25% (v/v) in vehicle	21	1944	2337.60 ± 601.30	4.19
	22	1653		
	23	2802		
	24	2187		
	25	3102		

CONCLUSION

The SI obtained for GF-4021 at all tested concentrations showed a less than three-fold increase over the control value. Therefore, GF-4021 did not demonstrate dermal sensitisation potential in the local lymph node assay.

Test item	Species	Strain	Sex	Route	Method	Result
GF-4021	Mouse	CBA/J	F	Dermal	Topical - Local lymph node assay	Dermal non sensitiser SI = 1.49, 1.84 and 2.04 at 2.5% (v/v), 5.0% (v/v) and 10.0% (v/v), respectively.

zRMS: no classification of product for skin sensitisation is warranted.

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

Not applicable.

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)

Not applicable.

A 2.11 Other/Special Studies

Not applicable.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for Halauxifen-methyl

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

Substance	Halauxifen-methyl	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0024 kg a.s. /ha	Spray dilution = 0.024 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 70	Dermal for in use dilution = 70	Oral = 100	Inhalation = 100	
RVNAS	0.058 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm ² per kg a.s./ha		DT50	30 days	

Table A 2: Estimation of longer-term operator exposure towards halauxifen-methyl according to EFSA guidance

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0209	% of RVNAS	36.02%	
	Acute systemic exposure mg/kg bw/day	0.5008	% of RVAAS		
Mixing and Loading	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No	
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No	
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0114	% of RVNAS	19.74%	
	Acute systemic exposure mg/kg bw/day	0.0466	% of RVAAS		
Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0209	% of RVNAS	36.02%	
	Acute systemic exposure mg/kg bw/day	0.5008	% of RVAAS		
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 (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0004	% of RVNAS	0.72%	
	Acute systemic exposure mg/kg bw/day	0.0317	% of RVAAS		

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0209	% of RVNAS	36.02%	
	Acute systemic exposure mg/kg bw/day	0.5008	% of RVAAS		
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No	
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No	
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0005	% of RVNAS	0.81%	
	Acute systemic exposure mg/kg bw/day	0.0070	% of RVAAS		

A 3.1.2 Calculations for Picloram

Table A 3: Input parameters considered for the estimation of operator exposure

Substance	Picloram	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.012 kg a.s. /ha	Spray dilution = 0.12 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 70	Dermal for in use dilution = 70	Oral = 100	Inhalation = 100	
RVNAS	0.3 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm ² per kg a.s./ha		DT50	30 days	

Table A 4: Estimation of longer-term operator exposure to picloram according to EFSA guidance

Operator Model		Estimation of longer term operator exposure to picrotin according to ECHA guidance		
	Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0694	% of RVNAS	23.13%
	Acute systemic exposure mg/kg bw/day	0.8878	% of RVAAS	
Mixing and Loading	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0399	% of RVNAS	13.31%
	Acute systemic exposure mg/kg bw/day	0.1615	% of RVAAS	
Operator Model		Mixing, loading and application AOEM		
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0694	% of RVNAS	23.13%
	Acute systemic exposure mg/kg bw/day	0.8878	% of RVAAS	
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 (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0013	% of RVNAS	0.44%
	Acute systemic exposure mg/kg bw/day	0.0417	% of RVAAS	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0694	% of RVNAS	23.13%	
	Acute systemic exposure mg/kg bw/day	0.8878	% of RVAAS		
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No	
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No	
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0020	% of RVNAS	0.66%	
	Acute systemic exposure mg/kg bw/day	0.0234	% of RVAAS		

A 3.1.3 Calculations for Aminopyralid

Table A 5: Input parameters considered for the estimation of operator exposure

Substance	Aminopyralid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.008 kg a.s. /ha	Spray dilution = 0.08 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 70 Dermal for in use dilution = 70		Oral = 100	Inhalation = 100	
RVNAS	0.26 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm ² per kg a.s./ha		DT50	30 days	

Table A 6: Estimation of longer-term operator exposure to aminopyralid according to EFSA guidance

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0512	% of RVNAS	19.71%	
	Acute systemic exposure mg/kg bw/day	0.7632	% of RVAAS		
Mixing and Loading	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No	
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No	
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0291	% of RVNAS	11.20%	
	Acute systemic exposure mg/kg bw/day	0.1180	% of RVAAS		
Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0512	% of RVNAS	19.71%	
	Acute systemic exposure mg/kg bw/day	0.7632	% of RVAAS		
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 (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0010	% of RVNAS	0.37%	
	Acute systemic exposure mg/kg bw/day	0.0385	% of RVAAS		

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0512	% of RVNAS	19.71%	
	Acute systemic exposure mg/kg bw/day	0.7632	% of RVAAS		
Mixing and Loading	Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No	
Application	Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No	
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day	0.0014	% of RVNAS	0.53%	
	Acute systemic exposure mg/kg bw/day	0.0172	% of RVAAS		

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for Halauxifen-methyl

Table A 7: Input parameters considered for the estimation of worker exposure

Worker exposure from residues on foliage for GF-4021	
Crop type	Oilseeds
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	0.0024 kg a.s./ha
Number of applications	1
Interval between multiple applications	365 days
Half-life of active substance	30 days
Multiple application factor	1.0
Dermal absorption of the product	70.00%
Dermal absorption of the in-use dilution	70.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0072 µg a.s./cm ²
Working hours	2 hr
Dermal transfer coefficient - Total potential exposure	12500 cm ² /hr
Dermal transfer coefficient - arms, body and legs covered	1400 cm ² /hr
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm ² /hr
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}

Table A 8: Estimation of longer-term worker exposure towards halauxifen-methyl according to EFSA guidance

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0021	% of RVNAS	3.62%
	Working clothing mg/kg bw/day	0.0002	% of RVNAS	0.41%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.2.2 Calculations for Picloram

Table A 9: Input parameters considered for the estimation of worker exposure

Worker exposure from residues on foliage for GF-4021	
Crop type	Oilseeds
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	0.012 kg a.s./ha
Number of applications	1
Interval between multiple applications	365 days
Half-life of active substance	30 days
Multiple application factor	1.0
Dermal absorption of the product	70.00%
Dermal absorption of the in-use dilution	70.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.036 µg a.s./cm ²
Working hours	2 hr
Dermal transfer coefficient - Total potential exposure	12500 cm ² /hr
Dermal transfer coefficient - arms, body and legs covered	1400 cm ² /hr
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm ² /hr
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}

Table A 10: Estimation of longer-term worker exposure towards picloram according to EFSA guidance

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0105	% of RVNAS	3.50%
	Working clothing mg/kg bw/day	0.0012	% of RVNAS	0.39%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.2.3 Calculations for Aminopyralid

Table A 11: Input parameters considered for the estimation of worker exposure

Worker exposure from residues on foliage for GF-4021	
Crop type	Oilseeds
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	0.008 kg a.s./ha
Number of applications	1
Interval between multiple applications	365 days
Half-life of active substance	30 days
Multiple application factor	1.0
Dermal absorption of the product	70.00%
Dermal absorption of the in-use dilution	70.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.024 µg a.s./cm ²
Working hours	2 hr
Dermal transfer coefficient - Total potential exposure	12500 cm ² /hr
Dermal transfer coefficient - arms, body and legs covered	1400 cm ² /hr
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm ² /hr
Inhalation transfer coefficient for automated applications	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10 ^{^(-3)}
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10 ^{^(-3)}

Table A 12: Estimation of longer-term worker exposure towards aminopyralid according to EFSA guidance

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0070	% of RVNAS	2.69%
	Working clothing mg/kg bw/day	0.0008	% of RVNAS	0.30%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for Halauxifen-methyl

Table A 13: Input parameters considered for the estimation of longer-term resident exposure

Resident exposure for GF-4021	
Croptype	Oilseeds
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Buffer strip	2-3 m
Application rate of the product	0.0024 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.024 g a.s./l
Dermal absorption of product	70.00%
Dermal absorption of in-use dilution	70.00%
Oral absorption	100.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0072 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Concentration in air	0.001 mg/m ³
Resident dermal spray drift exposure 75th percentile - adult	0.47 ml spray dilution/person
Resident dermal spray drift exposure 75th percentile - child	0.327 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - adult	0.00010 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - child	0.00022 ml spray dilution/person
Resident dermal spray drift exposure mean - adult	0.22318 ml spray dilution/person
Resident dermal spray drift exposure mean - child	0.18 ml spray dilution/person
Resident inhal. spray drift exposure mean - adult	0.00009 ml spray dilution/person
Resident inhal. spray drift exposure mean - child	0.00017 ml spray dilution/person
Exposure duration dermal	2 hours
Exposure duration inhalation	24 hours
Exposure duration entry into treated crops	0.25 hours
Light clothing adjustment factor	18.0%
Breathing rate adult	0.23 m ³ /day/kg
Breathing rate child (1-3 year old)	1.07 m ³ /day/kg
Drift percentage on surface (75th percentile)	5.60%
Drift percentage on surface (mean)	4.10%
Turf transferable residues percentage	5.00%
Transfer coeff. of surface deposits-adult	7300 cm ² /hour
Transfer coeff. of surface deposits-child (1-3 year old)	2600 cm ² /hour
Saliva extraction percentage	50.00%
Surface area of hands mouthed	20 cm ²
Frequency of hand to mouth activity	9.5 events/hour
Ingestion rate for mouthing of grass per day	25 cm ²
Dislodgeable residues percentage transferability for object to mouth	20.00%
Transfer coefficient for entry into treated crops (75th percentile) - adult	7500 cm ² /h
Transfer coefficient for entry into treated crops (75th percentile) - child	2250 cm ² /h
Transfer coefficient for entry into treated crops (mean) - adult	5980 cm ² /h
Transfer coefficient for entry into treated crops (mean) - child	1794 cm ² /h

Table A 14: Estimation of longer-term resident exposure towards halauxifen-methyl according to EFSA guidance

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	0.78%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	1.84%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.05%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	0.49%
	All pathways (mean) mg/kg bw/day	0.0016	% of RVNAS	2.70%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.19%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.40%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.02%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.27%
	All pathways (mean) mg/kg bw/day	0.0004	% of RVNAS	0.72%

A 3.3.2 Calculations for Picloram

Table A 15: Input parameters considered for the estimation of longer-term resident exposure

Resident exposure for GF-4021	
Croptype	Oilseeds
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Buffer strip	2-3 m
Application rate of the product	0.012 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.12 g a.s./l
Dermal absorption of product	70.00%
Dermal absorption of in-use dilution	70.00%
Oral absorption	100.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.036 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Concentration in air	0.001 mg/m ³
Resident dermal spray drift exposure 75th percentile - adult	0.47 ml spray dilution/person
Resident dermal spray drift exposure 75th percentile - child	0.327 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - adult	0.00010 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - child	0.00022 ml spray dilution/person
Resident dermal spray drift exposure mean - adult	0.22318 ml spray dilution/person
Resident dermal spray drift exposure mean - child	0.18 ml spray dilution/person
Resident inhal. spray drift exposure mean - adult	0.00009 ml spray dilution/person
Resident inhal. spray drift exposure mean - child	0.00017 ml spray dilution/person
Exposure duration dermal	2 hours
Exposure duration inhalation	24 hours
Exposure duration entry into treated crops	0.25 hours
Light clothing adjustment factor	18.0%
Breathing rate adult	0.23 m ³ /day/kg
Breathing rate child (1-3 year old)	1.07 m ³ /day/kg
Drift percentage on surface (75th percentile)	5.60%
Drift percentage on surface (mean)	4.10%
Turf transferable residues percentage	5.00%
Transfer coeff. of surface deposits-adult	7300 cm ² /hour
Transfer coeff. of surface deposits-child (1-3 year old)	2600 cm ² /hour
Saliva extraction percentage	50.00%
Surface area of hands mouthed	20 cm ²
Frequency of hand to mouth activity	9.5 events/hour
Ingestion rate for mouthing of grass per day	25 cm ²
Dislodgeable residues percentage transferability for object to mouth	20.00%
Transfer coefficient for entry into treated crops (75th percentile) - adult	7500 cm ² /h
Transfer coefficient for entry into treated crops (75th percentile) - child	2250 cm ² /h
Transfer coefficient for entry into treated crops (mean) - adult	5980 cm ² /h
Transfer coefficient for entry into treated crops (mean) - child	1794 cm ² /h

Table A 16: Estimation of longer-term resident exposure to picloram according to EFSA guidance

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0023	% of RVNAS	0.75%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.36%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.04%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0014	% of RVNAS	0.47%
	All pathways (mean) mg/kg bw/day	0.0035	% of RVNAS	1.18%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	0.18%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.08%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.02%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0008	% of RVNAS	0.26%
	All pathways (mean) mg/kg bw/day	0.0012	% of RVNAS	0.39%

A 3.3.3 Calculations for Aminopyralid

Table A 17: Input parameters considered for the estimation of longer-term resident exposure

Resident exposure for GF-4021	
Croptype	Oilseeds
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.
Buffer strip	2-3 m
Application rate of the product	0.008 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.08 g a.s./l
Dermal absorption of product	70.00%
Dermal absorption of in-use dilution	70.00%
Oral absorption	100.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.024 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa
Concentration in air	0.001 mg/m ³
Resident dermal spray drift exposure 75th percentile - adult	0.47 ml spray dilution/person
Resident dermal spray drift exposure 75th percentile - child	0.327 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - adult	0.00010 ml spray dilution/person
Resident inhal. spray drift exposure 75th percentile - child	0.00022 ml spray dilution/person
Resident dermal spray drift exposure mean - adult	0.22318 ml spray dilution/person
Resident dermal spray drift exposure mean - child	0.18 ml spray dilution/person
Resident inhal. spray drift exposure mean - adult	0.00009 ml spray dilution/person
Resident inhal. spray drift exposure mean - child	0.00017 ml spray dilution/person
Exposure duration dermal	2 hours
Exposure duration inhalation	24 hours
Exposure duration entry into treated crops	0.25 hours
Light clothing adjustment factor	18.0%
Breathing rate adult	0.23 m ³ /day/kg
Breathing rate child (1-3 year old)	1.07 m ³ /day/kg
Drift percentage on surface (75th percentile)	5.60%
Drift percentage on surface (mean)	4.10%
Turf transferable residues percentage	5.00%
Transfer coeff. of surface deposits-adult	7300 cm ² /hour
Transfer coeff. of surface deposits-child (1-3 year old)	2600 cm ² /hour
Saliva extraction percentage	50.00%
Surface area of hands mouthed	20 cm ²
Frequency of hand to mouth activity	9.5 events/hour
Ingestion rate for mouthing of grass per day	25 cm ²
Dislodgeable residues percentage transferability for object to mouth	20.00%
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500 cm ² /h
Transfer coefficient for entry into treated crops (75th percentile) - chi	2250 cm ² /h
Transfer coefficient for entry into treated crops (mean) - adult	5980 cm ² /h
Transfer coefficient for entry into treated crops (mean) - child	1794 cm ² /h

Table A 18: Estimation of longer-term resident exposure to aminopyralid according to EFSA guidance

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0015	% of RVNAS	0.58%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.41%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.03%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0009	% of RVNAS	0.36%
	All pathways (mean) mg/kg bw/day	0.0027	% of RVNAS	1.04%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	0.14%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.09%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.01%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	0.20%
	All pathways (mean) mg/kg bw/day	0.0008	% of RVNAS	0.33%

A 3.4 Combined exposure calculations for halauxifen-methyl, picloram, and aminopyralid

See point 6.6.5.

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 required to characterize the product.