REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product name(s): PYRIX 20 SL

Chemical active substance:

Pyriproxyfen, 20 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: AGROFARM SP. z o.o.

Submission date: 7 November 2025

MS Finalisation date: July 2026 (initial Core Assessment)

September 2026 (final Core Assessment)

Version history

When	What
07.11.2025	Initial version prepared by the Applicant.
July 2026	Initial zRMS assessment The report in the dRR format was prepared by the Applicant; therefore, all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes have been introduced directly into the text and highlighted in grey. Information that is not agreed or not relevant is ~~struck through~~ and shaded for transparency.
September 2026	Final report (Core Assessment updated following the commenting period) No additional information or assessments after the commenting period.

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General Reviewer's Introduction to Section B6 – Toxicology and Non-Dietary Exposure

Section B6 of the dossier provides a summary of the toxicological profile and non-dietary exposure (NDE) assessment for the plant protection product PYRIX 20 SL. The product is an soluble liquid [SL] formulated insecticide containing 20 g/L of the active substance pyriproxyfen. The intended use of PYRIX 20 SL is to control flies (Sciaridae) in mushroom cultivation. The product is intended for professional use.

The data support the application for zonal authorisation under Article 33 of Regulation (EC) No 1107/2009, both for national registration in Poland and for zonal evaluation, with Poland acting as the zonal Rapporteur Member State (zRMS). Administrative details are provided in Part A, Section 1.1.

The zRMS has assessed all relevant toxicological and exposure-related data necessary for regulatory decision-making. Toxicological profile has been concluded based on the classification of the mixture performed using the Additivity Formula, in accordance with Annex I, Section 3.1.3.6.1 of Regulation (EC) No 1272/2008 (CLP). Acute Toxicity Estimates (ATE) and converted ATE (cATE) values were applied to determine overall classification. More detailed discussion regarding hazard classification and evaluation of toxicological profile of the product please refer section 6.3 on page 6 of the dRR B6.

The results of the NDE calculations demonstrate that, under the proposed conditions of use and considering all relevant tasks associated with critical uses, the exposure levels for operators, workers, and B&R remain below the relevant toxicological reference values (e.g., AOEL, AAOEL). Therefore, safe use of the product PYRIX 20 SL can be concluded. Detailed information's regarding NDE assessment are provided under points 6.6.2, p.15 and 6.6.4, p.18.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on Pyrix 20 SL *

Product name and code	Pyrix 20 SL
Formulation type	SL
Active substance(s) (incl. content)	Pyriproxyfen 20 g/L
Function	insecticide
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 PYRIX 20 SL can be found in the confidential dRR Part C.**

Justified proposals for classification and labelling

Classification was made based on the concentration of the individual formulation components and their known toxicity classification.
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 PYRIX 20 SL according to Regulation (EC) No 1272/2008

~~Hazard class(es), categories~~	~~Not classified~~
~~Hazard pictograms:~~	~~GHS09~~
~~Signal word:~~	~~none~~
~~Hazard statement(s):~~	~~H411 – Toxic to aquatic life with long lasting effects~~
~~Precautionary statement(s):~~	~~P273 – Avoid release to the environment.~~ ~~P280 – Wear protective gloves~~ ~~P391 – Collect spillage.~~

	~~P501 – Dispose of contents/container in accordance with applicable national law.~~
~~Additional labelling phrases:~~	~~To avoid risks to man and the environment, comply with the instructions for use. [EUH401]~~

zRMS Reviewer comment: Classification derived by calculation (for details refer Part C, p.20)

Hazard class(es), categories	Eye irritation Hazard category 2
Hazard pictograms:	GHS07
Signal word:	Warning
Hazard statement(s):	H319: Causes serious eye irritation
Precautionary statement(s):	P264 Wash hands thoroughly after handling. P280 Wear eye protection/face protection. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P337 + P313 If eye irritation persists: Get medical advice/attention.
Additional labelling phrases:	To avoid risks to human and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for PYRIX 20 SL

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves during mixing/loading **Note:** However, the NDE assessment confirms safe use of the product. Due to the CLP classification of the product, it is advised to use eye/face protection during mixing and loading (M&L).
Workers	Acceptable	None
Residents	Acceptable	None
Bystanders	Acceptable	None

No unacceptable risk for operators was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in
zRMS Reviewer comment: Classification derived by calculation (for details refer Part C, p.20)

Hazard class(es), categories	Eye irritation Hazard category 2
Hazard pictograms:	GHS07
Signal word:	Warning
Hazard statement(s):	H319: Causes serious eye irritation
Precautionary statement(s):	P264 Wash hands thoroughly after handling. P280 Wear eye protection/face protection. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P337 + P313 If eye irritation persists: Get medical advice/attention.
Additional labelling phrases:	To avoid risks to human and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3 are applied.

No unacceptable risk for workers, residents and bystanders was identified when the product is used as intended. No specific PPE is necessary.

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

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

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	**Acceptability of exposure assessment**			
			Method / Kind (incl. application technique ***	**Max. number (min. interval between applications) a) per use b) per crop/ season**	**Max. application rate kg as/ha a) per use b) per crop/ season**	**Water L/ha min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
1	Mushrooms (fungi) Agaricus bisporus (overgrowth of cover by mushroom mycelium)	I	Spraying, automatised	a) 1 b) 1/1 cycle (3-4 throws = fruit harvest)	a) 0.3 g a.s./m² b) 0.3 g a.s./m²	1 L/m²	-	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032	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
 # Please refer zRMS reviewer comment point 6.4.1

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:

- None.

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)

	Pyiproxyfen
Common Name	Pyriproxyfen
CAS-No.	95737-68-1
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	~~Hazard classes (s), categories: Not classified~~ ~~Code(s) for hazard pictogram(s): none~~ ~~Signal word:none~~ ~~Hazard statement(s): none~~ ~~Precautionary statement(s): none~~ Not classified for health Annex VI (Regulation 1272/2008)
Additional C&L proposal	-
Agreed EU endpoints	
AOEL systemic	0.04 mg/kg bw/d (corrected for 40% oral absorption)

	Pyiproxyfen
AAOEL	0.4 mg/kg bw/d (corrected for 40% oral absorption)
Reference	EFSA Journal 2019;17(7):5732
Conditions to take into account/critical areas of concern with regard to toxicology	
According to Review Report/EFSA Conclusion for active substance	None

6.3 Toxicological Evaluation of Plant Protection Product

zRMS PL Reviewer comment:

The summary of the toxicological profile of the plant protection product Pyrix 20 SL provided by the applicant presents several interpretative challenges and, in its current form, cannot be fully considered in the evaluation of the registration dossier.

Reviewer's justification:
The applicant refers to selected excerpts from a report issued by the Australian National Registration Authority for Agricultural & Veterinary Chemicals (*Public Release Summary* "*Summary of the data reviewed and an outline of regulatory considerations for the proposed clearance and registration of the chemical pyriproxyfen in the product SUMILARV INSECT GROWTH REGULATOR*", APVMA Library Kingstone ACT 2604, Canberra, Australia). The cited Public Release Summary offers only a basic overview of the toxicity of the active substance pyriproxyfen and of the product SUMILARV INSECT GROWTH REGULATOR, registered in Australia in 1995. Given the age of this document, its relevance for the current EU regulatory context is limited.

Additionally, no comparison of the composition of the product under registration and the reference product has been provided (see dRR Part C). Therefore, the reviewer is not in a position to confirm the applicant's statement regarding the claimed identity of the two formulations.

In light of the above, the reviewer has prepared an independent hazard classification for Pyrix 20 SL in accordance with GHS/CLP principles, based on the actual chemical composition of the product.
It should also be noted that in dRR Part C, section 1.3.2 ("Table 1.3-1: Toxicological data for each co-formulant"), the applicant lists the co-formulants and indicates whether each component affects the classification, but does not provide the required scientific justification in line with EC Reg. 1272/2008. Consequently, referring in dRR B.6 to the CLP classification results presented in Part C leads to inconsistencies.

Therefore, the zRMS has prepared an independent hazard assessment using the ATEmix approach. The results have been inserted into Table 6.3-1: *Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for product code/name*, which the applicant had left empty**.**

EXPLANATION
During the EU review of active substance pyriproxyfen, the representative formulation was "pyriproxyfen 100g/L EC."
Pyrix 20 SL contains 5 times less active ingredient and is a Soluble Liquid formulation where the active ingredient is fully dissolved in water. Soluble liquid (SL) formulations are generally less toxic than emulsifiable concentrates (EC) because they use water as the solvent instead of organic solvents, which reduces the risk of phytotoxicity to plants and dermal toxicity to handlers.
Differences in leaf penetration and phytotoxicity between water-dissolved and solvent-dissolved active substances are determined by the properties of both the active ingredient pyriproxyfen and the solvent. Pyriproxyfen dissolved in a water-based solution must overcome the plant's natural, waxy cuticle, while a solvent-based solution may carry the directly through this barrier.
Phytotoxicity from water-based formulations
- Low inherent risk: Water itself is generally not phytotoxic. The phytotoxicity of a water-based formulation typically depends on the concentration and nature of the dissolved active substance.
- Increased risk with additives: While adjuvants like surfactants enhance penetration, they can also increase the risk of phytotoxicity, especially in high concentrations. Some surfactants have been shown to have toxic effects on plants.
- Formulation stability: Water-based formulations may present risks if they contain compounds susceptible to degradation, as byproducts could be phytotoxic.

• High concentration burn: If the water evaporates too quickly in hot weather, it can leave behind a concentrated deposit of the active substance and other ingredients, which can cause leaf burn.
Efficacy studies of Pyrix 20 SL (water-based formulation) in protecting mushrooms, applied once after the casing was applied, showed no phytotoxicity. No damage to the mushrooms was observed.
EC formulations are solvent-based and can be absorbed more easily through skin and can be corrosive to eyes or skin, while SL formulations are water-based, making them cleaner and safer for users and the environment.
The toxicology for the PYRIPORXYFEN 20g/L (2%) formulation was presented in the part of the registration dossier for the plant protection product Sumiarv Insect Growth Regulator of Hoechst Schering AgrEvo Pty Ltd and published by the Australian Registration Office. Product Sumiarv Insect Growth Regulator of Hoechst Schering is a water-based formulation like Agrofarm's Pyrix 20 SL.
Available toxicological data for each co-formulants of Pyrix 20 SL are presented in document PART C-Confidential Information.
Each co-formulants of Pyrix 20 SL are of no toxicological significance are of no toxicological significance/do not affect the toxicological properties of Pyrix 20 SL. They also have no significance for the classification of the product according to Regulation 1272. /do not affect the toxicological properties of Pyrix 20 SL. They also have no significance for the classification of the product according to Regulation 1272/2008.
Sumilarv Insect Growth Regulator of Hoechst Schering summary below:

Toxicology

The acute toxicity of pyriproxyfen, the active ingredient in Sumilarv, is low, with the only significant acute effect being slight irritation of the rabbit eye. Sumilarv, the 2% formulation of pyriproxyfen, may irritate the gastrointestinal tract if swallowed, or the nasal mucosa if inhaled, and is slightly irritating to the eye, and may cause defatting of the skin.

The main toxic effects in repeat-dose studies were on the liver. Kidney toxicity occurred in mice, but not in rats or dogs. Slight anaemia occurred in rats and dogs. Pyriproxyfen did not cause tumours or birth defects in laboratory animals, and was not toxic to genetic material (DNA).

Based on an assessment of the toxicology and the fact that there should be no dietary intake of residues, it was considered that there should be no adverse effects on human health from the proposed use of Sumilarv.

Occupational Health and Safety Aspects

Pyriproxyfen and its product SUMILARV INSECT GROWTH REGULATOR, are of low toxicity. They are not classified as hazardous substances or dangerous goods.

The main acute hazards of contamination with SUMILARV INSECT GROWTH REGULATOR are skin and eye irritation. The probability of workers developing adverse health effects following long term use is low.

Safety directions on the product label state that users should wear elbow-length PVC gloves when preparing the working strength spray. All workers should maintain good personal hygiene practices.

zRMS PL Reviewer comment: Part of the applicant's clarification/information regarding the NDE assessment has been moved by the reviewer from section 6.3 (p. 9) to section 6.6 (see p. 15).

(..)

zRMS PL Reviewer comment: see our detailed comment regarding CLP classification on page 4 of this dRR B6.

Toxicological classification of Pyrix 20 SL was made based on the concentration of the individual formulation components and their known toxicity classification according to the criteria given in Regulation (EC) No 1272/2008. Based on this classification, it can be said that Pyrix 20 SL create less hazard to humans than the "formulation 100g/L ".
Detailed information on the individual ingredients of the Pyrix 20 SL formulation can be found in Part C.

Agrofarm believes that conducting toxicological studies on animals (acute and chronic toxicity, eye/skin irritation, skin sensitization dermal absorption or inhalation) is not justifiable and is ethically unacceptable. Agrofarm made the assumption that toxicity of Pyrix 20 SL is comparable to the representative formulation "pyriproxyfen 100g/L EC." Given the explanations above, it can be assumed that it is certainly lower and we could use data and endpoints from the EU-level review.

zRMS PL Reviewer comment: In the reviewer's opinion, including a complete list of endpoints (LoEP) for the active substance pyriproxyfen in the context of the registration of Pyrix 20 SL products is unnecessary and creates confusion.

List of end points for the active substance and the representative formulation base on UE review of active substance Pyriproxyfen [EFSA Journal 2019;17(7):5732] **:

Acute toxicity (Regulation (EU) N° 283/2013, Annex Part A, point 5.2)

Rat LD_{50} oral	>5000 mg/kg bw (rat and mouse)	
Rat LD_{50} dermal	>2000 mg/kg bw (rat and mouse)	
Rat LC_{50} inhalation	>1.3 mg/L air /4h (*whole body, max. attainable concentration*) (rat and mouse)	
Skin irritation	Non-irritant	
Eye irritation	Non-irritant	
Skin sensitisation	Not sensitising (maximisation)	
Phototoxicity	Data gap (for UVB absorber)	

Short-term toxicity (Regulation (EU) N° 283/2013, Annex Part A, point 5.3)

Target organ / critical effect	Rat: liver (weight, hypertrophy), clinical chemistry, and haematological parameters Dog: liver (weight, hypertrophy), clinical chemistry	
Relevant oral NOAEL	Dog: 100 mg/kg bw per day (90-d) 10 mg/kg bw per day (1-yr) Rat: 23.5 mg/kg bw per day (90-d) 24.0 mg/kg bw per day (6-mo)	
Relevant dermal NOAEL	28-day, rat: 1000 mg/kg bw per day	
Relevant inhalation NOAEL	28-day, rat: 482 mg/m³ (equiv. to 86.8 mg/kg bw per day) based on salivation, reduced body weight gain, increased LDH and changes in organ weights (liver, spleen and lung)	

Genotoxicity (Regulation (EU) N° 283/2013, Annex Part A, point 5.4)

In vitro studies	Pyriproxyfen did not induce gene mutation in the Ames test or in the mammalian cell gene mutation	

	study (hamster V79 cells), was inactive to induce DNA damage in the UDS test with Hela S3 cell and did not induce chromosome aberrations in CHO cells.	
In vivo studies	Pyriproxyfen was not mutagenic in the mouse bone marrow micronucleus test.	
Photomutagenicity	Pending phototoxicity assessment	
Potential for genotoxicity	Pyriproxyfen is unlikely to be genotoxic	

Long-term toxicity and carcinogenicity (Regulation (EU) N°283/2013, Annex Part A, point 5.5)

Long-term effects (target organ/critical effect)	Rat: body weight, liver (weight, histopathology), clinical chemistry Mouse: liver (weight), systemic amyloidosis, kidneys (histopathology), reduced survival rate	
Relevant long-term NOAEL	2-year, rat: 27.2 mg/kg bw per day 78-week, mouse: LOAEL of 16.4 mg/kg bw per day	
Carcinogenicity (target organ, tumour type)	Liver haemangiosarcoma (mice) Unlikely to be carcinogenic to humans	
Relevant NOAEL for carcinogenicity	Rat: 138 mg/kg bw per day (high dose level) Mouse: 107.3 mg/kg bw per day	

Reproductive toxicity (Regulation (EU) N° 283/2013, Annex Part A, point 5.6)

Reproduction toxicity

Reproduction target / critical effect	Effects in rat multigeneration study: - Parental: increased liver weight - Reproductive: no adverse effect - Offspring: decreased pup weight at parental toxic doses	
Relevant parental NOAEL	13.3 mg/kg bw per day	
Relevant reproductive NOAEL	333.3 mg/kg bw per day (high dose level)	
Relevant offspring NOAEL	66.7 mg/kg bw per day	

Developmental toxicity

Developmental target / critical effect	**Rat**, combined dev/repro (study 1): - Maternal: clinical signs, decreased body weight gain and food consumption, increased water consumption, increased liver weight - Developmental: increased ambulation in open field test with male pups Rat, developmental study (study 2): - Maternal: decreased body weight gain and food consumption, increased water consumption, increased liver/kidney weight	

	– Developmental: increased incidence of opening of the foramen transversarium of the 7th cervical vertebra. **Rabbit**: – Maternal: increased abortions or premature deliveries, clinical signs, macroscopic findings – Developmental toxicity: increased incidence of visceral malformations	
Relevant maternal NOAEL	Rat, study 1: 100 mg/kg bw per day Rat, study 2: 100 mg/kg bw per day Rabbit: 100 mg/kg bw per day	
Relevant developmental NOAEL	Rat, study 1: 30 mg/kg bw per day Rat, study 2: LOAEL of 100 mg/kg bw per day Rabbit: 100 mg/kg bw per day	

Neurotoxicity (Regulation (EU) N° 283/2013, Annex Part A, point 5.7)

Acute neurotoxicity	Decreased total and ambulatory motor activity counts. Neurotoxic NOAEL: 300 mg/kg bw (males). Systemic NOAEL is 1000 mg/kg bw based on unkempt appearance.	
Repeated neurotoxicity	90 day, rat: no neurotoxic effects. Neurotoxic NOAEL 1111 mg/kg bw per day (males), 1212 mg/kg bw per day (females). Systemic NOAEL is 359 mg/kg bw per day based on decreased body weight and body weight gain.	
Additional studies (e.g. delayed neurotoxicity, developmental neurotoxicity)	None	

Source:
* National Registration Authority For Agricultural and Veterinary Chemicals : Public Release Summary – PYRIRPOXYFEN In the product Sumilarv Insect Growth Regulator – APVMA 363 1995
** EFSA Journal 2019;17(7):5732

zRMS Reviewer comment: A summary of the toxicological evaluation for product Pyrix 20 SL is given in the following tables.

Table 6.3-1: Summary of evaluation of the acute toxicity including irritancy and skin sensitisation for product Pyrix 20 SL

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral (ATEmix Calculation)	= 4853 mg/kg bw	Yes	None	According to Reg 1272/2008, see Part C
LD_{50} dermal (ATEmix Calculation)	= 3184 mg/kg bw	Yes	None	According to Reg 1272/2008, see Part C
LC_{50} inhalation (ATEmix calculation)	= 23.14 mg/L air	Yes	None	According to Reg 1272/2008, see Part C
Skin irritation	Non-irritant	Yes	None	According to

(additive calculation)				Reg 1272/2008, see Part C
Eye irritation (additive calculation)	Irritant	Yes	H319: Causes serious eye irritation	According to Reg 1272/2008, see Part C
Skin sensitisation, (additive calculation)	Non-sensitising	Yes	None	According to Reg 1272/2008, see Part C
Supplementary studies for combinations of plant protection products	No data – not required	--	--	--

Table 6.3-2: Additional toxicological information relevant for classification/labelling of product code/name

	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)	Pyriproxyfen (98.93%) CAS-No. 95737-68-1 pure 1,91% (w/w)** technical 1.93% (w/w)**	Hazard statement(s) Aquatic Acute 1; H400 Aquatic Chronic 1; H410 Not classified for health Annex VI (Regulation 1272/2008)	Harmonised classification and labelling * Reg. 1272/2008 ATP01	None***
Toxicological properties of non-active substance(s) (relevant for classification of product)	Propylene Glycol Phenyl Ether (refer Part C)	Hazard statement(s) H319 Causes serious eye irritation	REACH Joint 80.81% of industry notifications Last updated: 6-Aug-2024	Hazard statement(s) H319: Causes serious eye irritation
Further toxicological information	No data – not required	--	--	--

*ECHACHEM Database:
acces 02/07/2026: https://chem.echa.europa.eu/100.102.814/harmonised/87115?searchText=95737-68-1
** Based on the density of the formulation = 1.0458 g/cm^3
***considering only toxicological profile of the product for human

6.4 Toxicological Evaluation of Groundwater Metabolites

~~Not Applicable.~~

There is no possibility of pyriproxyfen and any metabolites being released into the environment and having an impact on the environment, especially for groundwater. In fact, Polish regulations require that wastes be collected and disposed in an appropriate manner such that no residues can enter the soil, the drainage water and/or the sewage systems. Under Polish regulations, such wastes include any solid waste such as used soil and compost, and liquid waste such as water used to clean chambers. Such wastes must be disposed of by an authorised waste management company or a wastewater treatment system. There is no need for an risk assessment for groundwater:

- no soil contamination, as spent substrate is classified as waste and must be disposed of properly under Polish law.
- no drainage or leaching pathways from shelves to soil or groundwater,

~~6.4.1 Metabolite 1~~

~~Not Applicable.~~

~~6.4.2 Metabolite 2~~

~~Not Applicable.~~

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in Pyrix 20 SL are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in Pyrix 20 SL

	Pyriproxyfen	
	Value	**Reference**
Concentrate	50%	EFSA Journal 2017;15(6):4873 and SANTE/2018/10591 rev.1
Dilution	50%	EFSA Journal 2017;15(6):4873

6.5.1 Justification for proposed values - Pyriproxyfen

No data on dermal absorption for Pyriproxyfen in Pyrix 20 SL is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for Pyriproxyfen

	Value	**Justification for value**	**Acceptability of justification**
Concentrate	50%	Default value for SL formulation, as the a.s. concentration is <50 g/L	Justification accepted. Endpoint can be used for current product
Dilution	50%	Default value for SL formulation	Justification accepted. Endpoint can be used for current product

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	PYRIX 20 SL
Formulation type	SL
Category	Insecticide
Active substance(s) (incl. content)	**Pyriproxyfen** 20 g/L
AOEL systemic	0.04 mg/kg bw/d*
AAOEL systemic	0.4 mg/kg bw/d*
Inhalation absorption	100%
Oral absorption	40%
Dermal absorption	Concentrate: 50% (as the a.s. concentration is <50 g/L) Dilution: 50% (Default)

*(Conclusion on the peer review of the pesticide risk assessment of the active substance pyriproxyfen. EFSA Journal 2019;17(7):5732, 26 pp.)

zRMS Reviewer comment: the following text regarding NDE assessment has been moved by the reviewer from section 6.3 to section 6.6.

Applicant discussion on NDE assessment (highlighted in pale grey, see below):

A summary of the exposure models used for estimation of operator, worker, resident and bystander exposure to the active substances during application of PYRIX 20 SL according to the critical use is presented in tables in this document. Detailed calculations are in Appendix 3.

In the EFSA calculator, the critical use is expressed as bare arable land.
As the downward spray application is automatized (remotely controlled by computer) with nobody present in the mushroom cultivation room during the application, operator exposure is only assessed during the mixing/loading phase. The potential total systemic exposure of the operator, dressed in work wear covering the body, arms and legs, at mixing and loading, with additional gloves corresponds to 9.0 % of the AAOEL for Pyriproxyfen, regarding the critical use in mushroom.

The potential total systemic exposure of the operator, dressed in work wear covering the body, arms and legs, at mixing and loading, with additional gloves corresponds to 8.2 % of the AOEL for Pyriproxyfen, regarding the critical use in mushroom. There is no unacceptable risk for operator wearing workwear and gloves during mixing and loading regarding the critical use in mushroom.
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.

The potential total systemic exposure of the worker, corresponds to 0.6% of the AOEL for regarding the critical use in mushroom.
Worker exposure when contact with soil is possible during their activities (e.g. manual mushroom harvest) is acceptable without work clothes or PPE/RPE. As good agricultural practice, wearing protective gloves is recommended when contact with soil is possible during worker activities.
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 per-formed.

No exposure of resident or bystander is expected considering the product will be applied automatically in completely closed isolated buildings, in controlled cultivation conditions preventing for potential air contamination and thus transfer from the mushroom house to the outside atmosphere is impossible.
Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for Pyriproxyfen 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.

6.6.1 Selection of critical use(s) and justification

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

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

Comments of zRMS:	The NDE (Non-Dietary Exposure) calculation performed by the Applicant using the EFSA online model OPEX (version 1.1.1) is considered acceptable. The zRMS Reviewer agrees with the conclusions presented. The risk to operators is deemed acceptable under the conditions of the proposed uses and taking into account the following risk mitigation measures, namely the wearing of workwear covering the arms, body, and legs during mixing, loading, and application (M, L, A). **Note**: Risk assessments were conducted on the assumption that standard workwear—covering the arms, body, and legs—is worn. Standard workwear is not classified as personal protective equipment (PPE) per se. As defined by EFSA (2022), “normal

	workwear consists of coveralls or a long-sleeved shirt and trousers made of cotton (≥ 300 g/m²), or cotton-polyester fabric containing at least 65% polyester (≥ 245 g/m²).”

A summary of the exposure models used for estimation of operator exposure to the active substances during application of PYRIX 20 SL according to the critical use is presented in Table 6.6-2. The outcome of the estimation is presented in
In the EFSA calculator, the critical use is expressed as bare arable land.
As the downward spray application is automatized (remotely controlled by computer) with nobody present in the mushroom cultivation room during the application, operator exposure is only assessed during the mixing/loading phase.

Table 6.6-3 (acute exposure) and Table 6.6-4 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Mushrooms (fungi) (max. 15 mL product/m², equivalent to 150 L product/ha)
Model(s)	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032; calculator version: opex 1.1.1

In the EFSA calculator, the critical use is expressed as bare arable land.
As the downward spray application is automatized (remotely controlled by computer) with nobody present in the mushroom cultivation room during the application, operator exposure is only assessed during the mixing/loading phase.

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

		Pyriproxyfen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AAOEL**
Bare arable land/Indoor/Downward spraying/Manual-hand held Drift reduction: 0% Crop density: Normal			
Application rate		3 kg a.s./ha	
Spray application (EFSA; 95th percentile) Body weight: 60 kg	M/L: Work wear (arms, body and legs covered)	0.52	129
	M/L: Work wear (arms, body and legs covered) + protected hands	0.0361	9.0

The potential total systemic exposure of the operator, dressed in work wear covering the body, arms and legs, at mixing and loading, with additional gloves corresponds to 9.0 % of the AAOEL for Pyriproxyfen, regarding the critical use in mushroom.

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

		Pyriproxyfen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Bare arable land/Indoor/Downward spraying/Manual-hand held Drift reduction: 0% Crop density: Normal			
Application rate		3 kg a.s./ha	

Spray application (EFSA**;** 75th percentile) Body weight: 60 kg	M/L: Work wear (arms, body and legs covered)	0.14	349
	M/L: Work wear (arms, body and legs covered) + protected hands	0.0033	8.2

The potential total systemic exposure of the operator, dressed in work wear covering the body, arms and legs, at mixing and loading, with additional gloves corresponds to 8.2 % of the AOEL for Pyriproxyfen, regarding the critical use in mushroom.

There is no unacceptable risk for operator wearing workwear and gloves during mixing and loading regarding the critical use in mushroom.

6.6.2.2 Measurement of operator exposure

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

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Comments of zRMS:	The NDE calculation (EFSA online model OPEX ver. 1.1.1) performed by the applicant is acceptable, and the zRMS reviewer agrees with the conclusions. Worker exposure (entry into previously treated areas or handling the crop according to the critical uses) is acceptable under the intended use conditions. The zRMS also agrees with the proposal that, considering good agricultural practice, wearing protective gloves is recommended when contact with soil may occur during worker activities. However, the NDE calculation confirms safe use even without workwear, nevertheless, the zRMS recommends that workers wear standard workwear, which is not classified as personal protective equipment (PPE) per se.

Table 6.6-5 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with PYRIX 20 SL according to the critical use(s). Outcome of the estimation is presented in Table 6.6-6 (acute exposure) and Table 6.6-7 (longer term exposure). Detailed calculations are in Appendix 3. In the current EFSA guidance, only short-term exposure is assessed for workers.

Table 6.6-5: Exposure models for intended uses

Critical use(s)	Mushrooms (fungi) (1 x 15 mL product/m², equivalent to 1 x 150 L product/ha)
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 calculator version: opex 1.1.1

Table 6.6-6: Estimated worker exposure (acute exposure)

According to the EFSA exposure guidance (EFSA Journal 2022;20(1):7032, 7 pp.,) for PPPs that are acutely toxic an acute worker exposure assessment is in principle needed, but in the current guidance insufficient data are available to perform it.

Table 6.6-7: Estimated worker exposure (longer term exposure)

		Pyriproxyfen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Contact with treated soil / Indoor Work rate: 8 hours/day Interval: NA TSF: NA mg a.s./h / kg a.s./ha			
Number of applications and application rate		1 x 3 kg a.s./ha	
Body weight: 60 kg	Potential TC: NA cm^2/person/h	0.0002	0.6

The potential total systemic exposure of the worker, corresponds to 0.6% of the AOEL for regarding the critical use in mushroom.

Worker exposure when contact with soil is possible during their activities (e.g. manual mushroom harvest) is acceptable without work clothes or PPE/RPE.
As good agricultural practice, wearing protective gloves is recommended when contact with soil is possible during worker activities.

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 mention PPE, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

zRMS Reviewer comment:

Mushroom-growing houses are modern, purpose-built facilities designed for efficient cultivation and are fully isolated from the external environment. Such buildings are completely enclosed, with non-transparent walls and a non-transparent roof, and equipped with tightly sealed, smooth concrete floors, typically covered with ceramic tiles. The growing rooms contain controlled air-conditioning and irrigation systems, including microclimate regulation. In addition, the active substance pyriproxyfen has a very low vapour pressure, particularly at mushroom-growing temperatures (13–16°C). As a result, exposure via air transport is negligible, and indirect exposure through long-range transport or dry re-deposition is also negligible.
Considering the above information, the zRMS reviewer is of the opinion that the specific characteristics of mushroom cultivation, together with the technical and structural requirements of mushroom-growing facilities, mean that non-dietary exposure (NDE) of bystanders and residents is not expected**.**

No exposure of resident or bystander is expected considering the product will be applied automatically in completely closed isolated buildings, in controlled cultivation conditions preventing for potential air contamination and thus transfer from the mushroom house to the outside atmosphere is impossible.

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 Pyriproxyfen 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.

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
All KCP 6.3	Australian National Registration Authority For Agricultural and Veterinary Chemicals	1995	Public Release Summary – PYRIRPOXYFEN In the product Sumilarv Insect Growth Regulator – APVMA 363 1995	N	Public Release Summary

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

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			National Registration Authority For Agricultural and Veterinary Chemicals : Public Release Sum-mary – PYRIRPOXYFEN In the product Sumilarv Insect Growth Regulator – APVMA 363 1995		
All KCP 6.3	EFSA	2019	Peer review of the pesticide risk assessment of the active substance pyriproxyfen. EFSA Journal 2019;17(7):5732 Published.	N	EFSA Public

List of data submitted by the applicant and not relied on

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

List of data relied on not submitted by the applicant but necessary for evaluation

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

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Agrofarm did not submit toxicological studies

Comments of zRMS:	Bridging is not applicable. Hazard classification via the application of bridging principles is not possible since data on a similar mixture are not available. Hazard assessment and proposed classification of the product based on content of ingredients of the mixture has been accepted (for details see Part C).

A 2.2 Acute oral toxicity (KCP 7.1.1)

Agrofarm did not submit acute oral toxicity studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (ATEmix formula) (for details see Part C).

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

Agrofarm did not submit dermal toxocoty studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (ATEmix formula) (for details see Part C).

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Agrofarm did not submit inhalation toxicity studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (ATEmix formula) (for details see Part C).

A 2.5 Skin irritation (KCP 7.1.4)

Agrofarm did not submit skin irritation studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).

A 2.6 Eye irritation (KCP 7.1.5)

Agrofarm did not submit eye irritation studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).

A 2.7 Skin sensitisation (KCP 7.1.6)

Agrofarm did not submit skin sensitisation studies

Comments of zRMS:	Hazard assessment and proposed classification of the product has been concluded considering content of relevant ingredients in the mixture (Additivity formula) (for details see Part C).

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

Not applicable.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

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

A 2.9.2 Available toxicological data for each co-formulant

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

A 2.10 Studies on dermal absorption (KCP 7.3)

Agrofarm did not submit dermal absorption studies.

A 2.11 Other/Special Studies

Not applicable

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

In the online EFSA calculator version 1.1.1, manual hand-held application on bare arable land was selected as being the most relevant for the use scenario on indoor mushrooms. However, the calculated exposure during the application phase is excluded from the total exposure because this phase is automated and there is no operator exposure during this phase. As a consequence, calculations are adjusted to the mixing/loading phase only in the General Report generated from the online calculator.

A 3.1.1 Calculations for pyriproxyfen

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

Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	**Name of active substance**	pyriproxyfen
Concentration of active substance in product [g a.s./l or kg]	20	**Crops**	Bare arable land
Area treated [ha/day]	1	**Application method**	Downward spraying
Dermal absorption [%] (concentrate)	50	**Application technique**	Manual-hand held
Dermal absorption [%] (dilution)	50	**Indoor/ outdoor**	Indoor
Oral absorption [%]	40	**Drift reduction [%]**	0
Inhalation absorption [%]	100	**Type of cultivation**	Normal
Body weight (kg)	60		
AOEL [mg/kg bw per day]	0.04		
AAOEL [mg/kg bw]	0.4		

Table A 2: Estimation of acute operator exposure towards pyriproxyfen according to EFSA guidance

Activity	Systemic exposure per body part	With work-wear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*Protected hands*
	Hands exposure	**501**	**19.7**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**6.7**	**6.7**
	Head protection	*None*	*None*
	Head exposure	**9.5**	**9.5**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.2**	**0.2**
Total *	Total systemic exposure [mg/kg bw per day]	0.52	0.036
	% of AAOEL	129	9.0

* calculated by hand (out of the online calculator)

Table A 3: Estimation of longer term operator exposure towards pyriproxyfen according to EFSA guidance

Activity	Systemic exposure per body part	With work-wear	With workwear + PPE/RPE
Mixing and loading (µg/kg bw per day)	*Hand protection*	*None*	*Protected hands*
	Hands exposure	**137**	**0.8**
	Body protection	*Workwear*	*Workwear*
	Body exposure	**0.8**	**0.8**
	Head protection	*None*	*None*
	Head exposure	**1.6**	**1.6**
	Inhalation protection	*None*	*None*
	Inhalation exposure	**0.08**	**0.08**
Total *	Total systemic exposure [mg/kg bw per day]	0.14	0.0033
	% of AOEL	349	8.2

* calculated by hand (out of the online calculator)

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for pyriproxyfen

Table A 4: Input parameters considered for the estimation of worker exposure

Indoor/ outdoor	Indoor	**AOEL [mg/kg bw per day]**	0.04
Re-entry activity	Contact with treated soil	**Dermal transfer coefficient - Total potential exposure [cm²/h]**	-
Crops	Bare arable land	**Dermal transfer coefficient - Arm, body and legs covered [cm²/h]**	-
Application method	Downward spraying	**Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]**	-
Application technique	Manual-hand held	**Dermal transfer coefficient - Hands covered, no workwear [cm²/h]**	-
Max. application rate of the product [l or kg/ha]	150	**Vapour pressure [Pa]**	0.001
Max. no. of applications	1	**Air concentration [mg/m³]**	0.001
Interval between multiple applications [days]	NA	**DFR refined worker [µg/cm² foliage per kg a.s./ha]**	3
Multiple application factor	1	**DT50 foliar worker [days]**	30
Body weight (kg)	60		
Name of active substance	pyriproxyfen		
Dermal absorption [%] (dilution)	50		
Inhalation absorption [%]	100		
Time [hours per day]	8		

Table A 5: Estimation of worker exposure towards pyriproxyfen according to EFSA guidance

Exposure route	Description	Potential	Workwear	Workwear and gloves	Gloves
Dermal	Systemic dermal exposure [mg a.s. per day]	0.0007	NA	NA	NA
Inhalation	Systemic inhalation exposure [mg a.s. per day]	0.01	NA	NA	NA
Total	Total systemic exposure [mg a.s. per day]	0.01	NA	NA	NA
	Total systemic exposure [mg/kg bw per day]	0.0002	NA	NA	NA
	% of AOEL	0.6	NA	NA	NA

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 applicable.