FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: **CHR/F/PYRA 250 EC**

Product name(s): **Etiuda 250 EC, Fermata 250 EC**

Chemical active substance:

Pyraclostrobin, 250 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Innvigo Sp. z o.o.

Submission date: March 2022

MS Finalisation date: 15/12/2022

Version history

When	What
December 2021	Dossier sent for evaluation
April 2022	Updates based on feedback from zRMS Poland
September 2022	zRMS evaluation of dRR
December 2022	Final version prepared by zRMS after Commenting period

Table of Contents

zRMS comments:
The text highlighted in grey was provided by the evaluator.

6 Mammalian Toxicology (KCP 7)

New informations were highlighted in yellow.
This document reviews the toxicological studies for the plant protection product CHR/F/PYRA 250 EC containing the active substance Pyraclostrobin which was included into Annex I of Directive 91/414 (Commission Directive 2004/30/EC of 10 March 2004, date of inclusion 01 June 2004). CHR/F/PYRA 250 EC is an EC-formulation containing 250 g/L Pyraclostrobin and acts as fungicide. A full risk assessment according to Uniform Principles is provided which demonstrates that the product is safe for operators, workers and bystanders.

6.1 Summary

Table 6.1-1: Information on CHR/F/PYRA 250 EC

Product name and code	CHR/F/PYRA 250 EC
Formulation type	Emulsifiable concentrate (EC)
Active substance(s) (incl. content)	Pyraclostrobin 250 g/l
Function	fungicide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	No
Product previously evaluated in another MS according to Uniform Principles	No

* Information on the detailed composition of CHR/F/PYRA 250 EC 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 CHR/F/PYRA 250 EC according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	~~**H315, H318, H332**~~ Skin Irrit. 2 Eye Dam. 1 Acute Tox. 4 (INH)
Hazard pictograms or Code(s) for hazard pictogram(s):	GHS05, GHS07
Signal word:	Danger
Hazard statement(s):	**H315 – Causes skin irritation** **H318 – Causes serious eye damage** **H332 – Harmful if inhaled**
Precautionary statement(s):	P261- Avoid breathing dust/fume/gas/mist/vapours/ spray. P264 - Wash contaminated body parts thoroughly after handling. P271 - Use only outdoors or in a well-ventilated area. P280 - Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352 - IF ON SKIN: Wash with plenty of water. P304 + P340 - IF INHALED: Remove person to fresh air and keep comfortable for breathing. P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P312 - Call a POISON CENTER or doctor/physician if you feel unwell.
Additional labelling phrases:	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
Other non-active ingredients relevant for classification	-Benzenesulfonic acid, C10-13-alkyl derivs., calcium salt; -Butan-1-ol -Hydrocarbons, C10-C13, aromatics, < 1% Naphthalene

Table 6.1-3: Summary of risk assessment for operators, workers, bystanders and residents for CHR/F/PYRA 250 EC

	Result	PPE / Risk mitigation measures
Operators	Acceptable	~~EFSA model:~~ Drift reduction, work wear during mixing & loading and application step. Protective clothes, protective gloves and face/eye protection at the mixing/loading step and handling due to hazard characterisation.
Workers	Acceptable	~~EFSA model:~~ ~~None~~ (Protective) clothes and gloves
Bystanders	Acceptable	~~EFSA model:~~ warning signs, drift reduction, 5m buffer strip
Residents	Acceptable	~~EFSA model:~~ warning signs, drift reduction, 5m buffer strip

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 kg as/ha** **a) a.s. 1**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
1, 2, 3, 4	Cereals (BBCH 25-69)	F	Spray, medium sprayer	a) 1 b) 2/21	a) 0.25 b) 0.50	100-400	35		R	R	R	R

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

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

Data gaps

Noticed data gaps are:

6.2 Toxicological Information on Active Substance(s)

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

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

	Pyraclostrobin
Common Name	Pyraclostrobin
CAS-No.	175013-18-0
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Hazard classes (s), categories: **Skin ~~i~~Irrit. 2~~, H315~~** **Acute Tox. 3*~~, H331~~** Code(s) for hazard pictogram(s): GHS06~~, GHS07~~ Signal word: Danger Hazard statement(s): H315: Causes skin irritation. H331: Toxic if inhaled.

	Pyraclostrobin
	Precautionary statement(s): P261 - Avoid breathing dust/fume/gas/mist/vapours/ spray. P264 - Wash contaminated body parts thoroughly after handling. P271 - Use only outdoors or in a well-ventilated area. P280 - Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352 - IF ON SKIN: Wash with plenty of water. P304 + P340 - IF INHALED: Remove person to fresh air and keep comfortable for breathing. P311 - Call a POISON CENTER/doctor.
Additional C&L proposal	EUH401- *To avoid risks to human health and the environment, comply with the instructions for use*
Agreed EU endpoints	
AOEL systemic	0.015 mg/kg bw/d
Reference	*SANCO/1420/2001-Final. 8. September 2004*
Conditions to take into account/critical areas of concern with regard to toxicology	
SANCO/1420/2001-Final. 8. September 2004	**Genotoxicity**: No genotoxic potential **Long term toxicity and carcinogenicity** Target / critical effect: Reduced body weight; (rat & mouse); liver cell necrosis (rat) Lowest relevant NOAEL: Chronic rat (75 ppm) 3 mg/kg bw/d Carcinogenicity: No carcinogenic potential **Reproductive toxicity** Target / critical effect - Reproduction: Reduced pup body weight gain in the presence of parental toxicity Lowest relevant reproductive NOAEL / NOEL: 75 ppm (8.2 mg/kg bw/d) Target / critical effect - Developmental toxicity: Developmental effects in rats and embryotoxicity (including malformations) in rabbits at maternally toxic doses Lowest relevant developmental NOAEL / NOEL: 5 mg/kg bw/d (rabbit) Lowest relevant maternal NOAEL / NOEL; 3 mg/kg bw/d (rabbit) **Delayed neurotoxicity**: No neurotoxic potential (rat, acute and 13wk studies)

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for CHR/F/PYRA 250 EC 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 CHR/F/PYRA 250 EC

Type of test, species, model system (Guideline)	Result	Classification (acc. to the criteria in Reg. 1272/2008)	Reference	Acceptability
LD_{50} oral, rat (calculation method –	> 2000 mg/kg bw	None	Estimation based on composition of the	Yes

alternative method)			product (additivity formula) see Part C, appendix 2	
LD_{50} dermal, rat (calculation method – alternative method)	No data – not required	None	Estimation based on composition of the product (additivity formula)-see Part C, appendix 2	Yes
LC_{50} inhalation, rat (calculation method – alternative method)	12.5 mg/L	**Acute Tox. 4, H332**	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Skin irritation, (calculation method – alternative method)	Irritant	**Skin Irrit. 2, H315**	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Eye irritation, (calculation method – alternative method)	Corrosive	**Eye Dam. 1, H318**	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Skin sensitisation (calculation method – alternative method)	No data – not required	None	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Specific target organ toxicity	None	None	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Aspiration toxicity	None	None	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes
Supplementary studies for combinations of plant protection products	No data – not required	None	Estimation based on composition of the product (additivity formula) see Part C, appendix 2	Yes

Table 6.3-2: Additional toxicological information relevant for classification/labelling of CHR/F/PYRA 250 EC

	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	Pyraclostrobin technical	Skin Irrit. 2 H315 Acute Tox. 3* H331	Reg. 1272/2008	Skin Irrit. 2 H315 Acute Tox. 4 H332

	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)**
active substance(s) (relevant for classification of product)	(24.06%)		/	
Toxicological properties of non-active substance(s) (relevant for classification of product)	Benzenesulfonic acid, C10-13-alkyl derivs., calcium salt (2.923 – 3.112%)	Skin Irrit. 2 H315 Eye Dam. 1 H318	~~Reg. 1272/2008 /~~ MSDS	Skin Irrit. 2 H315 Eye Dam. 1 H318
	Butan-1-ol (0.4715-0.7544%)	Skin Irrit. 2 H315 Eye Dam. 1 H318 Acute Tox. 4 H302 STOT SE 3 H335 STOT SE 3 H336	Reg. 1272/2008 /	Skin Irrit. 2 H315 Eye Dam. 1 H318
Further toxicological information	No data – not required			

6.4 Toxicological Evaluation of Groundwater Metabolites

Comments of zRMS:	Acceptable. Details in the dRR Part B10.

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 CHR/F/PYRA 250 EC are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in CHR/F/PYRA 250 EC

	Pyraclostrobin	
	Value	**Reference**
Concentrate	25 %	Default value, Guidance on Dermal Absorption (*EFSA Journal ~~2012; 10(4):2665~~ 2017;15(6):4873*)
Dilution	70 %	Default value, Guidance on Dermal Absorption (*EFSA Journal ~~2012; 10(4):2665~~ 2017;15(6):4873*)

6.5.1 Justification for proposed values

New dermal absorption study was performed for Pyraclostrobin in CHR/F/PYRA 250 and its presented in Appendix 2.

Table 6.5-2: Default dermal absorption rates for Pyraclostrobin

	Value	Justification for value	Acceptability of justification
Concentrate	25 %	~~A default dermal absorption value of 25% may be applied for products containing > 5% (50 g/kg for solids or 50 g/L for liquids) active substance.~~ According to the EFSA Guidance on Dermal Absorption (*EFSA Journal 2017;15(6):4873*) a default dermal absorption value of 25% may be applied for concentrated products that are organic solvent-formulated (including formulation type of emulsifiable concentrate EC).	Yes
Dilution	~~75 %~~ 70 %	~~A default value of 75% should be used in use dilutions containing ≤ 5% active substance.~~ According to the EFSA Guidance on Dermal Absorption (*EFSA Journal 2017;15(6):4873*) a default dermal absorption value of 70% may be applied for (in use) dilutions of organic solvent-formulated (includingformulation type of emulsifiable concentrate EC).	Yes
New data			
Concentrate	1.5 %	Ergon, C., 2021, S20-06511, *The dermal penetration of pyraclostrobin formulated as Pyraclostrobin 250 g/L through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 1.5 % (mean + k * SD) and 36 % for the formulation concentrate and the 1:2500 spray dilution, respectively, based on the EFSA guidance criteria.*	Yes
Dilution	36 %		Yes

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	CHR/F/PYRA 250 EC
Formulation type	EC
Category	Fungicide
Container size(s), short description	HDPE range from 250 ml to 5000 ml bottle/ 188 ml to 2000 ml Jar /3000 ml to 22000 ml conteiner/ 4000 ml to 20000 ml cannister COEX/EvOH range from 100 ml to 1000 ml bottle/

	5000 ml to 20000 ml conteiner HDPE/PA range from 120 ml to 5500 ml bottle/ 5000 ml canister/5850 ml to 10000 ml conteiner HDPE/F range from 120 ml to 5950 bottle/ 5880 to 10000 ml cannister
Active substance(s) (incl. content)	**Pyraclostrobin** 250 g/L
AOEL systemic	0.015 mg/kg bw/d
Inhalation absorption	100 %
Oral absorption	100 %
Dermal absorption	Concentrate: 1.5 % (Ergon, C., 2021, S20-06511) Dilution: 36 % (Ergon, C., 2021, S20-06511)

6.6.1 Selection of critical use(s) and justification

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

6.6.2 Operator exposure (KCP 7.2.1)

Comments of zRMS:	The operator exposure calculations for the proposed uses of CHR/F/PYRA 250 EC conducted by the Applicant using EFSA model are acceptable. The predicted longer term operator exposure to CHR/F/PYRA 250 EC applied for low crop via tractor mounted boom sprayer **using drift reduction technology** is within acceptable limit when the operator wearing workwear (arms, body and legs covered) both at the mixing/loading and application step. However, taking also into consideration the classification of the product (H315 – Causes skin irritation, H318 – Causes serious eye damage, H332 – Harmful if inhaled) protective clothes, protective gloves and face/eye protection is recommended to use for operator at the mixing/loading step and handling.

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 CHR/F/PYRA 250 EC according to the critical use(s) is presented in Table 6.6-2. Outcome of the estimation is presented in Table 6.6-3. Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Cereals (max. 2 x 1 L product/ha)
Model(s)	EFSA exposure model [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, European Food Safety Authority (EFSA), Parma, Italy, *EFSA Journal 2014;12(10):3874*]

Table 6.6-3: Estimated operator exposure- cereals

		Pyraclostrobin	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Vehicle mounted Drift Reduction downward spraying outdoors to low crops, Application rate: 2 × 0.25 kg a.s./ha			
EFSA exposure model Application volume 100-400 L/ha Body weight: 60 kg	No PPE (Potential exposure)	**0.0198**	**132.11**
	Work wear - arms, body and legs covered (mixing/loading and application) and drift reduction nozzels	0.0137	91.17

Conclusion

According to the calculations of the operator exposure with the EFSA exposure model, no undue risk is predicted for all uses supported in the EU central zone. In consideration of using work wear (arms, body and legs covered) during mixing and loading and application step and drift reduction nozzels, the estimated exposure of operators is below the AOEL for Pyraclostrobin (91.17 % of the AOEL).

6.6.3 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 considering above mentioned usage of work wear during mixing and loading, a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.4 Worker exposure (KCP 7.2.3)

Comments of zRMS:	The worker exposure calculations for the proposed uses of CHR/F/PYRA 250 EC conducted by the Applicant are acceptable. According to the calculation performed using EUROPOEM II Model the risk for worker is acceptable (48% of AOEL) provided that the worker uses (protective) clothes and gloves. As a standard rule, crops treated by CHR/F/PYRA 250 EC should not be re-entered before spray deposit on leaf surfaces has completely dried.

6.6.4.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with CHR/F/PYRA 250 EC according to the critical uses. Outcome of the estimation is presented in Table 6.6-5. Detailed calculations are in Appendix 3.
The exposure and risk assessments for workers were performed in consideration of the most critical GAP uses and re-entry scenarios covering all other intended GAP uses for which authorisation is

sought in the central zone.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Cereals (max. 2 x 1 L product/ha)
Model(s)	EFSA exposure model [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, European Food Safety Authority (EFSA), Parma, Italy, *EFSA Journal 2014;12(10):3874*] EUROPOEM II Model [~~Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, European Food Safety Authority (EFSA), Parma, Italy, *EFSA Journal 2014;12(10):3874*~~] [Hemmen et al. (2002) Post-application exposure of workers to pesticides in agriculture. Report of the re-entry working group. EUROPOEM II project. FAIR CT96-1406]

Table 6.6-5: Estimated worker exposure- EFSA exposure model

		Pyraclostrobin	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Number of applications and application rate:		2 × 0.25 kg a.s./ha	
2 hours/day (1), TC: 12500/1400 cm^2/person/h (2) Body weight: 60 kg	no PPE (3)	0.1818	**1211.68**
	with PPE (4)	0.0204	**135.71**

(1) ~~8~~ 2 h/day for professional applications for maintenance, inspection or irrigation activities etc.
(2) TC = 12500 (Total potential exposure)/1400 (Hands, arms, body and legs covered)cm2/person/ hour acc. to US Re-entry Agricultural TF data were used, TC: Transfer coefficient.
(3) Potential exposure
(4) Work wear - arms, body and legs covered

Table 6.6-6: Estimated worker exposure- EUROPOEM II model

		Pyraclostrobin	
Model data	**Level of PPE**	**Total absorbed dose (mg a.s. /day)**	**% of systemic AOEL**
Number of applications and application rate:		2 × 0.25 kg a.s./ha = 0.4 kg a.s./ha (MAF= 1.6)	
2 hours/day (1), TC: 2500 cm^2/person/h (2) Body weight: 60 kg Dermal absorption 36%	no PPE (3)	2.160	**240**
	with PPE (4)	0.432	48

(1) 2 h/day for professional applications for maintenance, inspection or irrigation activities etc. in cereals
(2) TC = 2500 cm2/person/ hour acc. to US Re-entry Agricultural TF data were used, TC: Transfer coefficient.
(3) Protective clothing
(4) Gloves

Conclusion

In calculations performed in EFSA model there is no possibility to use gloves by worker in opposite to EUROPOEM II. Current guidance *EFSA Journal 2014;12(10):3874* is missing data regarding TC value for worker equipped with gloves. New guideline *EFSA Journal 2022;20(1):7032* (not yet came into force) provides TC value for worker with covered body and **gloves**.
In accordance to ~~p~~Polish national requirements for toxicological section in case of multiple application of plant protection product **either** EFSA model **or** EUROPOEM II with MAF factor can be used:

*W przypadku, gdy proponowane jest wielokrotne zastosowanie środka w sezonie, do oceny narażenia pracownika należy zastosować model AOEM **lub** EUROPOEM II z uwzględnieniem współczynnika MAF.*

Considering that in EFSA model calculations risk was not accepted, and gloves could not be included EUROPOEM II calculations were presented.
According to the calculations of the worker exposure with the EUROPOEM II model, no undue risk is predicted for all uses supported in the EU central zone and applied with vehicle mounted sprayers. Estimated exposure of workers wearing work wear covering arms, body and legs and gloves is considered acceptable (48% AOEL).

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

No data on Dislodgeable foliar residue (DFR) refinement are available, therefore reference is made to the default value of 3 µg/cm^2 of foliage/kg a.s. applied/ha as indicated in the 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*).

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded 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.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

Comments of zRMS:	The resident exposure calculations for the proposed uses of CHR/F/PYRA 250 EC conducted by the Applicant using EFSA model including drift reduction and 5 meter buffer strip revealed that there is no acceptable risk resulting from entering into treated crops (child) after application of the product. The significant part of the resident exposure results from the entry into treated area, therefore this exposure could be lowered by installation of warning signs in prominent places informing about recent use of CHR/F/PYRA 250 EC together with information how long the entry into treated crops is prohibited. The drift reduction technology should include using low-drift nozzles and the generation of large spray droplets. The nozzles should be pointed back the direction of travel and spraying should be conducted at lowest possible high. As no AAOEL value was established for active substance pyraclostrobin, bystander's exposure is covered by resident's exposure.

6.6.5.1 Estimation of bystander and resident exposure

The exposure and risk assessments for bystanders and residents were performed in consideration of the most critical GAP use covering all other intended GAP uses for which authorisation is sought in the central zone. Table 6.6-6 shows the exposure model used for estimation of ~~bystander and~~ resident exposure to Pyraclostrobin. Outcome of the estimation is presented in Table 6.6-7. Detailed calculations are in Appendix 3.
Exposure of resident is used also for bystander because of no AAOEL was set up.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Cereals (max. 2 x 1 L product/ha)
Model(s)	EFSA exposure model [Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, European Food Safety Authority (EFSA), Parma, Italy, *EFSA Journal 2014;12(10):3874*]

Table 6.6-7: Estimated resident exposure

	Pyraclostrobin	
Model data	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Vehicle mounted-drift reduction downward spraying outdoors to low crops Application rate: 2 × 0.25 kg a.s./ha		
~~Bystanders (adult)~~ ~~Buffer strip: 5 m~~ ~~Body weight: 60 kg~~	~~0.0129~~	~~**86.20**~~
~~Bystanders (children)~~ ~~Buffer strip: 5 m~~ ~~Body weight: 10 kg~~	~~0.0303~~	~~**202.07**~~
Residents (adult) Buffer strip: 5 m weight: 60 kg	~~0.0129~~ All pathways 0.0120147	~~**86.20**~~ **80.10**
Residents (children) Buffer strip: 5 m Body weight:10 kg	~~0.0303~~ All pathways 0.0254722	~~**202.07**~~ **169.81**

An unacceptable risk for residents and bystanders was identified when the product is used as intended. The estimations performed according to AOEM, indicate that the systemic exposure to CHR/F/PYRA 250 EC exceeds the value of AOEL.

Therefore, additional counter-measures must be introduced to reduce resident and bystander exposure.

1. Based on the estimation according to AOEM, it can be concluded that the significant part of the resident exposure results from the entry to the treated area. Thus, to minimize the incidence of resident and bystander entry into the treated area, it is proposed to install warning signs informing about recent use of PPP next to the treated area and to inform the residents about the scheduled spraying action.

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0804700	0.0107000	0.0050210	0.2453650	0.2547222
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0080470	0.0010700	0.0005021	0.0245365	0.0254722
% of RVNAS	53.65%	7.13%	3.35%	163.58%	169.81%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0879271	0.0138000	0.0122065	0.8178834	0.7208844
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0014655	0.0002300	0.0002034	0.0136314	0.0120147
% of RVNAS	9.77%	1.53%	1.36%	90.88%	80.10%

2. The major of resident exposure to CHR/F/PYRA 250 EC includes spray drift of the applied formulation.

Following improvements of the application technique of CHR/F/PYRA 250 EC are recommended to reduce spray drift:

1. The application should result in generation of large spray droplets.
2. The application should be carried out using low-drift nozzles.
3. The nozzles should be pointed back the direction of travel.
4. The spraying should be conducted at lowest possible high.

Conclusion

According to the EFSA model calculations it can be concluded that there is no acceptable risk resulting from entering into treated crops to resident and bystanders (child) after application of CHR/F/PYRA 250 EC applied to cereals with a maximum rate of 0.25 kg a.s./ha, therefore warning signs informing about recent use of PPP should be installed in prominent places. As no AAOEL value was established for active substance pyraclostrobin, bystander's exposure is covered by resident's exposure.

6.6.5.2 Measurement of bystander and/or resident exposure

Since the bystander and/or resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for pyraclostrobin 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.

6.6.6 Combined exposure

Not relevant. The product contains only one active substance.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.1 – 7.1.10	Żero, K.	2021	*Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent substances; K. Żero; 2021* Not GLP Unpublished	N	Chemirol
KCP 7.2.1 KCP 7.2.2 KCP 7.2.3	Adamczak, A.	2021	*Toxicological calculations for CHR/F/PYRA 250 EC in cereals.* CHR1 Not GLP Unpublished	N	Chemirol
KCP 7.3	Egron, C.	2021	*IN-VITRO HUMAN SKIN PENETRATION OF 14C-PYRACLOSTROBIN IN PYRACLOSTROBIN 250 G/L* S20-06511 Eurofins Agroscience Services Chem SAS, Vergeze, France GLP Unpublished	N	Chemirol

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Not required.

A 2.2 Other/Special Studies

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation does not need to be classified as Acute Tox. 4 (H302).
Reference:	KCP 7.1.1
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent substances; K. Żero; 2021
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

According to point 7.1.1 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
" A test for acute oral toxicity shall be carried out, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, acute oral toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture."

The complete composition of the formulation with the classification of individual ingredients is available in part C.
Due to the fact, that all components of the formulation CHR/F/PYRA 250 EC are known, the acute oral toxicity test is not necessary.

We use the summation method using the formula:

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_i}}$$

Where:

- Ci - concentration of ingredient i (% w/w or % v/v)
- i – the individual ingredient from 1 to n
- n – the number of ingredients

- ATE_i - Acute Toxicity Estimate of ingredient i.

Table 3.1.2
Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for classification for the respective routes of exposure.

Exposure routes	Classification Category or experimentally obtained acute toxicity range estimate	Converted acute toxicity point estimate (see Note 1)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5 5 < Category 2 ≤ 50 50 < Category 3 ≤ 300 300 < Category 4 ≤ 2 000	0,5 5 100 500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50 50 < Category 2 ≤ 200 200 < Category 3 ≤ 1 000 1 000 < Category 4 ≤ 2 000	5 50 300 1 100
Gases (ppmV)	0 < Category 1 ≤ 100 100 < Category 2 ≤ 500 500 < Category 3 ≤ 2 500 2 500 < Category 4 ≤ 20 000	10 100 700 4 500
Vapours (mg/l)	0 < Category 1 ≤ 0,5 0,5 < Category 2 ≤ 2,0 2,0 < Category 3 ≤ 10,0 10,0 < Category 4 ≤ 20,0	0,05 0,5 3 11
Dust/mist (mg/l)	0< Category 1 ≤ 0,05 0,05 < Category 2 ≤ 0,5 0,5 < Category 3 ≤ 1,0 1,0 < Category 4 ≤ 5,0	0,005 0,05 0,5 1,5

Note 1
These values are designed to be used in the calculation of the ATE for classification of a mixture based on its components and do not represent test results.

Ingredients A_2, B and D_2 are classified in this class of hazard.

- A_2 – 0.4149% (Acute Tox. 4, H302)
- B – 22.90% (Acute Tox. 4 H302)
- D_2 – 0.7544% (Acute Tox. 4 H302)

For all ingredients the estimated values were taken.

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_{mix}}} = \frac{100}{\frac{22.90}{500} + \frac{0.7544}{500} + \frac{0.4149}{500}} = 2077 \frac{mg}{kg} b.w.$$

Conclusion

According to the table 3.1.2, a result (2 077 mg/kg bw > 2 000 mg/kg bw) **does not classify** the whole formulation as Acute Tox. 4, H302.

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

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The formulation does not contain compounds classified as acute dermal toxic, therefore the whole formulation does not need to be classified in this class of hazard.

According to point 7.1.2 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:

"A test for dermal toxicity shall be carried out on a case by case basis, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, acute dermal toxicity of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the toxic potential of the total mixture. Findings of severe skin irritation or corrosion in the dermal study may be used instead of performing a specific irritation study."

The complete composition of the formulation with the classification of individual ingredients is available in part C.

The active substances and the other co-formulants are not classified as acute dermal toxic, it can be assumed that entire formulation is not classified in this class. According to point 7.1.2 of part A of Annex Regulation No 284/2014, it is possible to waive from acute dermal toxicity test. Due to the fact, that all components of the formulation CHR/F/PYRA 250 EC are known, the acute dermal toxicity test is not necessary.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation need to be classified as Acute Tox. 4 (H332).

Reference:	KCP 7.1.3
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent sub-stances; K. Żero, 2021.
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

Inhalation study on CHRF/PYRA 250 EC is not required according to point 7.1.3 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products the inhalation test must be carried out since the preparation is:

- a gas or liquefied gas,
- a smoke generating formulation or fumigant,
- used with fogging equipment,
- a vapor releasing preparation,
- an aerosol,
- a powder containing a significant proportion of particles of diameter <50 µm (> 1% on a weight basis),
- to be applied from aircraft in cases where inhalation exposure is relevant,
- contains an active substance with a vapor pressure > $1x10^{-2}$ Pa and is to be used in enclosed spaces such as warehouses or glasshouses,
- to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 µm (> 1% on a weight basis).

The complete composition of the formulation with the classification of individual ingredients is available in part C.
Due to the fact, that all components of the formulation CHR/F/PYRA 250 EC are known, the acute inhalation toxicity test is not necessary.

Ingredient C is classified in this hazard class.

- C – 24.06 % (Acute Tox. 3 H331)

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_{mix}}} = \frac{100}{\frac{24.06}{3}} = 12.5\ mg/L$$

Conclusion

According to the table 3.1.2, the result (10.0 mg/L > **12.5 mg/L** < 20.0 mg/L) **classifies** the whole formulation as **Acute Tox. 4, H332**

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation need to be classified as Skin Irrit. 2 (H315).

Reference:	KCP 7.1.4
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent sub-stances; K. Żero, 2021.

Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

According to point 7.1.4 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
" The skin irritancy of the plant protection product shall be reported based on the tiered approach, unless the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, skin irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture."
The complete composition of the formulation with the classification of individual ingredients is available in part C.
Due to the fact, that all components of the formulation CHR/F/PYRA 250 EC are known, skin corrosive test is not necessary.

Table 3.2.3
Generic concentration limits of ingredients classified for skin corrosive/irritant hazard (Category 1 or 2) that trigger classification of the mixture as corrosive/irritant to skin.

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin Corrosive	Skin Irritant
	Category 1 (see note below)	Category 2
Skin Corrosive Categories 1A, 1B, 1C	≥ 5 %	≥ 1 % but < 5 %
Skin irritant Category 2		≥ 10 %
10 × Skin Corrosive Category 1A, 1B, 1C) + Skin irritant Category 2		≥ 10 %

Ingredients C, D_1 and D_2 are relevant.

- C – 24.06% (Skin Irrit., 2 H315)
- D_1 – 3.112% (Skin Irrit., 2 H315)
- D_2 – 0.7544 % (Skin Irrit., 2 H315)

We use the summation method, consisting in adding up the percentages of all ingredients classified in the each class.

$$\sum C_{SkinIrrit.} = 24.06\% + 3.112\% + 0.7544\% = 27.9264\%$$

Conclusion

The sum of concentrations (27.9264 %) is significantly higher than generic concentration level (10%). Therefore the formulation **is classified as Skin Irrit. 2, H315.**

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation need to be classified as Eye Dam. 1 (H318).
Reference:	KCP 7.1.5
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent sub-stances; K. Żero, 2021.
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

According to point 7.1.5 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:
" Eye irritation tests shall be provided, unless it is likely that severe effects on the eyes may be produced or the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, eye irritation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture."
The complete composition of the formulation with the classification of individual ingredients is available in part C.
Due to the fact, that all components of the formulation CHR/F/PYRA 205 EC are known, eye irritation test is not necessary.
For consideration of corrosive and irritant properties the following table applies:

Table 3.3.3
Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/ or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2).

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Category 1	Category 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C	≥ 3 %	≥ 1 % but < 3 %
Eye Effects Category 2		≥ 10 %
(10 × Eye Effects Category 1) + Eye effects Category 2		≥ 10 %
Skin Corrosive Category 1A, 1B, 1C +	≥ 3 %	≥ 1 % but < 3 %

Eye effects Category 1		
10 × (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

Ingredients D_1 and D_2 are relevant.

- D_1 – 3.112% (Eye Dam. 1, H318)
- D_2 – 0.7544% (Eye Dam. 1, H318)

We use the summation method, consisting in adding up the percentages of all ingredients classified in the each class.

$$\sum C_{SkinCorr.} + \sum C_{EyeDam} = 3.112\ \% + 0.7544\ \% = 3.8664\%$$

The sum of concentration (3.8664%) is higher than a generic concentration limit (3%). Therefore the whole formulation **is classified as corrosive to eyes (Eye Dam. 1 H318)**.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The formulation does not contain compounds classified as skin sensitiser, therefore the whole formulation does not need to be classified in this class of hazard.

According to point 7.1.6 of Part A of Annex to the Commission Regulation (EU) No 284/2013 as regards the data requirements for plant protection products:

"The skin sensitisation test shall be carried out unless the active substances or co-formulants are known to have sensitising properties or the applicant can justify an alternative approach under Regulation (EC) No 1272/2008. In the latter case, skin sensitisation properties of all components shall be provided or reliably predicted with a validated method. Consideration shall be given to the possible effects of components on the sensitising potential of the total mixture."

The complete composition of the formulation with the classification of individual ingredients is available in part C.

The active substances and the other co-formulants are not classified as skin sensitizers, it can be assumed that entire formulation is not classified in this class. According to point 7.1.6 of part A of Annex Regulation No 284/2014, it is possible to waive from skin sensitization. Due to the fact, that all components of the formulation CHR/F/PYRA 250 EC are known, the skin sensitisation test is not necessary.

A 2.8 Specific target organ toxicity (KCP 7.1.7)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation does not need to be classified as STOT SE 3 (H335) and STOT SE 3 (H336).

Reference:	KCP 7.1.7
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent substances; K. Żero, 2021.
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

For consideration of specific target organ toxicity the following table applies:

Table 3.8.3 Generic concentration limits of ingredients of a mixture classified as a specific target organ toxicant that trigger classification of the mixture as Category 1 or 2.

Ingredient classified as:	Generic concentration limits triggering classification of the mixture as:	
	Category 1	Category 2
Category 1 Specific Target Organ Toxicant	Concentration ≥ 10 %	1,0 % ≤ concentration < 10 %
Category 2 Specific Target Organ Toxicant		Concentration ≥ 10 % [(Note 1)]

Note 1 If a Category 2 specific target organ toxicant is present in the mixture as an ingredient at a concentration
≥ 1,0 % a SDS shall be available for the mixture upon request.

We also took into account the point 3.8.3.4.5.: "Care shall be exercised when extrapolating toxicity of a mixture that contains Category 3 ingredient(s). A generic concentration limit of 20 % is appropriate; however, it shall be recognised that this concentration limit may be higher or lower depending on the Category 3 ingredient(s) and that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20 % value. Expert judgement shall be exercised."

STOT SE 3, H335

The ingredient D_2 is classified as STOT SE 3. The concentration of the ingredient (0.7544%) is significantly lower than concentration triggering classification 20%. According to point 3.8.3.4.5. CLP Regulation the formulation is **not classified** as STOT SE 3, H335

STOT SE 3, H336

The ingredient D_2 is classified as STOT SE 3. The concentration of the ingredient (0.7544%) is significantly lower than concentration triggering classification 20%. According to point 3.8.3.4.5. CLP Regulation the formulation is **not classified** as STOT SE 3, H336.

A 2.9 Carcinogenicity (KCP 7.1.8)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation does not need to be classified as carcinogenic.
Reference:	KCP 7.1.8
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent substances; K. Żero, 2021.
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

The mixture will be classified as a carcinogen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 carcinogen and is present at or above the appropriate generic concentration limit as shown in Table 3.6.2 for Category 1A, Category 1B and Category 2 respectively.

For consideration of carcinogenicity the following table applies:
Table 3.6.2 Generic concentration limits of ingredients of a mixture classified as carcinogen that trigger classification of the mixture

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:		
	Category 1 carcinogen		Category 2 carcinogen
	Category 1A	Category 1B	
Category 1A carcinogen	≥ 0,1 %	-	-
Category 1B carcinogen	-	≥ 0,1 %	
Category 2 carcinogen	-	-	≥ 1,0 % [Note 1]

Note The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).
Note 1 If a Category 2 carcinogen is present in the mixture as an ingredient at a concentration ≥ 0,1 % a SDS shall be available for the mixture upon request.

Only ingredient A_2 is relevant.

- A_2 – 0.4149% (Carc. 2, H351)

Conclusion

A concentration of this compound is lower than concentration triggering classification. Therefore the formulation has **no classification** in this category.

A 2.10 Aspiration toxicity (KCP 7.1.9)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The calculations provided by Applicant are acceptable. According to the calculation result the formulation does not need to be classified as Asp. Tox 1 (H304).
Reference:	KCP 7.1.9
Report	Toxicological classification of product CHR/F/PYRA 250 EC based on calculation method taking into consideration health hazards of constituent substances; K. Żero, 2021.
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

For consideration of aspiration toxicity the following table applies:

Table 3.10.1
Hazard category for aspiration toxicity.

Category	Criteria
Category 1	Substances known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard A substance is classified in Category 1: (a) based on reliable and good quality human evidence or (b) if it is a hydrocarbon and has a kinematic viscosity of 20,5 mm^2/s or less, measured at 40 °C.

Only ingredient A_1 is relevant:

- A_1 – 41.49% (Asp. Tox 1, H304)

Viscosity of formulation: 0,2455 cm^2/s (40°C) = 24,55 mm^2/s (40°C)

Conclusion

Viscosity level of product is higher than generic concentration level (20,5 mm^2/s (40 °C)) Therefore the formulation is **not classified** as Asp. Tox 1, H304.

A 2.11 Reproductive toxicity (KCP 7.1.10)

Comments of zRMS:	The Applicant performed the toxicological assessment of the formulation CHR/F/PYRA 250 EC using the calculation method in accordance with CLP based on the composition of the formulation and taking into account the classification of each component of the mixture. The formulation does not contain compounds classified as toxic for reproduction, therefore the whole formulation does not need to be classified in this class of hazard.

The complete composition of the formulation with the classification of individual ingredients is available in part C.

The active substances and the other co-formulants of CHR/F/PYRA 250 EC are not classified as toxic for reproduction, it can be assumed that entire formulation is not classified in this class.

Summary

Having considered risk to the human health posed by ingredients of the preparation, product is classified as Acute Tox. 4, H332, Eye Dam. 1, H318, Skin Irrit. 2, H315.

A 2.12 Supplementary studies for combinations of plant protection products

Not required.

A 2.13 Data on co-formulants (KCP 7.4)

A 2.13.1 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 2.13.2 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 2.14 Studies on dermal absorption (KCP 7.3)

Comments of zRMS:	Study accepted. The *in vitro* study on dermal absorption of ^{14}C-Pyraclostrobin in Pyraclostrobin 250 G/L was performed according to the Regulation (EC) 440/2015 and OECD and EFSA guidance in compliance with GLP rules. No deviation was

	occurred during the study. The formulation was tested at the concentrated rate (250 g/L) and at the spray dilution 0.1 g/L. The results of the study revealed that the amount of applied dose penetrating within 24 hours was 1.5 % and 36 % for the formulation concentrate and the spray dilution, respectively, based on the EFSA guidance criteria.

Reference:	KCP 7.3
Report	*IN-VITRO HUMAN SKIN PENETRATION OF 14C-PYRACLOSTROBIN IN PYRACLOSTROBIN 250 G/L,* Camille Egron; 2021 Eurofins Agroscience Services Chem SAS 75B avenue de Pascalet 30310 Vergèze FRANCE STUDY CODE: S20-06511
Guideline(s):	- Regulation (EC) No 440/2008 – Test method B.45 - OECD guideline for the testing of chemicals: Test No. 428: Skin Absorption: in vitro Method (13 April 2004) - OECD guidance document for the conduct of skin absorption studies, OECD series on testing and assessment. Number 28, 05-Mar-2004 (ENV/JM/MONO(2004)2) - OECD Guidance notes on dermal absorption, 18 August 2011 (ENV/JM/MONO(2011)36) - Guidance on Dermal Absorption, EFSA Journal 2017; 15(6): 4873
Deviations:	No
GLP:	Yes
Acceptability:	Yes
Duplication (if vertebrate study)	No

Materials and methods:

Test item:

Test material		
Radiolabeled material	Name (Lot/Batch No.)	[-^{14}C]-Pyraclostrobin Batch 11660GXR009-3
	Test preparation	Spiking
	Specific activity	148.0 µCi/mg
	Radiochemical purity	96.9 %
Product	Name (Lot/Batch No.)	Pyraclostrobin 250 g/L Batch 04/2020
	Concentration a.s.	g/L or g/kg
	Formulation type	Emulsion Concentrate
Blank product	Name (Lot/Batch No.)	Batch 04/2020 B
	Concentration a.s.	0 g/L Pyraclostrobin

Test system:

Test system		
Diffusion cell	Cell type	Dynamic
	(if dynamic) Flow rate	1.5 ml/h
	Exposed skin area	1 cm²
	Cover	Unoccluded
Membrane	Skin type	Dermatomed
	Skin thickness range	356-396 µm
	Skin donors age	22 to 51 years old
	Skin donors sex	f
	Location	Abdomen
	Source	*Ex vivo*
	Integrity test	TEWL measurement
Receptor	Receptor medium	PBS 0.01M + 3% polyoxyethylene 20 oleyl ether
	Solubility in receptor medium	Yes
Sample Time	Exposure time	8h
	Observation time	24h
Sampling	Sample intervals	7 sampling times: 1h, 2h, 4h, 8h, 12h, 18h, 24h
Washing		Post exposure
Final Procedure	Tape stripping	Yes
	TS1-2 analysed separately	Yes
Remarks: None		

Test doses:

Tested doses	Concentrate	Spray dilution 1:2500
Target concentration [mg/ml]	250	0.1
Area dose [µg/cm²]	2500	1
Mean actual applied dose [µg/cm²]	2354	0.97
Specific activity [kBq/ml]	1176	555
No. of donors	4	4
No of cells used/valid cells*	8/8	8/8

Experimental design:

The aim of this study was to investigate the rate and extent of the in-vitro dermal absorption of pyraclostrobin following topical application of Pyraclostrobin 250 g/L test item, to the surface of human split-thickness skin mounted on flow-through diffusion cells, at the concentrated rate and one in-use spray dilution.

The "OECD guideline for the testing of chemicals: Test No. 428: Skin Absorption: in vitro Method (13 April 2004)" recommends using a radiolabelled substance to perform this type of study.

The study was also designed using recommendations from EFSA Guidance on Dermal Absorption (EFSA Journal 2017; 15(6): 4873).
The concentrate formulation and the spray dilution containing 14C-pyraclostrobin were applied to the surface of split-thickness human skin samples separating the donor and receptor chambers of a flow-through diffusion cell. The formulations remained on the skin for 8 hours before removal by an appropriate washing solution. The receptor fluid was sampled seven times at 1h, 2h, 4h, 8h, 12h, 18h and 24h from the commencement of application.
The radioactivity was measured in each compartment in order to recover a global mass balance.
The formulations were tested at two nominal concentrations:
– Concentrated rate : pyraclostrobin 250 g/L
– Diluted rate : pyraclostrobin 0.1 g/L

Results and discussion:

The mean results obtained are presented in the following table.

In-vitro dermal penetration of pyraclostrobin formulated as Pyraclostrobin 250 g/L through human skin - Recovery data

Dose group		High dose (Formulation concentrate) n=8		Low dose (Spray dilution 1:2500) n=8	
Target concentration	[mg/mL]	250		0.1	
Target dose	[µg/cm²]	2500		1	
Mean actual applied dose	[µg/cm²]	2354		0.97	
		Recovery [%]		Recovery [%]	
		Mean	S.D.	Mean	S.D.
Dislodgeable dose					
Skin washing after 8 h		101.18	2.72	58.87	12.60
Donor chamber wash		0.36	0.13	0.71	0.14
Dose associated to skin					
Tape strips: 1st sample, strips 1 + 2		0.12	0.04	12.84	5.86
Tape strips: 2nd sample; strips 3 - n		0.44	0.30	11.73	4.07
Skin preparation		0.28	0.14	13.79	11.30
Absorbed dose					
Receptor fluid		0.17	0.19	4.71	2.47
Receptor chamber wash		0.21	0.04	0.39	0.13
Total recovery [1]		102.71	2.60	100.10	3.16
Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at $t_{0.5}$]		No [55.4% ± 20.0]		No [58.7% ± 14.7]	
If no: Absorption estimates = absorbed dose + skin preparation + tape strips sample 2) [2]		1.05	0.47	27.7	9.67
If yes: Absorption estimates = absorbed dose + skin preparation		N/A	N/A	N/A	N/A
Absorption estimates used for risk assessment [3]		**1.5**		**36**	

[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.

[3] In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), total absorption = mean + k*SD, where k= 0.84 based on the number of replicates employed (n=8).

BLQ : below the limit of quantification ; N/A: not applicable ; SD: standard deviation

The dermal penetration of pyraclostrobin formulated as Pyraclostrobin 250 g/L through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 1.5 % (mean + k * SD) and 36 % for the formulation concentrate and the 1:2500 spray dilution, respectively, based on the EFSA guidance criteria.

Appendix 3 Exposure calculations

Table A 1: Estimation of operator exposure towards pyraclostrobin without PPE using EFSA Model ver. 30.03.2015

Operator exposure for Pyraclostrobin 250 EC outdoor spray applications

Application rate of active substance	0.25	kg a.s./ha	AppRate
Assumed area treated	50	ha/day	AreaTreated
Amount of active substance applied	12.5	kg a.s./day	AmountAS
Dermal absorption of the product	1.50%		AbsorpProduct
Dermal absorption of in-use dilution	36.00%		AbsorbUse
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	33946	127188	AOEM	
	Body	21056	150023	AOEM	
	Head	649	3557	AOEM	
	Protected hands (gloves)	178	2476	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	223	1828	AOEM	
	Protected head (hood and face shield)	10	201	AOEM	
	Inhalation	8	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		cl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	785	3567	AOEM	
	Body	161	164	AOEM	
	Head	6	14	AOEM	
	Protected hands (gloves)	13	72	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	6	6	AOEM	
	Inhalation	4	6	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted	

1. Total

	Without RPE/PPE	With RPE/PPE
Longer term		
Total systemic exposure from mixing, loading and application (mg a.s./day)	1.1889711	1.1889711
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0198162	0.0198162
% of RVNAS	132.11%	132.11%

Table A 1: Estimation of operator exposure towards pyraclostrobin with workwear at mixing and loading using EFSA Model ver. 30.03.2015

Operator exposure for Pyraclostrobin 250 EC outdoor spray applications

Application rate of active substance	0.25	kg a.s./ha	i_AppRate
Assumed area treated	50	ha/day	d_AreaTreated
Amount of active substance applied	12.5	kg a.s./day	i_AmountAS
Dermal absorption of the product	1.50%		i_AbsorpProduct
Dermal absorption of in-use dilution	36.00%		i_AbsorbUse
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	33946	127188	AOEM	
	Body	21056	150023	AOEM	
	Head	649	3557	AOEM	
	Protected hands (gloves)	178	2476	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	223	1828	AOEM	
	Protected head (hood and face shield)	10	201	AOEM	
	Inhalation	8	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	ork wear - arms, body and legs covered		cl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	785	3567	AOEM	
	Body	161	164	AOEM	
	Head	6	14	AOEM	
	Protected hands (gloves)	13	72	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	6	6	AOEM	
	Inhalation	4	6	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	ork wear - arms, body and legs covered		cl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted	

1. Total

	Without RPE/PPE	With RPE/PPE
Longer term		
Total systemic exposure from mixing, loading and application (mg a.s./day)	1.1889711	0.8205036
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0198162	0.0136751
% of RVNAS	132.11%	91.17%

Table A 3: Estimation of worker exposure towards pyraclostrobin using EUROPO-EM II Model

WORKER EXPOSURE			EUROPOEM II MODEL	
form	EC		Re-entry in the field	
a.s.	Pyraclostrobin			
Parameter		**Value**	**Unit**	**References, comments**
Re-entry activities in the field				
AR	Application rate	0.4	kg a.s./ha	summary of intended uses
Worker				
Duration				
T		2	hours / day	default: 6 h (Europoem II)
Inhalation Exposure				without PPE
	no model available	-		
Dermal Exposure				
DF	Dislodgeable foliar residue	30	mg a.s./m2/kg a.s./ha	default (Europoem II)
TC	Transfer coefficient	0.25	m2/ hour	vegetable (field): 0.25; ornamentals: 0.5; small fruit: 0.3; large fruit: 0.45 (Europoem II)
Dermal Exposure		**6**	mg a.s./ day	DE = DFR x AR x TC x T
Internal exposure				
DA	Dermal Absorption	36	%	
	PPE-factor dermal	5		gloves*
	AOEL	0.9	mg a.s./ day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s./ day]	[mg a.s./ day]	
	Inhalation	-	-	no model available
	Dermal	2.160	0.432	DE(int) = DE x (DA/100)
	Total	**2.160**	**0.432**	**sum**
	% AOEL			
	Inhalation	-	-	no model available
	Dermal	240	48	%AOEL = 100 x DE(int) / AOEL
	Total	**240**	**48**	**sum**

* It is assumed in the used TC values, that body exposure is already reduced by (protective) clothing. The use of gloves will result in an extra reduction factor of 5.

Table A 4: Estimation of worker exposure towards pyraclostrobin using EFSA Model

Worker exposure from residues on foliage for Pyraclostrobin 250 EC			
Crop type	Cereals		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.25	kg a.s./ha	i_AppRate
Number of applications	2		i_AppNo
Interval between multiple applications	21	days	i_AppInt
Half-life of active substance	30	days	d_HalfLifeAS
Multiple application factor	1.6		d_MAF
Dermal absorption of the product	1.50%		i_AbsorpProduct
Dermal absorption of the in-use dilution	36.00%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.75	µg a.s./cm²	d_DFR
Working hours	2	hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	12500	cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	1400	cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs coverec	available for this assessment	cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear – arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	10.9051124	1.2213726	no TC available for this	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.1817519	0.0203562		
% of RVNAS	1211.68%	135.71%		

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	10.9051124	0.1817519	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/10001*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	1.2213726	0.0203562	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/10001*i_AbsorpInuse	
Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/10001*i_AbsorpInuse	
Inhalation				Na for outdoor activities

Table A 5: Estimation of bystander and resident exposure towards pyraclostrobin using EFSA Model

Resident exposure for Pyraclostrobin 250 EC

Croptype	Cereals		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		i_AppEquip
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		i_FormVal
Buffer strip	5	m	i_Buffer
Application rate of the product	0.25	kg a.s./ha	i_AppRate
Concentration of active substance (in-use dilution for liquid applications)	2.5	g a.s./l	i_Conc_AS
Dermal absorption of product	1.50%		i_AbsorpProduct
Dermal absorption of in-use dilution	36.00%		i_AbsorpHours
Oral absorption	100.00%		i_AbsorpOralHours
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.75	µg a.s./cm²	i_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5*10-3Pa	Pa	i_Volat
Concentration in air	0.001	mg/m³	i_AirCon
Resident dermal spray drift exposure 75th percentile - adult	0.23798	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.2175	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.00009	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00017	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.12278	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.12	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.00008	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00014	ml spray dilution/person	
Exposure duration dermal	2	hours	i_ResExpDur
Exposure duration inhalation	24	hours	i_ResExpDurInhal
Exposure duration entry into treated crops	0.25	hours	i_ExpDurTreatCrop
Light clothing adjustment factor	18.0%		i_ClothAF
Breathing rate adult	0.23	m³/day/kg	i_BreathRAd
Breathing rate child (1-3 year old)	1.07	m³/day/kg	i_BreathRCh
Drift percentage on surface (75th percentile)	2.30%		
Drift percentage on surface (mean)	1.80%		
Turf transferable residues percentage	5.00%		i_Turf
Transfer coeff. of surface deposits-adult	7300	cm²/hour	i_TcTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm²/hour	i_TcTCCh
Saliva extraction percentage	50.00%		i_SalExt
Surface area of hands mouthed	20	cm²	i_AreaHM
Frequency of hand to mouth activity	9.5	events/hour	i_FreqHM
Ingestion rate for mouthing of grass per day	25	cm²	i_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.00%		i_DSF
Transfer coefficient for entry into treated crops (75th percentile) -	7500	cm²/h	i_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentile) -	2250	cm²/h	i_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm²/h	i_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1794	cm²/h	i_TcEntryCh

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0804700	0.0107000	0.0050210	0.2453650	0.2547222
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0080470	0.0010700	0.0005021	0.0245365	0.0254722
% of RVNAS	53.65%	7.13%	3.35%	163.58%	169.81%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0879271	0.0138000	0.0122065	0.8178834	0.7208844
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0014655	0.0002300	0.0002034	0.0136314	0.0120147
% of RVNAS	9.77%	1.53%	1.36%	90.88%	80.10%

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Not required.