REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: 19202

Product name(s): **KINVARA**

Chemical active substance(s):

MCPA, 233 g/L
Fluroxypyr, 50 g/L
Clopyralid, 28 g/L

Central Zone

Zonal Rapporteur Member State: Poland

ZONAL ASSESSMENT

(Reauthorisation according to Article 43)

Applicant: XXXX

Submission date: 31/01/2024

Evaluation date: October 2024

MS Finalisation date: March 2025

Version history

When	What
31.01.2024	Resubmision art.43
October 2024	Version evaluated by zRMS PL
March 2025	Version modified by zRMS PL to take into accout cMSs and the applicant

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6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on Kinvara *

Product name and code	Kinvara
Formulation type	Microemulsion [Code: ME]
Active substance(s) (incl. content)	MCPA; 233 g/L Fluroxypyr acid; 50 g/L Clopyralid; 28 g/L
Function	Herbicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	**Austria**: Kinvara Reg No. 4168-0
	Czech Republic: Kinvara Reg No. 5310-0 Arrva Reg No. 5310-1
	Hungary: Kinvara Reg No. 6300/19632-1/2019.NEBIH Arrva Reg No. 6300/20753-2/2019.NEBIH
	Ireland: Kinvara Reg No. 05381 Brittas Reg No. 06523 Pradera Reg No. 06524.
	Northern Ireland: Kinvara Reg No. 18436 Brittas Reg No. 18587
	Poland: Kinvara Reg No. R - 231/2019 Arrva Reg No. R-58/2020
	Romania: Kinvara Reg No. 560PC of 20.11.19 Arrva Reg No. 560PC of 20.11.19.

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

Hazard class(es), categories	Acute Tox. Cat. 4 ~~Skin Irrit. Cat. 2~~ Eye Irritant Cat. 2
Hazard pictograms or Code(s) for hazard pictogram(s)	 GHS07
Signal word	Warning
Hazard statement(s)	H302: Harmful if swallowed ~~H315: Causes skin irritation~~ H319: Causes serious eye irritation
Precautionary statement(s)	P264: Wash face and hands thoroughly after handling. P270: Do not eat, drink or smoke when using this product P280: Wear protective gloves /eye protection/face protection. P301 + P330: IF SWALLOWED: Rinse mouth. P312: Call a POISON CENTER/doctor, if you feel unwell ~~P302 + P352: IF ON SKIN: Wash with plenty of water~~ P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P337+P313: If eye irritation persists: Get medical advice/attention. ~~P362+P364: Take off contaminated clothing and wash it before reuse.~~ P391: Collect spillage P501: Dispose of contents/ container to … … in accordance with local/ regional/national/international regulation
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

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

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

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

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

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

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind (incl. application technique ***	**Max. number (min. interval between applications) a) per use b) per crop/ season**	**Max. application rate L product/ha**	**Water L/ha min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
1	Cereals Wheat, Barley, Rye, Triticale, Oats (BBCH 24-39)	F	Spraying, LCTM	1 ; 1	3.0	200 - 400	-	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032				

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

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

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

Explanation for column 10 "Acceptability of exposure assessment"

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

6.2 Toxicological Information on Active Substances

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

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

	Active substance 1	**Active substance 2**	**Active substance 3**
Common Name	MCPA	Fluroxypyr-meptyl	Clopyralid
CAS-No.	94-74-6	81406-37-3	1702-17-6
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes, categories: Acute Tox. 4, H302 Skin Irrit. 2, H315 Eye Dam. 1. H318 Code for hazard pictogram: GHS05, GHS07 Signal word: Danger Hazard statements: H302, H315, H318	No classification for health hazards.	Hazard class, category: Eye Dam. 1 Code for hazard pictogram: GHS05 Signal word: Danger Hazard statement: H318 Causes serious eye damage
Additional C&L proposal	None	None	None

	Active substance 1	Active substance 2	Active substance 3
Agreed EU endpoints			
AOEL systemic	0.04 mg/kg bw/d	0.8 mg/kg bw/d [acid]	0.15 mg/kg bw/d
Reference	Review report 2008 (SANCO/4062/2001-final)	EFSA Conclusion (EFSA Journal 2011;9(3):2091)	EFSA Conclusion (EFSA Journal 2018;16(8):5389)
Conditions to take into account/critical areas of concern with regard to toxicology			
According to EFSA Conclusion for active substance	None	None	None

6.3 Toxicological Evaluation of Plant Protection Product

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

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

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, classification by calculation	Classified	Yes	Acute Tox. 4; H302	Calculation Refer to Part C
LD_{50} dermal, classification by calculation	Not classified	Yes	None	Calculation Refer to Part C
LC_{50} inhalation, classification by calculation	Not classified	Yes	None	Calculation Refer to Part C
Skin irritation, classification by calculation	Classified	Yes	None ~~Skin Irrit. 2, H315~~	Calculation Refer to Part C
Eye irritation, BCOP and rabbit (OECD 437 & 405)	Irritant	Yes	~~H319~~ Eye Irrit. 2; H319	XXXX, 2015 XXXX, 2015
Skin sensitisation, classification by calculation	Non-sensitising	Yes	None	Calculation Refer to Part C
Supplementary studies for combinations of plant protection products	No data – not required	-	-	-

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

	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 dsubstance(s) (relevant for classification	MCPA (24.6% (w/w))	H302, ~~H315,~~ H318	MSDS*	H319 Acute Tox. 4; H302 Eye Irrit. 2; H319

	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)
of prouct)	Clopyralid (3.3% (w/w))	H318	MSDS*	~~H319~~ Eye Irrit. 2; H319
Toxicological properties of non-active substance(s) (relevant for classification of product)	Alcohols, C12-15, ethoxylated (16.8% (w/w))	H302, H318	MSDS*	~~H319~~ Eye Irrit. 2; H319
	Hydrocarbons, C10 aromatics, <1% naphthalene (8.9% (w/w))	STOT SE Cat. 3 - H336 (criteria ≥ 20%) Asp. Tox. Cat. 1 - H304 (criteria ≥ 10%)	MSDS*	None
Further toxicological information	No data – not required	-	-	-

* Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

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

6.5 Dermal Absorption (KCP 7.3)

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

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

	MCPA		Fluroxypyr		Clopyralid	
	Value	Reference	Value	Reference	Value	Reference
Concentrate	19%	New study reported in Appendix 2	16%	New study reported in Appendix 2	10%	New study reported in Appendix 2
Dilution (1:133)	11%		22%		8.7%	

6.5.1 Justification for proposed values - MCPA

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

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

Test	Concentrate	Spray dilution (1:133)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	19%	11%	Kinvara	Yes	Not required	Justification accepted. Endpoint can be used for current product	XXXX, 2016

* indicates that a study was reviewed at EU level

The dermal absorption value for spray dilutions that are more dilute than measured in the study were calculated using the pro-rata approach described in the 2017 EFSA Guidance on dermal absorption.

In the study, a dermal absorption value of 11% was obtained for a spray dilution of 1:133.

6.5.2 Justification for proposed values – Fluroxypyr

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

Table 6.5-3: Summary of the results of submitted dermal absorption studies for fluroxypyr

Test	Concentrate	Spray dilution (1:133)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	16%	22%	Kinvara	Yes	Not required	Justification accepted. Endpoint can be used for current product	XXXX, 2016

* indicates that a study was reviewed at EU level

The dermal absorption value for spray dilutions that are more dilute than measured in the study were calculated using the pro-rata approach described in the 2017 EFSA Guidance on dermal absorption.

In the study, a dermal absorption value of 22% was obtained for a spray dilution of 1:133.

6.5.3 Justification for proposed values - Clopyralid

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

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

Test	Concentrate	Spray dilution (1:133)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	10%	8.7%	Kinvara	Yes	Not required	Justification accepted. Endpoint can be used for current product	XXXX, 2016

* indicates that a study was reviewed at EU level

The dermal absorption value for spray dilutions that are more dilute than measured in the study were calculated using the pro-rata approach described in the 2017 EFSA Guidance on dermal absorption.

In the study, a dermal absorption value of 8.7% was obtained for a spray dilution of 1:133.

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	Kinvara		
Formulation type	ME		
Category	Herbicide		
Active substances (incl. content)	**MCPA** 233 g/L	**Fluroxypyr** 50 g/L	**Clopyralid** 28 g/L
AOEL systemic	0.04 mg/kg bw/d	0.8 mg/kg bw/d	0.15 mg/kg bw/d
Acute AOEL systemic	-	-	0.17 mg/kg bw/d
Inhalation absorption	100%	100%	100%
Oral absorption	100%	100%	100%
Dermal absorption	Concentrate: 19% Dilution (1:133): 11% (Based on product)	Concentrate: 16% Dilution (1:133): 22% (Based on product)	Concentrate: 10% Dilution (1:133): 8.7% (Based on product)

6.6.1 Selection of critical use(s) and justification

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

Justification

Kinvara is to be applied as a single application to cereals at a maximum rate of 3 L product/ha in 200-400 L water/ha. This application rate represents the critical GAP for operators, workers, bystanders and residents.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of Kinvara according to the critical use is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (acute exposure) and Table 6.6-4 (short term exposure). Detailed calculations are in Appendix 3.

At this time, no acute AOELs have been set for MCPA and fluroxypyr. Consequently, no acute risk assessment has been provided for these active substances.

Table 6.6-2: Exposure models for intended uses

Critical use	Tractor mounted boom spray application outdoors to low crops (max. 3 L product/ha)
Model	EFSA (European Food Safety Authority), Charistou A, Coja T, Craig P, Hamey P, Martin S, Sanvido O, Chiusolo A, Colas M and Istace F, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. https://doi.org/10.2903/j.efsa.2022.7032 OPEX version: 1.0.1

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

Model data	Level of PPE	Total absorbed dose [mg/kg bw]	% of systemic AAOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/95th percentile Crop density: Normal			
Clopyralid	Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption (concentrate): 10 % Dermal absorption (in-use dilution): 8.7 %		
	M/L: Workwear App: Workwear	0.1	82.8

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

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Field crops/Outdoor/Downward spraying/Vehicle-mounted/Drift reduction: 0 %/75th percentile Crop density: Normal			
MCPA	Number of applications and application rate: 1 x 0.699 kg a.s./ha Dermal absorption (concentrate): 19 % Dermal absorption (in-use dilution): 11 %		
	M/L: Workwear + Protected hands App: Workwear	0.02	49
Fluroxypyr	Number of applications and application rate: 1 x 0.15 kg a.s./ha Dermal absorption (concentrate): 16 % Dermal absorption (in-use dilution): 22 %		
	M/L: Workwear App: Workwear	0.08	10.6
	M/L: Workwear + Protected hands App: Workwear	0.006	0.8

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
		Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption (concentrate): 10 % Dermal absorption (in-use dilution): 8.7 %	
Clopyralid	M/L: Workwear App: Workwear	0.04	23.8
	M/L: Workwear + Protected hands App: Workwear	0.002	1.3
Combined exposure			Hazard index
	M/L: Workwear + Protected hands App: Workwear		0.5

zRMS:
The acute exposure calculated with the EFSA AOEM 2022 to Clopyralid of operator wearing a work clothing (long sleeved shirt, long trousers) during M/L and App. and applying formulation Kinvara on low crops at dose of 3.0L/ha, using tractor-mounted/trailed sprayer (downward spraying), amounted to 82.8 % of respective AAOEL, thus the risk is acceptable. No AAOEL has been set for other actives substances: MCPA and Fluroxypyr.

The short-term exposure calculated with the EFSA AOEM 2022 to MCPA of operator wearing a work clothing (long sleeved shirt, long trousers) during M/L and App. and protective gloves during M/L and applying formulation Kinvara on low crops at dose of 3.0L/ha, using tractor-mounted/trailed sprayer (downward spraying), amounted to 49 % of respective AOEL thus the risk is acceptable.

The short-term exposure calculated with the EFSA AOEM 2022 to Fluroxypyr of operator wearing a work clothing (long sleeved shirt, long trousers) during M/L and App. and applying formulation Kinvara on low crops at dose of 3.0L/ha, using tractor-mounted/trailed sprayer (downward spraying), amounted to 10.6 % of respective AOEL, thus the risk is acceptable.

The short-term exposure calculated with the EFSA AOEM 2022 to Clopyralid of operator wearing a work clothing (long sleeved shirt, long trousers) during M/L and App and applying formulation Kinvara on low crops at dose of 3.0L/ha, using tractor-mounted/trailed sprayer (downward spraying), amounted to 23.8 % of respective AOEL, thus the risk is acceptable.

The hazard index for the combined short-term exposure to all three active substances of operator wearing a work clothing (long sleeved shirt, long trousers) during M/L and App. and protective gloves during M/L calculated with the EFSA AOEM 2022 is 0.5, thus the resulting combined health risk is acceptable.

Given the toxicological properties and classification of the formulation Kinvara according to Regulation 1272/2008/EC) as ~~Skin Irrit. 2, H315 and~~ Eye Irrit. 2; H319 wearing protective gloves and eye protection/face protection is recommended when handling the concentrate.

6.6.2.2 Measurement of operator exposure

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

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Table 6.6-5 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with Kinvara according to the critical use. Outcome of the estimation is presented in Table 6.6-6 (short term exposure). There is no agreed approach for the estimation of acute worker exposure. Therefore, an acute exposure estimate has not been calculated. Detailed calculations are in Appendix 3.

Table 6.6-5: Exposure models for intended uses

Critical use	Inspection of cereals (max. 1 × 3 L product/ha)
Model	EFSA (European Food Safety Authority), Charistou A, Coja T, Craig P, Hamey P, Martin S, Sanvido O, Chiusolo A, Colas M and Istace F, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. https://doi.org/10.2903/j.efsa.2022.7032 OPEX version: 1.0.1

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

Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL	Re-entry restriction [days]
		Inspection, irrigation / Outdoor Work rate: 2 hours/day Interval: NA Body weight: 60 kg TC (potential): 12500 cm²/h TC (workwear (arms, body and legs covered)): 1400 cm²/h TC (workwear (arms, body and legs covered) and gloves): 1250 cm²/h TC (gloves): NA cm²/h	
MCPA		Number of applications & application rate: 1 x 0.699 kg a.s./ha Dermal absorption: 19 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.2	415	62
Workwear	0.02	46.5	0
Workwear and gloves	0.02	41.5	0
Hands covered, no workwear			
Fluroxypyr		Number of applications & application rate: 1 x 0.15 kg a.s./ha Dermal absorption: 22 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.04	5.2	0
Workwear	0.005	0.6	0
Workwear and gloves	0.004	0.5	0
Hands covered, no workwear			
Clopyralid		Number of applications & application rate: 1 x 0.084 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days	
Potential	0.01	7	0
Workwear	0.001	0.8	0
Workwear and gloves	0.001	0.7	0
Hands covered, no workwear			
Combined		Hazard index	
potential		4.3	63
Workwear		0.5	0
Workwear and gloves		0.4	0
Hands covered, no workwear			0

zRMS:
The exposure calculated with the EFSA AOEM 2022 to MCPA, an active substance of a product Kinvara of worker not wearing PPE (gloves) but wearing a work clothing (long sleeved shirt, long trousers) and entering for **2 hours** for inspection a field of cereals treated with this product at maximal dose 3.0 L product/ha as foreseen in GAP, is below AOEL of MCPA, thus does not pose a systemic health risk.

The potential exposure calculated with the EFSA AOEM 2022 to Fluroxypyr or Clopyralid, two active substances of a product Kinvara, of worker entering for **2 hours** for inspection a field of cereals treated with this product at maximal dose 3.0 L product/ha as foreseen in GAP, is below respective AOELs, thus does not pose a systemic health risk.

The hazard index for the combined exposure to all three active substances of Kinvara of worker wearing a work clothing (long sleeved shirt, long trousers) and entering for **2 hours** for inspection a field of cereals treated with this product at maximal dose 3.0 L product/ha as foreseen in GAP calculated with the EFSA AOEM 2022 is 0.5, thus the resulting combined health risk is acceptable.

Thus, it is concluded that the application of a product Kinavara does not pose an unacceptable risk to the health of worker due to its intended use within good agricultural practice providing that the worker is wearing a work clothing (long sleeved shirt, long trousers) during 2hrs inspection.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not required

6.6.3.3 Measurement of worker exposure

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

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

The acute exposure assessment for bystanders covers the exposure that a resident could reasonably be expected to incur in a single day. Therefore, there is no need for a separate acute risk assessment for residents.

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

Table 6.6-7 shows the exposure model used for estimation of resident and bystander exposure to MCPA, fluroxypyr and clopyralid. The outcome of the estimation is presented in Table 6.6-8 (acute bystander exposure) and Table 6.6-9 (short term resident exposure). Detailed calculations are in Appendix 3.

At this time, no acute AOELs have been set for MCPA and fluroxypyr. Consequently, no bystander (acute) risk assessment has been provided for these active substances.

Table 6.6-7: Exposure models for intended uses

Critical use	Tractor mounted boom spray application outdoors to low crops (max. 1 × 3 L product/ha)
Model	EFSA (European Food Safety Authority), Charistou A, Coja T, Craig P, Hamey P, Martin S, Sanvido O, Chiusolo A, Colas M and Istace F, 2022. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032, 134 pp. https://doi.org/10.2903/j.efsa.2022.7032 OPEX version: 1.0.1

Table 6.6-8: Estimated bystander exposure (acute exposure)

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AAOEL
			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 200 l
Clopyralid			Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.002	1.3
	Vapour (95th perc.)	0.0008	0.5
	Deposits (95th perc.)	0.0005	0.3
	Re-entry (95th perc.)	0.001	0.8
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0006	0.4
	Vapour (95th perc.)	0.0003	0.2
	Deposits (95th perc.)	0.0002	0.1
	Re-entry (95th perc.)	0.0008	0.5

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

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 200 l
MCPA			Number of applications and application rate: 1 x 0.699 kg a.s./ha Dermal absorption: 19 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	26.1
	Vapour (75th perc.)	0.0008	2
	Deposits (75th perc.)	0.003	6.3
	Re-entry (75th perc.)	0.02	56
	Sum (mean)	0.03	65.5
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.002	6.2
	Vapour (75th perc.)	0.0003	0.7
	Deposits (75th perc.)	0.0009	2.3
	Re-entry (75th perc.)	0.01	31.1
	Sum (mean)	0.01	30.1
Fluroxypyr			Number of applications and application rate: 1 x 0.15 kg a.s./ha Dermal absorption: 22 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.004	0.6
	Vapour (75th perc.)	0.0008	0.1
	Deposits (75th perc.)	0.0006	0.08
	Re-entry (75th perc.)	0.006	0.7
	Sum (mean)	0.008	1
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	0.1
	Vapour (75th perc.)	0.0003	0.03

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
	Deposits (75th perc.)	0.0002	0.03
	Re-entry (75th perc.)	0.003	0.4
	Sum (mean)	0.003	0.4
Clopyralid	Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days		
Resident child Body weight: 10 kg	Drift (75th perc.)	0.001	0.7
	Vapour (75th perc.)	0.0008	0.5
	Deposits (75th perc.)	0.0002	0.1
	Re-entry (75th perc.)	0.001	0.9
	Sum (mean)	0.003	1.7
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0002	0.2
	Vapour (75th perc.)	0.0003	0.2
	Deposits (75th perc.)	6e-05	0.04
	Re-entry (75th perc.)	0.0008	0.5
	Sum (mean)	0.001	0.7
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		0.3
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.06
	Re-entry (75th perc.)		0.6
	Sum (mean)		0.7
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.06
	Vapour (75th perc.)		0.009
	Deposits (75th perc.)		0.02
	Re-entry (75th perc.)		0.3
	Sum (mean)		0.3

zRMS:
The acute exposure of child and adult bystander to Clopyralid, an active substance of a product Kinvara applied on cereals in line with GAP at dose of 3.0 L/ha calculated with the EFSA AOEM 2022 demonstrates that such a exposure is well below AAOEL, therefore the application of product Kinvara does not pose an unacceptable risk to the health of bystanders for its intended use within good agricultural practice. No bystander acute exposure estimation for to MCPA and Fluroxypyr, two other active substances of a product Kinvara is required since no acute acceptable operator exposure values (AAOEL) has be set for any of this active substances.

The short-term exposure of child and adult residents to MCPA, Fluroxypyr and Clopyralid, three active substance of a product Kinvara applied on cereals in line with GAP at dose of 3.0 L/ha calculated with the EFSA AOEM 2022 demonstrates that such a exposure to each of these substances is below respective AOELs, therefore the application of product Kinvara does not pose an unacceptable risk to the health of residents for its intended use within good agricultural practice

The hazard index for the combined short-term exposure of residents to all three active substances (MCPA, Fluroxypyr and Clopyralid) of Kinvara applied on cereals in line with GAP at dose of 3.0 L/ha calculated with the EFSA AOEM 2022 is 0.7 for the child residents and 0.3 for adults residents , thus the resulting combined health risk is acceptable.

Summing up an application of a product Kinvara on cereals in line with GAP at dose of 3.0 L/ha using tractor-mounted/trailed boom sprayer does not pose an unacceptable health risk for residents and bystanders.

6.6.4.2 Measurement of resident and/or bystander exposure

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

6.6.5 Combined exposure

The product is a mixture of three active substances.

6.6.5.1 Exposure assessment of MCPA, Fluroxypyr and Clopyralid in Kinvara

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

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from Table 6.6-3 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Cumulative exposure to MCPA, fluroxypyr and clopyralid is calculated for operators, workers, and residents and is presented in Table 6.6-4, Table 6.6-6, and Table 6.6-9, respectively.

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

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 7.1.5	XXXX	2015	Arrva: The Bovine Corneal Opacity and Permeability (BCOP) Assay Doc No: 41502278 XXXX GLP Unpublished	N	XXXX
KCP 7.1.5	XXXX	2015	Arrva: acute Eye Irritation in the Rabbit Doc No: 41502279 XXXX GLP Unpublished	Y	XXXX
KCP 7.3	XXXX	2016	Kinvara: In Vitro Dermal Absorption Using Human Skin Doc. No. XY29FQ XXXX GLP Unpublished	N	XXXX

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

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

The following tables are to be completed by MS

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	Verte-brate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	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	Verte-brate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Not required.

Comments of zRMS:	Not required. See part C

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Kinvara warrant classification Acute Tox. 4; H302. See part C for justification.

No study required. Acute oral toxicity is estimated using the calculation method described in Globally Harmonised System CLP Regulation 1272/2008.

The content of the active substances and the co-formulants of Kinvara is considered strictly confidential and are presented in Part C. As per Table 3.1.1 (Annex I of CLP) the formulation will not be classified for oral toxicity.

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

Comments of zRMS:	Kinvara does not warrant classification for dermal toxicity. See part C for justification.

No study required. Acute dermal toxicity is estimated using the calculation method described in Globally Harmonised System CLP Regulation 1272/2008.

The content of the active substances and the co-formulants of Kinvara is considered strictly confidential and are presented in Part C. As per Table 3.1.1 (Annex I of CLP) the formulation will be not be classified for acute dermal toxicity.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Kinvara does not warrant classification for inhalation toxicity. See part C for justification

No study required. Acute inhalation toxicity is estimated using the calculation method described in Globally Harmonised System and CLP Regulation (EC) No. 1272/2008.

No co-formulants within Kinvara are classified for acute inhalation toxicity in accordance with Regulation (EC) No 1272/2008 therefore the formulation is not classified for acute inhalation toxicity according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Kinvara does not warrant classification Skin Irrit. 2; H315. See part C for justification

No study required. Skin irritation is estimated using the calculation method described in Globally Harmonised System CLP Regulation 1272/2008.

The content of the active substances and the co-formulants of Kinvara is considered strictly confidential and are presented in Part C. The formulation is not classified as causing skin corrosion/irritation according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The study Bovine Corneal Opacity and Permeability (BCOP) Assay **(KCP 7.1.5-01)** performed according to OECD TG 437 and in GLP conditions is acceptable. *In Vitro* Irritancy Score (IVIS) for tested formulation was 44.4, thus according to decision criteria no stand-alone prediction on eye irritancy can be made and *in vivo* assay is needed. It is noted that IVIS was below 55 which is a lower limit for substances which are capable according to OECD TG to cause serious eye damage The Arrva acute Eye Irritation in the Rabbit study (**KCP 7.1.5-02**) performed according to OECD TG 405 and in GLP conditions is acceptable. In 3 out of 3 tested animals the mean scores following grading at 24, 48 and 72 hours after instillation of the test material the conjunctival redness was 2; and in 2 out of 3 tested rabbits the conjunctival oedema (chemosis) was 2. These effects were fully reversed within an observation period of 14 days, therefore the criteria given in Table 3.3.2. of Regulation 1272/2008 for eye irritation category 2 are met. The scores for corneal opacity and iritis did not meet classification criteria for category 2 because corneal opacity was equal 1 in one rabbit, and iritis was below 1 in all three rabbits. Based on results of the acceptable *in vivo* study Kinvara (Arrva) warrants classification as Eye Irrit. 2; H319: Causes serious eye irritation.

A 2.6.1 Study 1

Reference	KCP 7.1.5-01
Report	Arrva: The Bovine Corneal Opacity and Permeability (BCOP) Assay, XXXX, 2015, document No. 41502278
Guideline(s)	Yes: OECD Guideline for the Testing of Chemicals No. 437 (updated 26 July 2013) “Bovine Corenal Opacity and Permeability Assay”. Method B.47 of Commission Regulation (EC) No. 440/2008
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	N/A

Materials and methods
Test System: Eyes from adult cattle (typically 12 to 60 months old) were obtained from a local abattoir as a by-product from freshly slaughtered animals. The eyes were excised by an abattoir employee after slaughter and were placed in Hanks’ Balanced Salt Solution (HBSS) supplemented with antibiotics (penicillin at 100 IU/mL and streptomycin at 100 µg/mL). They were transported to the test facility over ice packs on the same day of slaughter. The corneas were prepared immediately on arrival.

Test Item Formulation and Experimental Preparation: For the purpose of this study the test item was used as supplied.

Preparation of Negative and Positive Control Items: The negative control item, 0.9% w/v sodium chloride solution, was used as supplied. The positive control item, Ethanol, was used as supplied.

Preparation of Corneas: All eyes were macroscopically examined before and after dissection. Only corneas free of damage were used. The cornea from each selected eye was removed leaving a 2 to 3 mm rim of sclera to facilitate handling. The iris and lens were peeled away from the cornea. The isolated corneas were immersed in a dish containing HBSS until they were mounted in Bovine Corneal Opacity and Permeability (BCOP) holders. The anterior and posterior chambers of each BCOP holder were filled with complete Eagle's Minimum Essential Medium (EMEM) without phenol red and plugged. The holders were incubated at 32 ± 1 ºC for 60 minutes. At the end of the incubation period each cornea was examined for defects. Only corneas free of damage were used.

Selection of Corneas and Opacity Reading: The medium from both chambers of each holder was replaced with fresh complete EMEM. A pre-treatment opacity reading was taken for each cornea using a calibrated opacitometer (Appendix 1). The average opacity for all corneas was calculated. Three corneas with opacity values close to the median value of all corneas were allocated to the negative control. Three corneas were also allocated to the test item and three corneas to the positive control item.

Treatment of Corneas: The EMEM was removed from the anterior chamber of the BCOP holder and 0.75 mL of the test item or control items were applied to the appropriate corneas. The holders were gently tilted back and forth to ensure a uniform application of the item over the entire cornea. Each holder was incubated, anterior chamber uppermost, at 32 ± 1 ºC for 10 minutes. At the end of the exposure period the test item and control items were removed from the anterior chamber and the cornea was rinsed three times with fresh complete EMEM containing phenol red before a final rinse with complete EMEM without phenol red. The anterior chamber was refilled with fresh complete EMEM without phenol red. A post-treatment opacity reading was taken and each cornea was visually observed. The holders were incubated, anterior chamber facing forward, at 32 ± 1 ºC for 120 minutes. After incubation the holders were removed from the incubator, the medium from both chambers was replaced with fresh complete EMEM and a final opacity reading was taken. Each cornea was visually observed.

Application of Sodium Fluorescein: Following the final opacity measurement the permeability of the corneas to sodium fluorescein was evaluated. The medium from the anterior chamber was removed and replaced with 1 mL of sodium fluorescein solution (4 mg/mL). The dosing holes were plugged and the holders incubated, anterior chamber uppermost, at 32 ± 1 ºC for 90 minutes.

Permeability Determinations: After incubation the medium in the posterior chamber of each holder was decanted and retained.360 µL of medium representing each cornea was applied to a designated well on a 96-well plate and the optical density at 492 nm (OD492) was measured using the Anthos 2001 microplate reader.

Results and discussions

Corneal Epithelium Condition: The corneas treated with the test item or positive control item were cloudy post treatment and post incubation. The corneas treated with the negative control item were clear post treatment and post incubation.

In Vitro Irritancy Score: The *In Vitro* irritancy scores are summarized as follows:

Test Item	44.4
Negative Control	0.7
Positive Control	43.0

The positive control *In Vitro* Irritancy Score was within the range of 29.6 to 52.0. The positive control acceptance criterion was therefore satisfied. The negative control gave opacity of ≤ 2.9 and permeability

≤ 0.103. The negative control acceptance criteria were therefore satisfied.

Conclusion
No prediction of eye irritation can be made, hence the need for an acute eye irritation study in the rabbit via OECD 405.

A 2.6.2 Study 2

Reference	KCP 7.1.5- 02
Report	Arrva: acute Eye Irritation in the Rabbit, XXXX, 2015, document No. 41502279
Guidelines	Yes: OECD Guideline for the Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 02 October 2012) Method B5 Acute Toxicity (Eye Irritation) of Commission Regulation (EC) No. 440/2008
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	Kinvara (15-5845)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	No
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Individual Scores and Individual Total Scores for Ocular Irritation

Table 1 Individual Scores and Individual Total Scores for Ocular Irritation

Rabbit Number and Sex	75239 Male						75252 Male						75245 Male					
	IPR = 0						IPR = 0						IPR = 0					
Time After Treatment	1 Hr	24 Hr	48 Hr	72 Hr	7 Dys	14 Dys	1 Hr	24 Hr	48 Hr	72 Hr	7 Dys	14 Dys	1 Hr	24 Hr	48 Hr	72 Hr	7 Dys	14 Dys
CORNEA																		
E = Degree of Opacity	0	0	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0
F = Area of Cornea Involved	0	0	0	1	0	0	0	1	1	0	0	0	0	1	1	1	0	0
Score (E x F) x 5	0	0	0	5	0	0	0	5	5	0	0	0	0	5	5	5	0	0
IRIS																		
D	0	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0
Score (D x 5)	0	5	5	0	0	0	5	5	5	0	0	0	5	5	5	0	0	0
CONJUNCTIVAE																		
A = Redness	2	2	2	2	1	0	2	2	2	2	1	0	2	2	2	2	1	0
B = Chemosis	2	2	2	1	1	0	2	2	2	2	1	0	2	2	2	2	1	0
C = Discharge	2	1	1	1	0	0	2	2	2	1	0	0	2	2	3	2	0	0
Score (A + B + C) x 2	12	10	10	8	4	0	12	12	12	10	4	0	12	12	14	12	4	0
Total Score	12	15	15	13	4	0	17	22	22	10	4	0	17	22	24	17	4	0

IPR = Initial pain reaction
Hr = Hour(s)
Dy = Days

Mean scores following grading at 24, 48 and 72 hours after installation of the test material:

Animal 75239
- corneal opacity: 0.33
- iritis : 0.66
- conjunctival redness: 2
- conjunctival oedema (chemosis): 1.66

Animal 75252
- corneal opacity: 0.66
- iritis : 0.66
- conjunctival redness: 2
- conjunctival oedema (chemosis): 2

Animal 75245
- corneal opacity: 1
- iritis : 0.66
- conjunctival redness: 2
- conjunctival oedema (chemosis): 2

Clinical signs:	Ocular Reactions Diffuse corneal opacity was noted in two treated eyes at the 24 and 48-Hour observations. Diffuse corneal opacity persisted in one treated eye and developed in another treated eye at the 72-Hour observation. Iridial inflammation was noted in two treated eyes 1 hour after treatment and in all treated eyes at the 24 and 48-Hour observations. Moderate conjunctival irritation was noted in all treated eyes 1 hour after treatment and at the 24, 48 and 72-Hour observations with minimal conjunctival irritation noted at the 7-Day observation. All treated eyes appeared normal at the 14-Day observation. Body Weight No body weight gain was noted in one animal and two animals showed expected gain in body weight during the study.

Conclusion

Under the experimental conditions, Kinvara is an eye irritant. The test item produced a maximum group mean score of 20.3 and was classified as a moderate irritant (Class 5 on a 1 to 8 scale) to the rabbit eye

according to a modified Kay and Calandra classification system. Thus, classification is required according to Regulation (EC) No. 1272/2008. The test item was classified as Category 2A (irritating to eyes) according to the Globally Harmonized System of Classification and Labelling of Chemicals. The test item was also classified as Irritating to eyes (Category 2) according to Regulation (EC) No. 1272/2008, relating to the Classification, Labelling and Packaging of Substances and Mixtures. It is reasonable to assume that the Signal Word "Warning" and the Hazard Statement "H319: Causes serious eye irritation" are therefore required.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Kinvara does not warrant classification as Skin Sens. 1; H317. See part C for justification

No study required. Skin sensitisation is estimated using the method described in Globally Harmonised System CLP Regulation 1272/2008.

No co-formulants within Kinvara are classified for skin sensitisation in accordance with Regulation (EC) No 1272/2008 therefore the formulation is not classified for skin sensitisation according to Regulation (EC) No. 1272/2008.

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

Not required

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

A 2.10.1 Study 1 – MCPA, fluroxypyr and clopyralid in Kinvara

Comparative dermal absorption, in vitro using rat and human skin

Comments of zRMS:	The study performed according to internationally recognized OECD guidelines and in GLP conditions is acceptable. The final dermal absorption rates were derived according to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873).

	The dermal penetration estimates for MCPA to be used for risk assessment were set to be 19 % for formulation concentrate and 11 % for spray dilution. The dermal penetration estimates for fluroxypyr-meptyl to be used for risk assessment were set to be 16 % for formulation concentrate and 22 % for spray dilution. The dermal penetration estimates for clopyralid to be used for risk assessment were set to be 10% for formulation concentrate and 8.7% for spray dilution.

Reference	KCP 7.3
Report	Kinvara: *In Vitro* Dermal Absorption Using Human Skin, XXXX, 2016, document No. XY29FQ
Guideline(s)	Yes: OECD Guideline for the Testing of Chemicals No. 428 Guidance on Dermal Absorption, EFSA Journal 2017; 15(6):4873
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Summary

The rate and extent of absorption of clopyralid, fluroxypyr-meptyl and MCPA were investigated following dermal application to excised human skin at two dose concentrations for each active ingredient. The test formulation was applied as the commercially available microemulsion formulation (Kinvara) at a nominal level of 27.9 g a.s./L (clopyralid), 73.7 g a.s./L (fluroxypyr-meptyl) or 233.2 g a.s./L (MCPA) (high dose) and at a lower level corresponding to one in-use rate of the product nominally 0.210 g a.s./L (clopyralid), 0.554 g a.s./L (fluroxypyr-meptyl) or 1.753 g a.s./L (MCPA) (low dose).

Twelve static diffusion cells were prepared for each skin type at each dose level.

Dermatomed membranes (200 – 400 µm thickness were maintained in the cells at approximately 32 °C. The integrity of the membranes was first tested using tritiated water (^3H_2O). After removal of the residual ^3H_2O, the test formulation was applied to the unoccluded skin samples as a solution at 9.5 µL/cell (10 µL/cm^2).

The skin samples were exposed to the test material for 6 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid was collected at 0, 2, 4, 6, 12, and 24 hours after dosing. The solubility of clopyralid, fluroxypyr-meptyl and MCPA in the receptor fluid was demonstrated to be sufficient for the study and was not rate limiting to the absorption process. At the end of the study, the skin samples were tape stripped to remove residual surface dose and the stratum corneum.

Materials and methods

Twelve static diffusion cells were prepared for each skin type at each dose level. Dermatomed membranes (200 - 400 µm thickness) were maintained in the cells at approximately 32 °C. The integrity of the membranes was first tested using tritiated water (^3H_2O). After removal of the residual ^3H_2O, the test formulation was applied to the unoccluded skin samples as a solution at 9.5 µL per cell (10 µL/cm^2).

The skin samples were obtained from human donors following surgery and were supplied by the Tissue Solutions. They were stored at <-15 °C.

The specification associated with each skin sample was as follows:

Skin number	Sex	Anatomical region	Age	Receipt at Envigo
H1	Female	Abdominal	35	16 Nov 2015
H2	Female	Abdominal	48	1 Mar 2016
H3	Female	Abdominal	32	1 Mar 2016
H4	Female	Thigh	35	21 Jan 2016
H5	Female	Thigh	52	21 Jan 2016

The skin samples were exposed to the test material for 6 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid was collected at 0, 2, 4, 6, 12 and 24 hours after dosing. The solubility of clopyralid, fluroxypyr-meptyl and MCPA in the receptor fluid was demonstrated to be sufficient for the study and was not rate limiting to the absorption process. At the end of the experimental phase (24 hours after application) the skin membranes were tape-stripped using 3M Scotch 'Magic' tape. The initial tape strips (1 - 2) were collected into a glass vial separately and represented residual surface (non-absorbed) dose. Subsequent tape strips containing the stratum corneum were pooled as one batch and collected into sample pots. The remaining skin was retained separately. The diffusion cell components were also retained and analysed for mass balance purposes.

Measurement of the amounts of clopyralid, fluroxypyr meptyl and MCPA in the test samples was performed using validated analytical methodology. In outline, clopyralid, fluroxypyr meptyl and MCPA were extracted from diffusion cell components, skin, tape-strips and swab samples with; receptor fluid samples were diluted with water:dichloromethane (1:1), (clopyralid), water : methanol : acetic acid (75:25:1 v/v/v) (fluroxypyr-meptyl, MCPA). The receptor cell chamber components were soaked in 50 mL methanol and sonicated for 30 minutes. The same extraction procedure was repeated for the donor cells. The quantification of clopyralid, fluroxypyr meptyl and MCPA was performed using liquid chromatography with mass spectrometric detection (LC-MS).

Results and discussions

Absorption was measured for MCPA, fluroxypyr-meptyl and clopyralid.

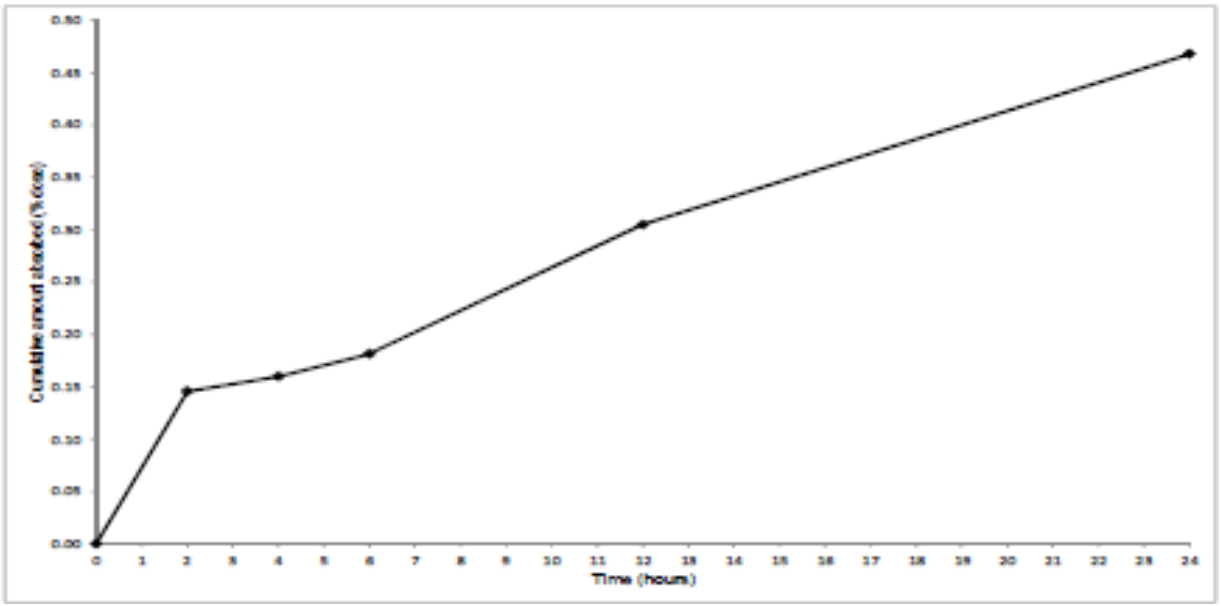
Assessment of dermal absorption of clopyralid - High level dose (27.9 g a.s./L)

Data were reported for 12 cells (dermatomed skin from 5 subjects).

Table A 2: Distribution of clopyralid (microemulsion formulation) detected following a single application at a nominal concentration of 279 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Dose on tape (s.corneum) (%)	Total absorbable (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	1	0.1	<0.1	nd	<LOQ	0.1	97.6	nd	0.1	97.7	97.8
H1	2	0.2	<0.1	nd	<LOQ	0.2	125.9	nd	0.1	126.0	126.2
H1	3	8.3	12.0	0.2	6.1	26.6	36.1	8.4	13.1	57.6	84.2
H2	4	1.8	0.3	nd	0.5	2.6	128.6	<LOQ	<0.1	128.6	131.2
H2	5	0.2	0.1	<0.1	3.3	3.6	80.4	7.7	2.6	90.7	94.3
H2	6	0.1	1.0	nd	3.0	4.1	82.0	4.0	0.9	86.9	91.0
H3	7	0.7	2.0	<0.1	2.2	4.9	55.7	15.7	16.0	87.4	92.3
H3	8	3.5	4.8	1.9	ns	10.2	43.9	0.8	0.4	45.1	55.3
H4	9	0.6	1.4	<0.1	0.5	2.5	90.6	1.3	0.8	92.7	95.2
H4	10	0.1	1.0	nd	1.6	2.7	86.7	0.9	0.8	88.4	91.1
H5	11	0.7	1.4	0.1	1.5	3.7	92.5	1.8	1.0	95.3	99.0
H5	12	1.1	1.1	0.1	1.7	4.0	103.1	2.9	1.2	107.2	111.2
	Mean	1.5	2.1	0.2	1.7	5.4	85.3	3.6	3.1	92.0	97.4
	sd	2.4	3.4	0.5	1.8	7.1	28.8	4.8	5.4	23.8	19.6
	%cv	160.0	161.9	250.0	105.9	131.5	33.8	133.3	174.2	25.9	20.1

Figure 1: Amount of clopyralid absorbed following a single application of Kinvara microemulsion at a nominal 279 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose

According to EFSA Guidance on dermal absorption (2017), since less than 75% of the absorption occurs within half the duration of the study:

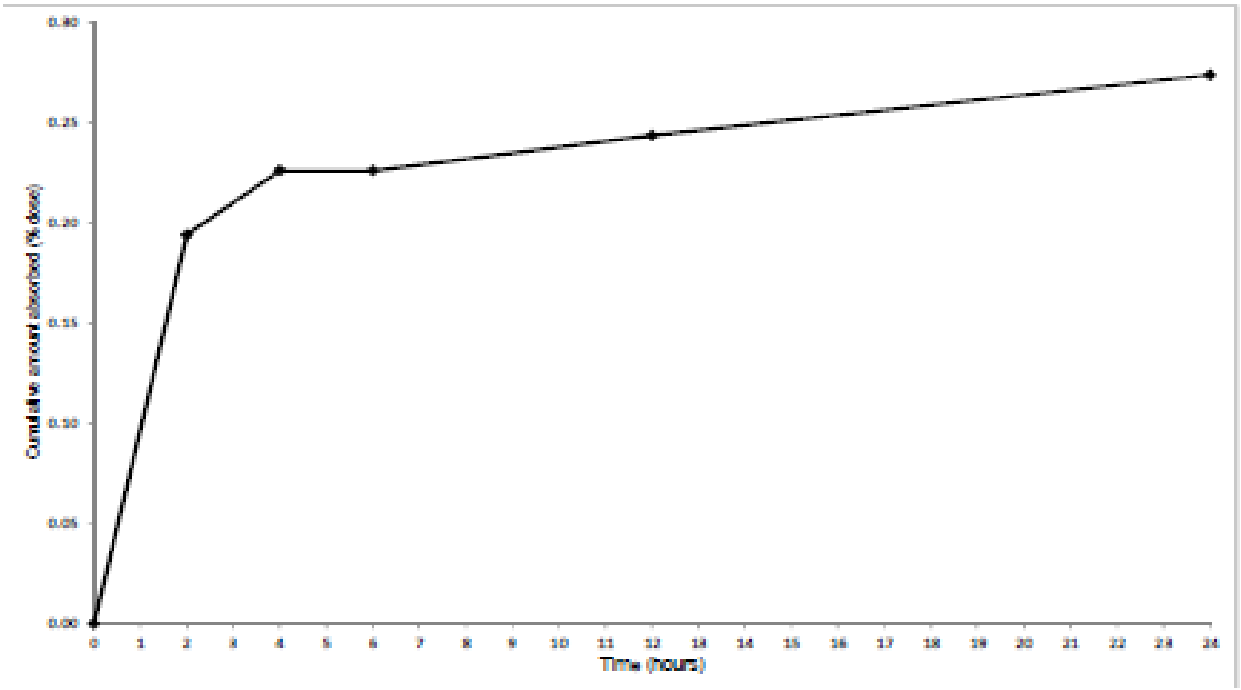
Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2)

<u>Assessment of dermal absorption of clopyralid - Low level dose (0.210 g a.s./L)</u>
Data are reported for 12 cells (from 5 subjects).

Table A 3: Distribution of clopyralid (microemulsion formulation) detected following a single application at a nominal concentration of 2.1 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Total absorbed (%)	Dose on tape (s.corneum) (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	13	0.4	16.7	nd	17.1	<LOQ	54.4	nd	8.0	62.4	79.5
H1	14	<LOQ	<LOQ	nd	<0.1	nd	94.4	nd	nd	94.4	94.4
H1	15	0.2	nd	nd	0.2	nd	88.9	nd	nd	88.9	89.1
H2	16	0.3	<LOQ	nd	0.3	nd	83.3	nd	nd	83.3	83.6
H2	17	nd	nd	nd	<0.1	<LOQ	94.4	nd	nd	94.4	94.4
H2	18	nd	<LOQ	nd	<0.1	<LOQ	100.0	nd	nd	100	100.0
H3	19	1.5	nd	nd	1.5	nd	94.4	nd	nd	94.4	95.9
H3	20	0.5	nd	nd	0.5	nd	100.0	nd	nd	100	100.5
H4	21	<LOQ	nd	nd	<0.1	nd	122.2	nd	nd	122.2	122.2
H4	22	<LOQ	nd	nd	<0.1	nd	122.2	nd	nd	122.2	122.2
H5	23	0.5	<LOQ	nd	0.5	nd	77.8	nd	3.1	80.9	81.4
H5	24	0.3	<LOQ	nd	0.3	nd	88.9	nd	1.6	90.5	90.8
	Mean	0.3	1.4	nd	1.7	nd	93.4	nd	1.1	94.5	96.2
	sd	0.4	4.8	-	4.9	-	18.2	-	2.4	16.5	13.9
	%cv	133.3	342.9	-	288.2	-	19.5	-	218.2	17.5	14.4

Figure 2: Amount of clopyralid absorbed following a single application of Kinvara microemulsion at a nominal 2.1 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose. When some cells are excluded (as in the study report), absorption appears to be complete (>75%) after half the study. However, according to the 2017 EFSA Guidance on Dermal absorption, cells should only be excluded if there is a plausible cause for them to be outliers, e.g. a membrane damaged during the experiment. No such observations were made during the Kinvara study. Therefore, all cells have been included. When all cells are included, less than 75% of the absoprtion occurs with half the duration of the study. Therefore, according to EFSA Guidance on dermal absorption (2017),

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2)

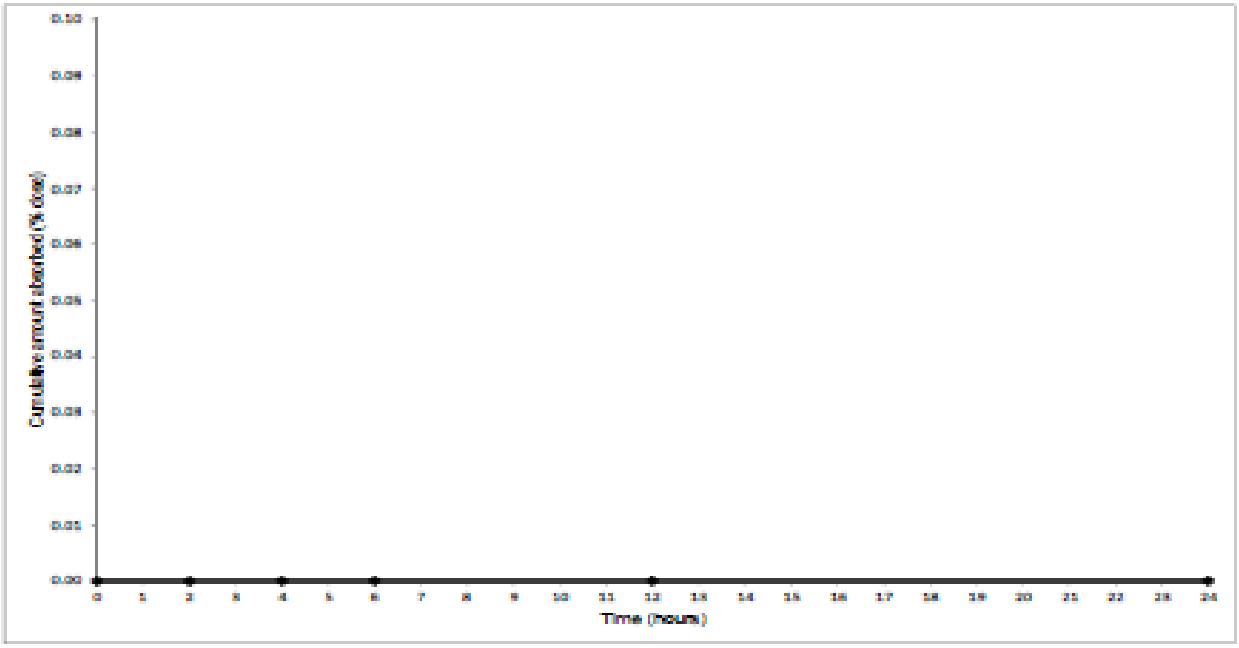
Assessment of dermal absorption of fluroxypyr-meptyl - High level dose (73.7 g a.s./L)

Data were reported for 12 cells (dermatomed skin from 5 subjects).

Table A 4: Distribution of fluroxypyr-meptyl (microemulsion formulation) detected following a single application at a nominal concentration of 737 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Total absorbed (%)	Dose on tape (s.corneum) (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	1	nd	7.4	<0.1	7.4	<LOQ	88.7	<LOQ	0.3	89.0	96.4
H1	2	nd	5.1	<0.1	5.1	<LOQ	91.5	<LOQ	0.1	91.6	96.7
H1	3	nd	15.8	1.3	17.1	12.7	31.7	12.0	20.2	63.9	93.7
H2	4	nd	12.5	<0.1	12.5	0.7	84.6	<LOQ	0.1	84.7	97.9
H2	5	nd	8.4	<0.1	8.4	3.9	67.5	9.9	3.1	80.5	92.8
H2	6	nd	3.6	<0.1	3.6	3.1	77.6	4.8	0.6	83.0	89.7
H3	7	nd	6.4	<0.1	6.4	3.1	52.0	21.4	12.8	86.2	95.7
H3	8	nd	11.4	5.1	16.5	ns	53.5	2.2	2.1	57.8	74.3
H4	9	nd	5.4	<0.1	5.4	<LOQ	81.8	2.4	0.7	84.9	90.3
H4	10	nd	7.1	<0.1	7.1	1.8	74.9	1.3	0.2	76.4	85.3
H5	11	nd	3.8	<0.1	3.8	1.6	77.7	4.1	0.5	82.3	87.7
H5	12	nd	4.7	0.1	4.8	1.7	75.9	4.0	0.7	80.6	87.1
	Mean	nd	7.6	0.5	8.2	2.4	71.5	5.2	3.5	80.1	90.6
	sd	-	3.8	1.5	4.7	3.5	17.5	6.4	6.4	9.9	6.6
	%cv	-	50.0	300.0	57.3	145.8	24.5	123.1	182.9	12.4	7.3

Figure 3: Amount of fluroxypyr absorbed following a single application of Kinvara microemulsion at a nominal 737 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose

According to EFSA Guidance on dermal absorption (2017), since more than 75% of the absorption occurs within half the duration of the study:

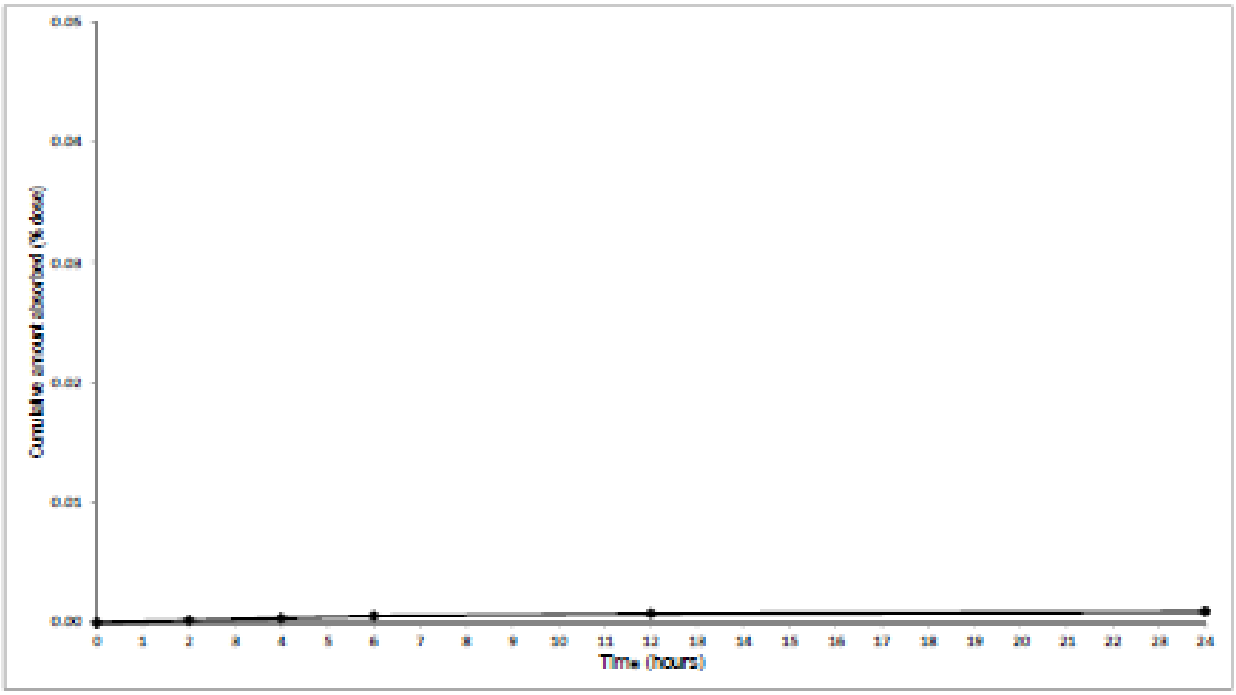
Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips)

Assessment of dermal absorption of fluroxypyr-meptyl - Low level dose (0.55 g a.s./L)
Data are reported for 12 cells (from 5 subjects).

Table A 5: Distribution of fluroxypyr-meptyl (microemulsion formulation) detected following a single application at a nominal concentration of 5.5 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Total absorbed (%)	Dose on tape (s.corneum) (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	13	nd	8.0	0.1	8.1	23.1	26.3	13.4	10.3	50.0	81.2
H1	14	nd	6.9	nd	6.9	17.4	43.2	21.2	3.1	67.5	91.8
H1	15	nd	4.1	nd	4.1	18.4	43.2	17.6	0.6	61.4	83.9
H2	16	nd	2.6	nd	2.6	20.9	43.2	15.8	2.8	61.8	85.3
H2	17	nd	2.6	nd	2.6	20.5	41.3	13.8	2.5	57.6	80.7
H2	18	nd	2.6	nd	2.6	14.7	45.0	18.0	1.7	64.7	82.0
H3	19	nd	1.0	nd	1.0	9.0	48.8	19.3	3.5	71.6	81.6
H3	20	nd	1.0	nd	1.0	17.7	35.6	24.7	1.5	61.8	80.5
H4	21	nd	2.6	nd	2.6	13.7	45.0	15.7	3.0	63.7	80.0
H4	22	nd	2.6	nd	2.6	7.7	60.0	10.3	1.7	72.0	82.3
H5	23	nd	0.9	nd	0.9	nd	69.4	6.7	3.4	79.5	80.4
H5	24	nd	0.8	nd	0.8	nd	65.7	7.3	2.3	75.3	76.1
	Mean	nd	3.0	<0.1	3.0	13.6	47.2	15.3	3.0	65.6	82.2
	sd	-	2.3	-	2.3	7.8	12.3	5.4	2.4	8.1	3.8
	%cv	-	76.7	-	76.7	57.4	26.1	35.3	80.0	12.3	4.6

Figure 4: Amount of fluroxypyr-meptyl absorbed following a single application of Kinvara microemulsion at a nominal 5.5 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose

According to EFSA Guidance on dermal absorption (2017), since more than 75% of the absorption occurs within half the duration of the study:

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips)

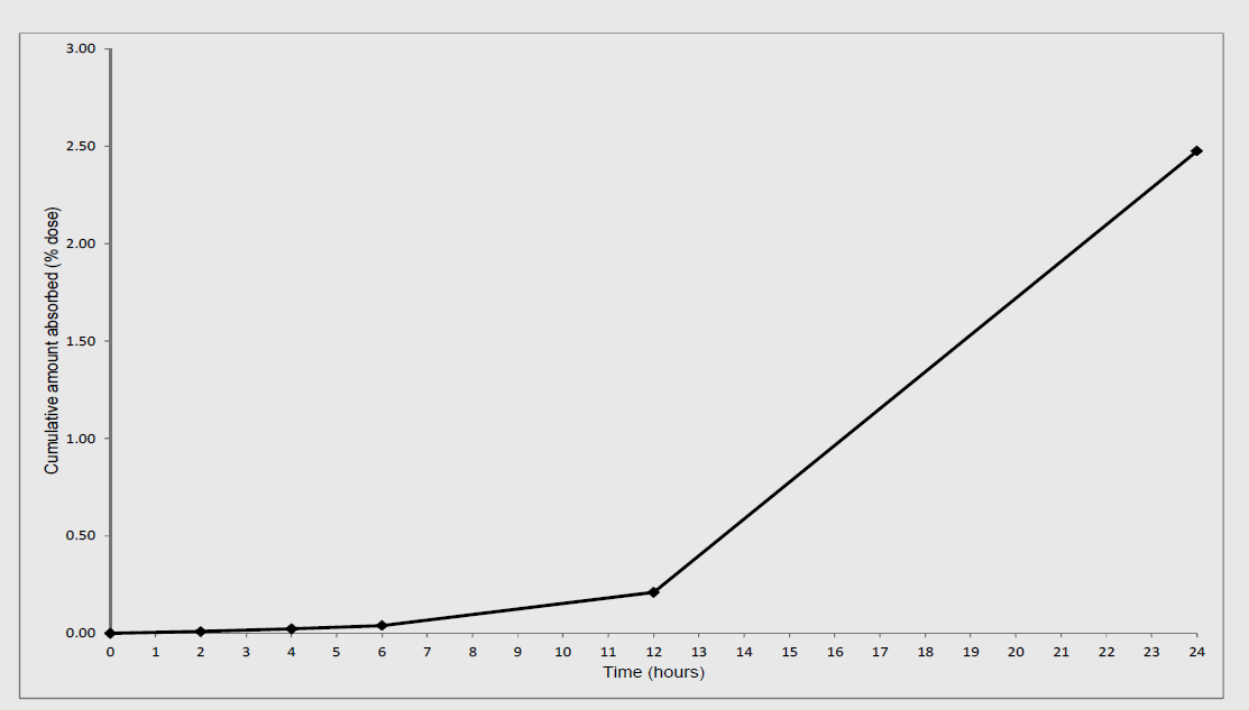
Assessment of dermal absorption of MCPA - High level dose (233.2 g a.s./L)

Data were reported for 12 cells (dermatomed skin from 5 subjects).

Table A 6: Distribution of MCPA (microemulsion formulation) detected following a single application at a nominal concentration of 2332 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Dose on tape (s.corneum) (%)	Total absorbable (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	1	0.2	0.6	<0.1	0.3	1.1	88.1	<LOQ	0.1	88.2	89.3
H1	2	0.3	0.5	<0.1	0.2	1.0	89.6	<LOQ	0.1	89.7	90.7
H1	3	6.0	11.3	0.2	7.7	25.2	29.3	8.1	19.2	56.6	81.8
H2	4	0.2	0.4	<0.1	0.4	1.0	92.5	0.2	<0.1	92.7	93.7
H2	5	0.4	0.4	<0.1	3.5	4.3	76.4	7.1	2.7	86.2	90.5
H2	6	0.8	0.7	<0.1	2.7	4.2	80.6	4.2	2.9	87.7	91.9
H3	7	5.4	1.7	<0.1	2.5	9.6	52.8	13.7	17.3	83.8	93.4
H3	8	9.8	5.1	3.6	ns	18.5	45.3	4.4	2.7	52.4	70.9
H4	9	8.0	2.0	<0.1	0.3	10.3	93.6	1.1	1.2	95.9	106.2
H4	10	0.3	0.8	<0.1	1.6	2.7	88.2	0.9	0.8	89.9	92.6
H5	11	0.8	0.9	<0.1	1.6	3.3	81.4	2.4	1.8	85.6	88.9
H5	12	13.3	0.9	0.1	1.7	16.0	79.7	3.1	1.5	84.3	100.3
	Mean	3.8	2.1	0.3	1.9	8.1	74.8	3.8	4.2	82.8	90.9
	sd	4.6	3.2	1.0	2.2	8.0	20.8	4.1	6.7	13.7	8.7
	%cv	121.1	152.4	333.3	115.8	98.8	27.8	107.9	159.5	16.5	9.6

Figure 5: Amount of MCPA absorbed following a single application of Kinvara microemulsion at a nominal 2332 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose

According to EFSA Guidance on dermal absorption (2017), since less than 75% of the absorption occurs within half the duration of the study:

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2)

Assessment of dermal absorption of MCPA - Low level dose (1.753 g a.s./L)

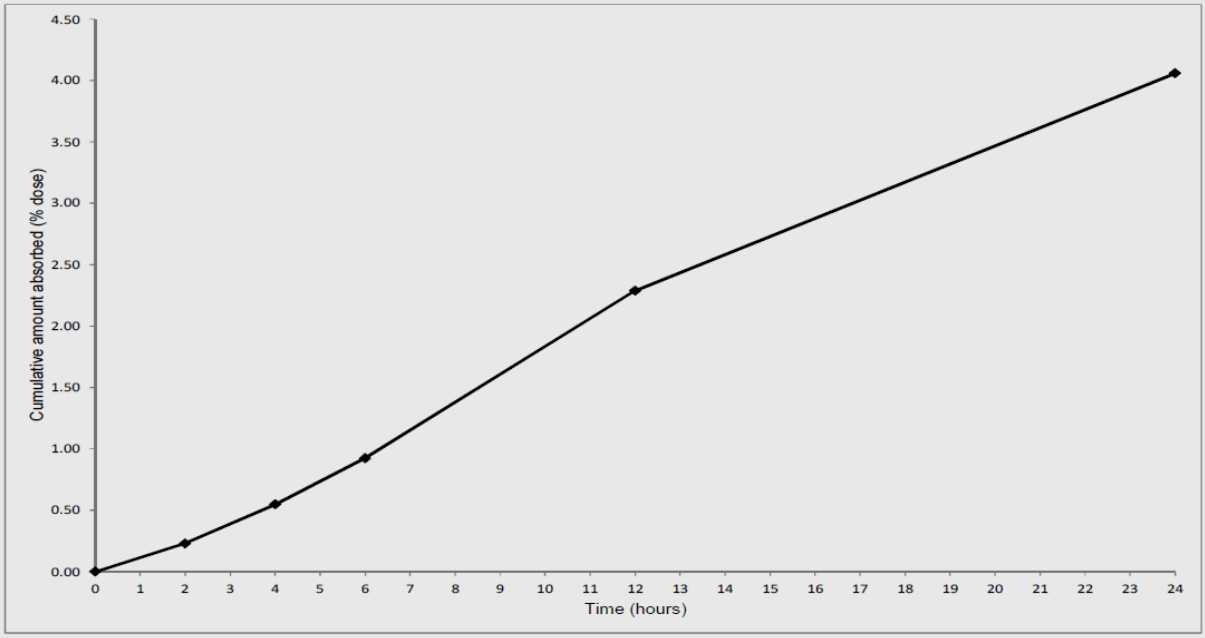
Data are reported for 12 cells (from 5 subjects).

Table A 7: Distribution of MCPA (microemulsion formulation) detected following a single application at a nominal concentration of 17.5 µg/cm² to dermatomed human skin - all cells.

Skin source	Cell number	Dose in receptor (0 - 24 hr) (%)	Dose remaining in skin (%)	Dose remaining on receptor chamber (%)	Dose on tape (s.corneum) (%)	Total absorbable (%)	Dose in skin swab (6 hr) (%)	Dose on tape (surface) (%)	Dose remaining on donor chamber (%)	Total non-absorbed (%)	Total recovery (%)
H1	13	4.5	22.4	0.1	<LOQ	27.0	80.1	<LOQ	19.2	99.3	126.3
H1	14	4.4	<LOQ	0.1	<LOQ	4.5	105.6	nd	0.2	105.8	110.3
H1	15	4.1	<LOQ	<0.1	<LOQ	4.1	100.6	nd	0.5	101.1	105.2
H2	16	2.1	2.5	0.1	<LOQ	4.7	77.6	nd	0.2	77.8	82.5
H2	17	3.8	<LOQ	0.1	<LOQ	3.9	96.9	nd	0.1	97.0	100.9
H2	18	3.5	1.9	0.1	<LOQ	5.5	87.6	nd	0.2	87.8	93.3
H3	19	3.7	<LOQ	<0.1	<LOQ	3.7	82.6	<LOQ	0.5	83.1	86.8
H3	20	1.4	<LOQ	<0.1	<LOQ	1.4	87.6	<LOQ	0.1	87.7	89.1
H4	21	3.1	<LOQ	0.1	nd	3.2	85.7	<LOQ	0.2	85.9	89.1
H4	22	4.6	<LOQ	0.1	nd	4.7	86.3	nd	0.9	87.2	91.9
H5	23	9.1	3.7	0.1	nd	12.9	71.4	<LOQ	4.5	75.9	88.8
H5	24	4.3	3.1	0.2	nd	7.6	83.2	nd	1.5	84.7	92.3
	Mean	4.1	2.8	0.1	-	6.9	87.1	-	2.3	89.4	96.4
	sd	1.9	6.3	0.1	-	6.9	9.7	-	5.5	9.4	12.4
	%cv	46.3	225.0	100.0	-	100.0	11.1	-	239.1	10.5	12.9

nd (less than limit of detection) 0.5 µg/sample (tape strips)
<LOQ (less than limit of quantification) 0.25 µg/sample (skin), 2.5 µg (tape strips)
- not applicable

Figure 6: Amount of MCPA absorbed following a single application of Kinvara microemulsion at a nominal 17.5 µg/cm² to dermatomed skin – selected cells



Results are expressed as mean cumulative percent applied dose

According to EFSA Guidance on dermal absorption (2017), since less than 75% of the absorption occurs within half the duration of the study:

Absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2)

Table A 8: *In-vitro* dermal penetration of clopyralid, fluroxypyr meptyl and MCPA formulated as Kinvara through human skin - Recovery data

	Clopyralid				Fluroxypyr meptyl				MCPA			
Dose group	High dose (Formulation concentrate)		Low dose (Spray dilution 1:133)		High dose (Formulation concentrate)		Low dose (Spray dilution 1:133)		High dose (Formulation concentrate)		Low dose (Spray dilution 1:133)	
Target concentration [mg/mL]	27.9		0.210		73.7		0.554		233		1.75	
Target dose [µg/cm²]	279		2.1		737		5.54		2330		17.5	
Mean actual applied dose [µg/cm²]	268		1.89		752		5.61		2343		16.9	
	Recovery [%]		Recovery [%]		Recovery [%]		Recovery [%]		Recovery [%]		Recovery [%]	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Dislodgeable dose												
Skin washing after 6 h	85.26	28.79	93.41	18.23	71.45	17.54	47.23	12.30	74.79	20.83	87.10	9.75
Donor chamber wash	3.36	5.61	4.23	3.35	3.45	6.36	3.03	2.45	4.57	6.84	2.34	5.45
Dose associated to skin												
Tape strips: 1st sample, strips 1 + 2	4.83	4.96	N/A	N/A	6.90	6.52	15.32	5.40	4.52	4.13	N/A	N/A
Tape strips: 2nd sample; strips 3 - n	2.27	1.73	N/A	N/A	3.58	3.83	16.31	5.05	2.05	2.18	N/A	N/A
Skin preparation	2.51	3.58	16.70	N/A	7.63	3.79	2.98	2.33	2.11	3.18	6.72	8.79
Absorbed dose												
Receptor fluid	1.45	2.37	0.53	0.44	N/A	N/A	N/A	N/A	3.79	4.59	4.05	1.87
Receptor chamber wash	0.58	0.88	N/A	N/A	2.17	2.61	0.10	N/A	1.30	1.99	0.11	0.03
Total recovery[1]	97.40	19.62	96.17	13.91	90.63	6.61	82.15	3.77	90.85	8.69	96.38	12.36
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]	No [47.68% ± 20.61]		No [52.51% ± 25.70]		Yes [No absorption detected]		Yes [No absorption detected]		No [11.28% ± 18.37]		No [41.04% ± 9.21]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2)[2]	5.43	7.14	2.91	6.27	N/A	N/A	N/A	N/A	8.10	7.99	6.93	6.93
If yes: Absorption estimates = absorbed dose + skin preparation)[2]	N/A	N/A	N/A	N/A	8.18	4.68	2.98	2.34	N/A	N/A	N/A	N/A
Absorption estimate normalised[3]	5.43 ± 7.14		2.91 ± 6.27		11.91 ± 5.68		18.79 ± 5.04		14.46 ± 7.00		6.93 ± 6.93	
Relevant absorption estimate[4]	10.005		8.683		15.545		22.019		18.938		11.371	
Absorption estimates used for risk assessment[5]	**10**		**8.7**		**16**		**22**		**19**		**11**	

[1] Values may not calculate exactly due to rounding of figures

[2] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the

absorption occurred in the first half of the study (see Table 7.6.2-1) Finally, the skin preparation is also considered potentially absorbable.

[3] According to the EFSA Guidance on Dermal Absorption, cells with insufficient recovery (< 95%) can be corrected by normalisation of absorption estimate to 100% recovery; explanation should be included.

[4.] In accordance with the EFSA Guidance on Dermal Absorption, one standard deviation (modified by the appropriate multiplication factor) was added to the mean% dermal penetration.

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

N/A: not applicable

Conclusion/endpoint:

The dermal penetration of clopyralid formulated as Kinvara through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 5.43 ± 7.14 and 2.91 ± 6.27 for the formulation concentrate and the 1:133 spray dilution, respectively. The dermal penetration estimates to be used for risk assessment were set at 10% and 8.7% for the formulation concentrate and the 1:133 spray dilution based on the EFSA guidance criteria (EFSA Journal 2017; 15(6):4873).

The dermal penetration of fluroxypyr-meptyl formulated as Kinvara through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 11.91 ± 5.68 and 18.79 ± 5.04 for the formulation concentrate and the 1:133 spray dilution, respectively. The dermal penetration estimates to be used for risk assessment were set at 16% and 22% for the formulation concentrate and the 1:133 spray dilution based on the EFSA guidance criteria (EFSA Journal 2017; 15(6):4873).

The dermal penetration of MCPA formulated as Kinvara through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 14.46 ± 7.00 and 6.93 ± 6.93 for the formulation concentrate and the 1:133 spray dilution, respectively. The dermal penetration estimates to be used for risk assessment were set at 19% and 11% for the formulation concentrate and the 1:133 spray dilution based on the EFSA guidance criteria (EFSA Journal 2017; 15(6):4873).

A 2.11 Other/Special Studies

Not required

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

Short term

Mixing/Loading	Application	MCPA (%AOEL)	Fluroxypyr (%AOEL)	Clopyralid (%AOEL)	Combined exposure (Hazard index)
		1080	16.2	35.6	11.3
		672	10.6	23.8	7.1
		49	0.8	1.3	0.5

Acute

Mixing/Loading	Application	MCPA (%AAOEL)	Fluroxypyr (%AAOEL)	Clopyralid (%AAOEL)
				186
				82.8
				11.2

A 3.1.1 Calculations for MCPA

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

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	**Name of active substance**	MCPA
Concentration of active substance [g a.s./l or kg]	233	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	19	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	11	**Indoor/outdoor**	Outdoor
Oral absorption [%]	100	**Drift reduction [%]**	0
Inhalation absorption [%]	100	**Type of cultivation**	Normal
Body weight (kg)	60		
AOEL [mg/kg bw/day]	0.04		
AAOEL [mg/kg bw]			

Table A 10: Estimation of operator exposure towards MCPA according to EFSA guidance

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*Protected hands*
	Hands exposure	**250**	**1**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**1.4**	**1.4**
	Head protection	*None*	*None*
	Head exposure	**7**	**7**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.2**	**0.2**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**9.5**	**9.5**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.1**	**0.1**
	Head protection	*None*	*None*
	Head exposure	**0.2**	**0.2**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Total	Total systemic exposure [mg/kg bw per day]	0.3	0.02
	% of AOEL	672	49

A 3.1.2 Calculations for fluroxypyr

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

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	**Name of active substance**	Fluroxypyr
Concentration of active substance [g a.s./l or kg]	50	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	16	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	22	**Indoor/outdoor**	Outdoor
Oral absorption [%]	100	**Drift reduction [%]**	0
Inhalation absorption [%]	100	**Type of cultivation**	Normal
Body weight (kg)	60		
AOEL [mg/kg bw/day]	0.8		
AAOEL [mg/kg bw]			

Table A 12: Estimation of operator exposure towards fluroxypyr according to EFSA guidance

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**78.7**	**78.7**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.5**	**0.5**
	Head protection	*None*	*None*
	Head exposure	**1.3**	**1.3**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**4.1**	**4.1**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.06**	**0.06**
	Head protection	*None*	*None*
	Head exposure	**0.1**	**0.1**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.05**	**0.05**
Total	Total systemic exposure [mg/kg bw per day]	0.08	0.08
	% of AOEL	10.6	10.6

A 3.1.3 Calculations for clopyralid

Table A 13: Input parameters considered for the estimation of operator exposure

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	**Name of active substance**	Clopyralid
Concentration of active substance [g a.s./l or kg]	28	**Crops**	Field crops
Area treated [ha/day]	50	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	10	**Application technique**	Vehicle-mounted
Dermal absorption [%] (dilution)	8.7	**Indoor/outdoor**	Outdoor
Oral absorption [%]	100	**Drift reduction [%]**	0
Inhalation absorption [%]	100	**Type of cultivation**	Normal
Body weight (kg)	60		
AOEL [mg/kg bw/day]	0.15		
AAOEL [mg/kg bw]	0.17		

Table A 14: Estimation of operator exposure towards clopyralid according to EFSA guidance – short term exposure

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**33.9**	**33.9**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.2**	**0.2**
	Head protection	*None*	*None*
	Head exposure	**0.4**	**0.4**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.09**	**0.09**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**0.9**	**0.9**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.01**	**0.01**
	Head protection	*None*	*None*
	Head exposure	**0.02**	**0.02**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.04**	**0.04**
Total	Total systemic exposure [mg/kg bw per day]	0.04	0.04
	% of AOEL	23.8	23.8

Table A 15: Estimation of operator exposure towards clopyralid according to EFSA guidance – acute exposure

Activity	Systemic exposure per body part	With workwear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**126**	**126**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**1.7**	**1.7**
	Head protection	*None*	*None*
	Head exposure	**2.7**	**2.7**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.3**	**0.3**
Application (µg/kg bw per day)	*Hand protection*	*None*	*None*
	Hands exposure	**9.5**	**9.5**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.03**	**0.03**
	Head protection	*None*	*None*
	Head exposure	**0.07**	**0.07**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.1**	**0.1**
Total	Total systemic exposure [mg/kg bw per day]	0.1	0.1
	% of AAOEL	82.8	82.8

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for MCPA

Table A 16: Input parameters considered for the estimation of worker exposure

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	0.04
Re-entry activity	Inspection, irrigation	**Dermal transfer coefficient - Total potential exposure [cm²/h]**	12500
Crops	Field crops	**Dermal transfer coefficient - Arm, body and legs covered [cm²/h]**	1400
Application method	Downward spraying	**Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]**	1250
Application technique	Vehicle-mounted	**Dermal transfer coefficient - Hands covered, no workwear [cm²/h]**	
Max. application rate of the product [l or kg/ha]	3	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	1	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	NA		
Multiple application factor	1		
Body weight (kg)	60		
Name of active substance	MCPA		
Dermal absorption [%] (dilution)	11		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Table A 17: Estimation of worker exposure towards MCPA according to EFSA guidance

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	10	1.1	1	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]				NA
Total	Total systemic exposure [mg a.s. per day]	10	1.1	1	NA
	Total systemic exposure [mg/kg bw per day]	0.2	0.02	0.02	NA
	% of AOEL	415	46.5	41.5	NA

A 3.2.2 Calculations for fluroxypyr

Table A 18: Input parameters considered for the estimation of worker exposure

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	0.8
Re-entry activity	Inspection, irrigation	**Dermal transfer coefficient - Total potential exposure [cm²/h]**	12500
Crops	Field crops	**Dermal transfer coefficient - Arm, body and legs covered [cm²/h]**	1400
Application method	Downward spraying	**Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]**	1250
Application technique	Vehicle-mounted	**Dermal transfer coefficient - Hands covered, no workwear [cm²/h]**	
Max. application rate of the product [l or kg/ha]	3	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	1	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	NA		
Multiple application factor	1		
Body weight (kg)	60		
Name of active substance	Fluroxypyr		
Dermal absorption [%] (dilution)	22		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Table A 19: Estimation of worker exposure towards fluroxypyr according to EFSA guidance

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	2.5	0.3	0.2	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]				NA
Total	Total systemic exposure [mg a.s. per day]	2.5	0.3	0.2	NA
	Total systemic exposure [mg/kg bw per day]	0.04	0.005	0.004	NA
	% of AOEL	5.2	0.6	0.5	NA

A 3.2.3 Calculations for clopyralid

Table A 20: Input parameters considered for the estimation of worker exposure

Indoor/outdoor	Outdoor	**AOEL [mg/kg bw/day]**	0.15
Re-entry activity	Inspection, irrigation	**Dermal transfer coefficient - Total potential exposure [cm²/h]**	12500
Crops	Field crops	**Dermal transfer coefficient - Arm, body and legs covered [cm²/h]**	1400
Application method	Downward spraying	**Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]**	1250
Application technique	Vehicle-mounted	**Dermal transfer coefficient - Hands covered, no workwear [cm²/h]**	
Max. application rate of the product [l or kg/ha]	3	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Max. no. of applications	1	**DT50 foliar worker [days]**	30
Interval between multiple applications [days]	NA		
Multiple application factor	1		
Body weight (kg)	60		
Name of active substance	Clopyralid		
Dermal absorption [%] (dilution)	8.7		
Inhalation absorption [%]	100		
Time [hours per day]	2		

Table A 21: Estimation of worker exposure towards clopyralid according to EFSA guidance

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	0.6	0.07	0.06	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]				NA
Total	Total systemic exposure [mg a.s. per day]	0.6	0.07	0.06	NA
	Total systemic exposure [mg/kg bw per day]	0.01	0.001	0.001	NA
	% of AOEL	7	0.8	0.7	NA

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

Table A 22: Estimation of acute bystander exposure according to EFSA guidance

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AA-OEL
			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 200 l
Clopyralid			Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Bystander child Body weight: 10 kg	Drift (95th perc.)	0.002	1.3
	Vapour (95th perc.)	0.0008	0.5
	Deposits (95th perc.)	0.0005	0.3
	Re-entry (95th perc.)	0.001	0.8
Bystander adult Body weight: 60 kg	Drift (95th perc.)	0.0006	0.4
	Vapour (95th perc.)	0.0003	0.2
	Deposits (95th perc.)	0.0002	0.1
	Re-entry (95th perc.)	0.0008	0.5

Table A 23: Estimation of short term resident exposure according to EFSA guidance

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
			Season: Not relevant Buffer zone: 2-3 m Drift reduction technology: 0 % Interval between treatments: NA Minimum volume of water: 200 l
MCPA			Number of applications and application rate: 1 x 0.699 kg a.s./ha Dermal absorption: 19 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days
Resident child Body weight: 10 kg	Drift (75th perc.)	0.01	26.1
	Vapour (75th perc.)	0.0008	2
	Deposits (75th perc.)	0.003	6.3
	Re-entry (75th perc.)	0.02	56
	Sum (mean)	0.03	65.5
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.002	6.2
	Vapour (75th perc.)	0.0003	0.7
	Deposits (75th perc.)	0.0009	2.3
	Re-entry (75th perc.)	0.01	31.1
	Sum (mean)	0.01	30.1

Model data	Level of PPE	Total absorbed dose [mg/kg bw per day]	% of systemic AOEL
Fluroxypyr	Number of applications and application rate: 1 x 0.15 kg a.s./ha Dermal absorption: 22 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days		
Resident child Body weight: 10 kg	Drift (75th perc.)	0.004	0.6
	Vapour (75th perc.)	0.0008	0.1
	Deposits (75th perc.)	0.0006	0.08
	Re-entry (75th perc.)	0.006	0.7
	Sum (mean)	0.008	1
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.001	0.1
	Vapour (75th perc.)	0.0003	0.03
	Deposits (75th perc.)	0.0002	0.03
	Re-entry (75th perc.)	0.003	0.4
	Sum (mean)	0.003	0.4
Clopyralid	Number of applications and application rate: 1 x 0.084 kg a.s./ha Dermal absorption: 10 % DFR: 3 µg/cm² foliage per kg a.s./ha DT50: 30 days		
Resident child Body weight: 10 kg	Drift (75th perc.)	0.001	0.7
	Vapour (75th perc.)	0.0008	0.5
	Deposits (75th perc.)	0.0002	0.1
	Re-entry (75th perc.)	0.001	0.9
	Sum (mean)	0.003	1.7
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0002	0.2
	Vapour (75th perc.)	0.0003	0.2
	Deposits (75th perc.)	6e-05	0.04
	Re-entry (75th perc.)	0.0008	0.5
	Sum (mean)	0.001	0.7
Combined exposure			Hazard index
Resident child Body weight: 10 kg	Drift (75th perc.)		0.3
	Vapour (75th perc.)		0.03
	Deposits (75th perc.)		0.06
	Re-entry (75th perc.)		0.6
	Sum (mean)		0.7
Resident adult Body weight: 60 kg	Drift (75th perc.)		0.06
	Vapour (75th perc.)		0.009
	Deposits (75th perc.)		0.02
	Re-entry (75th perc.)		0.3
	Sum (mean)		0.3