

REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: GF-3969

Chemical active substances:

Rimsulfuron, 148.15 g/kg

Thifensulfuron methyl, 92.6 g/kg

Isoxadifen-ethyl, 111.1 g/kg (safener)

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Corteva/DuPont/DowAgroScience/Pioneer*

Submission date: 18/12/2020

MS Finalisation date: December 2021 (initial Core Assessment)

May 2022 (final Core Assessment)

*Corteva Agriscience is new Legal Entity in most of EU countries and should be treated as an Applicant for GF-3969 registration. Information about Applicant for each country is provided in dRR Part A.

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Version history

When	What
18 December 2020	Applicant Initial dRR
December 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 .
May 2022	Final report (Core Assessment updated following the commenting period) Additional information/assessments included by the zRMS in the report in response to comments recieved from the cMS and the Applicant are highlighted in yellow. Information no longer relevant is struck through and shaded .

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Reviewer comments:

This part of dossier summarizes data related to the toxicological assessment and exposure data for the plant protection product GF-3969/Dragster and has been submitted to support registration according art. art. 33 of 1107/2009 in Poland.

Product was not a representative formulation reviewed during the Annex I inclusion/renewal of active substance(s) and has not been previously evaluated in any EU countries according to the Uniform Principles.

For the current product registration, applicant provided relevant data on the plant protection product GF-3969/Dragster regarding toxicological assessment based on *in vivo* toxicity studies also substantiated with composition prediction approach (ATE) and *in vitro* tests. The testing strategy takes into account methods compliant with the 3R concept for refinement, reduction and replacement of animal testing where applicable and acceptable (please refer Appendix 2 to this dossier).

Predictions for eye corrosion/irritation based on *in vitro* studies is not relevant due to inconclusive outcome. This approach is supported by following paper: Kolle S.N., van Cott A., van Ravenzwaay B. and Landsiedel R. (2017): *Lacking applicability of in vitro eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS*. Regulatory Toxicology and Pharmacology 85 (2017) 33-47. ~~However in vivo study showed no eye irritation properties but considering WoE and precautionary approach, ZRMS in this particular case (eye corrosion/irritation) decided take into account for hazard assessment predictions for eye corrosion/irritation based on composition of the product which estimation is indicative of eye irritation.~~

Considering comments and suggestions sent by the cMS during the commenting period on the dRR, ZRMS PL decided to take into account all proposals and reclassified the PPP Dragster in terms of eye irritation.

Based on the discussion regarding CLP classification final conclusions reflecting irritating potential was made on the basis of an *in vivo* test (Slonina, M., 2018 (DuPont-49964)), which confirmed the absence of eye irritation effect after exposure to the tested formulation.

Regarding skin corrosion/irritation based on *in vitro* studies ZRMS consider following outcome. In the OECD Test Guideline No. 439 *In Vitro* Skin Irritation: Reconstructed Human Epi-dermis Test Methods; revision 14 June 2021; section "Initial considerations and limitations" point 8, has been stated: (..) A study comparing *in vitro* and *in vivo* data for 65 agrochemical formulations revealed an overall accuracy of 54% (based on 65 agrochemical formulations), a sensitivity of 44% (based on 25 formulations) and a specificity of 60% (based on 40 formulations). This data indicates a lack of applicability of the RhE based in vitro skin irritation test for agrochemical formulations. (..).

In addition this is supported by following paper included in the references TG OECD 439: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). *Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations*. Regul.Toxicol. Pharmacol 89, 125-130.

Thus regarding mentioned above information, ZRMS decided not to take into account *in vitro* study Costin, G.E., Pham, R., Sadowski, N., 2018 and conclude hazard assessment for skin irritation outcome considering available *in vivo* study (Slonina, M., 2018).

Finally ZRMS decided take into account all information obtained from *in vivo* studies. ~~and one prediction based on composition (eye corrosion/irritation). ZRMS consider these results as complete data package relevant to conclude hazard assessment.~~ Product classification has been agreed using all accepted end-points.

ZRMS accepted already existing *in vivo* studies and do not request for the new one. 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-3969/Dragster (*water dispersible granules (WG) formulation containing 148.15 g/kg rimsulfuron and 92.60 g/kg thifensulfuron methyl and safener 111.1 g/kg isoxadifen-ethyl. The product is intended for use by professional users only on maize to control full grass spectrum and basic broad-leaved weeds (BLW) spectrum; refer dRR part B0) considering critical use(s), identify safe use of the product GF-3969/Dragster.*

Thifensulfuron methyl information belongs to FMC, but all datapoints originate from the EFSA conclusion. Unless otherwise specified, endpoints used in this section for isoxadifen-ethyl originate from Bayer CropScience and Corteva has a letter of access.

6 Mammalian toxicology (KCP 7)

Toxicology endpoints for the active substances in GF-3969, rimsulfuron, thifensulfuron methyl and isoxadifen-ethyl, used in risk assessments are derived from the respective review reports for these actives as indicated below.

For rimsulfuron: EFSA Scientific Report (2005) 45, 1-61. Conclusion regarding the peer review of the pesticide risk assessment of the active substance rimsulfuron. EFSA Journal 2018;16(5):5258 Peer review of the pesticide risk assessment of the active substance rimsulfuron.

For thifensulfuron methyl: EFSA Journal 2015;13(7):4201. Conclusion on the peer review of the pesticide risk assessment of the active substance thifensulfuron-methyl.

The evaluation of the safener isoxadifen-ethyl (IDF) was performed by RMS Germany and resulted in an evaluation report. Unless specified otherwise, endpoints were taken by the RMS Germany document (Summary of the German national evaluation of the safener isoxadifen-ethyl, 14th of August 2002, RMS: Germany - M-263999-01-1).

6.1 Summary

Table 6.1-1: Information on GF-3969

Product name and code	GF-3969 (DPX-V4B07 24.08WG)
Formulation type	Water dispersible granules [Code: WG]
Active substance(s) (incl. content)	Rimsulfuron, 148.15 g/kg Thifensulfuron methyl, 92.6 g/kg
Safener	Isoxadifen-ethyl, 111.1 g/kg
Function	Rimsulfuron and thifensulfuron methyl; herbicide Isoxadifen-ethyl; safener
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

NOTE: Information on the detailed composition of GF-3969 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-3969 according to Regulation (EC) No 1272/2008

	Proposal	Justification
Hazard class(es), categories:	Eye Irrit. 2	Eye Irritation Category 2 is applicable in accordance to Annex I – part 3 – points 3.3.3 to 3.3.3.6. of Regulation (EC) No. 1272/2008 and its corresponding ATPs.

Hazard pictograms or Code(s) for hazard pictogram(s):	 GHS07	The pictogram GHS07 is applicable to mixtures classified Eye Irritation Category 2 in accordance with articles 19 and 26, Annex I – Part 3 – point 3.3.4.1 and table 3.3.5 of Regulation (EC) No. 1272/2008 and its corresponding ATP's, and ECHA Guidance on labelling and packaging chapter 4, point 4.3
Signal word:	Warning	The signal word Warning is applicable to mixtures classified eye irritation Category 2 in accordance with Article 20, Annex I – Part 3 – Point 3.3.4.1. and Table 3.3.5 of Regulation (EC) No. 1272/2008 and its corresponding ATP's, and ECHA Guidance on labelling and packaging Chapter 4, Points 4.3.
Hazard statement(s):	H319	Hazard Statement H319 is assigned to mixtures classified Eye Irritation Category 2 in accordance to Annex I – part 3 – point 3.3.4.1. table 3.3.5 of Regulation (EC) No. 1272/2008 and its corresponding ATPs, and ECHA Guidance on labelling and packaging chapter 4, point 4.5.
Precautionary statement(s):	P280; P305 + P351 + P338; P337 + P313	Precautionary statement P280 is applicable to mixtures assigned H319 in accordance with Article 22, Annex I - part 3 - point 3.3.4.1. and table 3.3.5 of Regulation (EC) No. 1272/2008 and its corresponding ATPs, and ECHA Guidance on labelling and packaging chapter 4, point 4.6. and chapter 7 point 7.3.3.3. Precautionary statement P305 + P351 + P338 is applicable to mixtures assigned H319 in accordance with Article 22, Annex I – Part 3 – Point 3.3.4.1. Table 3.3.5. of Regulation (EC) No. 1272/2008 and its corresponding ATPs, and ECHA Guidance on labelling and packaging chapter 4, point 4.6. and chapter 7 point 7.3.3.3. Precautionary statement P337 + P313 is applicable to mixtures assigned H319 in accordance with Article 22, Annex I - Part 3- Point 3.3.4.1. Table 3.3.5. of Regulation (EC) No. 1272/2008 and its corresponding ATPs, and ECHA Guidance on labelling and packaging chapter 4, point 4.6. and chapter 7 point 7.3.3.3.
Additional labelling phrases:	EUH 208: Contains Isoxadifen-ethyl. May produce an allergic reaction. EUH 401: To avoid risks to man and the environment, comply with the instructions for use.	The label on the packaging of mixtures not classified as sensitising but containing at least one substance classified as sensitising and present in a concentration equal to or greater than that specified in table 3.4.6. of Annex I shall bear EUH208 statement. Supplemental hazard information assigned to plant protection products subject to 1107/2009/EC in accordance with Annex II, Part 4 of Regulation (EC) No. 1272/2008 and its corresponding ATPs.

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for GF-3969

	Result	PPE/ Risk mitigation measures
Operators	Acceptable	None; however, eyewear and gloves are required for mixing, loading, and application based on the hazard classification of the product.
Workers	Acceptable	None
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for operators, workers, bystanders and residents 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 bystanders/residents 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, bystander or resident 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 g a.s./ha a) a.s. 1 b) a.s. 2	Water L/ha min/ max			Operator	Worker	Bystander	Residents
1	Maize (ZEAMX) (silage & grain) BBCH 11 to BBCH 18	F	Hydraulic sprayer overall	a) 1 (n.a. ^a) b) 1 (n.a.)	a) 0.02 20 b) 0.0125 12.5	100 / 400	n.a.	Safener: formulated product contains 111.1 g/kg isoxadifen- ethyl (max. 15 g/ha) Adjuvant: application with max. 0.2% DPX-KG691 or vegetable oil				
14	Maize (ZEAMX) (silage & grain) BBCH 11 to BBCH 18	F	Hydraulic sprayer overall	a) 2 (7 days) b) 2 (7 days)	a) 0.02 20 b) 0.0125 12.5	100 / 400	n.a.	Safener: formulated product contains 111.1 g/kg isoxadifen- ethyl (max. 15 g/ha) Adjuvant: application with max. 0.2% DPX-KG691 or vegetable oil Split application possible without exceeding the total maximum of 135 g product/ha				

* 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

a n.a. = not applicable

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:

Not identify

6.2 Toxicological information on active substance(s)

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

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

	Rimsulfuron	Thifensulfuron methyl	Isoxadifen-ethyl
Common Name	Rimsulfuron	Thifensulfuron methyl	Isoxadifen-ethyl

	Rimsulfuron	Thifensulfuron methyl	Isoxadifen-ethyl
CAS-No.	122931-48-0	79277-27-3	163520-33-0
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Not classified in health hazard categories.	Not classified in health hazard categories.	Hazard classes (s), categories: Acute tox (oral) Cat. 4 Skin Sensitisation Cat. 1 Code(s) for hazard pictogram(s): GHS07 Signal word: Warning Hazard statement(s): H302 H317 Eye Irrit.2, H319*
Additional C&L proposal	Not applicable	Not applicable	Not applicable
Agreed EU endpoints			
AOEL systemic	0.07 mg/kg bw/d (corrected for 62% oral absorption)	0.07 mg/kg bw/d	0.02 mg/kg bw/d (corrected for 65% oral absorption)
Reference	EFSA Scientific Report (EFSA, 2005) Rimsulfuron SANCO/10528/2005 – rev. 2; 27 January 2006	EFSA Conclusion (EFSA, 2015)	German National Evaluation (2002)
Conditions to take into account/critical areas of concern with regard to toxicology			
Review Report/EFSA Conclusion for active substance	None	None	None

*This additional classification based on submitted MSDS, Du Pont (UK) Limited, has been added to reflect cMS comments

6.3 Toxicological evaluation of plant protection product

GF-3969 is a water dispersible granules formulation containing rimsulfuron, 148.15 g/kg, thifensulfuron methyl, 92.6 g/kg, and isoxadifen-ethyl, 111.1 g/kg. A summary of the toxicological evaluation for GF-3969 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.

Unless specifically indicated, all reports in this section are submitted to address mandatory data requirements for the approval of the plant protection product.

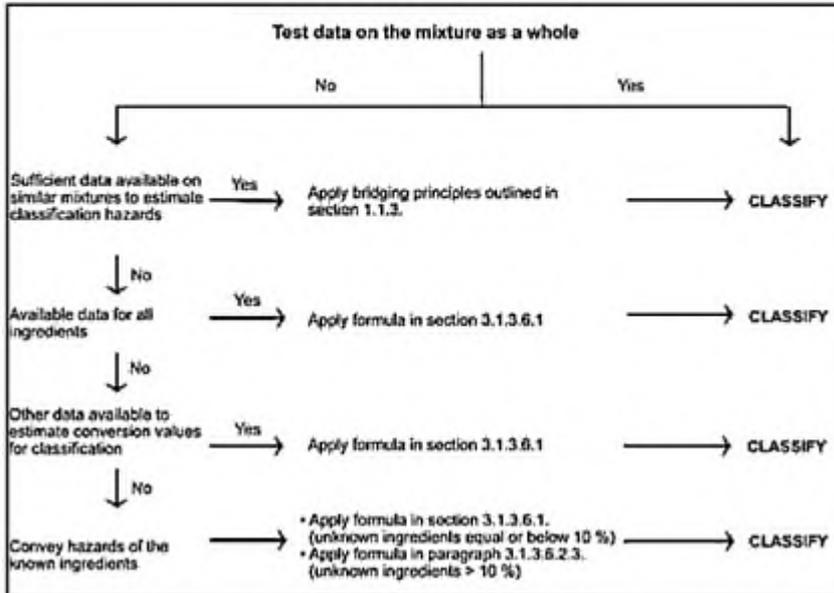
In accordance with Article 33.3.c the applicant confirms that no vertebrate studies were performed for the purpose of providing data on formulation GF-3969 in the EU. Acute *in vivo* studies are presented in this dossier which were not conducted to meet the requirements for assessment of acute mammalian toxicity under Regulation (EC) No. 1107/2009. Rather they were conducted to meet the requirements for registering GF-3969 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.

Unless specifically indicated, this section does not contain reports of studies duplicating previous tests on vertebrate animals.

The classification of the formulation GF-3969 for acute toxic effects based on the calculation method is presented in Table 6.3-1. Classification data for the components are found in the confidential dRR Part C.

Reviewer comments: for the purpose of hazard assessment ZRMS decided to take into account results obtained from existed *in vivo* studies which is in line with REACH regulation where is pointed out that in this case *in vivo* studies overruled ATE assessment. However considering different results of eye irritation assessment (*in vitro*, *in vivo* and ATE) and considering WoE also precautionary approach, in this particular case (eye corrosion/irritation), ZRMS decided to take into account for hazard assessment, predictions for eye corrosion/irritation based on composition of the product, which estimation is indicative of eye irritation. That is why only this calculation has been verified by the ZRMS. Remaining toxicity classification based on composition of the product (ATE) however available in the Part C of the dRR hasn't been verify.

Table 6.3-1: Summary of GF-3969 acute toxicity classification using ingredient data based on Regulation EC No. 1272/2008 (CLP) Section 3.1.3.6 mixture classification criteria

Endpoint	Classification based on additivity formula
Acute oral	Not classified Calculated ATE (if study data is not considered)= 12500 mg/kg * * < 10% of the mixture consists of unknown toxicity
Acute dermal	Not classified As per "relevant ingredients" definition in 3.1.3.3. of 1272/2008 as amended, this mixture does not contain relevant ingredients that should be considered for this hazard category. Calculation is not required.
Acute inhalation	Not classified As per "relevant ingredients" definition in 3.1.3.3. of 1272/2008 as amended, this mixture does not contain relevant ingredients that should be considered for this hazard category. Calculation is not required.
Endpoint	Classification based on components
Skin corrosion/irritation	Not classified As per "relevant ingredients" definition in 3.2.3.3.1. of 1272/2008 as amended, this mixture does not contain relevant ingredients that should be considered for this hazard category. Cumulative concentration of substances classified with Cat 2, H315 is < 1%. Classification is not triggered.
Eye corrosion/irritation	Category 2 Considering all classified substances in this hazard category and using the criteria given in Table 3.3.3. of 1272/2008 as amended: (10 x Eye Effects Category 1) + Eye Effects Category 2 ≥ 10% = Category 2, the result exceeds 10 and eye irritation Cat 2, H319 classification is triggered. Calculation in detail is available in Part C.
Respiratory Sensitisation	Not Classified
Skin sensitisation	Category 1 Product contains > 1% of Cat 1, H317 classified sensitising substance. Skin Sensitisation Category 1, H317 classification is triggered by calculation. This classification is omitted from the final product classification due to LLNA study (KCP 7.1.6; A 2.7.1) result that takes precedence. EUH208 statement is added instead.

ATE = Acute Toxicity Exposure

See Acute ATE Calculation Discussion in the confidential dRR Part C for additional details on how the ATE values were derived.

Table 6.3-2: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for GF-3969

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD ₅₀ oral, rat (OECD 425)	>5000 mg/kg bw	Yes	Not classified.	Fallers, M.N., 2018 (DuPont-49958)
LD ₅₀ dermal, rat (OECD 402)	>5000 mg/kg bw	Yes	Not classified.	Fallers, M.N., 2018 (DuPont-49959)
LC ₅₀ inhalation, rat (OECD 403)	>5.4 mg/L air	Yes	Not classified.	Kegelman, T.A., 2018 (DuPont-49960)
Skin irritation, rabbit (OECD 404)	Non-irritant	Yes	Not classified.	Slonina, M., 2018 (DuPont-49965)
Skin irritation, EpiDerm SIT model (OECD 439)*	Non-irritant	No	Not classified. Not applicable	Costin, G.E., Pham, R., Sadowski, N., 2018 (DuPont-50172)
Eye irritation, rabbit (OECD 405)**	Non-irritant	Yes	Not classified	Slonina, M., 2018 (DuPont-49964)
Eye irritation, EpiOcular EIT (OECD 492)***	Irritant	Supplementary	Inconclusive EpiOcular eye irritation test. Classification based on calculation. H319 Causes serious eye irritation.	Wilt, N., Pham, R., Sadowski, N., 2018 (DuPont-50173)
Skin sensitisation, mouse (OECD 429, LLNA)	Non-sensitising	Yes	Not classified.	Hoban, D., 2018 (DuPont-49966)
Supplementary studies for combinations of plant protection products. Induction of antioxidant-response-element dependent gene activity and cytotoxicity (using MTT) in the keratinocyte ARE-reporter cell line keratinosens	Non-sensitising Sensitizer	Supplementary	Not classified.	Ruwona, T., Sheehan, D., Koch, W.T., 2018 (DuPont-50245)

***Reviewer comments:** In the Test Guideline No. 439 *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Methods; revision 14 June 2021; in section “Initial considerations and limitations” point 8, has been stated: (..) *A study comparing in vitro and in vivo data for 65 agrochemical formulations revealed an overall accuracy of 54% (based on 65 agrochemical formulations), a sensitivity of 44% (based on 25 formulations) and a specificity of 60% (based on 40 formulations). This data indicates a lack of applicability of the RhE based in vitro skin irritation test for agrochemical formulations.* (..)

In addition this is supported by following paper: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). *Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations.* Regul.Toxicol. Pharmacol 89, 125-130.

Thus regarding mentioned above information, ZRMS decided not to take into account *in vitro* study Costin, G.E., Pham, R., Sadowski, N., 2018 and conclude hazard assessment skin irritation potential considering available *in vivo* study (Slonina, M., 2018).

** for detailed rationale see our comment Appendix 2 point A.2.2.6 and point 6.3 p.12 to this dRR.

** Predictions for eye corrosion/irritation based on *in vitro* studies is not relevant due to inconclusive outcome, thus ZRMS in this particular case (eye corrosion/irritation) decided to take into account for hazard assessment purpose predictions for eye corrosion/irritation based on *in vivo* study. composition of the product. More details see ZRMS General comment p.6 of this dRR.

Table 6.3-3: Additional toxicological information relevant for classification/labelling of GF-3969

	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)	Rimsulfuron (25.1% (w/w))	None	-	None
	Thifensulfuron methyl	None	-	None

	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)
for classification of product)	(49.8% (w/w)) Isoxadifen-ethyl (11.5% (w/w), technical)	Hazard statement(s) H302 H317	Reg. 1272/2008 as amended, Annex VI	EUH 208
Toxicological properties of non- active substance(s) (relevant for classification of product)	Benzenesulfonic acid, mono- C11-13-branched alkyl derivs. sodium salts (CAS No. 68608-89-9, <1%)	Acute tox. (oral) Cat 4, H302 Acute tox. (dermal) Cat 4, H312 Skin irritation Cat 2, H315 Eye damage Cat 1, H318	SDS*	Eye irritation Cat 2, H319
	Sodium carbonate (CAS No. 497-19-8, ≥1 - ≤5%)	Eye irritation Cat 2, H319	SDS*	Eye irritation Cat 2, H319
	Lignin, alkali, reaction products with disodium sulfite and formaldehyde (CAS 105859-97-0, ≥1 - ≤5%)	Eye irritation Cat 2, H319	SDS*	Eye irritation Cat 2, H319
	Barden clay (CAS 1332-58-7, ≥5 - ≤10%)	Not classified	SDS*	Not classified
Further toxicological information: GF-3969 tank mixed with adjuvant - Mixture classification	Non-ionic surfactant (DPX-KG691)	Acute tox. (oral) Cat 4, H302 Eye damage Cat 1, H318	SDS*	GF-3969 mixed with non- ionic surfactant DPX- KG691: In tank mix concentrations, classified components of DPX- KG691 would remain <1% and below the classification trigger criteria as laid out in 1272/2008 (as amended). No health hazard classification is expected to be applicable for the tank mix.
	Vegetable oil (Codacide)	Not classified.	SDS*	GF-3969 mixed with Vegetable oil Codacide: Codacide is not classified so it is not expected to contribute to hazard classification of the final tank mix.

* Safety data sheet by the applicant

NOTE: Considering comments and suggestions sent by the cMS during the commenting period on the dRR, ZRMS PL decided to take into account all proposals and reclassified the PPP Dragster in terms of eye irritation. Based on the discussion regarding CLP classification final conclusions reflecting irritating potential was made on the basis of an *in vivo* test (Slonina, M., 2018 (DuPont-49964)), which confirmed the absence of eye irritation effect after exposure to the tested formulation.

6.4 Toxicological evaluation of groundwater metabolites

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

Rimsulfuron metabolites

6.4.1 IN-70941

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-79041 is given in the following table. Full summaries of studies on the metabolite have previously been considered within an EU peer review process.

Table 6.4-1: Summary of the results of toxicity studies for IN-70941

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> (US EPA FIFRA Subdivision F, 84-2)	Negative	Yes	Reynolds, V.L., 1989 (HLR 344-89*)
<i>In vitro</i> mammalian cell mutagenicity, CHO-K1 cells (OECD 476)	Negative	Yes	San, R.H.C., Clarke, J.J., 2003 (DuPont-13387*/AA78YL.782.BTL)
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative	Yes	Gudi, R., Rao, M., 2004 (DuPont-13386, Revision No. 1/ AA78YL.341.BTL*)
Acute oral limit test (no guideline specified)	ALD >11000 mg/kg	Yes	Sarver, J.W., 1989 (HLR 199-89*)
Ten-dose oral subchronic (no guideline specified)	NOAEL not established because of hepatocellular hypertrophy in the only dose group (2200 mg/kg bw/day)	Yes	Sarver, J.W., 1989 (HLR 526-89*)

* indicates that a study was reviewed at EU level

6.4.2 IN-70942

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-70942 is given in the following table. Full summaries of studies on the metabolite have previously been considered within an EU peer review process.

Table 6.4-2: Summary of the results of toxicity studies for IN-70942

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> (OECD 471)	Negative	Yes	Wagner, V.O., III, VanDyke, M.R., 2013 (DuPont-36584*)
<i>In vitro</i> mammalian cell mutagenicity, CHO-K1 cells (OECD 476)	Negative	Yes	Clarke, J.J., 2013 (DuPont-36586*)
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative	Yes	Roy, S., Jois, M., 2013 (DuPont-36585*)

* indicates that a study was reviewed at EU level

6.4.3 IN-E9260

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-E9260 is given in the following table. A summary of the study on the metabolite that has not previously been considered within an EU peer review process is described in detail in Appendix 2. The remaining studies on the metabolite have had the full summaries previously considered within an EU peer review process.

Table 6.4-3: Summary of the results of toxicity studies for IN-E9260

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> (OECD 471)	Negative	Yes	Reynolds V.L., 1989 (HLR 108-89*)
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative	Yes	Forichon, A., 1992 (202380*)
<i>In vitro</i> mammalian cell mutagenicity, CHO-K1 cells (OECD 476) ^a	Negative	Yes	Clarke, J.J., 2013 (DuPont-36588*)
<i>In vitro</i> micronucleus (OECD 407)	Negative	Yes	Clare, 2018 (MNT00515)
<i>In vivo</i> Comet study (OECD 489)	Negative (2000 mg/kg bw/day)	Yes	Beevers, C., 2016 (8346539*)
Acute oral LD ₅₀ (OECD 401)	LD ₅₀ >2000 mg/kg	Yes	Lheritier, M., 1991 (110304*)
Acute dermal (OECD 402)	LD ₅₀ >2000 mg/kg	Yes	Lheritier, M., 1991 (110303*)
Skin irritation (OECD 404)	Non-irritant	Yes	Mercier, O., 1992 (201335*)
Eye irritation (OECD 405)	Slight eye irritant (not classified – EFSA, 2005)	Yes	Mercier, O., 1992 (201336*)
Skin sensitisation (M&K) (OECD 406)	Not sensitising	Yes	Mercier, O., 1992 (202355*)
Skin sensitization (LLNA) (OECD 429)	Not sensitising	Yes	Ladics, G.S., 2004 (DuPont-15258*)
28-day rat oral (OECD 407)	NOAEL <50 mg IN-E9260 kg/body wt Based on increased liver weights (Males) and decreased creatinine levels (Females)	Yes	Woehrlé, F., 1992, (35291*)

* indicates that a study was reviewed at EU level

a OECD 476 only specifies exposure for 3 hours. The result was negative following 3 hours' exposure.

Thifensulfuron methyl metabolites

6.4.4 IN-L9225

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-L9225 is given in the following table. These studies have been reviewed and are summarized in the Thifensulfuron-methyl RAR (2014).

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Negative ± S-9	Yes	Myhre, A., 2011 (DuPont-30758)*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Negative ± S-9	Yes	Donath, C., 2011 (EU TSM Task Force) (110127)*
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative ± S-9	Yes	Glover, K.P., 2011 (DuPont-30759)*
<i>In vitro</i> mammalian cell mutagenicity, CHO-K1 cells (OECD 476) ^a	Negative ± S-9	Yes	Clarke, J.J., 2011 (DuPont-30760)*
<i>In vitro</i> mammalian micronucleus test (OECD 487)	Negative ± S-9	Yes	May, 2012 (EU TSM Task Force) (DGV0080)*
Acute oral toxicity is Wistar Rats (OECD 420)	LD ₅₀ > 2000 mg/kg bw	Yes	RAR, 2014 (EU TSM, Task Force, 206 TIM) *

* indicates that a study was reviewed at EU level

6.4.5 IN-L9223

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-L9223 is given in the following table. These studies have been reviewed and are summarized in the Thifensulfuron-methyl RAR (2014).

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Negative ± S-9	Yes	Myhre, A., 2011 (DuPont-31622)*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Negative ± S-9	Yes	Donath, C., 2011 (EU TSM Task Force) (110128)*
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative ± S-9	Yes	Glover, K.P., 2011 (DuPont-31623)*
<i>In vitro</i> chromosomal aberration, human lymphocytes (OECD 473)	Negative ± S-9	Yes	Lloyd, 2011 (EU TSM Task Force) (8243962)*
<i>In vitro</i> mammalian cell mutagenicity, CHO-K1 cells (OECD 476) ^a	Negative ± S-9	Yes	Clarke, J.J., 2011 (DuPont-31624)*
<i>In vitro</i> mammalian cell mutagenicity, Mouse Lymphoma (L1578Y/TK) (OECD 476) ^a	Negative ± S-9	Yes	Lloyd, 2011 (EU TSM Task Force) (8243963)*

* indicates that a study was reviewed at EU level

6.4.6 IN-JZ789

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-JZ789 is given in the following table. These studies have been reviewed and are summarized in the Thifensulfuron-methyl RAR (2014).

Type of test, species (Guideline)	Result	Acceptability	Reference*
<i>In vitro</i> bacterial mutagenicity (Ames test), <i>Salmonella typhimurium</i> and <i>Escherichia coli</i> (OECD 471)	Negative ± S-9	Yes	May, K.,2012 (EU TSM Task Force) (DGV0081)*
<i>In vitro</i> mammalian micronucleus test (OECD 487)	Negative ± S-9	Yes	May, K., 2012 (EU TSM Task Force) (DGV0082)*

* indicates that a study was reviewed at EU level

Isoxadifen-ethyl metabolites

No metabolites predicted to occur in groundwater at concentrations above 0.1 µg/L.

6.5 Dermal absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in GF-3969 are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in GF-3969

	Rimsulfuron		Thifensulfuron methyl		Isoxadifen-ethyl	
	Value	Reference	Value	Reference	Value	Reference
Concentrate ^{a,b}	10%	Default for WG concentrated solution (>50 g a.s./kg)	10%	Default for WG concentrated solution (>50 g a.s./kg)	10%	Default for WG concentrated solution (>50 g a.s./kg)
Dilution ^{a,b}	50%	Default value for diluted WG solution (≤50 g a.s./L)	50%	Default value for diluted WG solution (≤50 g a.s./L)	50%	Default value for diluted WG solution (≤50 g a.s./L)

a SANTE/ 2018/ 10591 rev 1

b EFSA Journal 2017; 15(6):4873

6.5.1 Justification for proposed values - Rimsulfuron

No data on dermal absorption for rimsulfuron in GF-3969 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 rimsulfuron

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default value for undiluted WG formulation with active substance concentration >50 g/kg as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product.
Dilution	50%	Default value for diluted WG formulation with an active substance concentration ≤50 g/L	Justification accepted. Endpoint can be used for current product

	Value	Justification for value	Acceptability of justification
		as stated in the EFSA guidance document on dermal absorption	

6.5.2 Justification for proposed values - Thifensulfuron methyl

No data on dermal absorption for thifensulfuron methyl in GF-3969 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 thifensulfuron methyl

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default value for undiluted WG formulation with active substance concentration >50 g/kg as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product.
Dilution	50%	Default value for diluted WG formulation with an active substance concentration ≤50 g/L as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product.

6.5.3 Justification for proposed values - Isoxadifen-ethyl (safener)

No data on dermal absorption for isoxadifen-ethyl in GF-3969 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 isoxadifen-ethyl

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default value for undiluted WG formulation with active substance concentration >50 g/kg as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product
Dilution	50%	Default value for diluted WG formulation with an active substance concentration ≤50 g/L as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product

6.5.4 Justification for proposed values – DPX-KG691 (adjuvant)

No data on dermal absorption for adjuvant 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 6.5-5: Default dermal absorption rates for DPX-KG691

	Value	Justification for value	Acceptability of justification
Concentrate	10%	Default value for undiluted SL formulation with active substance concentration >50 g/L as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product.
Dilution	50%	Default value for diluted SL formulation with an active substance concentration ≤50 g/L as stated in the EFSA guidance document on dermal absorption	Justification accepted. Endpoint can be used for current product.

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-3969		
Formulation type	WG		
Category	Herbicide		
Active substance(s) (incl. content)	Rimsulfuron, 148.15 g/kg	Thifensulfuron methyl, 92.6 g/kg	Isoxadifen-ethyl, 111.1 g/kg
AOEL systemic	0.07 mg/kg bw/d	0.07 mg/kg bw/d	0.02 mg/kg bw/d
Inhalation absorption	100%	100%	100%
Oral absorption	70%	>80% (estimated)	65%
Dermal absorption ^{a,b} (Default based on EFSA guidance)	Concentrate: 10% Dilution: 50%	Concentrate: 10% Dilution: 50%	Concentrate: 10% Dilution: 50%

a SANTE/ 2018/ 10591 rev 1

b EFSA Journal 2017; 15(6):4873

Table 6.6-2: Adjuvant information and toxicological reference values used for exposure assessment

Product name and code	DPX-KG691	Codacide (MC001)	
Formulation type	SL		
Category	Non-ionic Adjuvant	Vegetable oil Adjuvant	
Active substance(s) (incl. content)	Isodecyl alcohol ethoxylate, 900 g/L	Canola Rape oil (95%)	Polyethoxylated Ester Emulsifier (5%)
AOEL systemic	0.75 ^a 0.5^c mg/kg bw/d	Contains no substance meeting the criteria for classification as hazardous under EU Directives (DSD 67/548/EC or CLP 1272/2008 EC). Not classified as dangerous according to Directive 67/548/EEC. All substances are REACH exempt. Not a hazardous product according to Globally Harmonized System (GHS).	
Inhalation absorption	100%		
Oral absorption	100%		
Dermal absorption ^{a,b} (Default based on EFSA guidance for SL formulations)	Concentrate: 10% Dilution: 50%		

a SANTE/ 2018/ 10591 rev 1

b EFSA Journal 2017; 15(6):4873

c DPX-KG691 – AOEL was derived from Study: Dufour P., (1999) Oral toxicity test after 28-day repeated administration in the rat. Report No. TF375/99-0777.

An AOEL for isodecyl alcohol ethoxylated, active substance in non-ionic adjuvant DPX-KG691 was determined from the 28-day rat feeding study NOAEL 150 mg/kg bw/day for female rat (Dufour P., 1999, Report No TF375/99-0777). Study summary is provided in Appendix 2.

On the basis of this study, the safety factor of 200 was derived according to the following different uncertainties:

- 10 inter-species (animal-to -human)
- 10 intra-specie (human-to-human)
- ≥ 3 duration of exposure (sub-acute to sub-chronic study).

For the exposure assessment, AOEL ~~0.75~~ 0.5 mg/kg/day was used for adjuvant DPX-KG691.

6.6.1 Selection of critical use(s) and justification

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

Justification

The Plant Protection Product GF-3969 is intended to be used in maize as an herbicide. The representative use pattern has been defined following evaluation of the individual GAPs in each relevant Member State. The representative GAP for this assessment is based on maximum application rate and minimum 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-3969.

6.6.2 Adjuvant Exposure

Since Codacide contains no substance meeting the criteria for classification as hazardous under CLP 1272/2008 EC, exposure assessment is only performed for DPX-KG691.

The recommended maximum application rate for DPX-KG691 is 0.2% v/v in the spray tank. Based on the water spray volumes (100 L/ha – 400 L/ha), application rates for DPX-KG691 range from 0.2 L to 0.8 L adjuvant/ha (0.2% of spray volumes). Since DPX-KG691 contains 900 g of isodecyl alcohol ethoxylate (IAE) per L of adjuvant, this translates to a minimum of 180 g IAE/L adjuvant and maximum of 720 g IAE/L adjuvant (e.g. maximum application rate = 0.8 L adjuvant/ha × 900 g IAE/L adjuvant = 720 g IAE/ha). Adjuvant exposure assessment has been conducted using the maximum application rate of adjuvant as that presents the highest exposure to the operator handling the concentrated adjuvant during mixing and loading. The EFSA model was used in order to assess the risk to human health for all subpopulations (operator, worker and resident). EFSA default dermal absorption values for an SL formulation of 10% (concentrate) and 50% (diluted product) have been used for the adjuvant. A summary of the results obtained for the adjuvant are summarized for each subpopulation below.

6.6.3 Operator exposure (KCP 7.2.1)

No unacceptable risk for operators from the supported uses of GF-3969 and the adjuvant was identified based on exposure estimates from the EFSA Model. However, eyewear must be worn when handling the concentrated product due to GF-3969 being classified as an eye irritant. Gloves should also be worn during mixing, loading, and application due to the skin sensitization hazard classification for GF-3969. Thus, the predicted operator exposure to rimsulfuron, thifensulfuron methyl, isoxadifen-ethyl (safener), and isodecyl alcohol ethoxylate (adjuvant) from tractor mounted applications was $\leq 5\%$ of the respective AOEL values, based on normal work wear and gloves worn during mixing, loading, and application.

6.6.3.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances

during application of GF-3969 according to the critical use(s) is presented in Table 6.6-3. Outcome of the estimation is presented in Table 6.6-4. Detailed calculations are in Appendix 3.

Table 6.6-3: Exposure models for intended uses

Critical use(s)	<ul style="list-style-type: none"> GF-3969: Maize (max. per application and per season = 0.135 kg product/ha, Minimum water volume = 100 L/ha) DPX-KG691: Maize (max. rate = 0.8 L adjuvant/ha in maximum water volume of 400 L/ha at 0.2% v/v)
Model(s)	EFSA 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)

Table 6.6-4: Estimated operator exposure: GF-3969

Spray application: Tractor mounted boom spray application outdoors to maize Area Treated: 50 ha/day (AOEM; 75 th percentile) Body weight: 60 kg						
Model Information	Rimsulfuron		Thifensulfuron methyl		Isoxadifen-ethyl (safener)	
Number of applications and application rate	1 × 0.02 kg a.s./ha		1 × 0.0125 kg a.s./ha		1 × 0.015 kg a.s./ha	
Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL	Total absorbed dose (mg/kg/day)	% of AOEL	Total absorbed dose (mg/kg/day)	% of AOEL
Work wear (arms, body and legs covered) M/L & A (no PPE)	0.0042	6%	0.0029	4%	0.0033	17%
Work wear (arms, body and legs covered) + Gloves for M/L & A	0.0011	2%	0.0009	1%	0.0010	5%

Table 6.6-5: Estimated operator exposure: DPX-KG691

Spray application: Tractor mounted boom spray application outdoors to maize Area Treated: 50 ha/day Body weight: 60 kg		
Model Information	Isodecyl alcohol ethoxylate (IAE)	
Number of applications and application rate	1 × 0.720 kg IAE/ha	
Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL
Work wear (arms, body and legs covered) M/L & A (no PPE)	0.1784	± 36%
Work wear (arms, body and legs covered) + Gloves for Mixing/Loading <i>only</i> and application	0.0093	+ 2%

6.6.4 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the respective acceptable operator exposure levels (AOEL) for all active substances in GF-3969 and DPX-KG691 will not be exceeded

under conditions of intended uses and considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.5 Worker exposure (KCP 7.2.3)

Since the maximum single application rate is the same as the maximum seasonal application rate (0.135 kg product/ha), the highest dislodgeable foliar residue, and hence the highest dermal exposure risk upon re-entry, is when the maximum amount of product is applied in one single application. When the product is split into two lower application rates with a 7-day interval in-between the two applications, some of the foliar residue from the first application will degrade before the second application resulting in re-entry exposure to foliar residue after the first or second application being lower than exposure from a single application at maximum dose rate. As such, the single application at maximum dose rate scenario represents the worst-case exposure scenario and, therefore, considered to be the most appropriate way of assessing re-entry worker exposure.

No unacceptable risk for workers from the supported uses of GF-3969 and DPX-KG691 was identified based on exposure estimates from the EFSA Model. The predicted operator exposure to rimsulfuron, thifensulfuron methyl, isoxadifen-ethyl (safener), and isodecyl alcohol ethoxylate (adjuvant) was ~~≤7%~~ **≤10%** of the respective AOEL values, based on normal work wear and no additional PPE.

6.6.5.1 Estimation of worker exposure

Table 6.6-6 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with GF-3969 according to the critical use(s). Outcome of the estimation is presented in Table 6.6-7. Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	<ul style="list-style-type: none"> GF-3969: Maize (max. per application and per season = 0.135 kg product/ha, Minimum water volume = 100 L/ha) DPX-KG691: Maize (max. rate = 0.8 L adjuvant/ha in maximum water volume of 400 L/ha at 0.2% v/v)
Model	EFSA 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)

Table 6.6-7: Estimated worker exposure: GF-3969

Inspection and irrigation Outdoor Work rate: 2 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha						
Model Information	Rimsulfuron		Thifensulfuron methyl		Isoxadifen-ethyl (safener)	
Number of applications and application rate	1 × 0.02 kg a.s./ha		1 × 0.0125 kg a.s./ha		1 × 0.015 kg a.s./ha	
Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL	Total absorbed dose (mg/kg/day)	% of AOEL	Total absorbed dose (mg/kg/day)	% of AOEL
Work wear (arms, body and legs covered) TC ^a : 1400 cm ² /person/h (no PPE ^b)	0.0014	2%	0.0009	1%	0.0011	5%

a EFSA default for crop inspection. TC: Transfer coefficient

b No PPE: Worker wearing long sleeved shirt, long trousers

Table 6.6-8: Estimated worker exposure: DPX-KG691

Inspection and irrigation Outdoor Work rate: 2 hours/day, DT ₅₀ : 30 days DFR: 3 µg/cm ² /kg a.s./ha			
Model Information		Isodecyl alcohol ethoxylate (IAE)	
Number of applications and active substance single application rate		1 × 0.720 kg IAE/ha	
Model data	Level of PPE	Total absorbed dose (mg/kg/d)	% of systemic AOEL
Work wear (arms, body and legs covered) TC ^a : 1400 cm ² /person/h (no PPE ^b)		0.0504	7 10%

a EFSA default for crop inspection. TC: Transfer coefficient

b No PPE: Worker wearing long sleeved shirt, long trousers

6.6.5.2 Refinement of generic DFR value (KCP 7.2)

A refinement of the generic dislodgeable foliar residues (DFR) was not necessary since the worker exposure estimations carried out indicated that the respective acceptable operator exposure levels (AOEL) for all active substances in GF-3969 and DPX-KG691 (adjuvant) will not be exceeded under conditions of intended uses.

6.6.5.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable worker exposure levels (AOEL) for all active substances in GF-3969 will not be exceeded under conditions of intended uses and considering above mentioned PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.6 Bystander and resident exposure (KCP 7.2.2)

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.

The toxicological assessment of the formulation GF-3969 based on Acute Toxicity Exposure (ATE) calculations triggers a category 1B skin sensitizer classification. Therefore, an assessment to confirm that the in use-spray dilution would not be classified as a skin sensitizer is required. There is a current understanding that if a formulation which is classified as a sensitizer (as in the case of GF-3969) is diluted to less than 1%, then the resulting mixture would not be considered a sensitizer. Considering the worst-case scenario GAP where the maximum product application rate (0.135 kg product/ha) is diluted in the minimum water volume (100 L water/ha), the product will constitute 0.14% of the in-use spray dilution ($[0.135 \text{ product/ha} \div 100 \text{ L water/ha}] \times 100\%$), which is less than the 1% cut-off. As such, the in-use spray dilution is not considered to be a skin sensitizer and therefore does not present a risk to bystanders/residents.

Resident exposure estimations carried out using the EFSA Model indicated that the acceptable exposure level will not be exceeded under conditions of intended use. Using the EFSA Model, the highest estimated all pathways mean exposure for residents (children) to rimsulfuron, thifensulfuron methyl, isoxadifen-ethyl (safener), isodecyl alcohol ethoxylate (adjuvant) was 6%, 4%, 16%, and ~~9%~~ 13% of the respective AOELs.

6.6.6.1 Estimation of bystander and resident exposure

Table 6.6-9 shows the exposure model(s) used for estimation of bystander and resident exposure to rimsulfuron, thifensulfuron methyl, and isoxadifen-ethyl (safener). Outcome of the estimation is presented in Table 6.6-10. Detailed calculations are in Appendix 3.

Table 6.6-9: Exposure models for intended uses

Critical use(s)	<ul style="list-style-type: none"> GF-3969: Maize (max. per application and per season = 0.135 kg product/ha, Minimum water volume = 100 L/ha) DPX-KG691: Maize (max. rate = 0.8 L adjuvant/ha in maximum water volume of 400 L/ha at 0.2% v/v)
Model	EFSA 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)

Table 6.6-10: Estimated bystander and resident exposure: GF-3969

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							
Model data		Rimsulfuron		Thifensulfuron methyl		Isoxadifen-ethyl (safener)	
		Total absorbed dose (mg/kg/d)	% of systemic AOEL	Total absorbed dose (mg/kg/d)	% of systemic AOEL	Total absorbed dose (mg/kg/d)	% of systemic AOEL
Number of applications and application rate		1 × 0.02 kg a.s./ha		1 × 0.0125 kg a.s./ha		1 × 0.015 kg a.s./ha	
Resident	Drift (75 th)	0.0027	4%	0.0017	2%	0.0020	10%

child Body weight: 10 kg	perc.)						
	Vapour (75 th perc.)	0.0011	2%	0.0011	2%	0.0011	5%
	Deposits (75 th perc.)	0.0002	0.2%	0.0001	0.1%	0.0001	0.6%
	Re-entry (75 th perc.)	0.0017	2%	0.0011	2%	0.0013	6%
	Sum (mean)	0.0040	6%	0.0033	4%	0.0033	16%
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0006	1%	0.0004	0.6%	0.0005	2%
	Vapour (75 th perc.)	0.0002	0.3%	0.0002	0.3%	0.0002	1%
	Deposits (75 th perc.)	0.0001	0.1%	0.0000	0.06%	0.0001	0.3%
	Re-entry (75 th perc.)	0.0009	1%	0.0006	1%	0.0007	4%
	Sum (mean)	0.0013	2%	0.0011	1%	0.0011	5%

Table 6.6-11: Estimated resident exposure (longer term exposure): DPX-KG691

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			
Model data		Isodecyl alcohol ethoxylate	
		Total absorbed dose (mg/kg/d)	% of systemic AOEL
Number of applications and application rate		1 × 0.720 kg IAE/ha	
Resident child Body weight: 10 kg	Drift (75 th perc.)	0.0242	3% 5%
	Vapour (75 th perc.)	0.0011	0.1% 0.2%
	Deposits (75 th perc.)	0.0058	1%
	Re-entry (75 th perc.)	0.0608	8% 12%
	Sum (mean)	0.0671	9% 13%
Resident adult Body weight: 60 kg	Drift (75 th perc.)	0.0058	1%
	Vapour (75 th perc.)	0.0002	0.03% 0.05%
	Deposits (75 th perc.)	0.0025	0.3% 0.5%
	Re-entry (75 th perc.)	0.0338	5% 7%
	Sum (mean)	0.0317	4% 6%

6.6.6.2 Measurement of bystander and/or resident exposure

Since the bystander and/or resident exposure estimations carried out indicated that the acceptable operator exposure levels (AOEL) for rimsulfuron, thifensulfuron methyl, isoxadifen-ethyl (safener), and isodecyl alcohol ethoxylate (adjuvant) will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of bystander/resident exposure was not necessary and was therefore not performed.

6.6.7 Combined exposure

The product is a mixture of two active substances (rimsulfuron and thifensulfuron methyl) and a safener (isoxadifen-ethyl). In the tank mix, GF-3969 is mixed with water (application rate of 0.135 kg fp/ha with spray volumes 100-400 L/ha). DPX-KG691 is then added (label rate of 0.2 L/ha – 0.8 L/ha) to the diluted formulation, resulting in dilution of the adjuvant in the tank mix with its overall concentration in the tank mix very low and thus reducing its hazard profile. Therefore, it is highly unlikely that the addition of DPX-KG691 will significantly change the toxicological profile of the product due to the very low concentrations of the adjuvants as well as the active substances. Furthermore, default dermal absorption values have been applied for all components in the risk assessment which presents a highly precautionary approach. Based on the specified use pattern, any cause for concern related to acute exposure to this tank mixture is not expected to lead to additional acute toxicity concerns for the user relative to that posed by the neat products individually.

6.6.7.1 Combined exposure assessment of rimsulfuron, thifensulfuron methyl, and isoxadifen-ethyl (safener) in GF-3969, and isodecyl alcohol ethoxylate (adjuvant)

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. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-12: Risk assessment from combined exposure

Application scenario	Active Ingredient	Estimated exposure/ AOEL (HQ)
Operators – Tractor mounted boom spray application (Gloves only worn during mixing, loading, and application)	Rimsulfuron	0.02
	Thifensulfuron methyl	0.01
	Isoxadifen-ethyl	0.05
	Isodecyl alcohol ethoxylate (adjuvant)	0.01 0.02
	Cumulative risk Operators (HI)	0.09 0.1
Workers – crop inspection and irrigation	Rimsulfuron	0.02
	Thifensulfuron methyl	0.01
	Isoxadifen-ethyl	0.05
	Isodecyl alcohol ethoxylate (adjuvant)	0.07 0.1
	Cumulative risk Workers (HI)	0.15 0.18
Resident Child – All pathways (mean)	Rimsulfuron	0.06
	Thifensulfuron methyl	0.04
	Isoxadifen-ethyl	0.16
	Isodecyl alcohol ethoxylate (adjuvant)	0.09 0.13
	Cumulative risk Resident Child – sum (mean) of all pathways (HI)	0.35 0.39
Resident Adult – All pathways (mean)	Rimsulfuron	0.02
	Thifensulfuron methyl	0.01

Application scenario	Active Ingredient	Estimated exposure/ AOEL (HQ)
	Isoxadifen-ethyl	0.05
	Isodecyl alcohol ethoxylate (adjuvant)	0.04 0.06
	Cumulative risk Resident Adult – sum (mean) of all pathways (HI)	0.12 0.14

The Hazard Index is <1 for all subpopulations. Thus, combined exposure to all active substances and safener in GF-3969 + adjuvant is not expected to present a risk for operators, workers, bystanders and residents provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied. No further refinement of the assessment is required.

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP Status Published or not	Vertebrate study Y/N	Owner
KCP, 7.1.4/02	Costin, G.E., Pham, R., Sadowski, N.	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50 SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Skin irritation test (SIT) using the epiderm skin model DuPont-50172 Institute for In Vitro Sciences, Inc. GLP: Yes Published: No	N	DuPont
KCP, 7.1.5/01	xxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Primary eye irritation in rabbits DuPont-49964 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
KCP, 7.1.5/02	Wilt, N., Pham, R., Sadowski, N.	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50 SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): epiocular™ eye irritation test (EIT) for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage DuPont-50173 xxxxxxxxxxxxxxxx GLP: Yes Published: No	N	DuPont
KCP, 7.1.6/01	xxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Local lymph node assay (LLNA) in mice DuPont-49966 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
KCP, 7.1.7/01	Clare, K.	2018	Rimsulfuron metabolite (IN-E9260) (CAS # 117671-01-9): Genetic toxicity evaluation using a micronucleus test in TK6 human lymphoblastoid cells MNT00515 Gentronix Limited GLP: Yes Published: No	N	Helm AG, SAPEC AGRO S.A., DuPont
KCP, 7.1.7/02	Ruwona, T., Sheehan, D., Koch, W.T.	2018	Rimsulfuron 25SG/thifensulfuron methyl 50SG/isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Induction of antioxidant-response-element dependent gene activity and cytotoxicity (using MTT) in the keratinocyte ARE-reporter cell line keratinosens DuPont-50245 Institute for In Vitro Sciences, Inc. GLP: Yes Published: No	N	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP Status Published or not	Vertebrate study Y/N	Owner
KCP 7.4/01	xxxxxxxxxxxxxxxxxxxx	1999	Oral toxicity test after 28-day repeated administration in the rat. TF375/99-0777 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	FMC

List of data submitted by the applicant and relied on – vertebrate studies

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP Status Published or not	Vertebrate study Y/N	Owner
KCP, 7.1.1/01	xxxxxxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% active): Acute oral toxicity study in rats - up-and-down procedure DuPont-49958 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
KCP, 7.1.2/01	xxxxxxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% active): Acute dermal toxicity study in rats DuPont-49959 xxxxxxxxxxxxxxxxxxxxGLP: Yes Published: No	Y	DuPont
KCP, 7.1.3/01	xxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Inhalation median lethal concentration (LC50) study in rats DuPont-49960 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
KCP, 7.1.4/01	xxxxxxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Primary skin irritation in rabbits DuPont-49965 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP Status Published or not	Vertebrate study Y/N	Owner
KCP, 7.1.5/01	xxxxxxxxxxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Primary eye irritation in rabbits DuPont-49964 xxxxxxxxxxxxxxxxxxxxxxxx Published: No	Y	DuPont
KCP, 7.1.6/01	xxxxxxxxxxxxxxxxxxxx	2018	Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Local lymph node assay (LLNA) in mice DuPont-49966xxxxxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
KCP 7.4/01	xxxxxxxxxxxxxxxxxxxxxxxx	1999	Oral toxicity test after 28-day repeated administration in the rat. TF375/99-0777 EViC-CEBA GLP: Yes Published: No	Y	FMC

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

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	xxxxxxxxxxxx	2016	IN-E9260: Rat alkaline Comet assay 8346539 xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	Helm AG and Sapec Agro SA DuPont
CP, 7.1.7	Clarke, J.J.	2013	IN-E9260: In vitro mammalian cell gene mutation test (CHO/HGPRT assay) DuPont-36588 BioReliance, Alliance Pharma, Inc. GLP: Yes Published: No	N	DuPont
CP, 7.1.7	Clarke, J.J.	2013	IN-70942: In vitro mammalian cell gene mutation test (CHO/HGPRT assay) DuPont-36586 BioReliance, Alliance Pharma, Inc. GLP: Yes Published: No	N	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Forichon, A.	1992	Test to evaluate the induction of chromosome aberrations in the human lymphocytes 202380 Hazleton (France) GLP: Yes Published: No	N	DuPont
CP, 7.1.7	Gudi, R., Rao, M.	2004	IN-70941: In vitro mammalian chromosome aberration study in human peripheral blood lymphocytes DuPont-13386, Revision No. 1 xxxxxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	N	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	2004	IN-E9260: Local lymph node assay (LLNA) in mice DuPont-15258 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	1991	Test to evaluate the acute toxicity following a single cutaneous application (Limit Test) in the rat 110303)xxxxxxxxxxxxxxxxGLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	1991	Test to evaluate the acute toxicity following a single oral administration (Limit Test) in the rat 110304 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	1992	Test to evaluate the acute ocular irritation and reversibility in the rabbit 201336 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Mxxxxxxxxxxxxxxxxxxxx	1992	Test to evaluate the acute primary cutaneous irritation and corrosivity in the rabbit 201335 Hazleton (France) GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Mercier, O.	1992	Test to evaluate sensitizing potential in the guinea-pig (Guinea-Pig Maximization Test) 202355 Hazleton (France) GLP: Yes Published: No	Y	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Reynolds, V.L.	1989	Mutagenicity testing of IN-E9260-1 in the Salmonella typhimurium Plate Incorporation Assay HLR 108-89 DuPont Haskell Laboratory GLP: Yes Published: No	N	DuPont
CP, 7.1.7	Reynolds, V.L.	1989	Mutagenicity testing of IN-70941 in the Salmonella typhimurium Plate Incorporation Assay HLR 344-89 DuPont Haskell Laboratory GLP: Yes Published: No	N	DuPont
CP, 7.1.7	Roy, S., Jois, M.	2013	IN-70942: In vitro mammalian chromosome aberration test in human peripheral blood lymphocytes (HPBL) DuPont-36585 BioReliance GLP: Yes Published: No	N	DuPont
CP, 7.1.7	San, R.H.C., Clarke, J.J.	2003	IN-70941: In vitro mammalian cell gene mutation test (CHO/HGPRT Test) DuPont-13387 BioReliance GLP: Yes Published: No	N	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	1989	Approximate Lethal Dose (ALD) of IN-70941 in rats HLR 199-89 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	1989	Ten-dose oral subchronic study of IN-70941 in rats HLR 526-89 xxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Wagner, V.O., III, VanDyke, M.R.	2013	IN-70942: Bacterial reverse mutation test DuPont-36584 BioReliance GLP: Yes Published: No	N	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	xxxxxxxxxxxxxxxx	1992	DPX-E9260 - 4 Week oral (gavage) toxicity study in the rat 35291 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont

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

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	xxxxxxxxxxxxxxxx	2016	IN-E9260: Rat alkaline Comet assay 8346539 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	Helm AG and Sapec Agro SA DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxx	2004	IN-E9260: Local lymph node assay (LLNA) in mice DuPont-15258 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxx	1991	Test to evaluate the acute toxicity following a single cutaneous application (Limit Test) in the rat 110303 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxx	1991	Test to evaluate the acute toxicity following a single oral administration (Limit Test) in the rat 110304 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	xxxxxxxxxxxxxxxx	1992	Test to evaluate the acute ocular irritation and reversibility in the rabbit 201336 xxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Mercier, O.	1992	Test to evaluate the acute primary cutaneous irritation and corrosivity in the rabbit 201335 xxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Mercier, O.	1992	Test to evaluate sensitizing potential in the guinea-pig (Guinea-Pig Maximization Test) 202355 xxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Sarver, J.W.	1989	Approximate Lethal Dose (ALD) of IN-70941 in rats HLR 199-89 xxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Sarver, J.W.	1989	Ten-dose oral subchronic study of IN-70941 in rats HLR 526-89 xxxxxxxxxxxxxxxxxxxxx GLP: Yes Published: No	Y	DuPont
CP, 7.1.7	Woehrle, F.	1992	DPX-E9260 - 4 Week oral (gavage) toxicity study in the rat 35291 xxxxxxxxxxxxxxxxxxxxx Published: No	Y	DuPont

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

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Myhre, A.	2011	IN-L9225: Bacterial reverse mutation test DuPont Haskell Laboratory DuPont-30758 GLP: Yes Published: No	N	FMC

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Glover, K.P.	2011	IN-L9225: In vitro mammalian chromosome aberration test in human peripheral blood lymphocytes DuPont Haskell Laboratory DuPont-30759 GLP: Yes Published: No	N	FMC
CP, 7.1.7	Clarke, J.J.	2011	IN-L9225: In vitro mammalian cell gene mutation test (CHO/HGPRT assay) BioReliance DuPont-30760, Revision No.1 GLP: Yes Published: No	N	FMC
CP, 7.1.7	Donath, C.	2011	Reverse mutation using bacteria (Salmonella typhimurium and Escherichia coli) with thifensulfuron acid. BSL Bioservice Scientific Laboratories GmbH, Germany. Study No.: 110127 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*
CP, 7.1.7	Donath, C.	2011	Reverse mutation using bacteria (Salmonella typhimurium and Escherichia coli) with 2-acid-3-sulfonamide BSL Bioservice Scientific Laboratories GmbH, Germany. Study No.: 110128 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*
CP, 7.1.7	Lloyd, M.	2011	2-acid-3-sulfonamide: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes Covance Laboratories Ltd, Harrogate, UK. Study No.: 8243962 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force
CP, 7.1.7	Lloyd, M.	2011	2-acid-3-sulfonamide: Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the microtitre® fluctuation technique Covance Laboratories Ltd, Study No: 8243963 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*
CP, 7.1.7	xxxxxxxxxxxxxx	2011	Acute oral toxicity (fixed dose procedure) - Limit test with Thifensulfuron acid Report No: 206 GLP: Yes Published: No	Y	EU TSM AIR 2 Task Force*
CP, 7.1.7	Myhre, A.	2011	IN-L9223: Bacterial reverse mutation test DuPont Haskell Laboratory DuPont-31622 GLP: Yes Published: No	N	FMC

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	Glover, K.P.	2011	IN-L9223: In vitro mammalian chromosome aberration test in human peripheral blood lymphocytes DuPont Haskell Laboratory DuPont-31623 GLP: Yes Published: No	N	FMC
CP, 7.1.7	Clarke, J.J.	2011	IN-L9223: In vitro mammalian cell gene mutation test (CHO/HGPRT assay) DuPont Haskell Laboratory DuPont-31624 GLP: Yes Published: No	N	FMC
CP, 7.1.7	May, K.	2012	Thifensulfuron Acid (IN-L9225): In vitro micronucleus test in human lymphocytes Huntingdon Life Sciences, Report No.: DGV0080 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*
CP, 7.1.7	May, K.	2012	O-Desmethyl Thifensulfuron Acid (IN-JZ789): Bacterial reverse mutation test Huntingdon Life Sciences, Report No.: DGV0081 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*
CP, 7.1.7	May, K.	2012	O-Desmethyl Thifensulfuron Acid (IN-JZ789): In vitro micronucleus test in human lymphocytes (amended report) Huntingdon Life Sciences, Report No.: DGV0082 GLP: Yes Published: No	N	EU TSM AIR 2 Task Force*

* Cheminova (now FMC) is owner of the study.

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

Data point	Author(s)	Year	Title Company Report No. Source GLP or GEP status Published or not	Vertebrate study Y/N	Owner
CP, 7.1.7	xxxxxxxxxxxxxxxxxxxx	2011	Acute oral toxicity (fixed dose procedure) - Limit test with Thifensulfuron acid Report No: 206 GLP: Yes Published: No	Y	EU TSM AIR 2 Task Force*

* Cheminova (now FMC) is owner of the study

List of isoxadifen-ethyl data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review – all documents

No studies previously submitted and relied upon.

List of isoxadifen-ethyl data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review – vertebrate studies

No vertebrate studies previously submitted and relied upon.

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

Unless specifically indicated, all reports in this section are submitted to address mandatory data requirements for the approval of the plant protection product.

Some of the submitted tests and studies which involve vertebrate animals and which address mandatory data requirements could have been met with alternative methods or by the calculation methods according to the CLP Regulation (EC No. 1272/2008); however, since this formulation is also being registered in regions that do not accept these alternative tests, the traditional tests were performed. These studies were included in the submission and used as a basis for the classification of the product when applicable as they provide representative data for the actual formulation. Studies were conducted according to prescribed guidelines.

Unless specifically indicated, this section does not contain reports of studies duplicating previous tests on vertebrate animals.

A 2.1 Statement on bridging possibilities

No bridging studies submitted.

Comments of zRMS:	Accepted. Previous Code number of the product DPX-V4B07 has been changed to GF-3969 due to the new owner Corteva, refer dRR Doc A point 2.1 p.7. Thus it is confirm that data package has been generated on the product applied for the current registration.
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A 2.2 Acute oral toxicity (KCP 7.1.1)

A 2.2.1 DuPont Report No.: DuPont-49958

Comments of zRMS:	Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. Study (Fallers, M.N., (2018) implements 3R rules minimizing the number of animals required to estimate the acute oral toxicity of a chemical. In addition estimation of LD ₅₀ and confidence intervals allows the observation of signs of toxicity. There is no deviation from studies protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference:	KCP 7.1.1/01
Report:	xxxxxxxxxxxxxxxxxxxxxxxxxxxx (2018); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% active): Acute oral toxicity study in rats - up-and-down procedure
DuPont Report No.:	DuPont-49958
Testing Facility Report No.:	DuPont-49958
Guidelines	OPPTS 870.1100 (2002), OECD 425 Section 4 (2008)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In an acute oral toxicity study of fasted female CrI:CD(SD) rats (approximately 10-11 weeks old at dosing) were given a single oral dose of GF-3969 suspended in 0.1% Tween 80 (v/v) in 0.5% methylcellulose at the limit dose of 5000 mg/kg body weight (3 females) and observed for 14 days.

No instances of mortality occurred.

Based on mortality results, acute toxicity estimates via oral route are:

Oral LD₅₀ Females = >5000 mg/kg body weight

MATERIALS AND METHODS

Test Item(s)

Test item (Common name): GF-3969
Purity: None for formulation
25.1% (w/w) of rimsulfuron active substance
49.8% (w/w) of thifensulfuron methyl active substance
50.4% (w/w) of isoxadifen-ethyl active substance
Description (physical state): Brown solid
Lot/batch no.: V4B07-001
Vehicle: 0.1% Tween 80 (v/v) in 0.5% methylcellulose

Test System

Species: Rat (*Rattus norvegicus*)
Strain: CrI:CD (SD)
Age and weight at dosing: Approximately 10-11 weeks old
Weight (g): Minimum 222.3, Maximum 231.5
Source: Charles River Laboratories, Raleigh, North Carolina, U.S.A.
Housing: Animals were housed individually in solid-bottom caging with bedding and appropriate species specific enrichment.
Feed and water: Feed: Certified Rodent LabDiet® (#5002) manufactured by PMI® Nutrition International, LLC, U.S.A. *ad libitum* except when fasted.
Water: *ad libitum*
Environmental conditions: Temperature: 20 to 25°C
Humidity: 30 to 70% relative humidity
Air changes: Not reported
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 4 days

Study Design

In-life dates

Start: 10 October 2017 End: 27 October 2017

Animal assignment and treatment

Animal assignment is shown in Table A 1.

Table A 1: Animal assignment

Dose (mg/kg body weight)	Females
5000	3

Following an overnight fast, a single dose of GF-3969, suspended in 0.1% Tween 80 (v/v) in 0.5% methylcellulose, was administered oral gavage to fasted female rats at a dose level 5000 mg/kg. Individual dose volumes were calculated using the fasted body weights obtained prior to dosing. The rats were dosed at a volume of 20 mL per kg of body weight. The rats were dosed one or two at a time at a minimum of 48-hour intervals.

Daily animal health observations were conducted throughout the study for mortality and signs of illness, injury, or abnormal behaviour. Animals were weighed on test days -1, 1, 8, and 15, and were observed for clinical signs at the beginning of fasting, just before dosing (test day 1), once during the first 30 minutes after dosing and 2 more times on the day of dosing, and once each day thereafter. On test day 15, the rats were euthanized and necropsied to detect grossly observable evidence of organ or tissue damage. The rats were euthanized by exsanguination while under isoflurane anaesthesia.

RESULTS AND DISCUSSION

Mortality

Mortality data are presented in the table below:

Table A 2: Dose, mortality/animals treated

Dose (mg/kg body weight)	Mortality - Female Rats (# affected /total)	Time range of deaths (hours or days)
5000	0/3	N/A

N/A: not applicable

No deaths occurred.

Clinical Observations

No clinical signs were observed.

Body Weight

No overall body weight losses were observed.

Necropsy Observations

No gross lesions were present at necropsy.

CONCLUSION

Under the conditions of this study, the oral LD₅₀ for GF-3969 was greater than 5000 mg/kg bw for female rats.

In accordance with Regulation (EC) No. 1272/2008, classification of GF-3969 for acute oral toxicity is not required.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Rat	CrI:CD(SD)	F	Oral	Gavage (diluted with 0.1% Tween 80 (v/v) in 0.5% methylcellulose)	LD ₅₀ = >5000 mg/kg body weight

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Unclassified
Regulation (EC) No. 1272/2008	Not classified

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

A 2.3.1 DuPont Report No.: DuPont-49959

Comments of zRMS:	Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. In the study (Fallers, M.N., (2018) tested material has not been administered at doses which cause pain and distress due to potential corrosive or severely irritant actions (note: GF-3969 is not classified as skin irritant). There is no deviation from studies protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference:	KCP 7.1.2/01
Report:	xxxxxxxxxxxxxxxxxxxxx (2018); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% active): Acute dermal toxicity study in rats
DuPont Report No.:	DuPont-49959
Testing Facility Report No.:	DuPont-49959
Guidelines	OPPTS 870.1200 (1998), OECD 402 (1987), EC Part B.3 440/2008 (2008), MAFF 12 Nousan 8147 (2000)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In an acute dermal toxicity study, young adult male and female Crl:CD (SD) rats were dermally exposed to GF-3969 for approximately 24 hours at the limit dose of 5000 mg/kg body weight. Animals then were observed for 14 days.

No instances of mortality occurred.

Based on mortality results, acute toxicity estimates via dermal route are:

Dermal LD₅₀ Combined (males and females) = >5000 mg/kg body weight

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	None for formulation 25.1% (w/w) of rimsulfuron active substance 49.8% of thifensulfuron methyl active substance 50.4% (w/w) of isoxadifen-ethyl active substance
Description (physical state):	Brown solid
Lot/batch no.:	V4B07-001
Vehicle:	Deionised water

Test System

Species:	Rat (<i>Rattus norvegicus</i>)
Strain:	Crl:CD (SD)
Age and weight at dosing:	Approximately 10 weeks old Weight (g): Male: Minimum 366.2, Maximum 387.8; Female: Minimum 218.5, Maximum 238.2
Source:	Charles River Laboratories, Raleigh, North Carolina, U.S.A.
Housing:	Animals were housed individually in solid-bottom caging with bedding and appropriate species-specific enrichment.
Feed and water:	Feed: Certified Rodent LabDiet® (#5002) manufactured by PMI® Nutrition International, LLC, U.S.A. <i>ad libitum</i> Water: Tap water <i>ad libitum</i>
Environmental conditions:	Temperature: 20 to 25°C Humidity: 30 to 70% relative humidity Air changes: Not reported Photoperiod: 12 hours dark/12 hours light
Acclimation period:	6 days

Study Design

In-life dates

Start: 11 October 2017 End: 25 October 2017

Animal assignment and treatment

Animal assignment is shown in Table A 3

Table A 3: Animal assignment

Dose (mg/kg body weight)	Males	Females
5000	5	5

Approximately 24 hours prior to dosing, the fur of each rat was closely shaved to expose the back from the scapular to the lumbar region. A calculated dose amount (5000 mg/kg bw) of GF-3969 (moistened with approximately 1.0 mL of deionised water) was applied directly to the skin (approximately 7.4×5 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 (2 ply) and stretch gauze bandage and self-adhesive bandage throughout the 24-hour exposure period to prevent any loss of the test item and also to ensure that the rats did not ingest it. At the end of the exposure period, the rats were removed from their cages, and the wrappings were removed. Excess test substance was washed from the dorsal skin of each rat with paper towels soaked in warm, soapy water, and the skin was dried. The rats were observed for clinical signs of toxicity and dermal response and returned to their cages. Dermal effects were scored according to the Draize Scale.

Observations for mortality and signs of illness, injury, and abnormal behavior were made daily throughout the study. Observations for clinical signs of toxicity and dermal irritation were made daily throughout the study (weekends and holidays excluded for dermal irritation). The rats were weighed prior to treatment (test day 1) and on test days 8 and 15. The rats were reshaved as needed during the study. All rats were euthanized at the end of the 15-day test period and examined to detect grossly observable evidence of organ or tissue damage. The rats were euthanized by exsanguination while under isoflurane anesthesia.

RESULTS AND DISCUSSION

Mortality

Mortality data are presented in the table below:

Table A 4: Dose, mortality/animals treated

Dose (mg/kg body weight)	Mortality - Male Rats (# affected /total)	Mortality - Female Rats (# affected /total)	Time range of deaths (hours or days)
5000	0/5	0/5	N/A

N/A: not applicable

There were no instances of mortality

Clinical Observations

Dehydration was noted between test days 14-15 in the female with body weight loss. Epidermal scaling was noted on one female between test days 3-6. No other clinical abnormalities were observed. No instances of edema and erythema were observed.

Body Weight

Overall body weight losses were observed in one male and one female due to an interruption in the water availability for these animals. There were no overall body weight losses observed in the animals with continuous water availability.

Necropsy

No gross lesions were observed at necropsy.

CONCLUSION

The acute dermal LD₅₀ for GF-3969 in rats was greater than 5000 mg/kg body weight for both male and female rats.

In accordance with Regulation (EC) No. 1272/2008, classification of GF-3969 for acute dermal toxicity is not required.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Rat	Crl:CD (SD)	M/F	Dermal	Topical (24-hour semi-occlusive exposure)	LD ₅₀ = >5000 mg/kg body weight

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Unclassified
Regulation (EC) No. 1272/2008	Not classified

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

A 2.4.1 DuPont Report No.: DuPont-49960

Comments of zRMS:	Data has been reviewed for compliance with the current guidelines, resulting from scientific progress. In the study (Kegelman, T.A., (2018) animals are exposed to one limit concentration for a predetermined duration (4 hours) and obtain sufficient information on the acute toxicity of test article to enable its classification and to provide lethality data (LC ₅₀) for both sexes as needed for quantitative risk assessments. There is no deviation from studies protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.
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Reference:	KCP 7.1.3/01
Report:	xxxxxxxxxxxxxxxxxxxxxxxxxx., (2018); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Inhalation median lethal concentration (LC ₅₀) study in rats
DuPont Report No.:	DuPont-49960
Testing Facility Report No.:	DuPont-49960
Guidelines	OPPTS 870.1300 (1998), OECD 403 (2009), EC Part B.2 440/2008, MAFF 2-1-3 Notification 12 Nousan 8147 (2000), MAFF 2-1-3 Notification 12 Nousan 8147 (2001)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In an acute inhalation toxicity study, groups of young adult male and female CrI:CD(SD) rats were exposed by inhalation route to GF-3969 for 4 hours to nose only at a concentration of 5.4 ± 0.50 mg/L air (dust aerosol). Animals then were observed for 16 days.

No deaths occurred during the study.

Based on mortality results, acute toxicity estimates via inhalation route are:

Inhalation LC₅₀ Males >5.4 mg/L air

Inhalation LC₅₀ Females >5.4 mg/L air

Inhalation LC₅₀ Males and Females Combined >5.4 mg/L air

MATERIALS AND METHODS

Test Item(s)

Test item (Common name): GF-3969
Purity: 25.1% (w/w) rimsulfuron, 49.8% (w/w) thifensulfuron methyl, 50.4% (w/w) isoxadifen-ethyl
Description (physical state): Mix of brown and light tan granules solid
Lot/batch no.: V4B07-002

Test System

Species: Rat (*Rattus norvegicus*)
Strain: CrI:CD(SD)
Age and weight at dosing: 8 weeks
Weight (g): Male: Minimum 292.0, Maximum 335.8; Female: Minimum 199.7, Maximum 239.1
Source: Charles River Laboratories International, Inc., Raleigh, North Carolina, U.S.A.
Housing: 1 rat/cage
Feed and water: Feed: PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002, *ad libitum* (except during exposure)
Water: Tap water, *ad libitum* (except during exposure)
Environmental conditions: Temperature: 20 to 25°C
Humidity: 30 to 70% relative humidity
Air changes: Not reported
Photoperiod: 12 hours dark/12 hours light
Acclimation period: 6 days

Study Design

In-life dates

Start: 29 November 2017 End: 15 December 2017

Animal assignment and treatment

Animal assignment is shown in Table A 5.

Table A 5: Animal assignment

Dose (mg/L air)	Males	Females	Combined
5.4	5	5	10

Animals were observed daily and body weights were recorded on Days 1, 2, 3, 4, 5, 6, 8, 15, and 17 after exposure. Animals were sacrificed and a necropsy was performed on all animals.

RESULTS AND DISCUSSION

Concentration Details in the Inhalation Chamber

During the exposure, rats were exposed to GF-3969 at total atmospheric concentration of 5.4 ± 0.50 mg/L (mean \pm standard deviation). The aerosol size was determined twice during the exposure. Mass median aerodynamic diameters (MMADs) were 3.5 and 3.4 μ m and geometric standard deviations were 2.1 and 2.2, respectively.

Mortality

Mortality data are presented in the following table.

Table A 6: 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
5.4	0/5	0/5	0/10	N/A	0/5	0/5	0/10

N/A: Not applicable

No deaths occurred during this study.

Clinical Observations

Rats displayed normal startle response throughout the exposure (test Day 1). There were no clinical signs of toxicity observed during the exposure. Common clinical signs observed when the rats were removed from their restrainers were test substance stained faces, heads and forelimbs and red nasal and ocular discharges. There were no adverse test substance related clinical signs of toxicity observed in the rats throughout the remainder of the 16-day recovery period.

Body Weight

All male rats displayed weight losses ranging from 9.5 to 20.0 grams and 3 of 5 female rats displayed bodyweight losses ranging from 3.8 to 8.8 grams the day after the exposure. One male rat lost 2.7 grams of body weight on test Day 4. One female lost 1.0 gram of body weight on test Day 4 and 3 females lost between 0.3 and 7.8 grams of body weight on test Day 5. There were no other bodyweight losses in any rats throughout the remainder of the 16-day recovery period.

Necropsy Observations

External

No treatment related findings were observed.

Internal

No gross findings were observed.

CONCLUSION

Under the conditions of this study, the 4-hour inhalation median lethal concentration (LC_{50}) for GF-3969 in male and female rats was greater than 5.4 mg/L.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Rat	CrI:CD(SD)	M/F	Inhalation	Nose only (4-hour)	$LC_{50} > 5.4$ mg/L air

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Not classified
Regulation (EC) No. 1272/2008	Not classified

A 2.5 Skin irritation (KCP 7.1.4)

A 2.5.1 Study 1, DuPont Report No.: DuPont-49965

Comments of zRMS:	<p>In the interest of both sound science and animal welfare, (..) <i>in vivo</i> testing should not be undertaken until all available data relevant to the potential dermal corrosivity/irritation of the test chemical have been evaluated in the tier approach assessment (..). Notifier provide two studies <i>in vitro</i> and <i>in vivo</i>. As we mentioned and explained in the our general comment (see p.6 to this dRR) <i>in vitro</i> study (Costin, G.E 2018) based on OECD 439 is not applicable for agrochemical formulations thus already existed <i>in vivo</i> study has been accepted and considered by the ZRMS as reliable for the hazard assessment. Study (Slonina, M., 2018) has been reviewed for compliance with the current guidelines, resulting from scientific progress.</p> <p>Test product was applied in a single dose to the skin of an experimental animal; untreated skin areas of the test animal serve as the control. The degree of irritation/corrosion was read and scored at specified intervals in order to provide a complete evaluation of the effects. The duration of the study was sufficient to evaluate the reversibility or irreversibility of the effects observed.</p> <p>There was no deviation from studies protocol. Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.</p>
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Reference:	KCP 7.1.4/01
Report:	xxxxxxxxxxxxxxxxxxxxxxxxxxxxx., (2018); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Primary skin irritation in rabbits
DuPont Report No.:	DuPont-49965
Testing Facility Report No.:	47001
Guidelines	OPPTS 870.2500 (1998), OECD 404 (2015), 12 NohSan No. 8147 (2000), EC No. 440/2008 Part B.4
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In a primary (acute) dermal irritation study, 3 young adult female New Zealand albino rabbits were dermally exposed to 0.5 g of GF-3969 moistened with distilled water, for 4 hours to approximately 6 cm² area of intact dorsal skin. Animals then were observed immediately after patch removal and at 30-60 minutes and 24, 48, and 72 hours and at 7, and 10 days after patch removal. Irritation was scored by the method of Draize (Draize, Woodard, & Calvery, 1944).

The mean dermal irritation scores at 24, 48 and 72 hours post patch removal, for the 3 rabbits respectively, were:

Mean Erythema Scores: [0.33, 0.33, 0.33] –

Mean Oedema Scores: [0.00, 0.00, 0.00]

Dermal irritation cleared from two dose sites by 30-60 minutes and from the remaining dose site by Day 10.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	25.1% (w/w) rimsulfuron, 50.4% (w/w) isoxadifen-ethyl, 49.8% thifensulfuron methyl
Description (physical state):	Solid granules
Lot/batch no.:	V4B07-002
Vehicle:	Distilled water

Test System

Species:	Rabbit (<i>Oryctolagus cuniculus</i>)
Strain:	New Zealand albino (NZA)
Age and weight at dosing:	13 or 14 weeks Weight (kg): Minimum 2.684, Maximum 2.957
Source:	Robinson Services Inc., Mocksville, North Carolina
Housing:	Individually
Feed and water:	Feed: Envigo Teklad certified Global High Fiber Rabbit Diet [®] #2031, approximately 150 grams/day Water: Filtered tap water, <i>ad libitum</i>
Environmental conditions:	Temperature: 19 to 22°C Humidity: 47 to 53% relative humidity Air changes: 13 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	13 or 19 days

Study Design

In-life dates

Start: 12 December 2017 End: 22 December 2017

Animal assignment and treatment

The pH of GF-3969 was found to be in the range of 2 and 11.5, which is considered acceptable for treatment.

A total of 3 female rabbits were assigned to treatment. A sequential testing strategy was adopted. Initially one rabbit was tested. Immediately after administration of the test item, assessments of any

initial local pain reactions were made. As severe effects were not observed in the first treated rabbit, two additional rabbits were subsequently treated in an identical manner.

A 0.5 g of GF-3969 moistened with distilled water 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) which were not more than 4-ply and were secured at the margins by non-irritating tape (3-inch Micropore 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, and the dose sites were gently cleansed with a 3% soap solution followed by tap water and a clean paper towel.

Irritation was scored by the method of Draize (Draize, Woodard, & Calvery, 1944) immediately following patch removal and at approximately 30-60 minutes, 24, 48, and 72 hours and 7 and 10 days post patch removal. General health condition and body weight were monitored.

RESULTS AND DISCUSSION

Dermal Irritation

Erythema (score of 1) was noted at all treated sites immediately after patch removal and at one treated site between the 30-60 minute and Day 7 scoring intervals. Oedema (score of 1) was noted at one treated site between the 30-60 minute and Day 7 scoring interval. Dermal irritation cleared from two dose sites by 30-60 minutes and from the remaining dose site by Day 10.

Individual animal irritation scores are presented in Table A 7.

Table A 7: Doses, scoring/animals treated

Rabbit No.	Observations after patch removal											
	Erythema						Oedema					
	Hours			Days			Hours			Days		
	30-60 mins	24	48	72	7	10	30-60 mins	24	48	72	7	10
3501	1	1	1	1	1	0	1	0	0	0	0	0
3502	0	0	0	0	N/A	N/A	0	0	0	0	N/A	N/A
3503	0	0	0	0	N/A	N/A	0	0	0	0	N/A	N/A

Key:

N/A: Not applicable

Erythema

0: No erythema

1: Very slight erythema (barely perceptible)

2: Well-defined erythema

3: Moderate to severe erythema

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

Maximum possible: 4

Oedema

0: No oedema

1: Very slight oedema (barely perceptible)

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

3: Moderate oedema (raised approximately 1 mm)

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

Maximum possible: 4

Systemic toxicity

All animals appeared active and healthy and gained body weight during the study. Apart from the dermal irritation noted below, there were no other clinical signs observed.

CONCLUSION

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Rabbit	NZA	F	Dermal	Topical (4-hour, semi-occlusive)	Mean Erythema Scores: 0.33, 0.33, 0.33 Mean Oedema Scores: 0.00, 0.00, 0.00 Recovery completed by 10 days

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Not classified
Regulation (EC) No. 1272/2008	Not classified

A 2.5.2 Study 2, DuPont Report No.: DuPont-50172

Comments of zRMS:	<p>Regarding skin corrosion/irritation based on <i>in vitro</i> studies we consider following outcome (for detailed explanation see our general comment on p.6 to this dRR). In the Test Guideline No. 439 <i>In Vitro</i> Skin Irritation: Reconstructed Human Epi-dermis Test Methods; revision 14 June 2021; section “Initial considerations and limitations” point 8, has been stated: <u>(..) a lack of applicability of the RhE based in vitro skin irritation test for agrochemical formulations.</u> (..). In addition this is supported by following paper included in the references TG OECD 439: Kolle S.N, van Ravenzwaay B. and Landsiedel R. (2017). <i>Regulatory accepted but out of domain: In vitro skin irritation tests for agrochemical formulations.</i> Regul.Toxicol. Pharmacol 89, 125-130.</p> <p>Thus regarding mentioned above information, ZRMS decided not to take into account <i>in vitro</i> study Costin, G.E., Pham, R., Sadowski, N., 2018 and conclude hazard assessment for skin irritation potential considering available <i>in vivo</i> study (Slonina, M., 2018).</p>
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Reference:	KCP 7.1.4/02
Report:	xx2018); Rimsulfuron 25SG/Thifensulfuron methyl 50 SG/Isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Skin irritation test (SIT) using the epiderm skin model
DuPont Report No.:	DuPont-50172
Testing Facility Report No.:	17AJ36.050082
Guidelines	OECD 439
Deviations:	None
GLP:	Yes
Acceptability:	No

STUDY SUMMARY

The Skin Irritation Test (SIT) using the EpiDerm™ Skin Model was used to predict the skin irritation potential of the test substance, GF-3969, in the context of classification of skin irritation hazard according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Irritation potential was determined by measuring the relative conversion of MTT (3-[4,5 - dimethylthiazol-2-yl] - 2,5 - diphenyltetrazolium bromide) in the test substance-treated tissues after exposure to the test substance for a 60-minute exposure period, followed by a 42-hour post-exposure expression period. Skin irritation potential of the test substance was predicted if the relative viability was less than or equal to 50%.

Two trials were conducted for the test substance. Even though the assay results generated in Trial 1 were considered valid per the OECD test guideline, the OD₅₇₀ value of the negative control-treated killed control tissues was unusually high, indicating that the quality of the killed control tissues used in Trial 1 was questionable. Therefore, Trial 2 was conducted with the Sponsor's approval and was considered valid per the OECD test guideline.

In Trial 2, the mean OD₅₇₀ of the negative control, sterile Calcium and Magnesium Free Dulbecco's Phosphate Buffered Saline (CMF-DPBS), was 2.057. The mean viability of the positive control, 5% sodium dodecyl sulfate (SDS), was 2.63%. The standard deviation calculated from individual percent tissue viabilities of the three identically treated replicates was <18% for the test substance and positive and negative controls. Since the mean positive control result met the criteria for classification as an irritant (*i.e.*, viability ≤50%) and the mean OD₅₇₀ value of the negative control was ≥0.8 and <2.8, the assay results were considered valid and were used to conclude on the skin irritation prediction of the test substance.

Based on the results of Trial 2, GF-3969 was predicted to be non-irritating to the skin, and thus would be considered unclassified according to the Globally Harmonized System of Classification and Labelling of Chemicals.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	Rimsulfuron: 14.82% (w/w) Thifensulfuron methyl: 9.26% (w/w) Isoxadifen-ethyl safener: 11.11% (w/w)
Description (physical state):	Light brown powder
Lot/batch no.:	V4B07-001

Test System

Kit:	EpiDerm™ Skin Kit
Source:	MatTek Corporation
Controls	
Positive:	5% Sodium Dodecyl Sulfate (SDS), 30 µL
Negative:	Sterile Calcium and Magnesium Free Dulbecco's Phosphate Buffered Saline (CMF-DPBS), 30 µL

Skin Irritation Test (SIT) Definitive Assay

The test substance, GF-3969, was tested in one valid definitive trial. After the overnight incubation for 18 ± 3 hours, the 6-well plates containing the EpiDerm™ tissues were removed from the incubator and placed at room temperature for at least 5 minutes prior to dosing.

The EpiDerm™ tissues were treated in triplicate with the test substance, GF-3969, for 60 ± 1 minutes. Since the test substance was a powder, immediately before application of the solid test substance, each

tissue surface was moistened with 25 μ L of sterile CMF-DPBS to improve contact of the tissue surface with the test substance. After adding the CMF-DPBS, 25 mg of the test substance was added to each of three tissues at 1-minute intervals per tissue using a 25 mg sharp spoon. The sharp spoon was filled with the test substance and then the spoon was levelled. After the three tissues were dosed with the test substance, the test substance was gently mixed and spread over the tissue surface using a sterile bulb-headed rod. The EpiDerm™ tissues were tested in triplicate with the positive or negative control for 60 ± 1 minutes. Thirty microliters of each control were applied to each of three tissues at 1-minute intervals per tissue. Immediately after control administration onto the tissue, a nylon mesh was placed gently over the dose to spread the negative and positive controls. The plates with dosed tissues were kept in the laminar flow hood until the last tissue was dosed. After the last tissue was dosed, all of the plates were transferred to the incubator for 35 ± 1 minutes at standard culture conditions. After 35 ± 1 minutes, all of the plates were removed from the incubator, placed into the laminar flow hood, and kept at room temperature until the exposure period was completed for the first dosed tissue.

After 60 ± 1 minutes of test or control substance exposure, the tissues were rinsed with sterile CMF-DPBS by filling and emptying the tissue insert 15 times. A stream of CMF-DPBS was directed onto the tissue surface. For the control substances where a mesh was used, the mesh was carefully removed with forceps (if necessary) after the fifth rinse. After the removal of the mesh, the rinsing procedure of the tissue continued for 10 times. After the 15th rinse, each of the three inserts per treatment group (test substance, positive control, and negative control) was completely submerged, gently swirled, and rinse media dumped in a beaker containing approximately 150 mL of CMF-DPBS and specifically assigned for each treatment group; this procedure was repeated three times for each insert of each treatment group. Finally, the tissues were rinsed once more on the inside and outside of the tissue insert with sterile CMF-DPBS from the wash bottle, and the excess CMF-DPBS was decanted. The bottoms of the tissue inserts were blotted on sterile paper towels and the inserts were transferred to new 6-well plates containing 0.9 mL of fresh warmed (to 37°C) EpiDerm™ Maintenance Medium. The tissue surface was carefully blotted with sterile cotton-tipped applicators to remove any excess moisture, and the tissue surface was visually observed for residual test substance using a dissecting scope. In cases where residual test substance was observed, sterile cotton-tipped applicators pre-moistened with CMF-DPBS were used to attempt to remove any residual test substance from the tissue surface. The tissues were then placed into the incubator at standard culture conditions for a post-treatment expression incubation of 42 ± 2 hours. After an initial 24 ± 1 hours of incubation, the 6-well plates were removed from the incubator and the tissues were transferred into new 6-well plates pre-filled with 0.9 mL fresh Maintenance Medium warmed to approximately 37°C. The tissues were placed back into the incubator at standard culture conditions for an additional 18 ± 1 hours for the remainder of the 42 ± 2 -hour post-treatment expression incubation.

MTT Preparation

A 10 \times stock of MTT prepared in phosphate buffered saline (PBS; filtered at time of batch preparation) was thawed and diluted in warm MTT Addition Medium (Dulbecco's Modified Eagle's Medium [DMEM] containing 2 mM L-glutamine) to produce a 1.0 mg/mL solution no more than 2 hours before use. Three hundred microliters of the MTT solution were added to each designated well of a pre-labelled 24-well plate.

After the total 42 ± 2 hours of post-exposure expression incubation, the 6-well plates were removed from the incubator. Each tissue was blotted on a sterile paper towel and transferred to an appropriate well containing 0.3 mL of MTT solution. The 24-well MTT plates were incubated at standard culture conditions for 3 ± 0.1 hours.

After the 3 ± 0.1 hours of incubation, the EpiDerm™ tissues were submerged, gently swirled, and rinse media decanted in a beaker containing approximately 150 mL of CMF-DPBS three times. The tissue was then blotted on absorbent paper, cleared of excess liquid, and transferred to a pre-labelled 24-well plate containing 2.0 mL of isopropanol in each designated well. The plate was covered with parafilm and shaken for 2–3 hours at room temperature to extract the MTT. At the end of the extraction period, the insert was gently agitated up and down in its extractant well. The tissues were pierced with forceps to allow the extract to flow back into the well from which the insert was removed, and the cell culture

inserts were discarded. The extract solution was mixed (homogenized by pipetting up and down three times) and two 200- μ L aliquots were transferred to the appropriate wells of a 96-well plate. Two hundred microliters of isopropanol were added to the wells designated as blanks. The absorbance at 570 nm (OD_{570}) of each well was measured with a Molecular Devices Vmax plate reader with the AUTOMIX function selected.

Killed Controls (KC)

To evaluate whether residual test substance was binding to the tissue and leading to a false MTT reduction signal, a functional check (using freeze-killed control tissue) was performed.

For the test substance, GF-3969, two killed tissues were treated with the test substance in the normal fashion for 60 ± 1 minutes. The rinsing, MTT exposure, and solvent extraction procedures were performed exactly as described for the viable tissues. Duplicate killed-control tissues were treated with the negative control for 60 ± 1 minutes. A small amount of MTT reduction is expected from the residual NADH and associated enzymes within the killed tissue. This background reduction of MTT will be compared to the MTT reduction observed in the test substance-treated killed-control tissues.

Evaluation of Test Results

The following Prediction Model was endorsed by the European Centre for the Validation of Alternative Methods (ECVAM) Scientific Advisory Committee (ESAC) for the prediction of skin irritation. A test substance was predicted to be an irritant (GHS Category 1 or 2) when the mean relative viability of the three treated tissues is less than or equal to 50% of the mean viability of the negative control. Additional testing (*e.g.*, reconstructed human epidermis [RhE] OECD TG 431) in a tiered testing approach would be warranted to discriminate between GHS Category 1 and GHS Category 2.

Table A 8: Skin irritation prediction model

<i>In vitro</i> result	<i>In vivo</i> prediction	GHS category
Mean tissue viability $\leq 50\%$	Irritant (I)	Category 1 or 2 ^a
Mean tissue viability $> 50\%$	Non-irritant (NI)	No category

^a Additional testing would be required to discriminate between a GHS Category 1 or 2 classification.

Criteria for a Valid Test

The assay was accepted when the following criteria were met: 1) the positive control (5% SDS) resulted in a mean tissue viability $\leq 20\%$, 2) the mean OD_{570} value of the negative control tissues was ≥ 0.8 and < 2.8 , and 3) the standard deviations of the positive and negative control calculated from individual percent tissue viabilities of the three identically treated replicates were $< 18\%$.

RESULTS AND DISCUSSION

The test substance, positive control, and negative control were exposed to the EpiDerm™ tissues in triplicate for 60 minutes, with a post-exposure time of 42 hours. The table below summarizes the results of the Skin Irritation Test (SIT) for the test substance and the positive control.

Two trials were conducted for the test substance. In Trial 1, the mean OD_{570} of the negative control, sterile CMF-DPBS, was 2.160. The mean viability of the positive control, 5% SDS, was 5.63%. The standard deviation calculated from individual percent tissue viabilities of the three identically treated replicates was $< 18\%$ for the test substance, positive control, and negative control. Since the mean positive control result met the criteria to be classified as an irritant (*i.e.*, viability $\leq 50\%$), the mean OD value of the negative control was ≥ 0.8 and < 2.8 , and the standard deviation calculated from the individual percent tissue viabilities was $< 18\%$, the assay results were considered valid per the OECD test guideline. However, the OD_{570} value of the negative control-treated killed control tissues was unusually high, indicating that the quality of the killed control tissues used in Trial 1 was questionable. Therefore, Trial 2 was conducted (Table A 9). In Trial 2, the mean OD_{570} of the negative control, sterile CMF-DPBS, was 2.057 (for the sample used to correct the assay positive control) and 2.059 (for the sample used to correct the test substance). The mean viability of the positive control, 5% SDS, was 2.63%. The standard deviation calculated from individual percent tissue viabilities of the three identically treated replicates was $< 18\%$ for the test substance, positive control, and negative control.

Since the mean positive control result met the criteria to be classified as an irritant (*i.e.*, viability $\leq 50\%$), the mean OD value of the negative control was ≥ 0.8 and < 2.8 , and the standard deviation calculated from the individual percent tissue viabilities was $< 18\%$ the assay results were considered valid. Although both trials were considered valid, only the results of Trial 2 are considered reliable for further interpretation.

Cotton-tipped applicators pre-wetted in sterile CMF-DPBS were used to attempt to remove residues of the test substance noted to persist on the tissues after rinsing (only in Trial 1). A dissecting scope was used to check for residual test substance before and after use of the pre-wetted cotton swabs. No residual test substance was observed to remain on the surface of the tissues.

The test substance was observed to directly reduce MTT in the absence of viable cells. Therefore, a killed-control experiment was performed in both trials. Additional calculations were performed to correct for the amount of MTT reduced directly by test substance residues. The test substance was not determined to be a colorant (was not considered to have potential interference with the MTT measurement) after centrifugation.

Table A 9: Skin Irritation Test (SIT) results using the EpiDerm™ Skin Model

Treatment	Mean viability (%)	Skin irritation prediction
GF-3969 ^a	104.8	Non-irritant
5% SDS ^a	2.63	Irritant

^a Results are from Trial 2 only.

CONCLUSION

Based on the results of Trial 2, GF-3969 was predicted to be non-irritating to the skin, and thus would be considered unclassified according to the Globally Harmonized System of Classification and Labelling of Chemicals.

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Not classified
Regulation (EC) No. 1272/2008	Not classified

A 2.6 Eye irritation (KCP 7.1.5)

A 2.6.1 Study 1, DuPont-49964

Comments of zRMS:	<p>In the interest of both sound science and animal welfare, <i>in vivo</i> testing should not be considered until all available data relevant to the potential eye irritation/serious eye damage of the test chemical have been evaluated in a weight-of-the-evidence (WoE) analysis as presented in the GD263.</p> <p>(..) If this WoE analysis is still inconclusive, analysis should be conducted with additional testing, starting with <i>in vitro</i> methods or in chemico method can be provided and finally <i>in vivo</i> testing is used as last resort. (..)</p> <p>(..) The <i>in vivo</i> animal test, if e.g. required by regulators, should be considered after conducting <i>in vitro</i> testing only when the test chemical is not directly identified as GHS Cat. 1, UN GHS Cat. 2 or as GHS No Cat. by currently adopted <i>in vitro</i> test methods and defined approaches.(..)</p> <p>(..) The test chemical cannot be tested with the currently available <i>in vitro</i> test methods or defined approaches due to the limitations of the test methods or when falling outside of the applicability domain of the test method or approach. (..)</p> <p>Due to the different outcomes obtained from <i>in vivo</i> and <i>in vitro</i> studies (the last one is inconclusive), ZRMS considered weight of the evidence (WoE) and decided as precautionary approach to take into account assessment of eye corrosion/irritation based on composition of the product. Considering all classified substances in this hazard category and using the criteria given in Table 3.3.3. of 1272/2008 as amended: (10 x Eye</p>
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Effects Category 1) + Eye Effects Category 2 $\geq 10\%$ = Category 2, the result exceeds 10% and eye irritation Cat 2, H319 classification is triggered. Calculation in detail is available in Part C.

Study (Slonina, M., (2018) has been reviewed only for compliance with the current requirements. We do not identify deviations from study protocol however despite this ZRMS do not considered study outcome to hazard assessment.

Considering comments and suggestions sent by the cMS during the commenting period on the dRR, ZRMS PL decided to take into account all proposals and reclassified the PPP Dragster in terms of eye irritation.

Based on the discussion regarding CLP classification, final conclusions reflecting irritating potential was made on the basis of an *in vivo* test (Slonina, M., 2018 (DuPont-49964)), which confirmed the absence of eye irritation effect after exposure to the tested formulation.

Reference:	KCP 7.1.5/01
Report:	xxxxxxxxxxxxxxxxxxxxxxxxxxxx); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Primary eye irritation in rabbits
DuPont Report No.:	DuPont-49964
Testing Facility Report No.:	47000
Guidelines	OPPTS 870.2400 (1998), OECD 405 (2012), JMAFF 12-Nousan-8147 (2000), EC No. 440/2008
Deviations:	None
GLP:	Yes
Acceptability:	Yes however not considered in hazard assessment.
Duplication (if vertebrate study)	No

STUDY SUMMARY

In a primary (acute) eye irritation study, 0.1 mL (0.087 grams) of GF-3969, was instilled into the conjunctival sac of 3 young female New Zealand albino rabbits. Animals were observed at 1, 24, 48, and 72 hours following instillation. Ocular irritation was evaluated by the Draize method of scoring (1944).

The mean eye irritation scores at 24, 48 and 72 hours post instillation, for the 3 rabbits respectively, were:

Conjunctival Redness: [1, 0.3, 0.0] - Conjunctival Chemosis: [0.3, 0.0, 0.0]

Corneal Opacity: [0.3, 0.0, 0.0] - Iris Inflammation: [0.0, 0.0, 0.0]

Recovery was completed in all rabbits by 72 hours post patch removal.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	Rimsulfuron (25.1% w/w) Isoxadifen-ethyl (50.4% w/w) Thifensulfuron methyl (49.8% w/w)
Description (physical state):	Solid granules
Lot/batch no.:	V4B07-001
Vehicle:	Test substance was instilled as received

Test System

Species:	Rabbit (<i>Oryctolagus cuniculus</i>)
Strain:	New Zealand albino (NZA)
Age and weight at dosing:	12 or 13 weeks Weight (kg): Minimum 2.425, Maximum 2.488
Source:	Robinson Services Inc., Mocksville, NC
Housing:	Individually
Feed and water:	Feed: Envigo Teklad Global High Fiber Rabbit Diet® #2031 (approximately 150 grams/day) and Premium Timothy Cube™ (Ontario Dehy Inc) Water: Filtered tap water <i>ad libitum</i>
Environmental conditions:	Temperature: 19 to 23°C Humidity: 42 to 50% relative humidity Air changes: Minimum 13 air changes/hour Photoperiod: 12 hours dark/12 hours light
Acclimation period:	6 to 8 days

Study Design

In-life dates

Start: 21 December 2017 End: 06 January 2018

Animal assignment and treatment

The pH of GF-3969 was found to be within a range of 2 to 11.5 (1% aqueous solution in distilled water at room temperature), which is considered acceptable for treatment.

A total of 3 rabbits (females) were assigned to treatment. A sequential testing strategy was adopted. Initially one rabbit was tested. Immediately after administration of the test item, assessments of any

initial local pain reactions were made. As severe effects were not observed in the first treated rabbit, two additional rabbits were subsequently treated in an identical manner.

Prior to the test item instillation, buprenorphine 0.1 mg/kg body weight was administered to the animals and at appropriate intervals to maintain therapeutic blood levels. Prior to the test item instillation, one or two drops of 0.5% tetracaine hydrochloride ophthalmic solution USP was applied to each eye.

A volume of 0.1 mL (0.087 g) of GF-3969 was instilled in the conjunctival sac after gently pulling the lower lid away from the eyeball. Then the lids were gently held together for about one second before releasing to minimize loss of the test substance. The contralateral (untreated) eye served as the control.

Buprenorphine 0.1 mg/kg body weight was administered to relieve potential discomfort associated with eye irritation which provides therapeutic relief for periods of up to 76 hours.

Irritation was scored by the Draize method of scoring at 1, 24, 48, and 72 hours after GF-3969 instillation. Fluorescein staining was used to assess the corneal epithelium damage at 24 hours after the test item instillation in all animals. General health conditions and body weights were monitored.

RESULTS AND DISCUSSION

Eye Irritation

Individual animal irritation scores are presented in Table A 10.

Table A 10: Grades for ocular lesions (eye treated with the test item)

Rabbit no.	3401							3402							3403						
	Right							Right							Right						
Reaction post application	Hours				Days			Hours				Days			Hours				Days		
	1	24	48	72	7	14	21	1	24	48	72	7	14	21	1	24	48	72	7	14	21
Conjunctivae (redness)	1	1	1	0	N/A	N/A	N/A	1	1	0	0	N/A	N/A	N/A	1	1	0	0	N/A	N/A	N/A
Conjunctivae (chemosis)	2	1	0	0	N/A	N/A	N/A	1	0	0	0	N/A	N/A	N/A	1	0	0	0	N/A	N/A	N/A
Cornea (degree of opacity)	0	1	0	0	N/A	N/A	N/A	0	0	0	0	N/A	N/A	N/A	0	0	0	0	N/A	N/A	N/A
Iris inflammation	0	0	0	0	N/A	N/A	N/A	0	0	0	0	N/A	N/A	N/A	0	0	0	0	N/A	N/A	N/A

Key: N/A: Not applicable

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

0: Normal

1: Some blood vessels hyperaemic (injected)

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

3: Diffuse beefy red

Maximum possible: 3

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

0: Normal

1: Some swelling above normal

2: Obvious swelling, with partial eversion of lids

3: Swelling, with lids about half closed

4: Swelling, with lids more than half closed

Maximum possible: 4

Opacity: degree of density

0: No ulceration or opacity

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

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

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

4: Opaque cornea; iris not discernible through the opacity

Maximum possible: 4

Iris

0: Normal

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

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

Maximum possible: 2

Systemic toxicity

All animals appeared active and healthy. Although one animal lost body weight, the two remaining animals gained body weight during the study. Apart from the eye irritation scores, there were no other clinical signs observed.

CONCLUSION

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Rabbit	NZA	F	Eye	Instillation (no washing)	Mean Redness Scores: 1, 0.3, 0.0 Mean Chemosis Scores: 0.3, 0.0, 0.0 Mean Corneal Scores: 0.3, 0.0, 0.0 Mean Iris Scores: 0.0, 0.0, 0.0 Recovery completed by 72 hours

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Not classified
Regulation (EC) No. 1272/2008	Not classified

A 2.6.2 Study 2, DuPont Report No.: DuPont-50173

Comments of zRMS:	<p>In the interest of both sound science and animal welfare, <i>in vivo</i> testing should not be considered until all available data relevant to the potential eye irritation/serious eye damage of the test chemical have been evaluated in a weight-of-the-evidence (WoE) analysis as presented in the GD263.</p> <p>(..) If this WoE analysis is still inconclusive, analysis should be conducted with additional testing, starting with <i>in vitro</i> methods or in chemico method can be provided and finally <i>in vivo</i> testing is used as last resort. (..)</p> <p>(..) The <i>in vivo</i> animal test, if e.g. required by regulators, should be considered after conducting <i>in vitro</i> testing only when the test chemical is not directly identified as GHS Cat. 1, UN GHS Cat. 2 or as GHS No Cat. by currently adopted <i>in vitro</i> test methods and defined approaches.(..)</p> <p>(..) The test chemical cannot be tested with the currently available <i>in vitro</i> test methods or defined approaches due to the limitations of the test methods or when falling outside of the applicability domain of the test method or approach. (..).</p> <p>Predictions for eye corrosion/irritation based on <i>in vitro</i> studies is not relevant due to inconclusive outcome thus ZRMS in this particular case (eye corrosion/irritation) decided to take into account for hazard assessment predictions for eye corrosion/irritation based on composition of the product. This approach is supported by following paper: Kolle S.N., van Cott A., van Ravenzwaay B. and Landsiedel R. (2017): <i>Lacking applicability of in vitro eye irritation methods to identify seriously eye irritating agrochemical formulations: Results of bovine cornea opacity and permeability assay, isolated chicken eye test and the EpiOcular™ ET-50 method to classify according to UN GHS</i>. Regulatory Toxicology and Pharmacology 85 (2017) 33-47.</p> <p>Due to the different outcomes obtained from <i>in vivo</i> and <i>in vitro</i> studies (the last one is inconclusive), ZRMS considered weight-of-the-evidence (WoE) and decided as precautionary approach to take into account assessment of eye corrosion/irritation based on <i>in vivo</i> study (Slonina, M., 2018 (DuPont-49964)), which confirmed the absence of eye irritation effect after exposure to the tested formulation.</p> <p>composition of the product. Considering all classified substances in this hazard category and using the criteria given in Table 3.3.3. of 1272/2008 as amended: (10 x Eye Effects Category 1) + Eye Effects Category 2 ≥ 10% = Category 2, the result exceeds 10 and eye irritation Cat 2. H319 classification is triggered.</p>
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	Calculation in detail is available in Part C- Study (Wilt, N., Pham, R., Sadowski, N., (2018) has been reviewed only for compliance with the current requirements. We do not identify deviations from study protocol how ever despite this ZRMS do not considered study outcome to hazard assessment.
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Reference:	KCP 7.1.5/02
Report:	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx (2018); Rimsulfuron 25SG/Thifensulfuron methyl 50 SG/Isxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): epiocular™ eye irritation test (EIT) for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage
DuPont Report No.:	DuPont-50173
Testing Facility Report No.:	17AJ36.015091
Guidelines	OECD 492 (2015)
Deviations:	None
GLP:	Yes
Acceptability:	Yes, however not considered in hazard assessment.

STUDY SUMMARY

The EpiOcular™ Eye Irritation Test (EIT) was used to evaluate the ocular irritation potential of the test substance, GF-3969, in the context of classification of ocular irritation according to the UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The ocular irritation potential was evaluated based upon measuring the relative conversion of MTT (3-[4, 5 - dimethylthiazol-2-yl] - 2,5 - diphenyltetrazolium bromide) in the test substance-treated tissues after exposure to the test substance for 6 hours, followed by an 18 ± 0.25 hour post-exposure expression period. Ocular irritation potential of the test substance was predicted if the relative viability was less than or equal to 60%. If the relative viability was greater than 60%, the test substance was predicted to not require classification or labelling for ocular irritation (GHS No Category). The protocol met the requirements of the OECD test guideline “Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage” (TG 492).

The test substance was tested in a valid definitive assay to determine the potential identification and classification of ocular irritation hazard.

The corrected mean OD₅₅₀ value for the negative control was 1.324, and the viability of the positive control, methyl acetate, was less than 50%; therefore, the assay results were considered valid.

Based on the viability value of 8.3% obtained for the test substance, GF-3969, the test substance is predicted to require classification or labelling for ocular irritation (GHS Category 1 or 2).

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	Rimsulfuron: 14.82% (w/w) Thifensulfuron methyl: 9.26% (w/w) Isoxadifen-ethyl safener: 11.11% (w/w)
Description (physical state):	Light brown powder
Lot/batch no.:	V4B07-001

Test System

Kit:	EpiOcular™ Eye Irritation Test (EIT)
Source:	MatTek Corporation
Controls	
Positive:	Methyl acetate, 50 µL
Negative:	Sterile deionised water, 50 µL

Test Substance Preparation

The test substance was administered to the test system without dilution.

Assessment of Direct Test Substance Reduction of MTT

The test substance was added to a 1.0 mg/mL MTT solution in warm Dulbecco's Modified Eagle's Medium (DMEM) containing 2 mM L-glutamine (MTT Addition Medium) to assess its ability to directly reduce MTT. Approximately 50 mg of the test substance was added to 1 mL of the MTT solution, and the mixture was incubated in the dark at standard culture conditions for 3 hours. A negative control, 50 µL of sterile deionised water, was tested concurrently. If the MTT solution colour turned blue/purple, the test substance was presumed to have reduced the MTT. The test substance was observed to reduce MTT directly in the absence of viable cells. A killed control experiment was performed concurrently in the assay to determine the extent of the direct MTT reduction (if any) by the test substance alone.

Colorant Control Test

The test substance's ability to interfere with the photometric MTT measurement was assessed. Approximately 50 mg of the test substance were added to 2.0 mL isopropanol in a 6-well plate and placed on an orbital plate shaker for 2–3 hours at room temperature. After shaking, 200- μ L aliquots of the isopropanol solutions and two blank samples of isopropanol were transferred to a 96-well plate and the absorbance was measured with a plate reader at the MTT measurement wavelength (550 nm). After the 2–3-hour shaking period, the test substance-isopropanol mixture was transferred into centrifuge tubes and centrifuged (*e.g.*, 14000 rpm, for 5 minutes at room temperature) prior to transfer to the 96-well plates for the absorbance determination. The absorbance of the test substance samples was determined by subtracting the mean isopropanol blank value from the absorbance of the test substance samples. If the OD₅₅₀ of the test substance sample was >0.08, the material was considered as possibly interacting with the MTT measurement. The test substance had a corrected OD₅₅₀ value of 0.000 after centrifugation and was not considered to have probable photometric MTT interference.

MTT Assay

The EpiOcular™ tissues were treated in duplicate with the test substance in one valid definitive trial. After the overnight incubation for 16–24 hours, the 6-well plates containing the EpiOcular™ tissues were removed from the incubator. The EpiOcular™ tissues were treated in duplicate with the test substance, positive control, or negative control. Prior to test substance or control substance applications, each tissue surface was moistened with 20 μ L of Ca⁺⁺Mg⁺⁺-free Dulbecco's Phosphate Buffered Saline (D-PBS) and incubated at standard culture conditions for 30 minutes. After incubation, the EpiOcular™ tissues were tested in duplicate with 50 μ L of the positive control or negative control. The EpiOcular™ tissues were tested in duplicate with approximately 50 mg of the test substance. The tissues were then placed back into the incubator after dosing and incubated at standard culture conditions for the remainder of the 6-hour exposure time.

At the end of the 6-hour treatment time, the test substance or controls were removed by extensively rinsing the EpiOcular™ tissues with Ca⁺⁺Mg⁺⁺-free D-PBS brought to room temperature, as described in the following details. Three specimen cups (plastic with >100 mL capacity), containing 100 mL each of Ca⁺⁺Mg⁺⁺-free D-PBS were used per test substance or control. Each test substance or control utilised a different set of three beakers. The cell culture insert containing the EpiOcular™ tissue was lifted out of the medium by grasping the upper edge of the plastic "collar" with fine forceps. Use of curved forceps facilitated handling and decanting.

At the end of the exposure period, the test or control substances were decanted from the EpiOcular™ tissue surface onto a clean paper towel and the culture dipped into the first beaker of Ca⁺⁺Mg⁺⁺-free D-PBS, swirled in a circular motion in the liquid for approximately 2 seconds, lifted out so that the cell culture insert was mostly filled with Ca⁺⁺Mg⁺⁺-free D-PBS, and the liquid decanted back into the container. This process was performed two additional times in the first beaker. The culture was then rinsed in the second and third beakers of Ca⁺⁺Mg⁺⁺-free D-PBS three times each in the same fashion. Any remaining liquid was decanted onto the clean paper towel. This process was repeated for every cell culture insert.

After rinsing, each cell culture insert was immediately transferred to 5 mL of Assay Medium, in a prelabelled 12-well plate for 25 minutes of immersion incubation (Post-Soak) at room temperature to remove any test substance absorbed into the tissue.

At the end of the Post-Soak immersion, each insert was removed from the Assay Medium, the medium decanted off the tissue, the insert blotted on absorbent material, and transferred to the appropriate well of the prelabelled 6-well plate containing 1 mL of warm Assay Medium. The tissues were incubated for 18 \pm 0.25 hours at Standard Culture Conditions (Post-Treatment Incubation).

A 1.0 mg/mL solution of MTT in warm MTT Addition Medium was prepared no more than 2 hours before use. Three hundred microliters of MTT solution were added to designated wells in a prelabelled 24-well plate. At the end of the Post-Treatment Incubation, the EpiOcular™ constructs were removed from the 6-well plates, gently blotted on absorbent material, and transferred to the appropriate wells

containing the 300 µL of MTT solution. The trays were incubated for 180 minutes at standard culture conditions.

After 180 minutes, each cell culture insert was removed from the plate, the bottom of the insert blotted on absorbent material, and then transferred to a prelabelled 24-well plate containing 2.0 mL of isopropanol in each designated well. The plates were sealed with parafilm and stored in the refrigerator (2–8°C) until the last exposure time was harvested. To extract the MTT, the plates were then placed on an orbital plate shaker and shaken for 2 to 3 hours at room temperature.

At the end of the extraction period, the liquid within the cell culture inserts was decanted into the well from which the cell culture insert was taken. The extract solution was mixed, and two aliquots of 200 µL were transferred to the appropriate wells of a 96-well plate. Two hundred microliters of isopropanol were added to the two wells designated as the blanks. The absorbance at 550 nm (OD₅₅₀) of each well was measured with a Molecular Devices Vmax plate reader.

Killed Controls (KC)

To evaluate whether residual test substance was binding to the tissue and leading to a false MTT reduction signal, a functional check (using freeze-killed control tissue) was performed.

For the test substance, duplicate killed tissues were treated with the test substance in the normal fashion for 6 hours. The rinsing, MTT exposure, and solvent extraction procedures were performed exactly as described for the viable tissues. Duplicate killed-control tissues were treated with the negative control for 6 hours. A small amount of MTT reduction is expected from the residual NADH and associated enzymes within the killed tissue. This background reduction of MTT was compared to the MTT reduction observed in the test substance-treated killed control tissues using calculations described below.

Presentation of Data

The mean OD₅₅₀ value of the blank control wells was calculated. The corrected OD₅₅₀ values of the negative control were determined by subtracting the mean OD₅₅₀ of the blank control from the negative control raw OD₅₅₀ values. The mean corrected OD₅₅₀ value of the negative control was determined. The corrected OD₅₅₀ values of the individual test substance OD₅₅₀ values and the positive control OD₅₅₀ values were determined by subtracting the mean OD₅₅₀ of the blank control from their raw OD₅₅₀s. The mean corrected OD₅₅₀ values for the positive control and test substance were determined.

The mean raw OD₅₅₀ value for the negative control killed control was subtracted from the mean raw OD₅₅₀ value for the test substance-treated killed controls, to determine the net OD₅₅₀ value of the test substance-treated killed controls.

The net OD₅₅₀ value represents the amount of reduced MTT due to direct reduction by test substance residues. The net OD₅₅₀ value was subtracted from the corrected mean OD₅₅₀ values of the viable test substance-treated tissues, to obtain a final corrected OD₅₅₀ value.

The following % of viability calculation was then performed:

$$\% \text{ Viability} = \frac{\text{Mean Corrected OD}_{550} \text{ of Test Substance or Positive Control}}{\text{Corrected Mean OD}_{550} \text{ of Negative Control}} \times 100$$

Evaluation of Test Results

If the test substance-treated tissue viability is >60% relative to negative control-treated tissue viability, the test substance is identified as not requiring classification and labelling according to UN GHS (No Category).

If the test substance-treated tissue viability is ≤60% relative to negative control-treated tissue viability, the test substance is identified as potentially requiring classification and labelling according to UN GHS (Category 1 or 2).

Table A 11: Eye irritation prediction model

<i>In vitro</i> result	GHS category
Mean tissue viability ≤60%	Category 1 or 2 ^a
Mean tissue viability >60%	No Category

a Additional testing would be required to discriminate between a GHS Category 1 or 2 classification.

Criteria for a Valid Test

The assay was accepted if the corrected mean OD₅₅₀ value of the negative control was >0.8 and <2.5, and the mean relative viability of the positive control was ≤50%.

RESULTS AND DISCUSSION

The EpiOcular™ cultures were treated in duplicate with the test substance for an exposure time of 6 hours. The negative and positive controls were also exposed in duplicate for 6 hours. Table A 12 summarises the percent viability results of the EIT using EpiOcular™ tissues for the test substance and the positive control, methyl acetate. Since the mean corrected OD₅₅₀ value for the negative control (1.324) was >0.8 and <2.5, and the viability for the positive control (16.7%) was less than 50%, the assay results were considered valid.

The test substance was observed to reduce MTT directly in the absence of viable cells; therefore, a killed control experiment was performed. Additional calculations were performed to correct for the amount of MTT reduced directly by test substance residues as described above. The test substance was not observed to be a colorant in isopropanol; therefore, a colorant control was not performed.

Table A 12: Results of the EpiOcular™ Eye Irritation Test (EIT)

Treatment	Concentration	Exposure time	Mean viability (%)	Ocular irritation prediction
GF-3969 ^a	Neat	6 hours	8.3	Irritant
Methyl acetate	Neat	6 hours	16.7	Irritant

a pH was not measured since the test substance is a solid.

CONCLUSION

The test substance resulted in a relative viability of 8.3% and is predicted to require classification or labelling for ocular irritation (GHS Category 1 or 2).

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Category 1 or 2
Regulation (EC) 1272/2008	No defined criteria. Since study result shows irritation potential but is inconclusive, classification has been based on calculated result.

A 2.7 Skin sensitisation (KCP 7.1.6)

A 2.7.1 DuPont Report No.: DuPont-49966

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:	xxxxxxxxxxxxxxxxxxxxxx); Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen ethyl 50WG (DPX-V4B07) A blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Local lymph node assay (LLNA) in mice
DuPont Report No.:	DuPont-49966
Testing Facility Report No.:	DuPont-49966
Guidelines	OPPTS 870.2600 (2003), OECD 429 (2010)
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In a dermal sensitization study with GF-3969 in N,N-Dimethylformamide (DMF), groups of 5 or 6 female CBA/JHsd mice were tested using the local lymph node assay. The positive control was HCA (α -hexylcinnamaldehyde) 25% (v/v).

No test substance-related changes in body weights were observed at any test concentration. On test day 6, individual body weight loss, between 25% and 32% was observed in 3/5 mice in test substance group 3. These animals also appeared dehydrated. This weight loss was attributed to the possibility that the individual cages were not pushed in the rack far enough for the mice to reach the water sipper. The water sipper was functioning properly. Since weight loss was not observed in other treatment groups, the lower body weight in group 3 mice on test day 6 were not considered test substance-related. One mouse in the 30% test substance group had 16% weight loss on test day 6. Other mice in this group did not have a similar weight loss nor was there weight loss observed in the 50% test substance group. Therefore, the lower body weight on test day 6 for animal was not considered test substance-related.

No clinical signs of toxicity were observed in the study. One mouse in the vehicle group had a swollen face. At sacrifice, this mouse had an enlarged lymph node on the right side. Three mice in group 3 appeared dehydrated on test day 6 due to insufficient access to water and four mice in group 5 had skin discoloration of the ears from the test substance.

No statistically significant increases in cell proliferation measurements compared to the vehicle group were observed at any test concentration. Stimulation indices (SI) for the groups treated with GF-3969 at the concentrations of 5, 15, 30 and 50% (w/v) in DMF were 1.50, 1.11, 1.38, and 0.55, respectively. Stimulation indices (SIs) of less than 3.0 were observed at all test concentrations of GF-3969. Therefore, the EC₃ value (the estimated concentration required to induce a threshold positive response, i.e., SI = 3) for the test substance under the conditions of this study was not calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice, (SI = 6.62). Therefore, the LLNA test system was valid for this study with GF-3969. Under the conditions of this study, GF-3969 did not produce a dermal sensitization response in mice.

In this study, GF-3969 was not a dermal sensitizer.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	25.1% w/w of rimsulfuron 49.8% w/w of thifensulfuron methyl 50.4% w/w of isoxadifen-ethyl
Description (physical state):	Paste Extruded Granules
Lot/batch no.:	V4B07-001

Vehicle/Control Item(s)

Vehicle/Negative control:	N,N-dimethylformamide (DMF)
Positive control:	α -hexylcinnamaldehyde, 25% v/v

Test System

Species:	Mouse (<i>Mus musculus</i>)
Strain:	CBA/JHsd
Age and weight at dosing:	10 weeks old Weight (g): Minimum 20.1, Maximum 24.6
Source:	The Jackson Laboratory, Bar Harbor, Maine, U.S.A.

Housing:	All animals were housed in solid-bottom cages with bedding and appropriate species-specific enrichment. During quarantine, animals were housed in groups of 5 or fewer. Animals were single housed for approximately 2 hours following each application of the vehicle, test substance, or positive control to allow additional time for drying and/or absorption. Following the 2-hour single-housing period, animals were returned to their group housing status
Feed and water:	Feed: PMI® Nutrition International, LLC Certified Rodent (LabDiet® 5002). <i>ad libitum</i> . Water: Tap water <i>ad libitum</i>
Environmental conditions:	Temperature: 20 to 25°C Humidity: 30 to 70% relative humidity Air changes: Not reported Photoperiod: 12 hours dark/12 hours light
Acclimation period:	8 days

Study Design

In-life dates

Start: 06 December 2017 End: 11 December 2017

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

Animal assignment and treatment

Four groups of female mice comprising 5 females per group were treated topically for three consecutive days (test days 1-3) on the dorsal surface of both ears (25 µL/ear) with GF-3969 at concentrations of 5%, 15%, 30% and 50% (w/v). Female mice with 5 or 6 animals from the vehicle control and positive control groups were maintained in similar conditions with treatment of DMF and 25% (v/v) of HCA, respectively.

Group	Number/ Group	Dosage (%) ^a
1	6	0 (Vehicle, N,N-Dimethylformamide)
2	5	5
3	5	15
4	5	30
5	5	50
6	6	25 (Positive Control, Hexylcinnamaldehyde)

a % = percent of test substance in vehicle (e.g., 100% = 1 g/mL, or neat test substance)

Approximately 5 hours after the injection, animals were sacrificed by isoflurane anesthesia followed by carbon dioxide inhalation, draining auricular lymph nodes were removed, and single cell suspensions were prepared. One mouse (152 in the vehicle group) was observed to have an enlarged lymph node during the removal of the lymph nodes; the lymph node data for this mouse were excluded from the statistical analysis. The single cell suspensions were incubated at 2-8°C overnight. On test day 7, the single cell suspensions were counted on a beta counter and reported as disintegrations per minute (dpm). The dpm value for one mouse (352 in the 15% test substance group) was deemed an outlier by statistical analysis. Exclusion of this data did not change the statistical significance and the date were, therefore, reported.

Study Parameter	Frequency
Body Weight	Test days 1 and 6
Daily Animal Health Observations	At least once daily
Careful Clinical Observations	Prior to dosing and prior to sacrifice
Dosing	Test days 1-3
Days of Rest	Test days 4-5
Injection of Radioactivity	Test day 6
Removal of Lymph Nodes	At sacrifice (test day 6)
Disintegrations per minute (dpm) data	Test day 7

Statistics

Significance was judged at $p < 0.01$. Lymph node dpm data were transformed to Log to obtain normality or homogenous variances

Parameter	Preliminary Test	Method of Statistical Analysis	
		If preliminary test is not significant	If preliminary test is significant
Lymph Node dpm Data ^a	Test for lack of trend	Sequential application of the Jonckheere-Terpstra trend test	Preliminary tests for pairwise comparison
	OR ^b		
	Levene's test for homogeneity and Shapiro-Wilk test for normality ^c	One-way analysis of variance followed by Dunnett's test	Kruskal-Wallis test followed by Dunn's test

a Positive control data were not included in the statistical analysis of the test substance groups.

b Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.

c If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.

RESULTS AND DISCUSSION

Clinical Observations and Irritation

No clinical signs of toxicity were observed in the study. One mouse in the vehicle group had a swollen face. At sacrifice, this mouse had an enlarged lymph node on the right side. Three mice in group 3 appeared dehydrated on test day 6 due to insufficient access to water and four mice in group 5 had skin discoloration of the ears from the test substance.

Body Weight

No test substance-related changes in body weights were observed at any test concentration. On test day 6, individual body weight loss, between 25% and 32% was observed in 3/5 mice in test substance group 3. These animals also appeared dehydrated. This weight loss was attributed to the possibility that the individual cages were not pushed in the rack far enough for the mice to reach the water sipper. The water sipper was functioning properly. Since weight loss was not observed in other treatment groups, the lower body weight in group 3 mice on test day 6 were not considered test substance-related. One mouse in the 30% test substance group (454) had 16% weight loss on test day 6. Other mice in this group did not have a similar weight loss nor was there weight loss observed in the 50% test substance group. Therefore, the lower body weight on test day 6 for animal 454 was not considered test substance-related.

Group Mean DPM

No statistically significant increases in cell proliferation measurements compared to the vehicle group were observed at any test concentration.

Stimulation Index (SI Value) and EC₃ Value

SIs of less than 3.0 were observed at all test concentrations of GF-3969. Therefore, the EC₃ value (the estimated concentration required to induce a threshold positive response, i.e., SI = 3) for the test substance under the conditions of this study was not calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice.

Individual and group mean values are reported in Table A 13.

Table A 13: Dose concentration, group mean DPM value and Stimulation Index

Test Material/ Dose concentration	Animal #	Individual Animal DPM	Group Mean \pm SD (DPM)	Stimulation Index (SI)
Vehicle (N,N-Dimethylformamide (DMF))	151	639.25	675.45 \pm 375.32	N/A
	153	359.25		
	154	1227.25		
	155	313.25		
	156	838.25		
[GF-3969] 5% [(w/v)] in DMF	251	781.25	1012.05 \pm 328.37	1.50
	252	1204.25		
	253	734.25		
	254	1497.25		
	255	843.25		
[GF-3969] 15% [(w/v)] in DMF	351	1232.25	747.05 \pm 453.23	1.11
	352	126.25		
	353	491.25		
	354	771.25		
	355	1114.25		
[GF-3969] 30% [(w/v)] in DMF	451	891.25	932.05 \pm 137.80	1.38
	452	1063.25		
	453	954.25		
	454	1034.25		
	455	717.25		
[GF-3969] 50% [(w/v)] in DMF	551	354.25	371.25 \pm 89.61	0.55
	552	293.25		
	553	290.25		
	554	416.25		
	555	502.25		
HCA (Positive control) 25% (v/v) in vehicle	651	3816.25	4473.42 \pm 1787.38	6.62
	652	3266.25		
	653	3991.25		
	654	8015.25		
	655	4420.25		
	656	3331.25		

CONCLUSION

Based on these data, and according to the guidance provided by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), GF-3969 is considered a dermal non-sensitizer in mice.

Test item	Species	Strain	Sex	Route	Method	Result
GF-3969	Mouse	CBA/JHsd	F	Dermal	Topical - Local lymph node assay	Dermal non-sensitizer SI = 1.50, 1.11, 1.38, and 0.55 at 5, 15, 30 and 50% (w/v) respectively.

Classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Not classified as skin sensitiser
Regulation (EC) 1272/2008	Not classified

A 2.8 Supplementary studies on the plant protection product (KCP 7.1.7)

No new or additional studies have been submitted.

A 2.9 Supplementary studies for combinations of plant protection products (KCP 7.1.8)

No new or additional studies have been submitted.

A 2.10 Data on co-formulants (KCP 7.4)

A 2.10.1 Safety data sheet for each co-formulant

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

A 2.10.2 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 2.10.3 TF375/99-0777

Comments of zRMS:	Study (DuFour, P., (1999)) has been submitted by the notifier to support determining an NOAEL for isodecyl alcohol ethoxylated, component of non-ionic adjuvant DPX-KG691, as basis for AOEL used in risk assessment (NDE). Study is relevant for risk assessment (setting NOAEL/AOEL) and hazard identification. The daily administration by gavage of the substance to SD rats over 28 days period did not induced significant signs of toxicity for all groups of treated M/F rats receiving 10, 50, or 150 mg/kg bw/day. For females receiving 450 mg/kg bw/d it was noted moderated increase in relative liver weight and AP activity. These changes was not follow-up histopathological abnormalities in liver. Thus under defined experimental conditions ZRMS supports 150 mg/kg bw/d as NOAEL for Female rats and 600 mg/kg bw/d for Male rats.				
	Relevant effect D28	Relative liver weight (brain weight ratio; mean value)		Biochemistry AP activity U/l	
	Sex	Female	Male	Female	Male
	Group 0 5 mg/kg bw/d vehicle	379.86±4.26	516.53±33.10	368.2±92.6	422.4±35.7

Group 1 10 mg/kg bw/d tested material	334.93±19.93	527.26±64. 32	282.0±67.7	417.8±104.4
Group 2 50 mg/kg bw/d tested material	373.34±38.84	515.67±55. 54	321.2±53.5	424.8±75.0
Group 3 150 mg/kg bw/d tested material	370.68±24.88	560.15±54. 15	348.0±54.8	431.4±69.4
Group 4 450 mg/kg bw/d F tested material	464.82±35.8* **	--	470.0±73.1*	--
Group 4 600 mg/kg bw/d M tested material	--	570.47±42. 98	--	471.8±90.4

Additionally due to lack of evident toxicity and clear signs of toxicity following administration of test substance ZRMS agree with proposed GHS classification. Study is sufficient for hazard assessment. Increase in the dose administered do not results in the development of severe toxic signs and mortality.
Results of the study and conclusions are adequate for risk assessment and classification purpose. Study accepted.

Reference:	KCP 7.4/01
Report:	DuFour, P., (1999); Oral toxicity test after 28-day repeated administration in the rat
DuPont Report No.:	TF375/99-0777
Testing Facility Report No.:	TF375/99-0777
Guidelines	OECD 407
Deviations:	None
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

STUDY SUMMARY

In a subchronic feeding study, isodecyl-alcohol ethoxylate was administered to male and female SPF (specific pathogen free) Sprague-Dawley rats (5 animals/sex/concentration) at concentrations of 0, 10, 50, 150 and 450 (females) or 600 ppm **mg/kg bw/day** (males) for 28 days. Parameters evaluated included body weight, body weight gain, food consumption, clinical signs, gross pathology, haematology, clinical chemistry, and organ weights.

No treatment-related adverse effects were observed over the 28-day interval in males or females at any dose.

The NOAEL for males was 600 ppm **mg/kg bw/day** and for females was 150 ppm **mg/kg bw/day**, the highest dose level tested. This NOAEL was based on the absence of adverse effects in males and females at 150 ppm **mg/kg bw/day** and below.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	Isodecyl-alcohol ethoxylate
Description:	Colourless liquid
CAS #:	61827-42-7
Stability of test compound:	Stable

Vehicle/Control Item(s)

Vehicle and/or positive control: Distilled water

Test System

Species: Rat
Strain: SPF (specific pathogen free) Sprague-Dawley albino female rats (OFA-SD)
Age at dosing: Approximately 6 weeks old
Weight at dosing: 240.6–249.5 g for males; 197.6–206.1 g for females
Source: IFFA-CREDO supplier (69592 L'Arbresle cedex, France)
Acclimation period: ≥5 days
Diet: Pelleted form (A04-10) delivered sterilized, *ad libitum*.
Water: Acidified tap water, *ad libitum*
Housing: 5 per cage, in 31 cm x 46 cm x 19 cm polypropylene cages with stainless steel lid. The bedding renewed regularly, was composed of wood shavings delivered dust-free and sterilized.

Environmental conditions
Temperature: 20–24°C
Humidity: 30–70%
Air changes: 10 cycles/hr
Photoperiod: Alternating 12-hour light and dark cycles

Study Design

In-life dates

Start: 08 June 1999 End: 10 August 1999

Animal assignment and treatment

Groups of 5 animals/sex/concentration were administered concentrations of 10, 50, 150 and 450 (females) or 600 ppm mg/kg bw/day (males) isodecyl-alcohol ethoxylate by oral gavage daily for 28 days. A negative control group received untreated diet.

Males			Females		
Group No.	No./ group	Conc. in diet (ppm mg/kg bw/day)	Group No.	No./ group	Conc. in diet (ppm mg/kg bw/day) ^a
I	5	0 (control)	II	5	0 (control)
III	5	10	IV	5	10
V	5	50	VI	5	50
VII	5	150	VII	5	150
VIII	5	600	VIII	5	450

Dosing formulations, preparation, and analysis

Formulations of test substance in distilled water were prepared fresh on each day of dosing and stored refrigerated until used. The homogeneity and concentration of isodecyl-alcohol ethoxylate in the dosing formulations were checked at the initial dose preparation. Towards the end of the study samples were taken to verify concentration. The test substance was at target concentrations and was homogeneous. Based on this information, it can be concluded that the animals received the targeted concentrations of test substance during the study.

Statistics

Body weight changes were analysed separately for each sex by a two-way analysis of variance for repeated measurements in time taking the "time" and "treatment factors" into consideration. If a statistically significant dosing effect was found, the mean of the control group was compared with that of the treated groups using the Fisher's test.

Hematology and clinical biochemistry data were analysed separately parameter by parameter. Once variance homogeneity between groups was confirmed (variation coefficient's analysis), the means were compared by analysis of variance.

If a statistically significant dosing effect was found, the control group was compared with each treated group using the Fisher's test.

If the application conditions of the test of analysis of variance were not respected, a non parametric test (Kruskal-Wallis) was used. If a statistically significant dosing effect was found, each treated group was compared to the control group using the Mann-Whitney's test.

Mean weights of tissues and organs removed on the necropsy day were analysed separately for each sex according to a process similar to the previous one.

Results of daily clinical findings, food consumption and macroscopic findings of organs at killing were discussed but not analysed statistically.

Observations

Animals were observed at least twice daily for mortality, morbidity and clinical signs of toxicity.

Body weights

All animals were weighed once per week.

Food consumption, food efficiency, and daily intake

Food consumption was recorded for each animal over the weighing interval. Food efficiency and daily intake were calculated from food consumption and body weight data.

Clinical pathology (haematology, clinical chemistry)

Blood samples were collected from all animals approximately 4 weeks after initiation of the study. At sacrifice, blood was collected for evaluation.

Sacrifice and pathology

On test Day 29, animals were anaesthetised and sacrificed. Gross examinations were performed on all study animals. The following organs were weighed: liver, kidneys, adrenal glands, thymus, brain, spleen, heart, testes, and epididymides. Organ weight/final body weight and organ weight/brain weight ratios were calculated.

RESULTS AND DISCUSSION

Observations

Clinical signs of toxicity

No compound-related clinical signs were noted at 10 mg/kg/day and 50 mg/kg/day.

Sporadically on week 2 and 3, some animals receiving 150 mg/kg/day salivated and burrowed in their bedding immediately after the end of dosing. On week 4, these signs associated with a slight piloerection and dirty coats were noted in all animals.

At 450 mg/kg/day (females) and 600 mg/kg/day (males), from day 4 to study termination, it was noted that all animals burrowed in their bedding and had hypersalivation immediately after dosing for several minutes.

From week 2, through the end of the study, a slight piloerection and dirty coats were also observed.

These post-dosing signs were considered to be without toxicological importance, since they are commonly noted with test substances bitter in taste when the route of administration is gastric intubation.

Mortality

The single mortality observed during the treatment period (one female treated at 450 mg/kg/day) was considered to be unrelated to administration of the test substance.

Body weight and body weight gain

There were no test substance-related or statistically significant differences on body weights or body weight gains.

Food consumption, food efficiency, and daily intake

No effects on food consumption were noted in the animals receiving the test substance.

Clinical pathology

Haematology

No differences of toxicological significance were observed between control and treated animals at the end of the treatment period.

Clinical chemistry

A moderate increase in alkaline phosphatase activity (+ 28 %) statistically significant was noted at the end of the treatment period in group 5 females (450 mg/kg/day). This change associated with a non-statistically significant increase in alanine aminotransferase (+ 34 %) was considered to be related to treatment.

Other differences from controls noted in treated groups of males and females were considered to be of no toxicological importance.

Sacrifice and pathology

Organ weight

Liver weights were statistically increased in females treated at 450 mg/kg/day in comparison with controls (+ 24 %). There were no other test substance-related effects on organ weights in either males or females.

Gross pathology

No test substance-related gross lesions were observed at necropsy.

CONCLUSION

Test item	Species	Strain	Sex	Route	Method	Result
Isodecyl-alcohol ethoxylate	Rat	OF A-SD	M F	Oral	Gavage (diluted with distilled water)	NOAEL = 600 mg/kg day for males NOAEL = 150 mg/kg day for females

GHS classification

Globally Harmonized System of Classification and Labelling of Chemicals (rev. 8, GHS 2019)	Category 5
Regulation (EC) No. 1272/2008	Not classified

A 2.11 Studies on dermal absorption (KCP 7.3)

No new or additional studies have been submitted.

A 2.12 Other/Special Studies (KCP 7.1.7)

Comments of zRMS:	<p>The key biological events underlying skin sensitisation has been summarised in the form of an (AOP), going from the molecular initiating event through the intermediate events up to the adverse health effect, i.e. allergic contact dermatitis in humans or contact hypersensitivity in rodents.</p> <p>1) the first key event molecular initiating event is the covalent binding of electrophilic substances to nucleophilic centres in skin proteins.</p> <p>2) <u>the second key event in this AOP takes place in the keratinocytes and includes inflammatory responses as well as gene expression associated with specific cell signalling pathways such as the antioxidant/electrophile response element (ARE)-dependent pathways.</u></p> <p>3) the third key event is the activation of dendritic cells, typically assessed by expression of specific cell surface markers, chemokines and cytokines.</p> <p>4) <u>the fourth key event is T-cell proliferation, which is indirectly assessed in the murine Local Lymph Node Assay. It has been address in the LLNA study Hoban, D., (2018) refer point A2.7.1 p.71 to this dRR.</u></p> <p>Study Ruwona, T., Sheehan, D., Koch, W.T., (2018); (ARE-Nrf2 luciferase test method) has been submitted to address the second key event as explained in above. Skin sensitisers have been reported to induce genes that are regulated by the antioxidant response element (ARE). Results of the study and conclusions are adequate for risk and hazard assessment. Study accepted.</p> <p>Results obtained in the mentioned above study Ruwona, T., at all (2018) supports conclusions from LLNA study, Hoban, D. (2018)</p>
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Reference:	KCP 7.1.7/02
Report:	Ruwona, T., Sheehan, D., Koch, W.T., (2018); Rimsulfuron 25SG/thifensulfuron methyl 50SG/isoxadifen ethyl 50WG (DPX-V4B07) a blend of paste extruded granules (14.82% + 9.26% + 11.11% active): Induction of antioxidant-response-element dependent gene activity and cytotoxicity (using MTT) in the keratinocyte ARE-reporter cell line keratinosens
DuPont Report No.:	DuPont-50245
Testing Facility Report No.:	17AJ36.170001
Guidelines	OECD TG442D
Deviations:	None
GLP:	Yes
Acceptability:	Yes

STUDY SUMMARY

The Induction of Antioxidant-Response-Element Dependent Gene Activity in the Keratinocyte ARE-Reporter Cell Line KeratinoSens assay was used to assess the skin sensitization potential of Rimsulfuron 25SG/Thifensulfuron methyl 50SG/Isoxadifen-ethyl 50WG blend of paste extruded granules (14.82% + 9.26% + 11.11% active) (GF-3969). The test substance, GF-3969, was tested in three definitive assays. Each definitive assay included a set of four plates (three for gene induction, one for cytotoxicity assessment). The test substance, GF-3969, was tested at 12 concentrations ranging from 0.977 to 2000 µM. The positive control, cinnamic aldehyde, was tested at five concentrations ranging from 4 to 64 µM. The mean EC1.5 (concentration for a statistically significant induction of 50% above solvent controls) and mean IC₅₀ (concentration leading to 50% viability as compared to solvent controls) for the test substance in the definitive assays were 368.24 µM and 1771.12 µM, respectively.

A test substance, was predicted to have sensitization potential if: 1) The EC1.5 value fell below 1000 μM in at least two of three repetitions; 2) at the lowest concentration with a gene induction above 1.5, cellular viability was greater than 70%; and 3) there was an apparent overall dose response which was similar between the three definitive assays. According to this current prediction model, GF-3969 was predicted to be a sensitizer.

MATERIALS AND METHODS

Test Item(s)

Test item (Common name):	GF-3969
Purity:	Rimsulfuron: 14.82% (w/w) Thifensulfuron methyl: 9.26% (w/w) Isoxadifen-ethyl safener: 11.11% (w/w)
Description (physical state):	White powder
Lot/batch no.:	V4B07-001

Test System

Cryopreserved KeratinoSens cells.

Negative (Vehicle) and Positive Control

The following controls were run concurrently with each test:

Control	Manufactured by	CAS No.	Purity (%)	Solvent	Concentration(s)	Negative/ Positive
1% DMSO (1% DMEM)	Sigma-Aldrich	67-68-5	99.97	DMSO	1%	Negative
Cinnamic aldehyde	Sigma-Aldrich	14371-10-9	99.1	DMSO	4, 8, 16, 32, 64 μL	Positive

DMSO = Dimethylsulfoxide

DMEM = Dulbecco's Modified Eagle Medium

Solubility Determination

The solubility of the test substance was tested in dimethylsulfoxide (DMSO) on the day of the initial definitive assay (at the highest 100 \times concentration of 200000 $\mu\text{g}/\text{mL}$). The highest 100 \times concentrations were described as dark brown non-viscous suspension.

MTT Direct Reduction Test

The ability of the test substance to directly reduce MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) was assessed at the same time as test substance treatment in the definitive assays. A 1.0 mg/mL MTT solution was prepared by dissolving a 10 mg/mL stock solution of MTT into warm MTT Addition Medium. Approximately 100 μL of the 100 \times (200000 μM) test substance concentration in DMSO was added to 1 mL of the MTT solution and then incubated in the dark at 37 $^{\circ}\text{C}$ for 1 to 3 hours. One hundred microliters of a negative control (*e.g.*, DMSO) was tested concurrently. If the MTT solution colour turned blue/purple, the test substance was presumed to have reduced the MTT. The test substance was darkly coloured and could not be accurately assessed in the MTT reduction assay.

Testing Concentrations

The test substance, GF-3969, had an assigned molecular weight of 500 g/mol and was diluted based on molarity. The 100 \times stock dilution was prepared to a top concentration of 200000 μM . The final 1 \times tested concentrations were 2000, 1000, 500, 250, 125, 62.5, 31.3, 15.6, 7.81, 3.91, 1.95, and 0.977 μM .

Definitive Assays

The test substance was tested in three definitive assays. Each definitive assay included a set of four plates (three for gene induction, one for cytotoxicity assessment). Each plate tested a range of 12 dosing concentrations for the test substance. Each plate also included five wells designated for the positive control (tested over a range of five dosing concentrations), six wells designated as the DMSO solvent control, and one well that was left blank.

Each definitive assay was performed independently but in parallel on the same day.

After approximately 24 hours of incubation, the Assay Medium was removed from the cells. The plates were decanted and gently blotted on sterile paper towels. One hundred and fifty microliters of fresh pre-warmed 1% Dulbecco's Modified Eagle Medium (DMEM) were added to all wells, including the blank. The plates were returned to the incubator until the dosing was initiated.

For the test substance, twelve decreasing doses were selected for the assay. For the positive control, five decreasing doses were prepared. For each experiment, the positive control (five doses), and the solvent control, a 100× DMSO master plate was made, followed by a 4× Master Plate. When added to the 150 µL of 1% DMEM already in each well, the addition of the 50 µL 4× dose brought the final dose on the plates to 1×.

Visual Observations

After approximately 48 hours of post-treatment incubation, visual observations of the cultures were performed for the cytotoxicity plate and recorded. The highest concentration from 500 to 2000 µM showed significant toxicity.

Treatment Termination and Luciferase Induction Determination

After 48 ± 1 hours of exposure, each white-walled culture plate was removed from the incubator and allowed to equilibrate to room temperature for at least 30 minutes. Once at room temperature, the treatment medium was decanted from each plate. The cultures were rinsed with 250 µL of Calcium and Magnesium Free Dulbecco's Phosphate Buffered Saline (CMF-DPBS; room temperature), the CMF-DPBS rinsate was decanted from the wells, and the plates were gently blotted onto paper towels.

Fifty microliters of CMF-DPBS was added to each well followed by 50 µL of ONE-Glo™ Reagent. The plates remained at room temperature in the dark for at least 5 minutes before being read by the luminometer. The plates were read within 45 minutes of addition of the ONE-Glo™ Reagent. The luminescence determination of each plate was performed by a Berthold Detection Systems luminometer initiated from an IBM-PC hosting the Windows-based Simplicity™ software. The light intensity in each well was measured at 565 nm in the form of relative light units (RLUs).

Treatment Termination: Cytotoxicity Using the MTT Endpoint

A 0.59 mg/mL MTT solution was prepared in 1% DMEM and used within 2 hours. After 48 ± 1 hours, the clear 96-well plates designated for the MTT endpoint were decanted and gently blotted on paper towels. No rinsing was performed. Two hundred microliters of 1% DMEM containing 0.59 mg/mL MTT was added to each well. The plate was incubated with a plate seal at standard culture conditions for approximately 4 hours.

After approximately 4 hours, the MTT solution was decanted, the plate was blotted, and 200 µL of 10% sodium lauryl sulfate (SLS) was added to each well. The plate was covered with a plate seal and incubated at standard culture conditions overnight.

After the overnight incubation, each plate was placed on a plate shaker and shaken for at least 20 minutes at room temperature. The absorbance at 570 nm (OD_{570}) of each well was measured with a Molecular Devices Vmax plate reader.

Criteria for Determination of a Valid Definitive Assay

The KeratinoSens assay was accepted when the positive control (cinnamic aldehyde) caused an EC1.5 value that fell within two standard deviations of the historical mean. Additionally, the results of the

three definitive trials for each plate were assessed using acceptance criteria that included: 1) variability in DMSO solvent control wells for each definitive assay was <20%; and 2) the positive control produced a statistically significant induction above 1.5-fold below 64 µM in each definitive assay.

There was a planned deviation in the acceptance criteria: Two out of 36 solvent wells for B1 and B2 were removed as they were deemed to be outliers. The Grubbs test was used to detect outliers and values were deemed significant outliers with a $p > 0.05$ value.

Evaluation of Test Results

A test substance was predicted to have sensitization potential if: 1) The EC1.5 value fell below 1000 µM in at least two of three repetitions; 2) at the lowest concentration with a gene induction above 1.5, cellular viability was greater than 70%; and 3) there was an apparent overall dose response which was similar between repetitions.

RESULTS AND DISCUSSION

The test substance, GF-3969, was tested in three definitive assays. Each definitive assay included a set of four plates (three for gene induction, one for cytotoxicity assessment). The test substance was tested at 12 concentrations ranging from 0.977 to 2000 µM. The positive control, cinnamic aldehyde, was tested at five concentrations ranging from 4 to 64 µM. A summary of the EC1.5 (concentration for a statistically significant induction of 50% above solvent controls) and IC₅₀ (concentration leading to 50% viability as compared to solvent controls) results of the definitive assays are presented in Table A 14. Additional luciferase induction information (which was not used for the current prediction model) that includes the I_{max} (the maximal fold induction) and the CI_{max} (the concentration at which the maximal fold induction occurs) is also presented in Table A 14.

The Induction of Antioxidant-Response-Element Dependent Gene Activity in the Keratinocyte ARE-Reporter Cell Line KeratinoSens assay was used to assess the skin sensitization potential of the test substance. A test substance was predicted to have sensitization potential if: 1) The EC1.5 value fell below 1000 µM in at least two of three repetitions; 2) at the lowest concentration with a gene induction above 1.5, cellular viability was greater than 70%; and 3) there was an apparent overall dose response which was similar between the three definitive assays. It is noted that the prediction model for the KeratinoSens assay was based on studies with neat chemicals, not extracts or mixtures. The prediction model presented based on pro-forma molecular weight of 500g and may not accurately assess mixtures.

Table A 14: EC1.5, IC₅₀, I_{max}, and CI_{max} mean summary

Treatment	Mean EC1.5 (µM)	Mean IC ₅₀ (µM)	Mean I _{max}	Mean CI _{max} (µM)	Potential sensitizer?
GF-3969	368.24	1771.12	6.39	2000	Yes
Cinnamic aldehyde	8.76	>64	NA	NA	Yes

NA = Not applicable

EC1.5 = Concentration for gene induction above the threshold (1.5-fold) as compared to the DMSO solvent controls.

IC₅₀ = Concentration leading to 50% relative viability compared to the DMSO solvent controls

I_{max} = Maximal induction, luciferase average maximal fold induction as compared to the DMSO solvent controls

CI_{max} = Concentration where average maximal fold induction occurred

CONCLUSION

According to the current prediction model, the test substance, GF-3969, was predicted to be a sensitizer.

A 2.12.1 Study 2, MNT00515

Comments of zRMS:	Study Clare, K. (2018); address aneugenicity regarding rimsulfuron metabolite (IN-E9260). This is in line with <u>EFSA Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology</u> . EFSA supporting
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	<p>publication 2016:EN-1074, 24 pp. refer point 2.3.2 (..)EFSA commented that the genotoxic potential of a metabolite should be clearly excluded, in particular when carcinogenicity and reproductive toxicity studies on the metabolite are not available(..) Thus study has been reviewed and accepted by the ZRMS and considered as reliable for assessing genotoxicity potential of rimsulfuron ground water metabolite IN-E9260. (see also dRR B10)</p>
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Reference:	KCP 7.1.7/01
Report:	Clare, K. (2018); Rimsulfuron metabolite (IN-E9260) (CAS # 117671-01-9): Genetic toxicity evaluation using a micronucleus test in TK6 human lymphoblastoid cells
DuPont Report No.:	MNT00515
Testing Facility Report No.:	MNT00515
Guidelines	OECD 487
Deviations:	None
GLP:	Yes
Acceptability:	Yes

STUDY SUMMARY

Rimsulfuron metabolite (IN-E9260) (CAS # 117671-01-9) was tested for its potential to induce micronucleus formation in TK6 human lymphoblastoid cells using the *in vitro* micronucleus test method with manual scoring of microscope slides.

Rimsulfuron metabolite (IN-E9260) was applied to the test system under three treatment Schedules. Treatment for 3 hours in both the absence and presence of an *in vitro* activation system based on S9 fraction obtained from Aroclor 1254-induced rat liver (S9 mix), and a continuous treatment in the absence of S9 mix. Cells were harvested for micronucleus analysis when cells in the solvent control treated cultures achieved between 1.5 and 2.0 normal cell cycles in the relevant exposure condition. In all treatments, the solvent used was dimethyl sulphoxide (DMSO).

In this study, TK6 human lymphoblastoid cells were not cytokinesis blocked and cell division was determined using a measure of relative population doubling (RPD). Duplicate cultures were used for each test concentration and micronuclei were scored in a minimum of 1000 mononuclear cells per culture, using two cultures per treatment concentration (2000 mononuclear cells in total), where possible.

The final dose ranges from which micronuclei were analysed for valid tests, were 888.9 to 2000 µg/mL for 3h with and without metabolic activation and 592.6 to 2000 µg/mL for continuous treatment (24h) without metabolic activation.

In all 3 treatment schedules cytotoxicity of less than 50% was observed (at precipitating concentrations).

Upon addition of test item to the culture medium in the initial test precipitate was observed at concentrations of 1333 µg/mL and above in all treatment schedules. At the end of the treatment period, precipitate was observed at a concentration of 2000 µg/mL in all treatment schedules.

In valid tests, none of the treatment schedules resulted in significant increases in micronucleus formation.

All criteria for a valid study were met as described in the protocol and are compliant with OECD 487 (2016). Based on the results generated under the conditions of this study, it is concluded that Rimsulfuron metabolite (IN-E9260) is negative for the induction of micronucleus formation both in the absence and presence of S9 metabolic activation in the *in vitro* mammalian cell micronucleus assay using the TK6 human lymphoblastoid suspension cell line (TK6).

MATERIALS AND METHODS

Dates of work

Start: 17 October 2018 End: 09 November 2018

Test Item(s)

Test item (Common name):	Rimsulfuron Metabolite (IN-E9260)
Purity:	99.73%
Description (physical state):	White Powder
Lot/batch no.:	EPP/LEE 425.1
Compound stability:	Expiry date according to CoA is 23-January-2019

Negative (Vehicle) and Positive Control

The vehicle used to deliver test substance to the test system was DMSO.

The following positive controls were run concurrently with each test:

Positive control	Treatment schedule	Genotoxic action	Solvent	Test concentration	Metabolic activation (\pm S9)
Cyclophosphamide (CP)	3h	Clastogen	DMSO	4 μ g/mL	+
Mitomycin C	3h	Clastogen		50 ng/mL	-
Mitomycin C	Continuous	Clastogen		30 ng/mL	-
Colchicine	Continuous	Aneugen		7.5 ng/mL	-

Tester System

Cell line	TK6 human lymphoblastoid suspension cell line (TK6)	
Source	Gentronix cell bank	
Maintenance	RPMI 1640 medium containing 10% heat-inactivated horse serum (Gibco Life Technologies, UK), antibiotics and Pluronic F68, incubation at 37°C and 5 CO ₂	
Metabolic activation	S9 fraction from Aroclor 1254 treated rats (Procured from Molecular Toxicology, Inc., USA), Protein Concentration: 30 mg/mL	
S9 mix:	Component	Final concentration in culture medium*
	NADP	0.25 mM
	Glucose-6-phosphate	1.25 mM
	S9 homogenate	1% v/v

Micronucleus Assay

Based on the results of the cytotoxicity test, the doses selected for testing in the micronucleus assay were as follows:

Treatment condition	Treatment time	Recovery time	Doses (μ g/mL)
Non-activated	3 hr	20 hr	888.9 to 2000
	24 hr	0 hr	592.6 to 2000
S9-activated	3 hr	20 hr	888.9 to 2000

Precipitation of the test substance dosing solution in the treatment medium was determined using unaided eye at the beginning and conclusion of treatment. The highest dose evaluated for micronuclei was selected based on the following:

3-hour (-S9)	3-hour (+S9)	24-hour (-S9)
55 \pm 5% cytotoxicity (CBPI relative to the vehicle control)	55 \pm 5% cytotoxicity (CBPI relative to the vehicle control)	55 \pm 5% cytotoxicity (CBPI relative to the vehicle control)

Acceptance Criteria

Before assay data were evaluated, all criteria for a valid assay must have been met. The following criteria were used to determine a valid assay:

Solvent (DMSO) controls:

The frequency of mononucleate cells with micronuclei for the solvent cultures must approximate those of the acceptable ranges from the Test Facility's historical control database and/or published values.

Positive controls:

The positive control chemicals must induce a statistically significant ($p < 0.05$) increase in the frequency of micronuclei in mononucleate cells compared with the concurrent solvent controls

Evaluation Criteria

If the criteria for assay validity were met, observed responses were evaluated as follows:

Criteria for a clearly positive response:

- At least one of the test concentrations exhibited a statistically significant increase compared with the concurrent solvent control.
- The increase was dose-related in at least one experimental condition when evaluated with an appropriate trend test.
- Any of the results were outside the historical solvent control range (Poisson-based 95% control limits)

Criteria for a clearly negative response:

- None of the test concentrations exhibited a statistically significant increase compared with the concurrent solvent control.

Statistics

The number of micronuclei analysed from 2000 mononuclear cells for each selected test item dose was compared with that from the concurrent solvent control. Pair-wise statistical analysis employing a one-sided Fisher's Exact test were used to evaluate statistical significance ($p < 0.05$). A linear trend test was employed (Cochran-Armitage) in order to confirm there was no dose related increase ($p < 0.05$).

RESULTS AND DISCUSSION

Negative and Positive Controls

All positive and vehicle control values were within acceptable ranges, and all criteria for a valid assay were met.

Cytotoxicity Assay

IN-E9260 was tested in a preliminary toxicity assay, with and without metabolic activation. TK6 human lymphoblastoid suspension cell line (TK6) were exposed to IN-E9260 at dose-levels ranging from 4.567 to 2000 $\mu\text{g/mL}$ in DMSO.

Visible precipitate was observed in treatment medium at the following doses:

Treatment condition	Treatment time (h)	Visible precipitate	
		At the beginning of treatment period	At the conclusion of treatment period
S9-activated	3	$\geq 1333 \mu\text{g/mL}$	2000 $\mu\text{g/mL}$
Non-activated	24	$\geq 1333 \mu\text{g/mL}$	2000 $\mu\text{g/mL}$
	3	$\geq 1333 \mu\text{g/mL}$	2000 $\mu\text{g/mL}$

The osmolality in treatment medium was measured as follows:

Osmolality (mOsm/kg)			
Time point	DMSO	1333 µg/mL	2000 µg/mL (P)
3 hour +S9 mix	462	446	442
3 hour -S9 mix	467	431	437
Continuous -S9 mix	464	442	436

(p) = precipitating concentration

The pH in treatment medium was measured as follows:

pH			
Time point	DMSO	1333 µg/mL	2000 µg/mL (P)
3 hour +S9 mix	7.45	7.48	7.43
3 hour -S9 mix	7.47	7.49	7.57
Continuous -S9 mix	7.52	7.69	7.53

(p) = precipitating concentration

Cytotoxicity of 12.85% was observed at a concentration of 2000 µg/mL. Lower concentrations of 1333 and 888.9 µg/mL, yielded cytotoxicity levels of -6.92 and -3.48%, respectively. These three concentrations were selected for slide analysis in the S9-activated 3-hour exposure group. Cytotoxicity of 32.23% was observed at a concentration of 2000 µg/mL. Lower test concentrations of 1333 and 888.9 µg/mL, yielded cytotoxicity levels of 2.69 and -5.07%, respectively. These three concentrations were selected for slide analysis in the non-activated 3-hour exposure group; and cytotoxicity of 47.00% was observed at a concentration of 2000 µg/mL. Lower test concentrations of 1333, 888.9 and 592.6 µg/mL, yielded cytotoxicity levels of 34.72, 26.96 and 17.30%, respectively. These four concentrations were selected for slide analysis in the non-activated 24-hour exposure group.

Micronucleus Assay

Cytotoxicity (CBPI relative to the vehicle control) was observed as follows:

Treatment	Concentration µg/mL (unless specified)	Micronuclei per culture			%RPD/ % cytotoxicity		
		S9+	S9-		S9+	S9-	
		3 h	3 h	24 h	3 h	3 h	24 h
DMSO	—	28/2000	18/2000	23/2000	100/N/A	100/N/A	100/N/A
IN-E9260	4.567	ND	ND	ND	ND/ND	ND/ND	ND/ND
	6.851	ND	ND	ND	ND/ND	ND/ND	ND/ND
	10.28	ND	ND	ND	ND/ND	ND/ND	ND/ND
	15.41	ND	ND	ND	ND/ND	ND/ND	ND/ND
	23.12	ND	ND	ND	ND/ND	ND/ND	ND/ND
	34.68	ND	ND	ND	ND/ND	ND/ND	ND/ND
	52.02	ND	ND	ND	ND/ND	ND/ND	ND/ND
	78.04	ND	ND	ND	ND/ND	ND/ND	ND/ND
	117.1	ND	ND	ND	ND/ND	ND/ND	ND/ND
	175.6	ND	ND	ND	ND/ND	ND/ND	ND/ND
	263.4	ND	ND	ND	ND/ND	ND/ND	88.92/11.08
	395.1	ND	ND	ND	103.54/-3.54	106.98/-6.98	87.95/12.05
	592.6	ND	ND	28/2000	111.96/-11.96	107.50/-7.50	82.70/17.30
888.9	24/2000	21/2000	30/2000	103.48/-3.48	105.07/-5.07	73.04/26.96	
1333	20/2000	20/2000	29/2000	106.92/-6.92	97.31/2.69	65.28/34.72	
2000	18/2000	26/2000	28/2000	87.15/12.85	66.77/32.23	53.00/47.00	
MMC ^a	30 ng/mL	--	--	118/2000	--	--	64.42/35.58
	50 ng/mL	--	79/2000	--	--	83.81/16.19	--
CP ^b	4	90/2000	--	--	13.97/ 86.03	--	--
COL ^c	7.5 ng/mL	--	--	141/2000	--	--	71.84/28.16

- a Mitomycin C
b Cyclophosphamide c
c Colchicine
NE: Not evaluated
NA: Not applicable

No statistically significant increase in micronuclei formation was observed at any test item concentration analysed, all micronucleus values fell within the 95% Poisson confidence limits of the solvent control historical range and there was no concentration related increase when evaluated with a Cochran-Armitage trend test. The criteria for a clearly negative result were met.

CONCLUSION

All criteria for a valid study were met as described in the protocol and are compliant with OECD 487 (2016). Based on the results generated under the conditions of this study, it is concluded that Rimsulfuron metabolite (IN-E9260) is negative for the induction of micronucleus formation both in the absence and presence of S9 metabolic activation in the *in vitro* mammalian cell micronucleus assay using the TK6 human lymphoblastoid suspension cell line (TK6).

Test item	Test	Test object	Concentrations (µg/mL)	Result
Rimsulfuron Metabolite (IN-E9260)	<i>In vitro</i> micronucleus	TK6 human lymphoblastoid suspension cell line (TK6)	4.567, 6.851, 10.28, 15.41, 23.12, 34.68, 52.02, 78.04, 117.1, 175.6, 263.4, 395.1, 592.6, 888.9, 1333, and 2000	Negative (±S9)

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for Rimsulfuron

Table A 15: Input parameters considered for the estimation of operator exposure: Rimsulfuron

Substance	Rimsulfuron	Formulation = Wettable granules, soluble granules	Application rate=0.02 kg a.s. /ha	Spray dilution = 0.2 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <math><5 \times 10^{-3}</math>Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 10	Dermal for in use dilution = 50	Oral = 70	Inhalation = 100	
RVNAS	0.07 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 16: EFSA calculator estimations of operator exposure: Rimsulfuron

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0069	% of RVNAS	9.79%	
	Acute systemic exposure mg/kg bw/day	0.0645	% 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	0.0042	% of RVNAS	5.93%	
	Acute systemic exposure mg/kg bw/day	0.0343	% of RVAAS		

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0069	% of RVNAS	9.79%	
	Acute systemic exposure mg/kg bw/day	0.0645	% 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	0.0011	% of RVNAS	1.59%	
	Acute systemic exposure mg/kg bw/day	0.0326	% of RVAAS		

A 3.1.2 Calculations for Thifensulfuron methyl

Table A 17: Input parameters considered for the estimation of operator exposure: Thifensulfuron methyl

Substance	Thifensulfuron Methyl	Formulation = Wetttable granules, soluble granules	Application rate-0.0125 kg a.s. /ha	Spray dilution = 0.125 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <math><5*10^{-3}</math>Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 10	Dermal for in use dilution = 50	Oral = 100	Inhalation = 100	
RVNAS	0.07 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 18: EFSA calculator estimations of operator exposure: Thifensulfuron methyl

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0048	% of RVNAS	6.84%	
	Acute systemic exposure mg/kg bw/day	0.0508	% 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	0.0029	% of RVNAS	4.15%	
	Acute systemic exposure mg/kg bw/day	0.0253	% of RVAAS		

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0048	% of RVNAS	6.84%	
	Acute systemic exposure mg/kg bw/day	0.0508	% 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	0.0009	% of RVNAS	1.30%	
	Acute systemic exposure mg/kg bw/day	0.0309	% of RVAAS		

A 3.1.3 Calculations for Isoxadifen-ethyl

Table A 19: Input parameters considered for the estimation of operator exposure: Isoxadifen-ethyl

Substance	Isoxadifen-ethyl	Formulation = Wetttable granules, soluble granules	Application rate-0.015 kg a.s./ha	Spray dilution = 0.15 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <math><5*10^{-3}</math>Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 10	Dermal for in use dilution = 50	Oral = 65	Inhalation = 100	
RVNAS	0.02 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 20: EFSA calculator estimations of operator exposure: Isoxadifen-ethyl

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0055	% of RVNAS	27.48%	
	Acute systemic exposure mg/kg bw/day	0.0556	% 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	0.0033	% of RVNAS	16.67%	
	Acute systemic exposure mg/kg bw/day	0.0284	% of RVAAS		

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0055	% of RVNAS	27.48%	
	Acute systemic exposure mg/kg bw/day	0.0556	% 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	4.91%	
	Acute systemic exposure mg/kg bw/day	0.0315	% of RVAAS		

A 3.1.4 Calculations for DPX-KG691

Input parameters considered for the estimation of operator exposure: DPX-KG691

Substance	Isodecyl alcohol ethoxylate	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.72 kg a.s./ha	Spray dilution = 1.8 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <math><5*10^{-3}</math>Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absorption	Dermal for product = 10	Dermal for in use dilution = 50	Oral = 100	Inhalation = 100	
RVNAS	0.5 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm ² per kg a.s./ha		DT50	30 days	

EFSA calculator estimations of operator exposure: DPX-KG691

Operator Model		Mixing, loading and application AOEM		
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.2755	% of RVNAS	55.10%
	Acute systemic exposure mg/kg bw/day	1.2364	% 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	0.1784	% of RVNAS	35.69%
	Acute systemic exposure mg/kg bw/day	0.7786	% of RVAAS	

Operator Model		Mixing, loading and application AOEM		
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.2755	% of RVNAS	55.10%
	Acute systemic exposure mg/kg bw/day	1.2364	% 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	0.0093	% of RVNAS	1.85%
	Acute systemic exposure mg/kg bw/day	0.0860	% of RVAAS	

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for Rimsulfuron

Table A 21: Input parameters considered for the estimation of worker exposure: Rimsulfuron

Crop type	Cereals
Indoor or outdoor	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Worker's task	Inspection, irrigation
Main body parts in contact with foliage	Hand and body
Application rate of active substance	0.02 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	10.00%
Dermal absorption of the in-use dilution	50.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.06 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 22: EFSA calculator estimations of worker exposure: Rimsulfuron

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0125	% of RVNAS	17.86%
	Working clothing mg/kg bw/day	0.0014	% of RVNAS	2.00%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.2.2 Calculations for Thifensulfuron methyl

Table A 23: Input parameters considered for the estimation of worker exposure: Thifensulfuron methyl

Crop type	Cereals
Indoor or outdoor	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Worker's task	Inspection, irrigation
Main body parts in contact with foliage	Hand and body
Application rate of active substance	0.0125 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	10.00%
Dermal absorption of the in-use dilution	50.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0375 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 24: EFSA calculator estimations of worker exposure: Thifensulfuron methyl

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0078	% of RVNAS	11.16%
	Working clothing mg/kg bw/day	0.0009	% of RVNAS	1.25%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.2.3 Calculations for Isoxadifen-ethyl (safener)

Table A 25: Input parameters considered for the estimation of worker exposure: Isoxadifen-ethyl

Crop type	Cereals
Indoor or outdoor	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Worker's task	Inspection, irrigation
Main body parts in contact with foliage	Hand and body
Application rate of active substance	0.015 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	10.00%
Dermal absorption of the in-use dilution	50.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.045 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 26: EFSA calculator estimations of worker exposure: Isoxadifen-ethyl

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0094	% of RVNAS	46.88%
	Working clothing mg/kg bw/day	0.0011	% of RVNAS	5.25%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.2.4 Calculations for Isodecyl alcohol ethoxylate (adjuvant)

Table A 27: Input parameters considered for the estimation of worker exposure: Isodecyl alcohol ethoxylate (adjuvant)

Crop type	Cereals
Indoor or outdoor	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Worker's task	Inspection, irrigation
Main body parts in contact with foliage	Hand and body
Application rate of active substance	0.72 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	10.00%
Dermal absorption of the in-use dilution	50.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	2.16 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 28: EFSA calculator estimations of worker exposure: Isodecyl alcohol ethoxylate (adjuvant)

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.4500	% of RVNAS	90.00%
	Working clothing mg/kg bw/day	0.0504	% of RVNAS	10.08%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A 3.3 Bystander and resident exposure calculations (KCP 7.2.2.1)

A 3.3.1 Calculations for Rimsulfuron

Table A 29: Input parameters considered for the estimation of resident exposure: Rimsulfuron

Croptype	Cereals
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Wettable granules, soluble granules
Buffer strip	2-3 m
Application rate of the product	0.02 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.2 g a.s./l
Dermal absorption of product	10.00%
Dermal absorption of in-use dilution	50.00%
Oral absorption	70.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.06 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa 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 30: EFSA calculator estimations of resident exposure: Rimsulfuron

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0027	% of RVNAS	3.84%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	1.53%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.23%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0017	% of RVNAS	2.41%
	All pathways (mean) mg/kg bw/day	0.0040	% of RVNAS	5.73%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0006	% of RVNAS	0.92%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.33%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.10%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0009	% of RVNAS	1.34%
	All pathways (mean) mg/kg bw/day	0.0013	% of RVNAS	1.90%

A 3.3.2 Calculations for Thifensulfuron methyl

Table A 31: Input parameters considered for the estimation of resident exposure: Thifensulfuron methyl

Croptype	Cereals
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Wettable granules, soluble granules
Buffer strip	2-3 m
Application rate of the product	0.0125 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.125 g a.s./l
Dermal absorption of product	10.00%
Dermal absorption of in-use dilution	50.00%
Oral absorption	100.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.0375 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa 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 32: EFSA calculator estimations of resident exposure: Thifensulfuron methyl

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0017	% of RVNAS	2.40%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	1.53%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.14%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	1.51%
	All pathways (mean) mg/kg bw/day	0.0029	% of RVNAS	4.16%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0004	% of RVNAS	0.57%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.33%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.06%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0006	% of RVNAS	0.84%
	All pathways (mean) mg/kg bw/day	0.0009	% of RVNAS	1.31%

A 3.3.3 Calculations for Isoxadifen-ethyl (safener)

Table A 33: Input parameters considered for the estimation of resident exposure: Isoxadifen-ethyl

Croptype	Cereals
Application method	Downward spraying
Application equipment	Vehicle-mounted
Formulation type	Wettable granules, soluble granules
Buffer strip	2-3 m
Application rate of the product	0.015 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	0.15 g a.s./l
Dermal absorption of product	10.00%
Dermal absorption of in-use dilution	50.00%
Oral absorption	65.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.045 µg a.s./cm ²
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10 ⁻³ Pa 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 34: EFSA calculator estimations of resident exposure: Isoxadifen-ethyl

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0020	% of RVNAS	10.07%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	5.35%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.61%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0013	% of RVNAS	6.33%
	All pathways (mean) mg/kg bw/day	0.0033	% of RVNAS	16.39%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	2.41%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.15%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.26%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0007	% of RVNAS	3.52%
	All pathways (mean) mg/kg bw/day	0.0011	% of RVNAS	5.29%

A 3.3.4 Calculations for Isodecyl alcohol ethoxylate (adjuvant)

Table A 35: Input parameters considered for the estimation of resident exposure: Isodecyl alcohol ethoxylate (adjuvant)

Resident exposure for Vivolt (DPX-KG691)	
Croptype	Cereals
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	0.72 kg a.s./ha
Concentration of active substance (in-use dilution for liquid applications)	1.8 g a.s./l
Dermal absorption of product	10.00%
Dermal absorption of in-use dilution	50.00%
Oral absorption	100.00%
Dislodgeable foliar residue (i_AppRate*i_DFR)	2.16 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 36: EFSA calculator estimations of resident exposure: Isodecyl alcohol ethoxylate (adjuvant)

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0242	% of RVNAS	4.83%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	0.21%
	Surface deposits (75th percentile) mg/kg bw/day	0.0058	% of RVNAS	1.17%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0608	% of RVNAS	12.15%
	All pathways (mean) mg/kg bw/day	0.0671	% of RVNAS	13.42%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0058	% of RVNAS	1.16%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.05%
	Surface deposits (75th percentile) mg/kg bw/day	0.0025	% of RVNAS	0.49%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0338	% of RVNAS	6.75%
	All pathways (mean) mg/kg bw/day	0.0317	% of RVNAS	6.34%

A 3.4 Combined exposure calculations for rimsulfuron, thifensulfuron methyl, and isoxadifen-ethyl (safener)

Please refer to Table 6.6-12 in this document for the risk assessment from combined exposure.