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| FINAL REGISTRATION REPORT  **Part B**  Section 6  Mammalian Toxicology  Detailed summary of the risk assessment |
| Product code: SAP250F  Product name(s): **Dyllis** (prev. INDOFIL Prothio 250 EC)  Chemical active substance(s):  Prothioconazole, 250 g/L |
| Central Zone  Zonal Rapporteur Member State: Poland |
| CORE ASSESSMENT |
| Applicant: Indofil Industries (Netherlands) BV  Submission date: 30/04/2021  MS Finalisation date: 08/2022; 07/2024; 11/2024 |

Version history

|  |  |
| --- | --- |
| When | What |
| April 2021 | V0 - Original version from applicant Indofil Industries (Netherlands) B.V. for submission to z-RMS in the frame of the PPP Authorization according to Article 33 of Regulation (EC) No 1107/2009. |
| August 2022 | zRMS first evaluation |
| January 2023 | Amendments after commenting period |
| July 2024 | Update human health risk assessment and product classification |
| July 2024 | zRMS assessment |
| November 2024 | The final Registration Report |

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# Mammalian Toxicology (KCP 7)

## Summary

Table 6.1‑1: Information on INDOFIL Prothio 250 EC \*

|  |  |
| --- | --- |
| Product name | ~~INDOFIL Prothio 250 EC~~ Dyllis |
| Product code | SAP250F / Prothioconazole 250 g/L EC |
| Formulation type | Emulsifiable concentrate [EC] |
| Active substance(s) (incl. content) | Prothioconazole; 250 g/L |
| Function | Fungicide |
| Product already evaluated as the ‘representative formulation’ during the approval of the active substance(s) | No |
| Product previously evaluated in another MS according to Uniform Principles | No |

\* Information on the detailed composition of Dyllis ~~INDOFIL Prothio 250 EC~~ can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1‑2: Justified proposals for classification and labelling for SAP250F / Prothioconazole 250 EC according to Regulation (EC) No 1272/2008

|  |  |
| --- | --- |
| Hazard class(es), categories | None  ~~Acute Tox. 3~~  ~~Skin Irrit. 2~~  ~~Eye Irrit. 2~~  ~~STOT SE 3~~ |
| Hazard pictograms or Code(s) for hazard pictogram(s) | None  ~~GHS06~~  ~~GHS07~~ |
| Signal word | None  ~~Danger~~ |
| Hazard statement(s) | None  ~~H331: Toxic if inhaled~~  ~~H315: Causes skin irritation~~  ~~H319: Causes serious eye irritation~~  ~~H335: May cause respiratory irritation.~~ |
| Precautionary statement(s) | WARNING SECTION OF THE LABEL (first page):  None  ~~P261: Avoid breathing vapours/ spray.~~  ~~P280: Wear protective gloves and eye protection/face protection.~~  ~~P302+P352: IF ON SKIN: Wash with plenty of water.~~  ~~P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.~~  Other section of the label:  ~~P261: Avoid breathing vapours/ spray.~~  P270 – Do not eat, drink or smoke when using this product.  P102: Keep out of reach of children.  ~~P271: Use only outdoors.~~  ~~P264: Wash hands thoroughly after handling.~~  ~~P362+P364: Take off contaminated clothing and wash it before reuse.~~  P391: Collect spillage;  ~~P403+P233: Store in a well-ventilated place. Keep container tightly closed.~~  ~~P405: Store locked up.~~  P501: Dispose of contents and/or their container according to the separated collection system used in your municipality.    And P280 as follows:  Operator:  *„Stosować rękawice ochronne, ~~ochronę oczu lub twarzy~~ oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w czasie wykonywania zabiegu”*  “Wear protective gloves, ~~eye/face shield~~ and work wear (~~arms, body and legs covered~~ coverall) during mixing/loading and work wear ~~(arms, body and legs covered)~~ during application”.  Worker:  *„Stosować ~~rękawice ochronne, ochronę oczu lub twarzy oraz~~ odzież roboczą (długie spodnie, koszula z długim rękawem~~.) oraz ograniczyć czas inspekcji terenu poddanego opryskowi do 2 godzin”.~~*  “Wear ~~protective gloves, eye protection/face protection and~~ workwear (arms, body and legs covered ~~long trousers, long-sleeve shirt~~) ~~and limit the time of inspection of treated area to 2 hours~~”.  ~~Bystander/resident:~~  ~~Warning board:~~  *~~“Zakaz wstępu na teren poddany zabiegowi do końca uprawy”.~~*  ~~“Do not enter the treated area till the end of the plant growth”~~  Section First aid:  P101: If medical advice is needed, have product container or label at hand.  ~~P304+P340, P311: IF INHALED: Remove person to fresh air and keep comfortable for breathing. Call a POISON CENTER/doctor.~~  ~~P302+P352: IF ON SKIN: Wash with plenty of water.~~  ~~P332+P313: If skin irritation occurs: Get medical advice/ attention.~~  ~~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 man and the environment, comply with the instructions for use. [EUH401] |

Table 6.1‑3: Summary of risk assessment for operators, workers, residents and bystanders for SAP250F / Prothioconazole 250 EC

|  | Result | PPE / Risk mitigation measures |
| --- | --- | --- |
| Operators | Acceptable | Work wear (arms, body and legs covered) and gloves during mixing and loading (M/L) and Work wear during application  ~~Classification: protective gloves, eye/face protection~~  ~~Exposure: protective gloves during mixing and loading~~ |
| Workers | Acceptable | None. Workwear (arms, body and legs covered)  ~~Classification: protective gloves, eye/face protection~~  ~~Exposure: Work wear amd protective gloves, inspection time: 2h~~ |
| Residents | Acceptable | None. Buffer zone fo field crops 2-3 m.  ~~no entry to the treated area till the end of the plant growth~~ |
| Bystanders | Acceptable | None. Buffer zone fo field crops 2-3 m.  ~~no entry to the treated area till the end of the plant growth~~ |

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. ~~No specific PPE is necessary.~~ Protective gloves are necessary for the operator when mixing and loading the product.

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 | 11 | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Use-No.\* | Crops and situation (e.g. growth stage of crop) | F, Fn, Fpn G, Gn, Gpn or I \*\* | Application | | Application rate | | | PHI (d) | Remarks:   (e.g. safener/synergist (L/ha))  critical gap for operator, worker, resident or bystander exposure based on [Exposure model] | Acceptability of exposure assessment | | | |
| Method / Kind  (incl. application technique \*\*\* | Max. number (min. interval between applications)  a) per use  b) per crop/ season | Max. application rate  L product/ha  a) a.s 1 | Max. application rate  kg as/ha   a) a.s. 1 | Water L/ha  min / max | Operator | Worker | Residents | Bystander |
| 1 | Wheat (spring and winter) (BBCH 25-69) | F | Spraying, LCTM | a) 3 (14)  b) 3 (14) | a) 0.8 L/ha | a) 0.200 | 150 – 400 | NA | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032 |  |  |  |  |
| 2 | Barley (spring and Winter)  (BBCH 25-69) | F | Spraying, LCTM | a) 2 (14)  b) 2 (14) | a) 0.8 L/ha | a) 0.200 | 150 – 400 | NA |  |  |  |  |
| 3 | Oat  (BBCH 25-69) | F | Spraying, LCTM | a) 2 (14)  b) 2 (14) | a) 0.8 L/ha | a) 0.200 | 150 – 400 | NA |  |  |  |  |
| 4 | Rye  (BBCH 25-69) | F | Spraying, LCTM | a) 3 (14)  b) 3 (14) | a) 0.8 L/ha | a) 0.200 | 150 – 400 | NA |  |  |  |  |
| 5 | Triticale  (BBCH 25-69) | F | Spraying, LCTM | a) 3 (14)  b) 3 (14) | a) 0.8 L/ha | a) 0.200 | 150 – 400 | NA |  |  |  |  |
| 6 | OSR  (BBCH 20-80) | F | Spraying, LCTM | a) 2 (14-21)  b) 2 (14-21) | a) 0.7 L/ha | a) 0.175 | 150 – 400 | 56 |  |  |  |  |

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

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

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

Explanation for column 10 “Acceptability of exposure assessment”

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

Data gaps

Data gaps should be listed in the summary to give an overview (especially for cMS).

Noticed data gaps are: None

## 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 | |
| RAC Opinion proposing harmonised classification and labelling at EU level of Prothioconazole (ISO), (March 2019) | Hazard classes (s), categories: Aquatic Acute 1 and Aquatic Chronic 1  Code(s) for hazard pictogram(s): GHS09  Signal word: Warning  Hazard statement(s): H400 and H410  Precautionary statement(s):  P101: If medical advice is needed, have product container or label at hand.  P102: Keep out of reach of children.  P273: Avoid release to the environment.  P391: Collect spillage;  P501: Dispose of contents and/or their container according to the separated collection system used in your municipality. |
| Additional C&L proposal | Please insert proposal for additional C&L if no (sufficient) harmonised classification is available |
| Agreed EU endpoints | |
| AOEL systemic | 0.2 mg/kg bw/d (corrected for 100% oral absorption) |
| Reference | EFSA Conclusion 2007 |
| Conditions to take into account/critical areas of concern with regard to toxicology | |
| According to EFSA Conclusion for Prothioconazole | None |

## Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for INDOFIL Prothio 250 EC is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

Table 6.3‑1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for SAP250F / Prothioconazole 250 EC

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Type of test, species, model system (Guideline) | Result | Acceptability | Classification  (acc. to the criteria in Reg. 1272/2008) | Reference\* |
| LD50 oral | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2) | | | Classification in accordance with Regulation 1272/2008 |
| LD50 dermal | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2) | | | Classification in accordance with Regulation 1272/2008 |
| LC50 inhalation | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2)) | | | Classification in accordance with Regulation 1272/2008 |
| Skin irritation | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2) | | | Classification in accordance with Regulation 1272/2008 |
| Eye irritation | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2) | | | Classification in accordance with Regulation 1272/2008 |
| Skin sensitisation | Not submitted, not necessary.  Estimation based on the composition of the product (additivity formula)  (Justification presented in Appendix 2) | | | Classification in accordance with Regulation 1272/2008 |
| Supplementary studies for combinations of plant protection products | No data – not required | | | |

\* Based on theoretical classification, according to Reg. 1272/2008. For details, please see Toxicological Classification document attached.

Table 6.3‑2: Additional toxicological information relevant for classification/labelling of INDOFIL Prothio 250 EC

|  | Substance (concentration in product, % w/w) | Classification of the  substance  (acc. to the criteria in Reg. 1272/2008) | Reference | Classification of product (acc. to the criteria in Reg. 1272/2008) |
| --- | --- | --- | --- | --- |
| Toxicological properties of active substance(s) (relevant for classification of product) | Prothioconazole (26% (w/w)) | Not classified for human health hazards | Opinion (March 2019) | - |
| Toxicological properties of Dippropylene Glycol Methyl Ether(1) | 25- <50% | Not classified | Reg. 1272/2008 | - |
| Further toxicological information | No data – not required |  |  |  |

(1) Equivalent to 255.1 g/kg of Prothioconazole

## Toxicological Evaluation of Groundwater Metabolites

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

## Dermal Absorption (KCP 7.3)

|  |  |
| --- | --- |
| Comment of ZRMS | Detailed comparison of the product SAP250F/Dyllis with the product used in the study provided by the Applicant (Prothioconazole-desthio in the Prothioconazole 250 EC, Imart C., 2021. Report No. S21-05182 (KCP 7.3/01) has not been carried out. However, the decision to use the rates of dermal absorption of prothioconazole-desthio is also supported by the results of studies obtained in trials with several other EC formulations (range: 14-20%). Additionally, Prthioconazole-desthio is not formed in the concentrated product; the conversion occurs during evaporation of water from diluted solutions of prothioconazole on surfaces. Considering that, the dermal absorption rate for PTZ-desthio in the concentrate should be 0%.  Taking into account all data presented above, the absorption values proposed by the Applicant for metabolite prothioconazole-desthio in the exposure assessment (9.4% for concentrate and 20% for spray dilution) are accepted and consedered as worst case scenario. |

A summary of the dermal absorption rates for the active substances in INDOFIL Prothio 250 EC are presented in the following table.

Table 6.5‑1: Dermal absorption rates for active substances in SAP250F / Prothioconazole 250 EC

|  | Prothioconazole | |
| --- | --- | --- |
|  | Value | Reference[[1]](#footnote-2) |
| Concentrate | 25% | Dermal Absorption 2017 |
| Dilution | 70% | Dermal Absorption 2017 |

**Table 6.5‑2: Dermal absorption rates for metabolite Prothioconazole-desthio (M04)**

|  | **Prothioconazole-desthio (M04)** | |
| --- | --- | --- |
|  | **Value** | **Reference** |
| Concentrate | 9.4%  ~~20%~~ | Based in a dermal absorption study – Imart C., 2021. Report No. S21-05182 (KCP 7.3/01) - Point A 2.10  ~~EFSA Scientific Report 2007; 106, 1-98~~ |
| Dilution  (0.4535 g/l) | 25%  ~~20%~~ | Based in a dermal absorption study – Imart C., 2021. Report No. S21-05182 (KCP 7.3/01) - Point A 2.10  ~~EFSA Scientific Report 2007; 106, 1-98~~ |

### Justification for proposed values - Prothioconazole

No data on dermal absorption for Prothioconazole in INDOFIL Prothio 250 EC 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 6.5‑3: Default dermal absorption rates for Prothioconazole

|  | Value | Justification for value | Acceptability of justification |
| --- | --- | --- | --- |
| Concentrate | 25% | A default dermal absorption value of 25% for concentrate and 70% for (in use) dilutions may be applied for that are organic solvent-formulated. For details, please see default values on point 6.1. (Table 2 – pag. 19) | yes |
| Dilution | 70% | yes |

### Justification for proposed values – Prothioconazole-desthio

The dermal absorption study (Imart C., 2021) investigated the rate and extent of the *in-vitro* dermal absorption of prothioconazole-desthio following topical application of Prothioconazole 250 EC test item, to the surface of human split-thickness skin mounted on flow-through diffusion cells, at the concentrated rate and one in-use spray dilution. Based on the results of this study, a 9.4% dermal absorption for the concentrate and a 25% dermal absorption for the dilution were considered appropriate for use in operator, worker and resident exposure calculations.~~According to EFSA Scientific Report 2007, a dermal absorption study in rhesus monkeys using an SC formulation containing M04, a 20% dermal absorption was considered appropriate for use in operator, worker and resident exposure calculations.~~

Table 6.5‑4: ~~Default~~ dermal absorption rates for Prothioconazole-desthio

|  | Value | Justification for value | Acceptability of justification |
| --- | --- | --- | --- |
| Concentrate | 9.4%  ~~20%~~ | Based on the dermal absorption study (Imart C., 2021), which investigated the rate and extent of the *in-vitro* dermal absorption of prothioconazole-desthio following topical application of Prothioconazole 250 EC test item, to the surface of human split-thickness skin mounted on flow-through diffusion cells, at the concentrated rate and one in-use spray dilution.  ~~No dermal absorption studies were performed and submitted with the representative formulation.~~  ~~Hence, for M04, a 20% dermal value has been derived from a dermal absorption study in monkeys~~ | Yes, see comments above. |
| Dilution (1:500) 0.4535 g/L | 25%  ~~20%~~ | Yes, see comments above. |

## 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 | ~~INDOFIL Prothio 250 EC~~ Dyllis | |
| Product name and code | SAP250F / Prothioconazole 250 g/L EC | |
| Formulation type | EC | |
| Category | Fungicide | |
| Active substance(s) and Relevant Metabolite (incl. content) | **Prothioconazole**  250 g/L | **Prothioconazole-desthio** (JAU 6476-desthio)  ~~181.4 g/L~~ 226.75 |
| AOEL systemic | 0.2 mg/kg bw/d | 0.01 mg/kg bw/d |
| Inhalation absorption | 100% | 100% |
| Oral absorption | 100% | 100% |
| Vapour pressure | < 4 x 10-7 Pa at 20 °C\*  < 4 x 10-7 Pa at 25 °C | 0.001 (OPEX default value) |
| Dermal absorption | Concentrate: 25%  Dilution: 70%  (Default values) | Concentrate: 9.5%  Dilution: 25%  (Based on dermal absorption study Imart C., 2021 - Report No. S21-05182)  ~~Concentrate: 0%~~  ~~Dilution: 20%~~  ~~(EFSA Scientific Report 2007; 106, 1-98)~~ |

\* EFSA Scientific Report (2007) 106, 1-98, Conclusion on the peer review of prothioconazole

According to the EFSA conclusion (EFSA Scientific Report 2007; 106, 1-98) the metabolite JAU 6476-desthio (M04) is considered more toxic than the parent. Therefore, a detailed risk assessment for all population groups is required for JAU 6476-desthio.

***Relevant notes for prothioconazole-desthio risk assessment:***

|  |  |
| --- | --- |
| Comment of ZRMS | ~~The approach suggested by Applicant to assess the exposure to metabolite prothioconazole-desthio represents the worst scenario (maximal conversion rate of parent substance). The assumptions used in the calculations are accepted.~~  The conversion rate of the parent compound to Prthioconazole-desthio amounts to 45% (as proposed in „Pesticide peer review meeting“ of September, 2020). This rate should be used in the assessment (prothioconazole: 0.11 kg/ha and 0.08163 kg/ha for prothioconazole-desthhio). Concluding, the scenario presented by the Applicant (anticipating maximal conversion rate of the parent substance) can be accepted as an overestimated scenario. |

Since the conversion rate of prothioconazole to prothioconazole-desthio is not known, a conservative approach was applied, and the following assumptions were used in the exposure calculations:

* For the exposure assessment to prothioconazole-desthio a total conversion of prothioconazole to prothioconazole-desthio was assumed. To calculate the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio);
* ~~For the operator exposure calculation, formation of prothioconazole – desthio is not expected in the concentrate, thus during the M/L task the dermal absorption of prothioconazole-desthio was not considered and a dermal absorption value of 0% was applied to remove this from calculation.~~
* No conversion of prothioconazole-desthio to prothioconazole was considered for the exposure assessment of prothioconazole.
* For the combined risk assessment a conversion rate of 50% is considered from prothioconazole to prothioconazole-desthio.

**APPROACH USED FOR WORKER AND RESIDENT**

To achieve an acceptable risk in all exposition groups (operator, worker and resident/bystander), the following approach were used to refine worker and residents in order to have a more realistic and acceptable risk.

**For the worker and the resident**, a DFR study was used to refine the prothioconazole-desthio assessment (For study details please see point 2.11). This study was performed with a similar formulation (Prothioconazole + Folpet) which the objective is to generate specimens on decline of Prothioconazole, its metabolite (Prothio-desthio) and Folpet in dislodgeable foliar residues (DFR) from cereals.

### Selection of critical use(s) and justification

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

Justification

The applications use selected (Cereals) offers the worst-cases scenario for exposure to operator, worker, resident and bystander. The values used were considered to be the worst-case of each scenario.

### Operator exposure (KCP 7.2.1)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~The estimations of operator exposure to prothioconazole contained in SAP250F/INDOFIL Prothio 250 EC (based on AOEM) performed by the Applicant are correct.~~  ~~Conclusions:~~  ~~According to the estimation based on AOEM, the use of SAP 250F/INDOFIL Prothio 250 EC containing prothioconazole (250 g/kg)~~ **~~causes acceptable health risk for unprotected operator.~~** ~~The potential exposure to the active substance amounts to the value lower than the AOEL set for this substance. If the nozzles with drift-reduction are used, the exposure of unprotected operator amounts to 25%.~~  ~~However,~~ ~~taking into account the classification of the product, protective gloves, eye/face shield and work wear during M&L and product application are mandatory.~~  ~~Thus, the following sentence regarding the use of PPE is recommended by the evaluator to be placed in the label:~~  ~~„~~*~~Stosować rękawice ochronne, ochronę oczu lub twarzy oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz wykonywania zabiegu~~*~~”~~  ~~“Wear protective gloves, eye/face shield and work wear (coverall) during mixing/loading and application”.~~  The estimations of operator exposure to prothioconazole contained in SAP250F/Dyllis (based on EFSA Journal 2022;20(1):7032OPEX calculator v1.0.2) performed by the Applicant are accepted (see also zRMS comments above).  Conclusions:  According to the estimation results, the use of SAP 250F/Dyllis containing prothioconazole (250 g/kg) **causes acceptable health risk for operator equipped with work wear and protective gloves during mixing/loading and work wear during application.**  Thus, the following sentence regarding the use of PPE is recommended by the evaluator to be placed in the label:  „*Stosować rękawice ochronne, oraz odzież roboczą (kombinezon) w trakcie przygotowywania cieczy roboczej oraz odzież roboczą w czasie wykonywania zabiegu*”  “Wear protective gloves and work wear (coverall) during mixing/loading and work wear during application”. |

#### Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of INDOFIL Prothio 250 EC according to the critical use(s) is presented in Table 6.6‑2. The outcome of the estimation is presented in 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) | Field crops: Cereals (3 x 0.8 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 2014;12(10):3874~~  ~~calculator version: 30/03/2015~~  Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032  OPEX calcuator v1.0.2 (29/04/2024) |

Estimated operator exposure (acute exposure)

An AAOEL was not allocated for prothioconazole and its metabolite (prothioconazole-desthio). Therefore, estimates of the acute exposure to operators has not been conducted.

Table 6.6‑3: Estimated operator exposure (longer term exposure)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CEREALS |  | Prothioconazole | | Prothioconazole-desthio | |
| Model data | Level of PPE | Total absorbed dose  (mg/kg/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Vehicle-mounted: Downward spraying  Outdoor, normal  **Number of applications:** 3  **Interval between applications:** 14 days  **Crop:** Cereals  *Oilseed rape are also covered by this assessment.* | | | | | |
| Application rate | | 3 x 0.2 kg a.s./ha | | 3 x 0.1814 kg a.s./ha ~~(100% conversion\*)~~ | |
| **Spray application** (AOEM**;** 75th percentile)  Body weight: 60 kg | Potenial exposure  ~~No PPE~~ | 0.3  ~~0.2239~~ | 131  ~~111.95~~ | 0.09  ~~0.0777~~  ~~0.0073~~~~\*~~ | 913  ~~776.71~~  ~~72.81~~ |
| Work wear (arms, body and legs covered) M/L and Application | 0.2  ~~0.1402~~ | 84.7  ~~70.12~~ | 0.0586  ~~0.0486~~  ~~0.0048~~~~\*~~ | 594  ~~485.57~~  ~~48.43~~ |
| Gloves + Work wear (arms, body and legs covered) M/L and Work wear during Application | 0.026  ~~0.218~~ | 11.2  ~~10.89~~ | 0.007  ~~0.0072~~ | 74.6  ~~72.37~~ |

~~\*~~ ~~Assuming 100% conversion of prothioconazole to prothioconazole-desthio and 0% dermal absorption from formulation (concentrate).~~

**CONCLUSION**

According to the calculations above (Table 6.6‑3), it can be concluded that there is an acceptable risk for operator when adequate working clothing (arms, body and legs covered) is considered during mixing and loading (M/L) and application and gloves during M/L.

#### 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.

### Worker exposure (KCP 7.2.3)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~The estimations of worker exposure to the active substance contained in SAP 250F/INDOFIL Prothio 250 EC (based on AOEM) performed by the Applicant are accepted. Taking into account, that the worst scenario was used (100 % conversion of prothioconazole to prothioconazole-destho), the proposed PPE ensures worker safety during crop inspection.~~  ~~Conclusions:~~  ~~According to the estimation results, the use of SAP250F/INDOFIL Prothio 250 EC containing prothioconazole (250 g/kg)~~ **~~does not~~****~~cause unacceptable health risk for a worker wearing work wear and protective gloves~~** ~~during field inspection with maximum exposure time of 2h. In addition, due to the classification of the product, the use of eye/face shield is recommended.~~  ~~Nevertheless, it is forbidden to re-enter area treated with SAP250F/INDOFIL Prothio 250 EC until spray deposit on plant surfaces has dried.~~  ~~Following sentence regarding the use of PPE is recommended by the evaluator to be placed in the~~ **~~section of precautions for the workers~~**~~:~~  ~~„~~*~~Stosować rękawice ochronne, ochronę oczu lub twarzy oraz odzież roboczą (długie spodnie, koszula z długim rękawem) oraz ograniczyć czas inspekcji terenu poddanego opryskowi do 2 godzin~~*~~.”~~  ~~“Wear protective gloves, eye/face shield and workwear (long trousers, long-sleeve shirt) and limit the time of inspection of treated area to 2 hours”.~~  In the estimations of worker exposure to the active substance contained in SAP 250F/Dyllis (based on EFSA Journal 2022;20(1):7032OPEX calculator v1.0.2) performed by the Applicant, the DFR value for prothioconazole-desthio was used based on the results of the study by Gaffney V. (2022). Taking into account the conditions of the trial (scenario for Southern Europe, treatment: two applications, application rate of prothioconazole: 180 g/ha), the use of default value (3 µg/cm2/kg) for prothioconazole-desthio is more appropriate and justified. The rate of conversion of the parent compound to Prthioconazole-desthio amounts to 45% (as proposed in „Pesticide peer review meeting“ of September, 2020). This rate should be used in the assessment (application rate prothioconazole: 0.11 kg/ha and 0.08163 kg/ha for prothioconazole-desthhio).  The results of the assessment are presented below:  Prothioconazole:  Prothioconazole-desthio:  The combined exposure of the worker to prothioconazole and prothioconazole-desthio (assuming 2h exposure during inspection and irrigation) wearing work wear amounts to 63.5% of AOEL (0.64 HQ).  Conclusions:  According to the estimation results, the use of SAP250F/Dyllis containing prothioconazole (250 g/kg) **does not** **cause unacceptable health risk for a worker wearing work wear** during field inspection with exposure time of 2h. Still, bearing in minds the hygienic rules, the use protective gloves **is also recommended by** the evaluator during inspection of the treated area.  Nevertheless, it is forbidden to re-enter area treated with SAP250F/Dyllis until spray deposit on plant surfaces has dried. |

#### Estimation of worker exposure

Table 6.6‑4 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with INDOFIL Prothio 250 EC according to the critical use(s). Outcome of the estimation is presented in Table 6.6‑5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6‑4: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Field crops: Cereals (3 x 0.8 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 2014;12(10):3874~~  ~~calculator version: 30/03/2015~~  Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032  OPEX calcuator v1.0.2 (29/04/2024) |

Estimated worker exposure (acute exposure)

An AAOEL was not allocated for prothioconazole and its metabolite (prothioconazole-desthio). Therefore, estimates of the acute exposure to workers has not been conducted.

Table 6.6‑5: Estimated worker exposure (longer term exposure)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Prothioconazole | | | | Prothioconazole-desthio | | |
| Model data | Level of PPE | Total absorbed dose (mg/kg bw/day) | | % of systemic AOEL | | Total absorbed dose (mg/kg bw/day) | | % of systemic AOEL |
| Inspection, irrigation  Outdoor  Work rate: 2 hours/day,  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha  Interval between treatments: 14 days  *Oilseed rape are also covered by this assessment.* | | | | | | | | |
| Number of applications and application rate | | 3 x 0.2 kg a.s./ha | | | | 3 x 0.1814 kg a.s./ha ~~(100% conversion\*)~~ | | |
| Body weight: 60 kg | Potential  TC: 12500 cm2/person/h | 0.4  ~~0.3933~~ | | 197  ~~196.64~~ | | 0.1  ~~0.1274~~  ~~0.1019~~ | | 1275  ~~1273.93~~  ~~1019.14~~ |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.04  ~~0.0440~~ | | 22.1  ~~22.02~~ | | 0.01  ~~0.0143~~  ~~0.0114~~ | | 143  ~~142.68~~  ~~114.14~~ |
| Work wear (arms, body and legs covered) and gloves  TC: 1250 cm2/person/h | 0.04 | | 19.7 | | 0.01 | | 128 |
| ~~Work wear (arms, body and legs covered) and gloves~~  ~~TC:~~ **~~None~~** ~~cm~~~~2~~~~/person/h~~ | **~~no TC available for this assessment~~** | | | | | | |
| ~~Work wear (arms, body and legs covered) and gloves~~  ~~90% protection from gloves~~ | ~~0.0044~~ | **~~2.20~~** | | ~~0.0011~~ | | **~~11.41~~** | |

~~\*~~ ~~Assuming 100% conversion of prothioconazole to prothioconazole-desthio and 0% dermal absorption from formulation (concentrate).~~

**CONCLUSION**

~~Taking into account the classification proposal as Repro cat 2, R61 (Repr. 1B H360) for prothioconazole-desthio (EFSA Scientific Report (2007) 106, 1-98, Conclusion on the peer review of prothioconazole) and the potential exposure of workers to this metabolite, the use of gloves is proposed.~~

~~Overall, the following phrase should be included in the product label:~~

~~“~~*~~Treated crops should not be re-entered before spray deposits on leaf surfaces have completely dried. In case a worker enters the treated area, protective gloves, long trousers and long-sleeved shirt should be worn.~~*~~”.~~

~~Although there is no TC available for calculating the worker exposure when using gloves within the EFSA model, it is possible to apply the default protection afforded by using gloves (90%) to the calculate the total absorbed dose and % of the AOEL for the worker using work wear and gloves. This is presented in the table above.~~

~~The risk for the worker re-entering the crops treated with INDOFIL Prothio 250 EC is considered as acceptable.~~

According to the calculations above (Table 6.6‑5), it can be concluded that there is an unacceptable risk for worker when adequate working clothing is considered. Therefore, refinement of the generic DFR value using a DFR study is necessary.

#### Refinement of generic DFR value (KCP 7.2)

~~Not Required.~~

A Dislodgable Foliar Residue (DFR) study was carried out to determine the decline of prothioconazole, prothioconazole-desthio and folpet dislodgeable foliar residues in cereals (wheat and barley) following two applications of SAP2101F containing Prothioconazole 12% w/v (=120 g/L) + Folpet 30% w/v (=300 g/L) was applied between BBCH 32-61 at a rate of 1.5 L/ha (=180 g Prothioconazole/ha + 450 g Folpet/ha) onto the crop in open field conditions. The interval between applications was 14 ± 1 day with the last application applied 42 days before commercial harvest (=DBCH). The formulation was applied using appropriate application equipment at the proposed normal use rates and timings.

The field trials were performed at 3 field sites: 2 field sites in Spain and 1 field site in Portugal.

For the calculations of prothioconazole-desthio amount in µg/cm2 of foliage/kg a.s. applied/ha a 100% of conversion was considered. Therefore, 163.26 g prothio-desthio/ha (=180 g Prothioconazole/ha x 0.907) was considered as maximum rate applied for prothio-desthio.

**For DFR calculations the higher residue value (0DAA2) was considered for the risk assessment.**

**DFR CALCULATIONS**

**0 DAA2 – Maximum residue value – DFR CALCULATION**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **LabRP  Sample Code** | **Days** | **Corrected Mean**  **Protioconazole-desthio (µg/cm2)** | **Mean**  **Protioconazole-desthio (µg/cm2)** | **Maximum**  **“Applied” dose of prothio-desthio (kg as/ha)** | **DFR value (µg/cm2 kg as/ha)** |
| 452/DFR12/21 | 0 DAA2 | 0.025 | 0.019(6) | 0.16326 kg prothio-desthio/ha | **0.1207** |
| 453/DFR12/21 |
| 454/DFR12/21 |
| 509/DFR12/21 | 0 DAA2 | 0.013 |
| 510/DFR12/21 |
| 511/DFR12/21 |
| 602/DFR12/21 | 0 DAA2 | 0.021 |
| 603/DFR12/21 |
| 604/DFR12/21 |

**The DFR value considered to refine the risk of prothioconazole-desthio based on a conversion factor of 100% of prothioconazole into prothio-desthio was 0.31443 µg/cm2 kg as/ha, 0 days after application 2 (0 DAA2).**

Table 6.6‑6: Estimated worker exposure (longer term exposure)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Prothioconazole | | Prothioconazole-desthio | |
| Model data | Level of PPE | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Inspection, irrigation  Outdoor  Work rate: 2 hours/day,  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha (Prothioconazole)  DFR: 0.1207 µg/cm2/kg a.s./ha (Prothioconazole-desthio)  Interval between treatments: 14 days  *Oilseed rape are also covered by this assessment.* | | | | | |
| Number of applications and application rate | | 3 x 0.2 kg a.s./ha | | 3 x 0.1814 kg a.s./ha (100% conversion) | |
| Body weight: 60 kg | Potential  TC: 12500 cm2/person/h | 0.4  ~~0.3933~~ | 197  ~~196.64~~ | 0.005  ~~0.0051~~ | 51  ~~51.25~~ |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.04  ~~0.0440~~ | 22.1  ~~22.02~~ | 0.0006 | 5.7 |
| Work wear (arms, body and legs covered) and gloves  TC: 1250 cm2/person/h | 0.04 | 19.7 | 0.0005 | 5.1 |
| ~~Work wear (arms, body and legs covered) and gloves~~  ~~TC:~~ **~~None~~** ~~cm~~~~2~~~~/person/h~~ | **~~no TC available for this assessment~~** | | | |

**CONCLUSION**

According to the calculations above (Table 6.6‑6), it can be concluded that there is an acceptable risk for worker when adequate working clothing (arms, body and legs covered) is considered and using the refined DFR value for prothioconazole-desthio, available from the DFR study (Gaffney, V. 2022).

#### 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.

### Resident and bystander exposure (KCP 7.2.2)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~The reference values acutely toxic active substance (RVAAS) for the prothioconazole and protoconazole-desthio are not allocated. Consequently, it is assumed that the estimation of bystander exposure is covered by the calculation of resident exposure towards active substance and its metabolite.~~  ~~The estimations of resident exposure to prothioconazole-desthio has not been accepted. The buffer zone amounts to 10 m is unrealistic, the maximum allowable zone is 5 m. Thus, a new calculation for prothioconazole was performed and the results are presented below:~~    ~~Prothioconazole: The results of the exposure estimations suggest that the use of SAP 250F/INDOFIL Prothio 250 EC according to the list of intended uses presented in GAP Table cause acceptable health risk for bystander and resident (adult and child) according AOEM.~~  ~~Prothioconazole-desthio: The results of the exposure estimations suggest that the use of SAP 250F/INDOFIL Prothio 250 EC according to the list of intended uses presented in GAP Table, may cause~~ **~~unacceptable health risk for bystander and resident (child)~~** ~~according AOEM. The exposure value to prothioconazole-desthio amounts to 134 % of AOEL (if buffer zone of 5m is applied).~~ ~~However, it should be noted that the majority of the exposure is supposed to occur if a resident/bystander enters into the treated area. Thus,~~ ~~the incidental short-time exposure of bystander and resident to prothioconazole-desthio is acceptable if the~~ **~~warning boards~~** ~~forbidding entry of bystander/resident into the treated area are installed and remain till the end of cultivation.~~  ~~Taking into account the results and conclusions of the estimations it is mandatory to install a warning board informing:~~  ~~“~~*~~Zakaz wstępu na teren poddany zabiegowi do końca uprawy~~*~~”.~~  ~~“Do not enter the treated area till the end of the plant growth”~~  The reference values acutely toxic active substance (RVAAS) for the prothioconazole and protoconazole-desthio are not allocated. Consequently, it is assumed that the estimation of bystander exposure is covered by the calculation of resident exposure towards the active substance and its metabolite.  In the estimations of bystander/resident exposure to the active substance contained in SAP 250F/Dyllis (based on EFSA Journal 2022;20(1):7032OPEX calculator v1.0.2) performed by the Applicant, the DFR value for prothioconazole-desthio was used based on the results of the study by Gaffney V. (2022). Taking into account the conditions of the trial (scenario for Southern Europe, treatment: two applications, application rate of prothioconazole 180 g/ha), the use of default value (3 µg/cm2/kg) for prothioconazole-desthio is more appropriate and justified. The conversion rate of the parent compound to Prthioconazole-desthio amounts to 45% (as proposed in „Pesticide peer review meeting“ of September, 2020) and this value should be used in the assessment (application rate prothioconazole: 0.11 kg/ha and 0.08163 kg/ha for prothioconazole-desthhio).  The results of estimations are presented below:  Prothioconazole:    Prothioconazole-desthio:    The exposure of the resident/bystander to prothioconazole and prothioconazole-desthio amounts to 96% AOEL (0.96 HQ) and 43.1% AOEL (0.43 HQ) for child and adult, respectively.  Conclusions:  The results of the exposure estimations suggest that the use of SAP 250F/Dyllis according to the list of intended uses presented in GAP Table, causes acceptable health risk for bystander and resident (adult and child). |

#### Estimation of resident and bystander exposure

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

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

Table 6.6‑6 shows the exposure model(s) used for estimation of resident and bystander exposure to prothioconazole and its metabolite (prothioconazole-desthio). The outcome of the estimation is presented in Table 6.6‑7 (longer term resident exposure). Detailed calculations are in Appendix 3.

Table 6.6‑6: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Field crops: Cereals (3 x 0.8 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 2014;12(10):3874~~  ~~calculator version: 30/03/2015~~  Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment of plant protection products. EFSA Journal 2022;20(1):7032  OPEX calcuator v1.0.2 (29/04/2024) |

Table 6.6‑7: Estimated resident exposure (longer term exposure)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Prothioconazole | | 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: Downward spraying  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha (Prothioconazole)  DFR: 0.1207 µg/cm2/kg a.s./ha (Prothioconazole-desthio)  Interval between treatments: 14 days  Minimum volume of water: 150 L  *Oilseed rape are also covered by this assessment.* | | | | | |
| Buffer zone: 2-3 (m)  Drift reduction technology: No | | | | Buffer zone: 2-3 (m)  Drift reduction technology: No  ~~Buffer zone: 10 (m)~~  ~~Drift reduction technology: Yes~~ | |
| Number of applications and application rate | | 3 x 0.2 kg a.s./ha | | 3 x 0.1814 kg a.s./ha ~~(100% conversion\*)~~ | |
| Resident child  Body weight: 10 kg | Drift (75th perc.) | 0.03  ~~0.0251~~ | 12.6  ~~12.53~~ | 0.008  ~~0.0081~~  ~~0.0018~~ | 82  ~~81.33~~  ~~17.89~~ |
| Vapour (75th perc.) | 0.00005  ~~0.0011~~ | 0.02  ~~0.54~~ | 0.0008  0.0011  ~~0.0011~~ | 8  10.70  ~~10.70~~ |
| Deposits (75th perc.) | 0.005  ~~0.0049~~ | 2.5  ~~2.47~~ | 0.002  ~~0.0018~~  ~~0.0002~~ | 18.2  ~~18.15~~  ~~1.76~~ |
| Re-entry (75th perc.) | 0.05  ~~0.0531~~ | 26.6  ~~26.55~~ | 0.0007  ~~0.0138~~ | 6.9  ~~137.58~~ |
| **Sum (mean)** | 0.06  ~~0.0608~~ | 29.9  ~~30.41~~ | 0.007  ~~0.0074~~  ~~0.0132~~ | 71.6  ~~74.13~~  ~~131.74~~ |
| Resident adult  Body weight: 60 kg | Drift (75th perc.) | 0.0060 | 3.00 | 0.002  ~~0.0019~~  ~~0.0003~~ | 19.4  ~~19.44~~  ~~3.38~~ |
| Vapour (75th perc.) | 0.00002  ~~0.0002~~ | 0.008  ~~0.12~~ | 0.0003  ~~0.0002~~  ~~0.0002~~ | 2.7  ~~2.30~~  ~~2.30~~ |
| Deposits (75th perc.) | 0.002  ~~0.0021~~ | 1.1  ~~1.07~~ | 0.0007  ~~0.0001~~ | 7  ~~0.64~~ |
| Re-entry (75th perc.) | 0.03  ~~0.0295~~ | 14.8  ~~14.75~~ | 0.0004  ~~0.0076~~ | 3.8  ~~76.44~~ |
| **Sum (mean**) | 0.03  ~~0.0282~~ | 14  ~~14.08~~ | 0.0020  ~~0.0066~~ | 20  ~~19.69~~  ~~65.56~~ |

~~\*~~ ~~Assuming 100% conversion of prothioconazole to prothioconazole-desthio and 0% dermal absorption from formulation (concentrate).~~

~~Since an unacceptable risk has been identified for a child resident even when risk mitigation measures have been considered (drift-reduction (50%)/10 m buffer strip), below it is proposed two different approaches that demonstrate, as a weight of evidence, an acceptable risk for resident, based on more realistic endpoints.~~

**~~APPROACH A. RESIDENT REFINEMNT – NEW TC VALUES~~**

~~In the EFSA Calculator 2015, for the estimation of the resident exposure during entry into treated crops, the TC value for a worker performing inspection activities is used, i.e. 7500 cm~~~~2~~~~/h (75th percentile); 5980 cm~~~~2~~~~/h (mean).~~

~~Considering the stage of crop (pre-emergence/early post-emergence) and season the PPP, the contamination of a child re-entering treated crops is unlikely. In case it occurs, the assumption of wearing clothes covering arms, body and legs has been considered for this specific case. Therefore, a refinement is proposed, for resident exposure during “entry into treated crops” using the TC values for a worker re-entering the field for inspection/irrigation tasks assuming arms body and legs are covered, i.e. 1400~~ ~~cm2~~~~/h (75th percentiles); 1116.27 cm~~~~2~~~~/h (mean). Since there are no TC values available for children, a factor of 0.3 is applied to adult TC values, i.e. 420 cm~~~~2~~~~/h (75th percentiles); 334.88 cm~~~~2~~~~/h (mean).~~

~~A refinement on ‘reentry into treated crop’ parameter was performed considering the new TC values. The main aim of this refinement is to achieve a realistic scenario for the residents when exposure to INDOFIL Prothio 250 EC. With this refinement, new values on “all pathways mean” were also found. For detailed calculations please see Appendix 4.~~

**~~APPROACH B. 40% CONVERSION RATE TO PROTHIOCONAZOLE-DESTHIO~~**

~~The risk assessment for the metabolite JAU 6476-desthio in the previous steps was performed assuming a total transformation of Prothioconazole into such metabolite.~~

~~Haas and Bornatsch (2000), Haas (2001b) and Haas (2001c), referred in the DAR (2004; sections B7.1.1 and B.7.1.5), studied the residue formation after spray application of Prothioconazole in wheat, peanut or confined rotational crops (wheat, chard and turnip seedlings were planted at 28, 146 and 269 days after Prothioconazole application, simulating three rotations), respectively.~~

~~Various crop matrices were collected for residue measurement in all studies. For the metabolite JAU 6476-desthio, the maximum residue content measured was 35.49% in wheat fodder. Therefore, and as a worst-case approach, the following refinement was made assuming a 40% transformation rate from the parent to the metabolite in foliar matrices. From these results the total amount of Prothioconazole to be applied, 200g as described in the GAP, would correspond to 181.4g for cereals of JAU 6476-desthio which would be transformed into 72.6g for cereals of JAU 4676-desthio (40%). The refinement with these more realistic values was considered and is presented in table below.~~

**~~Table 6.6-8: Overall - resident exposure to Prothioconazole-desthio – With Re-entry and Sum parameters refined~~**

|  |  |  |  |
| --- | --- | --- | --- |
|  | | **~~Prothioconazole-desthio~~** | |
| **~~Model data~~** | | **~~Total absorbed dose (mg/kg bw/day)~~** | **~~% of systemic AOEL~~** |
| ~~Vehicle-mounted: Downward spraying~~  ~~DT50: 30 days~~  ~~DFR: 3 µg/cm2/kg a.s./ha~~  ~~Interval between treatments: 14 days~~  ~~Buffer zone: 10 (m)~~  ~~Drift reduction technology: Yes~~  *~~Oilseed rape are also covered by this assessment.~~* | | | |
| ~~Number of applications and application rate~~ | | ~~3 x 0.0726 kg a.s./ha (40% conversion)~~ | |
| ~~Resident child~~  ~~Body weight: 10 kg~~ | ~~Drift (75~~~~th~~ ~~perc.)~~ | ~~0.0007~~ | **~~7.16~~** |
| ~~Vapour (75~~~~th~~ ~~perc.)~~ | ~~0.0011~~ | **~~10.70~~** |
| ~~Deposits (75~~~~th~~ ~~perc.)~~ | ~~0.0001~~ | **~~0.71~~** |
| ~~Re-entry (75~~~~th~~ ~~perc.)~~ | ~~0.0055~~ | **~~55.06~~** |
| **~~Sum (mean)~~** | ~~0.0059~~ | **~~59.14~~** |
| ~~Resident adult~~  ~~Body weight: 60 kg~~ | ~~Drift (75~~~~th~~ ~~perc.)~~ | ~~0.0001~~ | **~~1.35~~** |
| ~~Vapour (75~~~~th~~ ~~perc.)~~ | ~~0.0002~~ | **~~2.30~~** |
| ~~Deposits (75~~~~th~~ ~~perc.)~~ | ~~0.0000~~ | **~~0.26~~** |
| ~~Re-entry (75~~~~th~~ ~~perc.)~~ | ~~0.0031~~ | **~~30.59~~** |
| **~~Sum (mean)~~** | ~~0.0028~~ | **~~27.62~~** |

**CONCLUSION**

According to EFSA calculator, an acceptable risk was determined for residents (child and adults) during treatments with INDOFIL Prothio 250 EC.

#### 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) 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.

### Combined exposure

~~Not relevant.~~ The product contains only one active substance. However, as the active substance prothioconazole has the relevant metabolite prothioconazole-desthio, a combined exposure is calculated and presented. A conversion of 50% from prothioconazole to prothioconazole-desthio is considered for this calculation.

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

Table 6.6‑13: Risk assessment from combined exposure (longer term exposure)

| Application scenario | Active ingredient | Estimated exposure / AOEL (HQ) |
| --- | --- | --- |
| Operators – ~~e.g. handheld application~~  Gloves + Work wear (arms, body and legs covered) M/L and Work wear (arms, body and legs covered) during Application | Prothioconazole | 0.112  ~~0.1089~~ |
| Prothioconazole-desthio | 0.746  ~~0.3708~~ |
| **Cumulative risk operators (HI)** | **0.9**  **~~0.4797~~** |
| Workers – ~~e.g. hand-harvesting vegetable crops~~  Workwear (arms, body and legs covered) | Prothioconazole | ~~0.221~~ 0.12  ~~0.2202~~ |
| Prothioconazole-desthio | ~~0.057~~ 0.54  ~~0.0287~~ |
| **Cumulative risk workers (HI)** | **~~0.3~~ 0.66**  **~~0.2489~~** |
| Resident - child | Prothioconazole |  |
| Drift | ~~0.126~~ 0.07  ~~0.1253~~ |
| Vapour | ~~0.0002~~ 0.004  ~~0.0054~~ |
| Deposits | ~~0.025~~ 0.014  ~~0.0247~~ |
| Re-entry | ~~0.266~~ 0.146  ~~0.2655~~ |
| Sum of all pathways | ~~0.299~~ 0.168  ~~0.304~~ |
| Prothioconazole-desthio |  |
| Drift | ~~0.82~~ 0.295  ~~0.4067~~ |
| Vapour | 0.08  ~~0.107~~ |
| Deposits | ~~0.182~~ 0.068  ~~0.0907~~ |
| Re-entry | ~~0.069~~ 0.62  ~~0.0346~~ |
| Sum of all pathways | ~~0.716~~ 0.79  ~~0.4241~~ |
| **Cumulative risk resident – child (HI)** |  |
| ~~Drift~~ | ~~0.9~~  ~~0.532~~ |
| ~~Vapour~~ | ~~0.08~~  ~~0.1124~~ |
| ~~Deposits~~ | ~~0.2~~  ~~0.1154~~ |
| ~~Re-entry~~ | ~~0.3~~ |
| **Sum of all pathways** | **0.96**  **~~1~~**  **~~0.7281~~** |
| Resident - adult | Prothioconazole |  |
| Drift | ~~0.03~~ 0.016 |
| Vapour | ~~0.008~~ 0.001  ~~0.0012~~ |
| Deposits | ~~0.011~~ 0.006  ~~0.0107~~ |
| Re-entry | ~~0.148~~ 0.08 |
| Sum of all pathways | ~~0.14~~ 0.078 |
| Prothioconazole-desthio |  |
| Drift | ~~0.194~~ 0.07  ~~0.0972~~ |
| Vapour | 0.027  ~~0.023~~ |
| Deposits | ~~0.07~~ 0.025  ~~0.0347~~ |
| Re-entry | ~~0.038~~ 0.34  ~~0.0192~~ |
| Sum of all pathways | ~~0.20~~ 0.35  ~~0.1099~~ |
| **Cumulative risk resident – adult (HI)** |  |
| ~~Drift~~ | ~~0.2~~  ~~0.1272~~ |
| ~~Vapour~~ | ~~0.03~~  ~~0.0242~~ |
| ~~Deposits~~ | ~~0.08~~  ~~0.0454~~ |
| ~~Re-entry~~ | ~~0.2~~  ~~0.1667~~ |
| **Sum of all pathways** | **~~0.3~~ 0.43**  **~~0.2507~~** |

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

1. Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

MS to blacken authors of vertebrate studies in the version made available to third parties/public.

List of data submitted by the applicant and relied on

| Data point | Author(s) | Year | Title Company Report No.  Source (where different from company) GLP or GEP status Published or not | Vertebrate study  Y/N | Owner |
| --- | --- | --- | --- | --- | --- |
| KCP 7.3/01 | Imart C., | 2021 | *In-Vitro* Human Skin Penetration Of Prothioconazole-Desthio In Prothioconazole 250 Ec  Eurofins Agroscience Services Chem SAS  Report No: S21-05182  GLP  Unpublished | N | ASCENZA AGRO, S.A. |
| KCP 7.2/01 | Torres M., | 2022 | SAP2101F (PROTHIOCONAZOLE 120 G/L + FOLPET 300 G/L) – DISLODGEABLE FOLIAR RESIDUE DECLINE STUDY ON CEREALS (WHEAT OR BARLEY) IN SOUTHERN EUROPE IN 2021  SynTech Research Spain S.L  Report No: 512SRES21X01  GLP  Unpublished | N | ASCENZA AGRO, S.A. |
| KCP 7.2/02 | Gaffney V. | 2022 | Determination of the Decline of Prothioconazole, Prothioconazole-desthio and Folpet Dislodgeable Foliar Residues on Cereals (Wheat and Barley) in Southern Europe in 2021 after Application of SAP2101F  Laboratório de Resíduos de Pesticidas ASCENZA AGRO, S.A.  Report No: DFR12/21  GLP  Unpublished | N | ASCENZA AGRO, S.A. |

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

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

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

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

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

1. Detailed evaluation of the studies relied upon

|  |  |
| --- | --- |
| Comments of zRMS: | New data for co-formulant ATLAS G-5002L-LQ-(CQ) was provided by the Applicant. According to information presented above, data identifying the ingredient in the co-formulant has been amended in the dRR part C. The update of data for the ingredient affected its toxicological characteristics and therefore, the classification of the formulation SAP250F (Dyllis) presented below and in dRR part C. |

* 1. Statement on bridging possibilities

Not required.

* 1. Acute oral toxicity (KCP 7.1.1)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~Only one ingredient contained in the product SAP250F/ INDOFIL Prothio 250 EC was taken into account for the purpose of product classification in regards to acute oral toxicity:~~  ~~For this component the ATE value of 500 mg/l (acc. To the table 3.1.2 of the Regulation EC No. 1272/2008) is used.~~  ~~The ATE~~~~mix~~ ~~of the product amounts to~~ **~~2,066 mg/kg bw.~~**  ~~Conclusion:~~  ~~Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F / INDOFIL Prothio 250 EC~~ **~~does not require classification in regards to oral acute toxicity.~~**  Product SAP250F/Dyllis does not contain ingredients classified in regards to acute oral toxicity.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F / Dyllis **does not require** classification in regards to oral acute toxicity. |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for acute oral toxicity, according to Regulation EC 1272/2008.

* 1. Acute percutaneous (dermal) toxicity (KCP 7.1.2)

|  |  |
| --- | --- |
| Comments of zRMS: | The formulation SAP250F / Dyllis does not contain co- formulants classified in regards to acute dermal toxicity.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F/ Dyllis **does not require classification in regards to dermal acute toxicity.** |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for acute dermal toxicity, according to Regulation EC 1272/2008.

* 1. Acute inhalation toxicity (KCP 7.1.3)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~Only one ingredient contained in the product SAP250F/ INDOFIL Prothio 250 EC was taken into account for the purpose of product classification in regards to acute inhalation toxicity:~~  ~~For this component the ATE value of 0.5 mg/l (acc. to the table 3.1.2 of the Regulation EC No. 1272/2008) is used.~~  ~~The ATE~~~~mix~~ ~~of the product amounts to~~ **~~2.07 mg/l~~**  ~~Conclusion:~~  ~~Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F/ INDOFIL Prothio 250 EC~~ **~~requires classification in regards to inhalation acute toxicity (Acute Tox 3, H331).~~**  Product SAP250F / Dyllis does not contain ingredients classified in regards to acute inhalation toxicity.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F / Dyllis **does not require** classification in regards to inhalation acute toxicity. |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for acute inhalation toxicity, according to Regulation EC 1272/2008.

* 1. Skin irritation (KCP 7.1.4)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~Only one ingredient contained in the product SAP250F/ INDOFIL Prothio 250 EC was taken into account for the purpose of product classification.~~  ~~Taking into account the worst scenario that must apply in the case of calculation method/additivity formula (the order in which the toxicological data are taken into account) and the provisions of Regulation EC No. 1272/2008, the concentration value of the relevant ingredient is above the generic concentration limit that triggers classification of the mixture in regards to skin irritation (≥ 10%).~~  ~~Taking into account the composition of the product, the formulation SAP250F/ INDOFIL Prothio 250 EC~~ **~~requires classification in regards to skin irritation (Skin Irrit. 2, H315).~~**  Product SAP250F / Dyllis does not contain ingredients classified in regards to skin corrosion/irritation.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F / Dyllis does not require classification in regards to skin corrosion/irritation. |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for skin irritation, according to Regulation EC 1272/2008.

* 1. Eye irritation (KCP 7.1.5)

|  |  |
| --- | --- |
| Comments of zRMS: | ~~Only one ingredient contained in the product SAP250F/ INDOFIL Prothio 250 EC was taken into account for the purpose of product classification.~~  ~~Taking into account the worst scenario that must apply in the case of calculation method/additivity formula (the order in which the toxicological data are taken into account) and the provisions of Regulation EC No. 1272/2008, the concentration value of the relevant ingredient is above generic concentration limit that triggers classification of the mixture in regards to the eye irritation (≥ 10%).~~  ~~Taking into account the composition of the product, the formulation SAP250F/ INDOFIL Prothio 250 EC~~ **~~requires classification in regards to eye irritation ( Eye Irrit. 2, H319).~~**  Product SAP250F / Dyllis does not contain ingredients classified in regards to eye irritation.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F / Dyllis **does not require** classification in regards to eye irritation. |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for eye irritation, according to Regulation EC 1272/2008.

* 1. Skin sensitisation (KCP 7.1.6)

|  |  |
| --- | --- |
| Comments of zRMS: | The formulation SAP250F / INDOFIL Prothio 250 EC does not contain co- formulants classified in regards to skin sensitization.  Conclusion:  Taking into account the composition of the product and the provisions of the Regulation EC No. 1272/2008, the formulation SAP250F/ INDOFIL Prothio 250 EC **does not require classification in regards to skin sensitization.** |

The studies to assess the acute toxicity of the plant protection product INDOFIL Prothio 250 EC were judged to be not necessary in the interest of animal welfare, according to Article 62 of Regulation (EC) No 1107/2009. The assessment has been conducted according to Regulation EC 1272/2008 requirements.

Therefore, a case for the classification and labelling of INDOFIL Prothio 250 EC for human health effects, based on existing data for all formulation components is provided in Part C, Toxicological Classification document of this registration report.

**Conclusion**

Following the assessment of the formulants properties, it is proposed that INDOFIL Prothio 250 EC **should not be** classified for skin sensitisation, according to Regulation EC 1272/2008.

* 1. Supplementary studies for combinations of plant protection products (KCP 7.1.7)

Not required.

* 1. Data on co-formulants (KCP 7.4)
     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).

* + 1. 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).

* 1. Studies on dermal absorption (KCP 7.3)

|  |  |
| --- | --- |
| Comments of zRMS: | See comments in the section 6.5. |

According to the EFSA Guidance on Dermal Absorption (2017), the default dermal absorption value of 25% for the undiluted product and 70% for the spray dilution was considered for the active substance prothioconazole since INDOFIL Prothio 250 EC is an Emulsifiable Concentrate [EC]. For details, please see default values on point 6.1. (Table 2 – pag. 19).

|  |  |
| --- | --- |
| **Report** | KCP 7.3/01 Imart C., 2021 |
| **Title** | *IN-VITRO* HUMAN SKIN PENETRATION OF PROTHIOCONAZOLE-DESTHIO IN PROTHIOCONAZOLE 250 EC |
| **Document No.** | S21-05182 |
| **Guidelines:** | - 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 |
| **GLP:** | Yes |

**OBJECTIVE:**

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

The methodology used for the metabolite of prothioconazole is based on the assumption that all prothioconazole is degraded to desthio-metabolite. Therefore, the dermal absorption was tested for a concentration that mimics a 100 % degradation of prothioconazole in the formulation.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RESULTS:**  The mean results obtained are presented in the following table.  *In-vitro* dermal penetration of prothioconazole-desthio formulated as Prothioconazole 250 EC through human skin - Recovery data   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | **Dose group** | | High dose | | Low dose | | | (Formulation concentrate) n=8 | | (Spray dilution 1:500) n=8 | | | Target concentration | [mg/mL] | 226.75 | | 0.4535 | | | Target dose | [µg/cm²] | 2267.50 | | 4.54 | | | Mean actual applied dose | [µg/cm²] | 2304.54 | | 4.68 | | |  | | Recovery [%] | | Recovery [%] | | |  | | Mean | S.D. | Mean | S.D. | | **Dislodgeable dose** | |  |  |  |  | | Skin washing after 8 h | | 92.04 | 7.99 | 66.54 | 8.95 | | Donor chamber wash | | 4.04 | 2.34 | 0.92 | 0.87 | | **Dose associated to skin** | |  |  |  |  | | Tape strips: 1st sample, strips 1 + 2 | | 0.89 | 0.23 | 10.10 | 3.20 | | Tape strips: 2nd sample; strips 3 - n | | 1.58 | 0.64 | 5.43 | 2.06 | | Skin preparation | | 3.71 | 4.19 | 10.01 | 7.70 | | **Absorbed dose** | |  |  |  |  | | Receptor fluid | | 0.48 | 0.20 | 8.88 | 3.01 | | Receptor chamber wash | | 0.01 | 0.04 | 0.16 | 0.13 | | **Total recovery 1** | | 102.57 | 2.25 | 101.37 | 2.58 | | Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at t0.5] | | No  [55.12% ± 12.72] | | Yes  [77.48% ± 7.71] | | | If no: Absorption estimates  = absorbed dose + skin preparation + tape strips sample 2) 2 | | 5.59 | 4.51 | NA | NA | | If yes: Absorption estimates  = absorbed dose + skin preparation | | NA | NA | 19.05 | 7.52 | | **Absorption estimates used for risk assessment 3** | | **9.4** | | **25** | |   1 Values may not calculate exactly due to rounding of figures  2 In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study.  3 In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873), total absorption = mean + k\*SD, where k= 0.84 based on the number of replicates employed (n=8).  NA: not applicable; SD: standard deviation |

**CONCLUSION:**

The dermal penetration of prothioconazole-desthio formulated as Prothioconazole 250 EC through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating within   
24 hours was determined to be 9.4 % (mean + k \* SD) and 25 % for the formulation concentrate and the 1:500 spray dilution, respectively, based on the EFSA guidance criteria.

Dermal absorption study for Prothioconazole Desthio to be added.

* 1. Other/Special Studies

No applicable. DFR study summarized in Appendix 4.

1. Exposure calculations

 

1. 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)

|  |  |
| --- | --- |
| Comments of zRMS: | See comments in the section 6.6.3 and 6.6.4. |

* 1. DFR studies (KCP 7.2 DFR)

|  |  |
| --- | --- |
| **Report** | Torres M., 2022 |
| **Title** | SAP2101F (PROTHIOCONAZOLE 120 g/L + FOLPET 300 g/L) –  DISLODGEABLE FOLIAR RESIDUE DECLINE STUDY ON CEREALS  (WHEAT OR BARLEY) IN SOUTHERN EUROPE IN 2021 |
| **Document No.** | 512SRES21X01 |
| **Guidelines:** | • Regulations (EU) No. 283/2013 and 284/2013 implementing Regulation (EC) No. 1107/2009 of the European Parliament.  • "Commission Working Document 7029/VI/95 Rev. 5, General Recommendations for the Design, Preparation and Realization of Residue Trials, July 22, 1997.  • OECD Guideline for the testing of chemicals on Crop Field Trial (TG 509 published in September 2009).  • OECD Series on Testing and Assessment No. 9 “Guidance document on the conduct of studies of occupational exposure to pesticides during agricultural application”, Paris 1997. OCDE/GD(97)148.  • U.S. EPA Series 875.2100 Occupational and Residential Exposure Test Guidelines, Foliar Dislodgeable Residue Dissipation.  • SANTE/2019/12752, Technical guidelines on data requirements for setting maximum residue levels, comparability of residue trials and extrapolation of residue data on products from plant and animal origin, 01/01/2021. |
| **GLP:** | Yes |

**SUMMARY**

SAP2101F (Prothioconazole 120 g/L + Folpet 300 g/L) is a fungicide effective against a diseases caused by ascomycetes (Septoria and Helminthosporium), basidiomycetes, and deuteromycetes in crops of commercial importance developed by ASCENZA. Prothioconazole is a broad spectrum anti-fungal agent of triazolinthione family; it has been widely used in crop protection especially in cereals, with preventive, curative, eradicating effects and long residual activity. Folpet is a contact fungicide with a broad spectrum of action derived from phthalimide and trichloromethylsulfenyl chloride with foliar fungicidal activity and preventive action. The objective of this study was to generate specimens on decline of Prothioconazole, its metabolite Prothioconazole-desthio (sum of isomers) and Folpet in dislodgeable foliar residues (DFR) from wheat and/or barley in order to support the registration of market value of plant protection products applied according good agricultural practice (GAP). Three decline curve trials coded as SRES21-144-512FX, SRES21-145-512FX and SRPT21-075-512FX were conducted in Mahora (Albacete - Spain), Barracas (Castellon– Spain) and Torres Vedras (Lisboa - Portugal) during 2021, respectively, and the dislodging and storage areas were done at Test Facility for spanish trials and the portuguese trial at the Field Test Site SynTech Research Portugal, respectively. Two foliar applications of the formulated product SAP2101F containing Prothioconazole 12% w/v (=120 g/L) + Folpet 30% w/v (=300 g/L) were applied at a target rate of 1.5 L/ha (=(80 g Prothioconazole/ha + 450 g Folpet/ha) onto the crop in open field conditions starting between 58 and 60 days before normal commercial harvest (NCH). Applications were done following the study timing with 13 and 14 days between them and last application between 44 and 46 days before commercial harvest (=DBCH), with BBCH 51-71 The formulation was applied using appropriate application equipment at the proposed normal use rates and timings. Untreated samples (leave pieces corresponding to a surface of 400 cm2 , based on a mean weight test) were collected at 0 DBA1 (days before application 1) and 14 ±1 DAA2 (days after application 2), while treated samples were collected, at 0 DBA1 (days before application), 0 DAA1 (days after application 1), 0 DBA2, 0 DAA2, 24 HAA2 (hours after application 2), 3 DAA2, 5 DAA2, 7 DAA2 and 14±1 DAA2. Untreated samples were also collected for field fortifications purposes at 0 DBA1 (days before application 1), 0 DBA2, 3 DAA2 (days after application 2) and between 13 DAA2 and 14 DAA2. The specimens (untreated & treated) were stored separated and deep frozen [max: -17.7ºC, min: -29.4ºC] until their shipment to the Test Facility Laboratorio de Residuos ASCENZA AGRO S.A., Portugal to be analysed in a different GLP study coded as DFR12/21 being the Study Director Vanessa Gaffney. Shipment was done in insulated boxes with dry ice and samples were received in perfect conditions with dry ice presence. There were no unusual events that affected this study.

**FIELD PHASE**

A summary of application details is given below. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range described in study plan

Table

Description automatically generated

|  |  |
| --- | --- |
| **Report** | Gaffney V., 2022 |
| **Title** | Determination of the Decline of Prothioconazole, Prothioconazole-desthio and Folpet Dislodgeable Foliar Residues on Cereals (Wheat and Barley) in Southern Europe in 2021 after Application of SAP2101F |
| **Document No.** | DFR12/21 |
| **Guidelines:** |  |
| **GLP:** | Yes |

**OBJECTIVE**

The objective of this study is to determine the decline of prothioconazole, prothioconazole-desthio and folpet dislodgeable foliar residues in cereals (wheat and barley) following two applications of SAP2101F at a rate of 1.5 L/ha onto the crop in open field conditions.

Leaf disc wash solutions and leaf disc wash field fortified solutions were analysed for residues of prothioconazole, prothioconazole-desthio and folpet. The analytical method was validated within the scope of this study.

Samples were generated in 3 trials, 2 in Spain and 1 in Portugal, during the field phase of study 512SRES21X01 from SynTech Research Spain S.L. which is directed by Manuel Torres.

This analytical phase was conducted by an independent study from the field phase.

**Summary**

Leaf disc wash solutions and leaf disc wash field fortified solutions were sent frozen to the Laboratório de Resíduos de Pesticidas (LabRP) in order to analyse the magnitude of prothioconazole, prothioconazole-desthio and folpet in dislodgeable foliar residues in cereals leaves, generated under three field trials, 2 in Spain and 1 trial in Portugal by SynTech Research Spain S.L., under the direction of Manuel Torres.

The solutions were obtained by washing leaf discs from grapevine leaves with an aqueous solution of a surfactant after three applications of the formulated products SAP2101F.

According to the field information, sampling has been taken in the untreated modality, immediately before first application, 0 DBA 1 (DBA – days before application), and before second application 0 DBA 2, immediately after second application, 0 DBA2, and 14 days after second application, 14 DAA2 (DAA – days after application). Regarding treated modalities sampling has been performed at 0 DBA 1, 0 DAA1, 0 DBA2, 0 DAA2, 24 HAA2 (HAA – hours after third application), 3 DAA2, 5 DAA2, 7 DAA2 and 14 DAA2.

To assess the stability of prothioconazole, prothioconazole-desthio and folpet residues under field, storage and transport conditions, leaf disc wash field fortified solutions were also delivered together with the specimens described above. In this interim report the results regarding the stability of protioconazole and protioconazole-desthio in leaf disc wash solutions will be reported.

After reception, all samples were stored at ≤ -18 ºC until analysis.

The validation assays were performed under the current study. Validation results are presented on **Table 8** of this report.

Specimens were analysed by direct injection into UPLC-TQ-S-micro. The analytical procedure followed is described at point **7.6** of this report.

Moreover, the quantification of prothioconazole and prothioconazole-desthio in the samples was performed using a linear regression analytical calibration with matrix matched calibration standards.

Procedural recovery tests in control specimens were injected concurrently with the analytical specimens.

The results were in accordance with the requirements on SANTE/2020/12830, Rev 1.

Final results are compiled in the table below.



**Table 1** - Summary of results for Prothioconazole from trial SRPT21-144-512FX-Spain.



**Table 2** - Summary of results for Prothioconazole-desthio from trial SRPT21-144-512FX-Spain.



**Table 4** - Summary of results for Prothioconazole from trial SRPT21-145-512FX-Spain.



**Table 5** - Summary of results for Prothioconazole-desthio from trial SRPT21-145-512FX-Spain.



**Table 7** - Summary of results for Prothioconazole from trial SRPT21-075-512FX-Portugal



**Table 8** - Summary of results for prothioconazole-desthio from trial SRPT21-075-512FX-Portugal

**CONCLUSIONS**

An analytical method validated under the scope of this study was used to determine the magnitude of prothioconazole, prothioconazole-desthio and folpet in dislodgeable foliar residues in cereals leaves generated under SynTech Research study 512SRES21X01. For this purpose, leaf disc wash solutions and leaf disc wash field fortified solutions were analysed for residues of prothioconazole, prothioconazole-desthio and folpet.

The results of the field recovery tests demonstrated that the residues protioconazole, protioconazole-desthio and folpet in grapevine leaf disc wash solutions are stable under field, storage and transport conditions and also during the experimental work performed in this study.

The performance of the analytical method was demonstrated by recovery tests injected concurrently with the samples. The results achieved fulfill with the criteria set on SANTE/2020/12830 Rev 1.

All the analytical work has been conducted in accordance with GLP principles.

~~Not required.~~

**~~APPROACH A. RESIDENT REFINEMNT – NEW TC VALUES~~**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **~~TC default~~** | **~~TC default - Refined~~** | **~~TC default (mean)~~** | **~~TC default (mean) - Refined~~** |
| ~~Adult~~ | ~~7500 cm~~~~2~~~~/h~~ | *~~1400 cm~~~~2~~~~/h~~* | ~~5980 cm~~~~2~~~~/h~~ | *~~1116.27 cm~~~~2~~~~/h~~* |
| ~~Children~~ | ~~2250 cm~~~~2~~~~/h~~ | *~~420 cm~~~~2~~~~/h~~* | ~~1794 cm~~~~2~~~~/h~~ | *~~334.88 cm~~~~2~~~~/h~~* |

|  |  |  |
| --- | --- | --- |
| ~~Calculation of the new mean TC values~~~~\*~~~~:~~  = 1.254180602  = 1.254180602 ↔ x = 1116.27 - Adult    = 1.254180602 ↔ x = 334.88 - Child     |  | | --- | |  | |  | |
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |
|  |

~~A refinement on ‘reentry into treated crop’ parameter was performed considering the new TC values. The main aim of this refinement is to achieve a realistic scenario for the residents when exposure to INDOFIL Prothio 250 EC. With this refinement, new values on “all pathways mean” were also founded, as shown below:~~

1. ~~Re-entry into treated crop – Refinement~~

~~The method used should be the same as for worker. Residents exposure from contact with residues when re-entering into treated crop should assessed using the following formula:~~

~~Entry into treated crop exposure = (DFR \* MAF \* ReTC \* ReExpDurTreatCrop)/1000 \* DA~~

~~DFR – Dislodgeable foliar residue (App. Rate \* initial DFR)~~

~~MAF – Multiple application factor (value of 2.25 used as default)~~

~~ReTC – Re-entry Transfer coefficient~~

~~ReExpDurTreatCrop – Exposure duration entry into treated crops (value of 15 minutes used as default)~~

~~DA - Dermal Absorption~~

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **~~TC default~~** | **~~TC default - Refined~~** | **~~Dose~~** | **~~Weight~~** | **~~DFR~~~~initial~~** | **~~Volume~~** | **~~Nºapp./Int. between app.~~** | **~~Drift-reduction (50%)~~** | **~~Buffer-zone~~** |
| ~~Adult~~ | ~~7500 cm~~~~2~~~~/h~~ | *~~1400 cm~~~~2~~~~/h~~* | ~~3.5 L pf/ha~~ | ~~60 kg~~ | ~~3~~ | ~~150 L~~ | ~~3/14~~ | ~~Yes~~ | ~~10 m~~ |
| ~~Children~~ | ~~2250 cm~~~~2~~~~/h~~ | *~~420 cm~~~~2~~~~/h~~* | ~~10 kg~~ |

**~~Children~~**

~~= 0.0257 / 10 =~~ **~~0.00257 mg/kg bw/day~~**

**~~Adult~~**

~~= 0.0856/ 60 =~~ **~~0.00143 mg/kg bw/day~~**

1. ~~All pathways (mean) – Refinement~~

~~According to EFSA 2014:~~

~~“Summing all the exposure pathways, each one being conservative (considering high percentiles of exposure), would result in an overly conservative and unrealistic result. This is particularly true for bystanders, considering that is extremely unlikely that all exposures occur together. However, for residents, it might be appropriate to sum up the mean exposures from each pathway, where available.”~~

~~Below is presented the sum of each pathway for children and adults. (The ‘entry into treated crop’ parameter was refined using new mean TC values)~~

~~Re-entry into treated crop (mean) – Refinement~~

~~The method used should be the same as for worker. Residents exposure from contact with residues when re-entering into treated crop should assessed using the following formula:~~

~~Entry into treated crop exposure = (DFR \* MAF \* ReTC \* ReExpDurTreatCrop)/1000 \* DA~~

~~DFR – Dislodgeable foliar residue (App. Rate \* initial DFR)~~

~~MAF – Multiple application factor (value of 2.25 used as default)~~

~~ReTC – Re-entry Transfer coefficient~~

~~ReExpDurTreatCrop – Exposure duration entry into treated crops (value of 15 minutes used as default)~~

~~DA - Dermal Absorption~~

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **~~TC default~~** | **~~TC default - Refined~~** | **~~Dose~~** | **~~Weight~~** | **~~DFR~~~~initial~~** | **~~Volume~~** | **~~Nºapp./Int. between app.~~** | **~~Drift-reduction (50%)~~** | **~~Buffer-zone~~** |
| ~~Adult~~ | ~~5980 cm~~~~2~~~~/h~~ | *~~1116.27 cm~~~~2~~~~/h~~* | ~~0.1814 kg a.s./ha~~ | ~~60 kg~~ | ~~3~~ | ~~150 L~~ | ~~3/14~~ | ~~Yes~~ | ~~10 m~~ |
| ~~Children~~ | ~~1794 cm~~~~2~~~~/h~~ | *~~334.88 cm~~~~2~~~~/h~~* | ~~10 kg~~ |

**~~Children~~**

~~= 0.0205 / 10 =~~ **~~0.00205 mg/kg bw/day~~**

**~~Adult~~**

~~= 0.0683 / 60 =~~ **~~0.00114 mg/kg bw/day~~**

**~~All pathways - Mean~~**

*~~Calculations – formula~~*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ~~Summing of exposure pathways mean~~ | **~~Systemic exposure (mg a.s. /bw/day)~~** | | | | | | |
| **~~Spray drift~~** | **~~Vapour~~** | **~~Surface deposits~~** | | | **~~Entry into treated crops~~** ~~Dermal~~ | **~~All pathways (mean)~~**  ~~Calculated~~ |
| ~~Dermal~~ | ~~Hand to mouth~~ | ~~Object to mouth~~ |
| ~~1-3 year old child~~ | ~~0.0009983~~ | ~~0.0010700~~ | ~~0.0001060~~ | ~~0.0000194~~ | ~~0.0000102~~ | ~~0.0020477~~ | ~~0.0042516~~ |
| ~~Adult~~ | ~~0.0001821~~ | ~~0.0002300~~ | ~~0.0000496~~ | ~~-~~ | ~~-~~ | ~~0.0011376~~ | ~~0.0015993~~ |

**~~Overall - resident exposure to Prothioconazole-desthio – With Re-entry and Sum parameters refined~~**

|  |  |  |  |
| --- | --- | --- | --- |
|  | | **~~Prothioconazole-desthio~~** | |
| **~~Model data~~** | | **~~% of systemic AOEL~~** | **~~Total absorbed dose (mg/kg bw/day)~~** |
| ~~Vehicle-mounted: Downward spraying~~  ~~DT50: 30 days~~  ~~DFR: 3 µg/cm2/kg a.s./ha~~  ~~Interval between treatments: 14 days~~  ~~Buffer zone: 10 (m)~~  ~~Drift reduction technology: Yes~~  *~~Oilseed rape are also covered by this assessment.~~* | | | |
| ~~Number of applications and application rate~~ | | ~~3 x 0.1814 kg a.s./ha~~ | |
| ~~Resident child~~  ~~Body weight: 10 kg~~ | ~~Drift (75~~~~th~~ ~~perc.)~~ | ~~0.0017894~~ | **~~17.89~~** |
| ~~Vapour (75~~~~th~~ ~~perc.)~~ | ~~0.0010700~~ | **~~10.70~~** |
| ~~Deposits (75~~~~th~~ ~~perc.)~~ | ~~0.0001762~~ | **~~1.76~~** |
| ~~Re-entry (75~~~~th~~ ~~perc.)~~ | ~~0.0025682~~ | **~~25.68~~** |
| **~~Sum (mean)~~** | ~~0.0042516~~ | **~~42.52~~** |
| ~~Resident adult~~  ~~Body weight: 60 kg~~ | ~~Drift (75~~~~th~~ ~~perc.)~~ | ~~0.0003378~~ | **~~3.38~~** |
| ~~Vapour (75~~~~th~~ ~~perc.)~~ | ~~0.0002300~~ | **~~2.30~~** |
| ~~Deposits (75~~~~th~~ ~~perc.)~~ | ~~0.0000645~~ | **~~0.64~~** |
| ~~Re-entry (75~~~~th~~ ~~perc.)~~ | ~~0.0014268~~ | **~~14.27~~** |
| **~~Sum (mean)~~** | ~~0.0015993~~ | **~~15.99~~** |

1. EFSA Journal 2017; 15(6):4873 [↑](#footnote-ref-2)