FINAL REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: **CHR/ZF/PROTI 100 FS**

Product name(s):

Gamelan 100 FS

Doraltes 100 FS

Chemical active substance(s):

Prothioconazole, 100 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Innvigo Sp. z o.o.

Submission date: 07.2021

MS Finalisation date: 05/09/2022

Version history

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

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

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on CHR/ZF/PROTI*

Product name and code	CHR/ZF/PROTI
Formulation type	FS (Flowable concentrate for seed treatment)
Active substance(s) (incl. content)	Prothioconazole; 100 g/L
Function	Fungicide seed treatment
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/ZF/PROTI 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/ZF/PROTI according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Skin Sens. 1A Aquatic Chronic 2
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS07, GHS09
Signal word	Warning
Hazard statement(s)	H317 - May cause an allergic skin reaction. H411 - Toxic to aquatic life with long-lasting effects
Precautionary statement(s)	P261 - Avoid breathing mist/vapours/spray. P272 - Contaminated work clothing should not be allowed out of the workplace. P280 – Wear protective gloves/protective clothing/eye protection/face protection P302 + P352- IF ON SKIN: Wash with plenty of water with soap. P333+P313 - If skin irritation or rash occurs: Get medical advice/attention. P362+P364 - Take off contaminated clothing and wash it before reuse. P391 – Collect spillage. ~~OPERATOR:~~ ~~*„Stosować rękawice ochronne oraz odzież roboczą w trakcie przygotowywania cieczy użytkowej oraz w trakcie wykonywania zabiegu."*~~ ~~"Wear protective gloves work wear during mixing and loading and application."~~ ~~For polish version: see the label~~
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]
	Contains: 2-methyloisothiazol-3(2H)-on, 1,2-benzisothiazol-3(2H)-on

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for CHR/ZF/PROTI

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Coverall Gloves during mixing/loading, calibration and cleaning. Due to the hazard characterisation gloves also during bagging.
Workers	Acceptable	~~None~~ Coverall
Residents	Acceptable	None
Bystanders	Acceptable	

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

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

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

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ******	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****)**	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/100 kg seeds** **a) a.s. 1** **b) a.s. 2**	**Water L/100 kg seeds** **min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
3, 4, 5	Winter wheat, winter rye, winter triticale (BBCH 00)	F	Seed dressing	n/a	0.01 kg prothioconazole /100 kg seeds Max. 250 kg treated seeds/ha	0.7	n/a	Operator, worker: SeedTropex model Bystander/resident: 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	R	R	A	A

* 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 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)

	Prothioconazole
Common Name	Prothioconazole
CAS-No.	178928-70-6
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	**Hazard classes (s), categories**: Aquatic Acute 1 Aquatic Chronic 1 **Code(s) for hazard pictogram(s): GHS09** **Signal word:**

	Prothioconazole
	Warning **Hazard statement(s):** H400 – Very toxic to aquatic life H410 – Very toxic to aquatic life with long lasting effects **Precautionary statement(s):** P273 – Avoid release to the environment P391 – Collect spillage
Additional C&L proposal	Not required. Opinion proposing harmonised classification and labelling at EU level of Prothioconazole (ISO) – Adopted 15 March 2019
Agreed EU endpoints	
AOEL systemic	0.2 mg/kg bw/d (for active substance) 0.01 mg/kg bw/d (for Prothioconazole-desthio)
Reference	EFSA Scientific Report (2007) 106, 1-98, SANCO/3923 /07 – final (2021)
Conditions to take into account/critical areas of concern with regard to toxicology	
According to EFSA Scientific Report (2007) 106, 1-98 for prothioconazole	The metabolite prothioconazole-desthio is more toxic than Prothioconazole in the rat and rabbit developmental studies (the classification Repro cat 2, R61 is proposed)

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for CHR/ZF/PROTI 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/ZF/PROTI

Type of test, species, model system (Guideline)	**Result**	**Acceptability**	**Classification (acc. to the criteria in Reg. 1272/2008)**	**Reference**
LD_{50} oral, rat (calculation method)	> 2000 mg/kg bw	Yes	None	M. Kolodziej, 2021
LD_{50} dermal, rat (calculation method)	> 2000 mg/kg bw	Yes	None	M. Kolodziej, 2021
LC_{50} inhalation, rat (calculation method)	> 20 mg/L air	Yes	None	M. Kolodziej, 2021
Skin irritation, (calculation method)	Not Irritant	Yes	None	M. Kolodziej, 2020
Eye irritation, (calculation method)	Not Irritant	Yes	None	M. Kolodziej, 2021
Skin sensitisation, (calculation method)	Sensitising	Yes	Skin Sens. 1A, H317	M. Kolodziej, 2021

Supplementary studies for combinations of plant protection products	No data – not required		None	

Table 6.3-2: Additional toxicological information relevant for classification/labelling of CHR/ZF/PROTI

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	-	-	-	-
Toxicological properties of non-active substance(s) (relevant for classification of product)	2-methylisothiazol-3(2H)-one (0.003-0.005%)	Acute Tox. 3, H301 Acute Tox. 3, H311 Acute Tox. 2, H330 Skin Corr. 1B, H314 Eye Dam. 1, H318 Aquatic Acute 1, H400 (M=10); Aquatic Chronic 1, H410 (M=1) Skin Sens. 1A, H317 C≥0.0015%	~~M. Kolodziej, 2021~~ Regulation 1272/2008 /MSDS**	Skin Sens. 1A, H317
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

Comments of zRMS:	Accepted.

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

6.5 Dermal Absorption (KCP 7.3)

Prothioconazole-desthio is a relevant metabolite of prothioconazole with toxic effects but is not part of the formulation *per se*. Non-dietary risk assessment to this metabolite has to be conducted but not for tasks/scenarios where the concentrate product is involved. Only dermal absorption for the diluted metabolite has to be considered.

A summary of the dermal absorption rates for the active substance in CHR/ZF/PROTI 100 FS is presented in the following table.
New dermal absorption study was performed ~~and presented during the inclusion process~~ for Prothioconazole-desthio formulated as CHR/ZF/PROTI 100 FS.

Table 6.5-1: Dermal absorption rates for Prothioconazole and Prothioconazole-desthio in CHR/ZF/PROTI

	Prothioconazole		Prothioconazole-desthio	
	Value	**Reference**	**Value**	**Reference**
Concentrate	10%	EFSA default value*	-	RAR 2018# Formation of prothioconazole – desthio is not expected in the concentrate. According to DAR (2004) it may be formed in diluted prothioconazole formulations, particularly on clothing, skin or on certain plant surfaces during the drying process.
Dilution (dilution factor)	50%	EFSA default value*	50%	EFSA default value* Assuming 100% conversion of prothioconazole to prothioconazole-desthio
New data				
Concentrate	N/A	N/A	2.3%	C. Imart, 2021, Study number S21-03902 (prothioconazole-desthio 100 g/L)
Dilution (dilution factor)	N/A	N/A	~~1.8~~ 4.5%	C. Imart, 2021, Study number S21-03902 (prothioconazole-desthio 14 g/L)

- not applicable (see introduction above)
* Guidance on dermal absorption (EFSA Journal 2017;15(6):4873)
# EC Draft (Renewal) Assessment Report – Prothioconazole – RMS UK and Co-RMS France – February 2018

6.5.1 Justification for proposed values - Prothioconazole

New dermal absorption study was performed ~~and presented during the inclusion process~~ for Prothioconazole-desthio formulated as CHR/ZF/PROTI 100 FS.

Table 6.5-2: Default dermal absorption rates for Prothioconazole and Prothioconazole-desthio

	Value	Justification for value	Acceptability of justification
Prothioconazole			
Concentrate	10%	The product is a FS formulation containing 100 g	Yes

	Value	Justification for value	Acceptability of justification
Prothioconazole			
		active substance/L and then the default value for "Water-based/dispersed or solid" formulation concentrate applies (Guidance on dermal absorption (EFSA Journal 2017;15(6):4873))	
Dilution	50%	The product is a FS formulation and then the default value for "Water-based/dispersed or solid" formulation dilution applies (Guidance on dermal absorption (EFSA Journal 2017;15(6):4873))	Yes
Prothioconazole-desthio			
Concentrate	2.3%	The dermal penetration of prothioconazole-desthio formulated as CHR/ZF/PROTI 100 FS through human dermatomed skin was determined in vitro (C. Imart, 2021, Study number S21-03902). The amount of applied dose penetrating within 24 hours was determined to be 2.3 % (mean + k * SD) and ~~1.8~~ 4.5%for the formulation concentrate (100g/L) and the 1:7.14 spray dilution (14g/L), respectively, based on the guidances criteria: Guidance on Dermal Absorption, EFSA Journal 2017; 15(6): 4873. 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).	Yes
Dilution	~~1.8~~ 4.5%		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/ZF/PROTI 100 FS	
Formulation type	FS	
Category	Fungicide	
Active substance(s) (incl. content)	Prothioconazole 100 g/L	
AOEL systemic	Prothioconazole : 0.2 mg/kg bw/d	Prothioconazole-desthio : 0.01 mg/kg bw/d
Inhalation absorption	100%	
Oral absorption	100%	
Dermal absorption	Prothioconazole : Concentrate: 10% Dilution: 50%	Prothioconazole-desthio : Concentrate: 2.3% Dilution: ~~1.8~~ 4.5%

	(Default based on Guidance on dermal absorption (EFSA Journal 2017;15(6):4873))	(Based on the study result (C. Imart, 2021, Study number S21-03902) conducted for product CHR/ZF/PROTI 100 FS (formulation))

6.6.1 Selection of critical use(s) and justification

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

Justification
The critical GAP is for the same use rate used on winter wheat, winter rye and winter triticale seeds as seed dressing. The sowing rate of 250 kg seeds/ha will be considered for bystander and resident risk assessment.

6.6.2 Operator exposure (KCP 7.2.1)

Comments of zRMS:	Prothioconazole-desthio is formed after application of the product containing prothioconazole, therefore the risk assessment is also performed for Prothioconazole-desthio. In the line with the conservative approach, for the calculation of the exposure to Prothioconazole no conversion to Prothioconazole-desthio was assumed, whilst for the calculation of the exposure to Prothioconazole-desthio, 100% conversion from Prothioconazole was assumed. The Applicant calculated the operator exposure using the SeedTropex model declaring possession of a license to access human exposure assessment model (exposure data generated and owned by an industry task force). It is noted, that according to the document EFSA Agreement Number EFSA/PPR/2007/01 Final Report (28 November 2008) the SeedTropex exposure model is a predictive exposure model, based on proprietary data (SeedTropex Steering Group), for exposure evaluation for operators using seed treatment products and also those involved in sowing seed which has been treated with plant protection products. The exposure studies in the database were conducted in accordance with OECD guidelines and are GLP compliant. Seed treatment exposure scenarios are not covered by *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). According to the *Public consultation on the draft scientific opinion on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products* (Annex G, EFSA Journal 2022;20(1):7032) the new calculator EFSA still does not include a harmonized Seed Treatment Model. The new roadmap on the next step to be undertaken in the field of non-dietary exposure to PPPs being preparing be EFSA will be a chance to highlight such needs. It is noted that the SeedTropex Task Force has not yet finalised the work on the new model. According to the calculation performed by Applicant the risk for operator is acceptable provided that the operator uses coverall and protective gloves during all tasks (M/L, calibration and cleaning) except bagging (only coverall). The calculated exposure is 24% of the AOEL of prothioconazole and 75% of the AOEL of prothioconazole-desthio. Taking the above into account as well as the classification of the product CHR/ZF/PROTI 100 FS (Skin Sens.1A, H317) and good agriculture rules gloves are recommended also during bagging.

6.6.2.1 Estimation of operator exposure

A summary of the exposure model used for estimation of operator exposure to the active substance during

application of CHR/ZF/PROTI 100 FS according to the critical use(s) is presented in **Błąd! Nieprawidłowy odsyłacz do zakładki: wskazuje na nią samą.**. The outcome of the estimation is presented in

Critical use(s)	Winter wheat, winter rye and winter triticale (0.1 L product / 100 kg seeds)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 SeedTropex model , Unpublished, UK—FR, Industry data (1996)

Table 6.6-3. Detailed calculations are in A 2.2.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Winter wheat, winter rye and winter triticale (0.1 L product / 100 kg seeds)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 SeedTropex model , Unpublished, UK—FR, Industry data (1996)

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

		Prothioconazole		**Metabolite (prothioconazole-des-thio)**	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Seed dressing					
Application rate		0.01 kg a.s./100 kg seeds		0.00907 kg a.s./100 kg seeds (taking into account the molar ratio of prothio-conazole-desthio to prothioconazole 312.2/344.3=0.907)	
Spray application (SeedTropex model; geometric mean) Body weight: 60 kg	~~Work wear (arms, body and legs covered)~~ Coverall during M/L, calibration, bagging and cleaning + protective gloves during M/L, calibration and cleaning	0.0487	24	~~0.00704~~ 0.00753	~~70~~ 75

In the SeedTropex studies, operators wore working coveralls and protective gloves during all tasks except during bagging when only coveralls were worn.
Without any additional protective equipment, the risk is acceptable ~~is considered~~ and represents 24% of the AOEL of prothioconazole or 7~~0~~5% of the AOEL of prothioconazole-desthio.

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)

Comments of zRMS:	Prothioconazole-desthio is formed after application of the product containing prothioconazole, therefore the risk assessment is also performed for Prothioconazole-desthio. In the line with the conservative approach, for the calculation of the exposure to Prothioconazole no conversion to Prothioconazole-desthio was assumed, whilst for the calculation of the exposure to Prothioconazole-desthio, 100% conversion from Prothioconazole was assumed. The Applicant calculated the predicted potential worker exposure using the SeedTropex model declaring possession of a license to access human exposure assessment model (exposure data generated and owned by an industry task force). According to the calculation performed by Applicant the risk for worker is acceptable provided that the worker uses coverall. The calculated exposure during loading and sowing of treated seeds by CHR/ZF/PROTI 100 FS is 32% of the AOEL of prothioconazole and 56% of the AOEL of prothioconazole-desthio. Taking into account the good agriculture rules gloves are recommended during loading of seeds.

6.6.3.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model used for estimation of worker exposure handling a crop treated with CHR/ZF/PROTI 100 FS according to the critical use(s). Outcome of the estimation is presented in Table 6.6-5. Detailed calculations are in A 2.2.

Table 6.6-4: Exposure models for intended uses

Critical use(s)	Winter wheat, winter rye and winter triticale (0.1 L product / 100 kg seeds)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 SeedTropex model , Unpublished, UK—FR, Industry data (1996)

Table 6.6-5: Estimated worker exposure

		Prothioconazole		**Metabolite (prothioconazole-desthio)**	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Loading and sowing treated seeds Work rate: 10 hours/day					
Application rate		0.01 kg a.s./100 kg seeds		0.00907 kg a.s./100 kg seeds (taking into account the molar ratio of prothioconazole-desthio to prothioconazole 312.2/344.3=0.907)	
Loading and sowing (SeedTropex model; geometric mean)	~~Work wear (arms, body and legs covered)~~ Coverall	0.0644	32	0.00557	56

Body weight: 60 kg					

Four among the nineteen monitored workers wore gloves during loading and sowing.
The risk is acceptable for workers wearing a working coverall for prothioconazole and for its metabolite prothioconazole-desthio.
During loading of seeds, protective gloves could be recommended as a general good practice.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not applicable.

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 mentioned 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)

Comments of zRMS:	Prothioconazole-desthio is formed after application of the product containing prothioconazole, therefore the risk assessment is also performed for Prothioconazole-desthio. In the line with the conservative approach, for the calculation of the exposure to Prothioconazole no conversion to Prothioconazole-desthio was assumed, whilst for the calculation of the exposure to Prothioconazole-desthio, 100% conversion from Prothioconazole was assumed. No bystander and resident exposure is expected during and after the sowing of the treated seeds, however the Applicant calculated the resident exposure resulted from vapour using EFSA calculator. The predicted total systemic exposure to a child and adult resident calculated both for Prothioconazole and Prothioconazole-desthio is within acceptable limits, therefore the sowing of the seeds treated by CHR/ZF/PROTI 100 FS does not cause an unacceptable health risk. According to EFSA 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) 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. Therefore, exposure assessment for residents also covers bystander exposure.

6.6.4.1 Estimation of resident and bystander exposure

Exposure of resident is used also for bystander because of no AAOEL was set up.

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.

There are no specific bystander or resident exposure data for seed treatment products in the EFSA Guidance Document. The SeedTropex model (1996) does neither include exposure data for residents. As a surrogate for the time being, the most relevant way to conduct this evaluation is to consider that treated seeds are granules which are applied in-furrow. With this approach, the EFSA calculator can be used. Only the vapour pathway is considered.

Default value of dermal absorption was used for prothioconazole ~~-desthio~~ (Guidance on dermal absorption (EFSA Journal 2017;15(6):4873)) as a worst case scenario and values obtained in the study (C. Imart, 2021, Study number S21-03902) for prothioconazole-desthio.

Błąd! Nieprawidłowy odsyłacz do zakładki: wskazuje na nią samą. shows the exposure model(s) used for estimation of resident ~~and bystander~~ exposure to prothioconazole and prothioconazole-desthio. The outcome of the estimation is presented in Table 6.6-7 (longer term resident exposure) ~~and in **Błąd! Nie można odnaleźć źródła odwołania.** (acute bystander exposure).~~ Detailed calculations are in A 2.2.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Winter wheat, winter rye and winter triticale (0.1 L product / 100 kg seeds; max. sowing density of 250 kg seeds/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-7: Estimated resident ~~and bystander~~ exposure

		Prothioconazole		**Metabolite (prothioconazole-desthio)**	
Model data		**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Vehicle mounted in-furrow application of granules					
Number of applications and application rate		1 x 0.025 kg a.s./ha		1 x 0.022675 kg a.s./ha (taking into account the molar ratio of prothioconazole-desthio to prothioconazole 312.2/344.3=0.907)	
Resident child Body weight: 10 kg	Vapour (75th perc.)	0.00107	0.54	0.00107	11
Resident adult Body weight: 60 kg	Vapour (75th perc.)	0.000230	0.12	0.000230	2.3

6.6.4.2 Measurement of resident and/or bystander exposure

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

6.6.5 Combined exposure

Not relevant. The product contains only one active substance.
Exposure has to be considered either to prothioconazole or to its metabolite.

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 7.1.1 KCP 7.1.2 KCP 7.1.4 KCP 7.1.5 KCP 7.1.6	– Kolodziej, M.	2021	Toxicological classification of product CHR/ZF/PROTI based on calculation method taking into consideration health hazards of constituent substances; Chemirol Sp. z o.o. Non GLP Unpublished	N	Chemirol Sp. z o.o.
KCP 7.3	Imart, C.	2021	IN-VITRO HUMAN SKIN PENETRATION OF ^{14}C-PROTHIOCONAZOLE-DESTHIO IN CHR/ZF/PROTI 100 FS Eurofins Agroscience Services Chem SAS, Vergèze, France Study code: S21-03902 GLP Published	N	Chemirol Sp. z o.o.

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Not required.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Comments of zRMS:	Acceptable. Acute oral toxicity was determined taking into consideration valid data available on each of the components in the mixture. Since the calculated ATEmix for CHR/ZF/PROTI 100 FS is significantly higher than generic concentration level (2000 mg/kg bw), the formulation does not need to be classified as acute oral toxic according to the Regulation EC 1272/2008.

Reference:	KCP 7.1.1
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 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/ZF/PROTI 100 FS are known, the acute oral toxicity test is not necessary.

Materials and methods

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.

We use the table:

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 body-weight)	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 bod-yweight)	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.

Two ingredients are classified in this class of hazard.

- Acute Tox. 3, H301, ATE = 100 mg/kg
- Acute Tox. 4, H302, ATE = 500 mg/kg

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} ATE_i} = 1\ 666\ 667$$

Results and discussions

According to the table 3.1.2, the result (1 666 667 mg/kg bw) is significantly higher than generic concentration level (2 000 mg/kg bw).

Conclusion

According to the table 3.1.2, the result (1 666 667 mg/kg bw) is significantly higher than generic concentration level (2 000 mg/kg bw). Therefore the formulation is not classified as Acute Tox. 4, H302.

According to point 7.1.1 of part A of Annex Regulation No 284/2014, it is possible to waive from performing acute oral toxicity tests.

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

Comments of zRMS:	Acceptable. Acute dermal toxicity was determined taking into consideration valid data available on each of the components in the mixture. Since the calculated ATEmix for CHR/ZF/PROTI 100 FS is significantly higher than generic concentration level (2000 mg/kg bw), the formulation does not need to be classified as acute dermal toxic according to the Regulation EC 1272/2008.
Reference:	KCP 7.1.2
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 2021
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

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.

Due to the fact, that all components of the formulation CHR/ZF/PROTI 100 FS are known, the acute dermal toxicity test is not necessary.

Materials and methods

Only one ingredient is classified in this hazard class.

- Acute Tox. 3, H311

We use the values from table.

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_{mix}}} = 6\,000\,000$$

Results and discussions

According to the table 3.1.2, the result (6 000 000 mg/kg bw > > 2000 mg/kg bw) is significantly higher than concentration triggering classification.

Conclusion

According to the table 3.1.2, the result (6 000 000 mg/kg bw > > 2000 mg/kg bw) is significantly higher than concentration triggering classification and therefore the whole formulation is not classified as Acute Tox. 4, H312.

According to point 7.1.2 of part A of Annex Regulation No 284/2014, it is possible to waive from performing acute dermal toxicity tests.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Comments of zRMS:	Acceptable. Acute inhalation toxicity was determined taking into consideration valid data available on each of the components in the mixture. Since the calculated ATEmix for CHR/ZF/PROTI 100 FS is significantly higher than generic concentration level (20.0 mg/L), the formulation does not need to be classified as acute inhalation toxic according to the Regulation EC 1272/2008.

Reference:	KCP 7.1.3
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 2021
Guideline(s):	Regulation (EC) No. 1272/2008
Deviations:	-
GLP:	No
Acceptability:	Yes
Duplication (if vertebrate study)	No

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 study shall not be required if the applicant can justify an alternative approach under Regulation (EC) No 1272/2008, where applicable. For this purpose, acute inhalation 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/ZF/PROTI 100 FS are known, the acute inhalation toxicity test is not necessary.

Materials and methods

Two ingredients is classified in this hazard class.

- Acute Tox. 2, H330
- Acute Tox. 2, H330

LD_{50} is not known. Therefore the estimated values were used to the calculation.

$$ATE_{mix} = \frac{100}{\sum_{i=1}^{n} \frac{C_i}{ATE_{mix}}} = 5\,000$$

Results and discussions

According to the table 3.1.2, the result (5 000 mg/L > 20.0 mg/L) is significantly higher than generic concentration level.

Conclusion

According to the table 3.1.2, the result (5 000 mg/L > 20.0 mg/L) is significantly higher than generic concentration level. Therefore the formulation is not classified in this class of hazard.

According to point 7.1.3 of part A of Annex Regulation No 284/2014, it is possible to waive from performing acute inhalation toxicity tests.

A 2.5 Skin irritation (KCP 7.1.4)

Comments of zRMS:	Acceptable. Skin irritation was determined taking into consideration valid data available on each of the components in the mixture. According to the calculation result for CHR/ZF/PROTI 100 FS significantly lower than concentration triggering classification, the formulation does not need to be classified as skin irritant according to the Regulation EC 1272/2008.

A 2.5.1 Study 1

Reference:	KCP 7.1.4
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 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/ZF/PROTI 100 FS are known, skin corrosive test is not necessary.

SKIN CORROSION:

Materials and methods

One ingredient is classified in this hazard class.

- Skin Corr. 1B, H314

According to the table 3.2.3, the result (0.005%) is significantly lower than concentration triggering classification (1%).

Results and discussions

According to the table 3.2.3, the result is significantly lower than concentration triggering classification (1%).

Conclusion

According to the table 3.2.3, the result (0.005%) is significantly lower than concentration triggering classification (1%). Therefore the formulation is not classified as Skin Corr. 1B, H314.
According to point 7.1.4 of part A of Annex Regulation No 284/2014, it is possible to waive from performing skin irritation tests.

SKIN IRRITANT:

Materials and methods

Ingredient is classified as corrosive to skin. Additionally one ingredient is classified as irritant to skin.

- Skin Corr. 1B, H314
- Skin Irrit. 2, H315

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

$$10 \times \sum C_{SkinCorr.} + \sum C_{SkinIrrit.} = 0.055\%$$

Results and discussions

According to the table 3.2.3, the result (0.055%) is significantly lower than concentration triggering classification (10%).

Conclusion

According to the table 3.2.3, the result (0.055%) is significantly lower than concentration triggering classification (10%). Therefore the formulation is not classified as Skin Irrit. 2, H315.
According to point 7.1.4 of part A of Annex Regulation No 284/2014, it is possible to waive from performing skin irritation tests.

A 2.6 Eye irritation (KCP 7.1.5)

Comments of zRMS:	Acceptable. Eye irritation was determined taking into consideration valid data available on each of the components in the mixture. According to the calculation result for CHR/ZF/PROTI 100 FS significantly lower than concentration triggering classification, the formulation does not need to be classified as eye irritant according to the Regulation EC 1272/2008.

A 2.6.1 Study 1

Study 1

Reference:	KCP 7.1.5
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 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 pro-duced 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/ZF/PROTI 100 FS are known, eye irritation test is not necessary.

Materials and methods

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 + Eye effects Category 1	≥ 3 %	≥ 1 % but < 3 %
10 × (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		≥ 10 %

EYE CORROSION:
Two ingredients are classified in this class of hazard.

- Eye Dam. 1, H318
- Eye Dam. 1, H318

$$\sum C_{EyeDam.} = 0.01\%$$

Conclusion

The sum of the concentration of components classified as corrosive to eyes (0.01%) is lower than generic concentration level (1%). Therefore the whole formulation is not classified as corrosive to eyes.
According to point 7.1.5 of part A of Annex Regulation No 284/2014, it is possible to waive from performing eye corrosion tests.

EYE IRRITANT:
Three ingredients are classified in this class of hazard.

- Eye Irrit. 2, H319
- Eye Dam. 1, H318
- Eye Dam. 1, H318

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

$$10 \times \sum C_{EyeCorr.} + \sum C_{EyeIrrit} = 3.8\%$$

Conclusion

The sum of concentration (3.8%) is higher than a concentration triggering classification. Therefore the whole formulation is not classified as irritant to eyes.
According to point 7.1.5 of part A of Annex Regulation No 284/2014, it is possible to waive from performing eye corrosion tests.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Acceptable. Skin sensitizing potential was determined taking into consideration valid data available on each of the components in the mixture. One component of formulation is classified as sensitizer at the concentration higher than the specific concentration limit (0.0015%). Therefore the formulation CHR/ZF/PROTI 100 FS is classified as sensitizing (Skin Sens. 1A, H317) according to the Regulation EC 1272/2008.

A 2.7.1 Study 1

Reference:	KCP 7.1.6
Report	Toxicological classification of product CHR/ZF/PROTI 100 FS based on calculation method taking into consideration health hazards of constituent substances; M. Kolodziej; 2021

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

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.

Due to the fact, that all components of the formulation CHR/ZF/PROTI 100 FS are known, the skin sensitisation test is not necessary.

One component is classified as sensitizer with the specific concentration limit at the concentration of 0.0015%. The content of the ingredient exceeds the specific concentration limit and therefore whole formulation is classified as sensitizing (Skin Sens. 1A, H317).

Conclusion

The whole formulation is classified as sensitizing (Skin Sens. 1A, H317).
According to point 7.1.6 of part A of Annex Regulation No 284/2014, it is possible to waive from skin sensitisation test.

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 2.10 Studies on dermal absorption (KCP 7.3)

Comments of zRMS:	Study accepted with remarks below. The *in vitro* study on dermal absorption of Prothioconazole-desthio in CHR/ZF/PROTI 100 FS was performed according to the Regulation (EC) 440/2015

	and OECD and EFSA guidances in compliance with GLP rules. No deviation was occurred during the study, but in the study one cell was excluded from the calculation due to abnormal absorption value identified using Dixon Test. The formulation was tested at the concentrated rate (100g of prothioconazole-desthio/L) and the diluted rate (14g of prothioconazole-desthio/L). The dilution rate is comparable with the dilution of product CHR/ZF/PROTI 100 FS used for seed treatment (0.1 L formulation plus 0.7 L water, dilution factor 8, 12.5g of prothioconazole-desthio/L). However, analyzing the obtained results for the cell N (RF 24h) (diluted formulation) in Dixon Test and using the formula (Q=gap/range) it seems that the obtained result for cell N should not be excluded. The value of 0.395 obtained in calculations according to the Dixon Test (8 observations) is less than Q_{table} value of 0.468 at 90% confidence. Therefore this result should not be considered as an outlier. Taking above into account, the amount of applied dose penetrating within 24 hours should be 2.3 % for the formulation concentrate (number of replicates n=8) and 4.5% instead of 1.8% for dilution (number of replicates n=8 instead of n=7, no cell excluded), based on the EFSA guidance criteria (mean + k * SD).

Reference: KCP 7.3

Report

IN-VITRO HUMAN SKIN PENETRATION OF ^{14}C-PROTHIOCONAZOLE-DESTHIO IN CHR/ZF/PROTI 100 FS

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STUDY CODE: S21-03902

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]-prothioconazole-desthio Batch XXVII/5/A/1
	Test preparation	Spiking
	Specific activity	208.57 µCi/mg
	Radiochemical purity	100 %
Product	Name (Lot/Batch No.)	CHR/ZF/PROTI 100 FS Batch 202003
	Company code	Not Applicable
	Concentration a.s.	104.8 g/L prothioconazole
	Formulation type	FS
Blank product	Name (Lot/Batch No.)	Not Applicable
	Concentration a.s.	0 g/L prothioconazole

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	352-400 µm
	Skin donors age	33 to 49 years old
	Skin donors sex	f
	Location	Abdomen
	Source	*Ex vivo*
	Integrity test	TEWL measurement
Receptor	Receptor medium	PBS 0.01M
	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 (1:7.14)
Target concentration [mg/ml]	100	14
Area dose [µg/cm²]	1000	140
Mean actual applied dose [µg/cm²]	901	135
Specific activity [kBq/ml]	1083	943
No. of donors	4	4
No of cells used/valid cells*	8/8	7/8

* One cell was excluded from the calculation due to abnormal absorption value in the total skin compartment.

Experimental design:

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 ^{14}C-prothioconazole-desthio 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 : prothioconazole-desthio 100 g/L
– Diluted rate : prothioconazole-desthio 14 g/L

For each tested concentration, 8 diffusion cells were used. A total of 16 cells were used for this study.

Results and discussion:

BLQ values were considered as 0 for calculations.

Mean concentrations were calculated (when calculable, *i.e.* $n \geq 2$) using individual concentration and were expressed with the corresponding standard deviation value and variation coefficient (when calculable, *i.e.* $n \geq 3$).

When possible, the maximum flux was considered based on the calculation of the slope of the linear portion of the cumulative absorption in the receptor fluid as a function of time curve. It should not include the lag-phase or plateau.
The dermal penetration of prothioconazole-desthio formulated as CHR/ZF/PROTI 100 FS through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating within 24 hours was determined to be 2.3 % (mean + k * SD) and 1.8% for the formulation concentrate and the 1:7.14 spray dilution, respectively, based on the EFSA guidance criteria.

A 2.11 Other/Special Studies

A 2.11.1 Specific target organ toxicity

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

The EFSA guidance document[1] refers to the SeedTropex model for operator exposure assessment during seed treatment. The notifier of CHR/ZF/PROTI holds a license to access human exposure assessment using the SeedTropex model. This evaluation is detailed here below.
The Seed TROPEX model applies to the evaluation of operator exposure in industrial seed treatment plants. In addition, this model is suitable only for liquid preparations. Then it is suitable for risk assessment of CHR/ZF/PROTI.

- **Input data for seed treatment with CHR/ZF/PROTI**

The product contains 100 g prothioconazole/L. It is used diluted: 100 mL product + 700 mL water. The application rate is 0.1 L of product per quintal seeds, equivalent to 10 g prothioconazole/quintal seeds.
For the purpose of this evaluation, it is considered that the total duration of a working day is 9 hours with 8 hours devoted to bagging, the remainder (one hour) to calibration, four mixing/loadings and cleaning.

- **Synopsis of the 1993 studies used to build the SeedTropex model**

In the UK, four sites were used for the seed treatment study, three involving static treatment equipment and one involving a mobile treater. The bag size for treated seed was generally 50 kg, although at two sites 500 kg bags were also used. In France, two static treatment plants were studied and the seed bags sizes were 25 and 50 kg.
The test substance used in the UK was 'Baytan', FS type, containing the active substances triadimenol 185 g/L and fuberidazole 22.5 g/L supplied in 10-litre packs. The application rate was 2 L/ton. The reasons for its choice included firstly the wide usage on cereal seed in the UK and secondly a validated and simple method of analysis of triadimenol on these sampling media.
In France 'Germinate Double,' FS type, was used containing the active substances anthraquinone 250 g/L and copper oxyquinolate 150 g/L supplied in 200-litre drums. The product is widely used on cereal seeds in France. The application rate was 2 L/t. Anthraquinone was used as the marker for exposure.
The methodology used in the studies was that recommended by the current OECD guidelines. The studies were carried out in accordance with the principles of Good Laboratory Practice (GLP) as applied to field studies. Data from all studies have been reported and have been archived in the UK and France.
Dermal and inhalation exposure was evaluated using whole body dosimeters and filter samples with personal pumps, respectively.
The potential dermal exposure of the body (excluding hands and head) was measured using cotton overall representative of that which operators would normally wear under these conditions as collection devices. Actual dermal exposure was measured using cotton underclothing. This last measurement was only performed on a dozen individuals.
Cotton sampling gloves (UK studies) and hand washing (French studies) were used to measure the actual exposure of the hands. Potential hand exposure was measured on nitrile working gloves where these were worn.
Head exposure was measured using a hood.
Inhalation exposure was evaluated by a personal air sampling technique using portable pumps connected to cassettes containing glass fibre filters placed in the operators' breathing zones.

[1] EFSA "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[55 pp.]

- **Generic exposure on the basis of the SeedTropex model**

Calibration: Such operation is performed at a maximum once a day at the outset of treatment with this product (in the most modern stations calibration is automatic). Exposure is expressed in term of mg/operation as calibration is a procedure of short term duration. It is considered that there is only exposure to diluted product during this procedure. The generic unit of exposure is therefore **mL diluted product/operation**.
In this evaluation the most concentrated product is considered (worst case situation), *i.e.* when 0.1 formulation ~~water~~ is used along with 0.7 L ~~formulation~~ water. The dilution factor is then 8.

Mixing/loading: Mixing loading into the seed treater is performed on diluted product (if any dilution of the formulation is performed) and is done twice per day, at the beginning of the morning and the beginning of the afternoon shifts. Exposure is expressed in term of mg/operation. It is considered that there is only exposure to the formulated product and not to diluted product during this procedure. The generic unit of exposure is therefore **mL product/operation**.

Notes: - Based on an intermediate pack size of 20 L and 10 tons of seeds treated per hour, the number of mix/loads is 4.

- ***No exposure to prothioconazole-desthio is considered during the mixing/loading as this substance does not exist in the concentrate product.***

Bagging: Bagging of treated seeds represents the main job activity in terms of exposure and is therefore expressed in term of mg/unit time.
The duration of exposure is taken as 8 hours over the working day as the three other procedures would take a total of one hour of the 9 hour shift. The physical nature of the contamination of the worker is likely to be a combination of dust and material on contaminated surfaces with which he/she comes into contact. It is therefore inappropriate to consider either the formulated product or the diluted product as the only source of exposure. The generic unit of exposure is therefore **mg active ingredient/h** without adjustment for the differing concentrations of active ingredients in either formulated or diluted products.
Note: According to the recommendations for the choice of dermal absorption values in the EFSA Guidance for dermal absorption (EFSA Journal 2017;15(6):4873), "dermal absorption value for exposures to dried dispersed residue should be the higher of the values for the concentrate and the in-use dilution." This is not strictly proposed for seed treatment products.

- ***For prothioconazole, a default value of 50% will be considered even if probably conservative.***
- ***For prothioconazole-desthio, the highest value is 2.3% in the dermal absorption study recently conducted.***

Cleaning of the treatment equipment: Such operation takes place at the end of the treatment shift and usually takes up to half an hour to complete. As it is of comparatively short duration exposure is expressed in terms of mg/operation. It is considered that there is only exposure to the diluted product during cleaning. The generic unit of exposure is therefore **mL diluted product/operation**.

A 3.1.1 Calculations for prothioconazole

Table A 1: Calculated operator exposure to prothioconazole from the use of CHR/ZF/PROTI (geometric means)

Task	Total Potential Dermal Exposure (mg/op)*	Estimated Actual Dermal Exposure (mg/op)*	Inhalation Exposure (mg/op)*	***Frequency of operation ** / day***	Total Potential Dermal Exposure (mg/day)	Estimated Actual Dermal Exposure (mg/day)	Inhalation Exposure (mg/day)
Calibration	0.407	0.178	0.0173	1	0.407	0.178	0.0173
Mixing / Loading	0.469	0.114	0.0102	4	1.88	0.457	0.0408
Bagging	1.19	0.472	0.0150	8	9.51	3.77	0.120
Cleaning	10.9	1.04	0.198	1	10.9	1.04	0.198
Total route specific exposure (mg/person/day)					22.7	5.45	0.376
Total absorbed dose (10% or 50% dermal penetration # and 100% inhalation absorption; 60 kg person) (mg/kg bw/day)						0.0424	0.00627
Total absorbed dose (mg/kg bw/day)						**0.0487**	

* exposure during bagging in mg/hour
** frequency during bagging in hours/day
# 10% dermal absorption is considered during mixing/loading (concentrate product) and 50% dermal absorption is considered for the other tasks (diluted product).

A 3.1.2 Calculations for prothioconazole-desthio

Table A 2: Calculated operator exposure to prothioconazole-desthio from the use of CHR/ZF/PROTI (geometric means)

Task	Total Potential Dermal Exposure (mg/op)*	Estimated Actual Dermal Exposure (mg/op)*	Inhalation Exposure (mg/op)*	***Frequency of operation ** / day***	Total Potential Dermal Exposure (mg/day)	Estimated Actual Dermal Exposure (mg/day)	Inhalation Exposure (mg/day)
Calibration	0.369	0.161	0.0157	1	0.369	0.161	0.0157
Bagging	1.19	0.472	0.0150	8	9.51	3.77	0.120
Cleaning	9.88	0.945	0.180	1	9.88	0.945	0.180
Total route specific exposure (mg/person/day)					19.8	4.88	0.316
Total absorbed dose (~~1.8~~ 4.5% or 2.3% dermal penetration # and 100% inhalation absorption; 60 kg person) (mg/kg bw/day)						~~0.00178~~ 0.00227	0.00526
Total absorbed dose (mg/kg bw/day)						**~~0.00704~~**	

	0.00753

* exposure during bagging in mg/hour
** frequency during bagging in hours/day
# 2.3% dermal absorption is considered during bagging (highest concentration; dried residues) and ~~1.8~~ 4.5% dermal absorption is considered for the other tasks (diluted product).

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

When considering seed treatment, the worker exposure corresponds to the exposure of persons loading and sowing seeds.
The EFSA guidance document[2] refers to the SeedTropex model for worker exposure assessment during loading and sowing seeds. The notifier of CHR/ZF/PROTI holds a license to access human exposure assessment using the SeedTropex model. This evaluation is detailed here below.
The Seed TROPEX model applies to the evaluation of worker exposure during the loading and sowing of seeds. Then it is suitable for risk assessment of CHR/ZF/PROTI.

Exposure measurements for seed sowing and loading were conducted on thirteen farms in the UK and six farms in France. Triadimenol (370g/ton of seed) was used in the UK while anthraquinone (500 g/ton of seeds) was used in France. In France seeds were packed in 25 kg bags while in the UK, 50, 500, 1000 kg bags, bulk or even mixed type of packs were used. The farms selected in the UK were significantly larger than in France and the areas treated per day, in addition to the quantities sown, were significantly higher in these farms.

For modelling purposes, unless field area and type of application are well defined, the appropriate parameter for normalisation is the working day. The maximum exposure potential exists for the worker who conducts both loading and sowing procedures. A conservative assumption of 10 hours duration of work is used.

When considering the seed sowing task, possible dermal exposure is to the fully dried product residue on seeds. According to the recommendations for the choice of dermal absorption values in the EFSA Guidance for dermal absorption (EFSA Journal 2017;15(6):4873), "*dermal absorption value for exposures to dried dispersed residue should be the higher of the values for the concentrate and the in-use dilution*." This is not strictly proposed for seed treatment products.

- For prothioconazole, a default value of 50% will be considered even if probably conservative.
- For prothioconazole-desthio, the highest value is 2.3% in the study recently conducted.

A 3.2.1 Calculations for prothioconazole

Table A 3: Generic exposure calculations during seed loading and sowing (geometric means)

Task	Total Potential Dermal exposure (mg/hr)	Estimated Actual Dermal exposure (mg/hr)	Inhalation exposure (mg/hr)
Loading / sowing	1.48	0.733	0.0200

[2] EFSA "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[55 pp.]

Table A 4: Calculated exposure to prothioconazole from the use of CHR/ZF/PROTI treated seeds (geometric means)

Loading / sowing	Total Potential Dermal	Estimated Actual Dermal	Inhalation
Exposure (mg/day)	14.8	7.33	0.200
Absorbed dose (mg/day) *		3.665	0.200
Absorbed dose (mg/kg bw/day)		0.0611	0.00333
Total absorbed dose (mg/kg bw/day)		**0.0644**	

* considering 50% dermal absorption

A 3.2.2 Calculations for prothioconazole-desthio

Table A 5: Generic exposure calculations during seed loading and sowing (geometric means)

Task	Total Potential Dermal exposure (mg/hr)	Estimated Actual Dermal exposure (mg/hr)	Inhalation exposure (mg/hr)
Loading / sowing	1.34	0.665	0.0181

Table A 6: Calculated exposure to prothioconazole-desthio from the use of CHR/ZF/PROTI treated seeds (geometric means)

Loading / sowing	Total Potential Dermal	Estimated Actual Dermal	Inhalation
Exposure (mg/day)	13.4	6.65	0.181
Absorbed dose (mg/day) *		0.153	0.181
Absorbed dose (mg/kg bw/day)		0.00255	0.00302
Total absorbed dose (mg/kg bw/day)		**0.00557**	

* considering 2.3% dermal absorption

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

There are no specific bystander or resident exposure data for seed treatment products in the EFSA Guidance Document. The SeedTropex model (1996) does neither include exposure data for bystanders and residents. As a surrogate, the most relevant way to conduct this evaluation is to consider that treated seeds are granules of product which are applied in-furrow. With this approach, the EFSA calculator can be used.

Among the four pathways of exposure usually taken into account for bystander and resident exposure, only this to vapour applies to in-furrow granule application.

A 3.3.1 Calculations for prothioconazole

Table A 7: Input parameters considered for the estimation of resident exposure to prothioconazole

Resident exposure for CHR/ZF/PROTI				
Croptype	Bare soil			
Application method	In furrow application of granules			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Granules, fine granules			*i_FormVal*
Buffer strip	2-3	m		*i_Buffer*
Application rate of the product	0.025	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	#DIV/0!	kg a.s./kg		*d_ConcAS*
Dermal absorption of product	10.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	50.00%			*i_AbsorpInuse*
Oral absorption	100.00%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.075	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	NA	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	NA	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	NA	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	NA	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	NA	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	NA	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	NA	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	NA	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	NA			
Drift percentage on surface (mean)	NA			
Turf transferable residues percentage	1.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) -	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) -	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

Table A 8: Estimation of resident exposure towards prothioconazole according to EFSA guidance

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)	**NA**	**0.0107**	**NA**	**NA**	**NA**
Total systemic exposure per kg body weight (mg/kg bw/day)	**NA**	**0.00107**	**NA**	**NA**	**NA**
% of RVNAS		**0.54%**			
1.2 Adult					
	Spray drift	**Vapour**	**Surface deposits**	**Entry into treated crops**	**All pathways (mean)**
Total systemic exposure (mg a.s./day)	**NA**	**0.0138**	**NA**	**NA**	**NA**
Total systemic exposure per kg body weight (mg/kg bw/day)	**NA**	**0.000230**	**NA**	**NA**	**NA**
% of RVNAS		**0.12%**			

A 3.3.2 Calculations for prothioconazole-desthio

Table A 9: Input parameters considered for the estimation of resident exposure to prothioconazole-desthio

Resident exposure for CHR/ZF/PROTI				
Croptype	Bare soil			
Application method	In furrow application of granules			
Application equipment	Vehicle-mounted			*i_AppEquip*
Formulation type	Granules, fine granules			*i_FormVal*
Buffer strip	2-3	m		*i_Buffer*
Application rate of the product	0.022675	kg a.s./ha		*i_AppRate*
Concentration of active substance (in-use dilution for liquid applications)	#DIV/0!	kg a.s./kg		*d_ConcAS*
Dermal absorption of product	0.00%			*i_AbsorpProduct*
Dermal absorption of in-use dilution	2.30%			*i_AbsorpInuse*
Oral absorption	1.80%			*i_AbsorpOralInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.068025	µg a.s./cm^2		*d_DFR*
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure	Pa		*i_Volat*
Concentration in air	0.001	mg/m^3		*d_AirCon*
Resident dermal spray drift exposure 75th percentile - adult	NA	ml spray dilution/person		
Resident dermal spray drift exposure 75th percentile - child	NA	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - adult	NA	ml spray dilution/person		
Resident inhal. spray drift exposure 75th percentile - child	NA	ml spray dilution/person		
Resident dermal spray drift exposure mean - adult	NA	ml spray dilution/person		
Resident dermal spray drift exposure mean - child	NA	ml spray dilution/person		
Resident inhal. spray drift exposure mean - adult	NA	ml spray dilution/person		
Resident inhal. spray drift exposure mean - child	NA	ml spray dilution/person		
Exposure duration dermal	2	hours		*d_ReExpDur*
Exposure duration inhalation	24	hours		*d_ReExpDurInhal*
Exposure duration entry into treated crops	0.25	hours		*d_ExpDurTreatCrop*
Light clothing adjustment factor	18.0%			*d_ClothAF*
Breathing rate adult	0.23	m^3/day/kg		*d_BreathRAd*
Breathing rate child (1-3 year old)	1.07	m^3/day/kg		*d_BreathRCh*
Drift percentage on surface (75th percentile)	NA			
Drift percentage on surface (mean)	NA			
Turf transferable residues percentage	1.00%			*d_Turf*
Transfer coeff. of surface deposits-adult	7300	cm^2/hour		*d_ReTCAd*
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour		*d_ReTCCh*
Saliva extraction percentage	50.00%			*d_SalExt*
Surface area of hands mouthed	20	cm^2		*d_AreaHM*
Frequency of hand to mouth activity	9.5	events/hour		*d_ReFreqHM*
Ingestion rate for mouthing of grass per day	25	cm^2		*d_MouthGrass*
Dislodgeable residues percentage transferability for object to mouth	20.00%			*d_DRP*
Transfer coefficient for entry into treated crops (75th percentile) -	7500	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (75th percentile) -	2250	cm^2/h		*d_TcEntryCh*
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm^2/h		*d_TcEntryAd*
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h		*d_TcEntryCh*

Table A 10: Estimation of resident exposure towards prothioconazole-desthio according to EFSA guidance

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)	**NA**	**0.0107**	**NA**	**NA**	**NA**
Total systemic exposure per kg body weight (mg/kg bw/day)	**NA**	**0.00107**	**NA**	**NA**	**NA**
% of RVNAS		**11%**			
1.2 Adult					
	Spray drift	**Vapour**	**Surface deposits**	**Entry into treated crops**	**All pathways (mean)**
Total systemic exposure (mg a.s./day)	**NA**	**0.0138**	**NA**	**NA**	**NA**
Total systemic exposure per kg body weight (mg/kg bw/day)	**NA**	**0.000230**	**NA**	**NA**	**NA**
% of RVNAS		**2.3%**			

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)