REGISTRATION REPORT

**Part B**

**Section 6**

# Mammalian Toxicology

Detailed summary of the risk assessment

Product code: A23282A

Product name: **KAYAK ERA**

Chemical active substances:

Cyprodinil, 225 g/L
Prothioconazole, 75 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(New product authorization)

Applicant: XXXX

Submission date: June 2022

Evaluation date: March 2023

MS Finalisation date: December 2023

# Version history

| When | What |
|---|---|
| | |
| March 2023 | Version evaluated by PL zRMS |
| December 2023 | Version revised by zRMS to take into account comments submitted by cMS and the applicant |
| | |

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# 6 Mammalian Toxicology (KCP 7)

## 6.1 Summary

**Table 6.1-1: Information on A23282A/KAYAK ERA ***

| | |
|---|---|
| Product name and code | A23282A/KAYAK ERA |
| Formulation type | Emulsifiable Concentrate (EC) |
| Active substance(s) (incl. content) | Cyprodinil, 225 g/L<br>Prothioconazole, 75 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 A23282A/KAYAK ERA 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 A23282A/KAYAK ERA according to Regulation (EC) No 1272/2008**

| | |
|---|---|
| Hazard class(es), categories | Skin irritation, Category 2<br>Serious eye damage, Category 1<br>Skin sensitisation, Category 1<br>Specific target organ toxicity - single exposure, Category 3, Respiratory system |
| Hazard pictograms or Code(s) for hazard pictogram(s) | GHS05, GHS07, |
| Signal word | Danger |
| Hazard statement(s) | H315: Causes skin irritation<br>H318: Causes serious eye damage<br>H317: May cause an allergic skin reaction<br>H335: May cause respiratory irritation |
| Precautionary statement(s) | Prevention:<br>P261 Avoid breathing ~~dust/ fume/ gas/ mist/ vapours/~~ spray.<br>P264 Wash skin thoroughly after handling<br>P280 Wear protective gloves/ eye protection/ face protection<br>P271 Use only outdoors or in a well-ventilated area<br>P272 Contaminated work clothing should not be allowed out of the workplace.<br><br>Response<br>P302 + P352 IF ON SKIN: Wash with plenty of soap and water.<br>P304 + P340 + P312 IF INHALED: remove person to fresh air and keep comfortable for breathing. Call a POISON CENTER/doctor if you feel unwell<br>P305 + P351 + P338 + P310 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor.<br>P332 + P313 If skin irritation occurs: Get medical advice/attention.<br>P362 Take off contaminated clothing and wash before reuse<br><br>Storage<br>P403 + P233 Store in a well-ventilated place. Keep container tightly closed.<br>P405 Store locked up.<br><br>Disposal<br>P501 Dispose of contents/container to … |
| Additional labelling phrases | Hazardous components which must be listed on the label:<br>Mixture of octanoic acid- decanoic acid- N,N-dimethylamide<br>cyprodinil (ISO)<br>benzenesulfonic acid, C10-13-alkyl derivs., calcium salts<br>2-ethylhexan-1-ol |

**Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for A23282A/KAYAK ERA**

| | Result | PPE / Risk mitigation measures |
|---|---|---|
| Operators | Acceptable | ~~None~~<br>Protective gloves, eye protection/face protection during mixing/loading operations or when directly contacting surface of equipment contaminated with concentrated product |
| Workers | Acceptable | None ( please see zRMS evaluation below) |
| Residents | Acceptable | None, if 50% conversion of prothioconazole to prothioconazole-desthio is asumed.<br>In case of assuming 100% conversion of prothioconazole to prothioconazole-desthio a drift reduction technology or a buffer zone of |

| | Result | PPE / Risk mitigation measures |
|---|---|---|
| | | 5 m are required ( please see zRMS evaluation below) |
| Bystanders | Acceptable | None |

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

**zRMS**:

***Assuming 100% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio as a theoretical worst case***

**Operators.** The application of product Kayak Era ( A23282A) in accordance with GAP does not pose an unacceptable risk to the health of operator during its intended use within good agricultural practice providing that operator is wearing work wear covering arms, body and legs during mixing/loading and application, and protective gloves during mixing/loading. Since the product classified as Eye Dam. 1, Skin Irrit.2 and Skin Sens. 1 the operator should wear work wear covering arms, body and legs during mixing/loading and application, protective gloves, eye protection/face protection during mixing/loading operations or when directly contacting surface of equipment contaminated with concentrated product.

**Workers:**
The application of a product Kayak Era ( A23282A) in accordance with GAP does not pose an unacceptable risk to the health of worker due to its intended use within good agricultural practice providing that the worker is wearing a work clothing (long sleeved shirt, long trousers).

**Residents:**
The health risk of residents ( adult and child) caused by the application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha is acceptable when risk mitigation measures are used such as a drift reduction technology or a buffer zone of 5 m.

***Assuming 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio as requested by DE***

**Operators.** The application of product Kayak Era ( A23282A) in accordance with GAP does not pose an unacceptable risk to the health of operator during its intended use within good agricultural practice providing that operator is wearing work wear covering arms, body and legs during mixing/loading and application, and protective gloves during mixing/loading. Since the product classified as Eye Dam. 1, Skin Irrit.2 and Skin Sens. 1 the operator should wear work wear covering arms, body and legs during mixing/loading and application, protective gloves, eye protection/face protection during mixing/loading operations or when directly contacting surface of equipment contaminated with concentrated product.

**Workers:**
The application of a product Kayak Era ( A23282A) in accordance with GAP does not pose an unacceptable risk to the health of worker due to its intended use within good agricultural practice providing that the worker is wearing a work clothing (long sleeved shirt, long trousers).

**Residents:**
In case when 50% conversion of prothioconazole to prothioconazole-desthio is assumed the application of a product Kayak Era ( A23282A) in accordance with GAP does not pose an unacceptable risk to the health of residents ( adult and child) due to its intended use within good agricultural practice. In case 100% conversion of prothioconazole to prothioconazole-desthio is assumed a drift reduction technology or a buffer zone of 5 m are required ( please see zRMS evaluation below).

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) Cyprodinil b) Prothioconazole** | **Water L/ha min / max** | | | **Operator** | **Worker** | **Residents** | **Bystander** |
| AT5 | Winter wheat (BBCH 30-69) | F | Spraying, LCTM | 1 ; 1 | a) 0.45<br>b) 0.15 | 100 - 400 | N/A | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 | R | A | R | A |

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

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

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

Explanation for column 10 "Acceptability of exposure assessment"

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

### Data gaps

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

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)**

| | **Cyprodinil** | **Prothioconazole** |
|---|---|---|
| Common Name | Cyprodinil | Prothioconazole |
| CAS-No. | 121552-61-2 | 178928-70-6 |
| **Classification and proposed labelling** | | |
| With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as | **Hazard classes (s), categories:** Skin sensitisation, Category 1<br>**Code(s) for hazard pictogram(s):** | **Hazard classes (s), categories:** n/a<br>**Code(s) for hazard pictogram(s):** n/a<br>**Signal word:** n/a |

| | Cyprodinil | Prothioconazole |
|---|---|---|
| amended) | GHS07<br>**Signal word:** Warning<br>**Hazard statement(s):**<br>H317: May cause an allergic skin reaction.<br>**Precautionary statement(s):**<br>**Prevention:** P261 Avoid breathing dust. P280 Wear protective gloves.<br>**Response:** P333 + P313 If skin irritation or rash occurs: Get medical advice/ attention. P362 + P364 Take off contaminated clothing and wash it before reuse. | **Hazard statement(s):** n/a<br>**Precautionary statement(s):** n/a |
| Additional C&L proposal | This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher<br>The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher | n/a |
| **Agreed EU endpoints** | | |
| AOEL systemic | 0.03 mg/kg bw/d (corrected for >82% oral absorption) | 0.2 mg/kg bw/d (corrected for 90% oral absorption following oral dosing) |
| Reference | EFSA Scientific report (2005) 51, 1-78 | EFSA Scientific report (2007) 106, 1-98 |
| **Conditions to take into account/critical areas of concern with regard to toxicology** | | |
| Review Report/EFSA Conclusion for active substance | At the moment a final specification for the max content of non-relevant impurities cannot be set. | The metabolite prothioconazole-desthio is more toxic than prothioconazole in the rat and rabbit developmental studies (the classification Repro cat 2, R61 is proposed). |

## 6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for A23282A/KAYAK ERA 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 A23282A/KAYAK ERA**

| Type of test, species, model system (Guide-line) | Result | ATE & Additivity Calculation Result | Acceptability | Classification (acc. to the criteria in Reg. 1272/2008) | Reference |
|---|---|---|---|---|---|
| $LD_{50}$ oral | n/a | >2000 mg/kg<br>Not Classified | Yes | None | n/a<br>(see Appendix 2 and part C) |
| $LD_{50}$ dermal | n/a | >2000 mg/kg<br>Not Classified | Yes | None | n/a<br>see Appendix 2 and part C) |
| $LC_{50}$ inhalation | n/a | >5 mg/L<br>Not Classified | Yes | None | n/a<br>see Appendix 2 and part C) |
| Skin irritation | n/a | Cat. 2 | Yes | H315 | n/a<br>see Appendix 2 and part C) |
| Eye irritation | n/a | Cat. 1 | Yes | H318 | n/a<br>see Appendix 2 and part C) |
| Skin sensitisation) | n/a | Cat. 1 | Yes | H317 | n/a<br>see Appendix 2 and 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 A23282A/KAYAK ERA**

| | 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) | Cyprodinil (>= 30 - < 50% (w/w)) | Hazard statement<br>Skin Sens. 1; H317 | Reg. 1272/2008 / MSDS** / EFSA conclusion | ~~Hazard statements~~<br>Skin Irrit.2; H315 Causes skin irritation.<br>Skin Sens.1; H317 May cause an allergic skin reaction.<br>Eye Dam. 1; H318 Causes serious eye damage.<br>STOT SE 3; H335 May cause respiratory irritation.<br><br>(see part C for more detailed justification ) |
| | Prothioconazole (>= 10 - < 20% (w/w)) | Hazard statement<br>n/a | | |
| Toxicological properties of non-active substance(s) (relevant for classification of product) | Mixture of octanoic acid-decanoic acid-N,N-dimethylamide (CAS No. 1118-92-9, >= 50 - < 70% (w/w))* | Hazard statements<br>Skin Irrit. 2; H315<br>Eye Dam. 1; H318<br>STOT SE 3; H335 | | |
| | benzenesulfonic | Hazard statements | | |

| | 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) |
|---|---|---|---|---|
| | acid, C10-13-alkyl derivs., calcium salts (CAS No. 1335202-81-7, >= 3 - < 10% (w/w))* | Skin Irrit. 2; H315<br>Eye Dam. 1; H318 | | |
| | 2-ethylhexan-1-ol (CAS No. 104-76-7, >= 1 - < 10% (w/w))* | Hazard statements<br>Acute Tox. 4; H332<br>Skin Irrit. 2; H315<br>Eye Irrit. 2; H319<br>STOT SE 3; H335 | | |
| Further toxicological information | No data – not required | | | |

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

## 6.4 Toxicological Evaluation of Groundwater Metabolites

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

## 6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in A23282A/KAYAK ERA are presented in the following table.

**Table 6.5-1: Dermal absorption rates for active substances in A23282A/KAYAK ERA**

| | Cyprodinil | | Prothioconazole | | Desthio | |
|---|---|---|---|---|---|---|
| | **Value** | **Reference** | **Value** | **Reference** | **Value** | **Reference** |
| Concentrate | 1.5% | New study reported in Appendix 2 | 2.8% | New study reported in Appendix 2 | n/a | n/a |
| Dilution 1 (1:50) | 10% | New study reported in Appendix 2 | 16% | New study reported in Appendix 2 | 14% | New study reported in Appendix 2 |
| Dilution 2 (1:200) | 13% | New study reported in Appendix 2 | 11% | New study reported in Appendix 2 | 16% | New study reported in Appendix 2 |

### 6.5.1 Justification for proposed values - Cyprodinil

Proposed dermal absorption rates for **Cyprodinil** is based on a dermal absorption study conducted with the current product/formulation. The study results are summarized in the following table. Full summary of the study on the dermal absorption of **Cyprodinil/Prothioconazole/Desthio EC (A23282A)** are described in detail in Appendix 2.

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

| Test | Concentrate (225g/L) | Spray dilution 1 (1:50) | Spray dilution 2 (1:200) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference* |
|---|---|---|---|---|---|---|---|---|
| In vitro (human) | 1.5% | 10% | 13% | A23282A/ KAYAK ERA | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product | Stephen C., 2021 |

### 6.5.2 Justification for proposed values - Prothioconazole

Proposed dermal absorption rates for **Prothioconazole** is based on a dermal absorption study conducted with the current product/formulation. The study results are summarized in the following table. Full summary of the study on the dermal absorption of **Cyprodinil/Prothioconazole/Desthio EC (A23282A)** are described in detail in Appendix 2.

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

| Test | Concentrate (75g/L) | Spray dilution 1 (1:50) | Spray dilution 2 (1:200) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference* |
|---|---|---|---|---|---|---|---|---|
| In vitro (human) | 2.8% | 16% | 11% | A23282A/ KAYAK ERA | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product /. | Stephen C., 2021 |

### 6.5.3 Justification for proposed values - Desthio

Proposed dermal absorption rates for **Desthio** is based on a dermal absorption study conducted with the current product/formulation. The study results are summarized in the following table. Full summary of the study on the dermal absorption of **Cyprodinil/Prothioconazole/Desthio EC (A23282A)** are described in detail in Appendix 2.

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

| Test | Spray dilution 1 (1:50) | Spray dilution 2 (1:200) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference* |
|---|---|---|---|---|---|---|---|
| In vitro (human) | 14% | 16% | A23282A/ KAYAK ERA | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product | Stephen C., 2021 |

## 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 | A23282A/KAYAK ERA | |
| Formulation type | EC | |
| Category | Fungicide | |
| Active substance (incl. content) | **Cyprodinil** 225 g/L | |
| AOEL systemic | 0.03 mg/kg bw/d | |
| Inhalation absorption | 100% | |
| Oral absorption | >82% | |
| Dermal absorption | Concentrate: 1.5%<br>Dilutions:<br>10% (4.5 g/L) measured value<br>13.0% (1.125 g/L) measured value<br>Based on product (formulation)) | |
| Active substances (incl. content) | **Prothioconazole** 75 g/L | ***Prothioconazole-desthio** |
| AOEL systemic | 0.2 mg/kg bw/d | 0.01 mg/kg bw/day |
| Inhalation absorption | 100% | 100% |
| Oral absorption | 100% | 100% |
| Dermal absorption | Concentrate: 2.8%<br>Dilutions:<br>16% (1.5 g/L) measured value<br>11.0% (0.375 g/L) measured value<br>Based on product (formulation) | Concentrate: ~~2.8%~~ n/a<br>Dilutions:<br>14% (1.5 g/L) measured value<br>16.0% (0.375 g/L) measured value<br>Based on product (formulation) |

*First tier estimates of exposure assume as a theoretical worst case that there is 100% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio. For this conversion 1 kg prothioconazole yields 0.907 kg prothioconazole-desthio. This conversion can only occur after a drying process so for spray operators the exposure assessment only considers exposure from application of the spray solution and not mixing and loading

### 6.6.1 Selection of critical use 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**

Operator

For operators, the critical GAP is dependent on the amount of product handled and the application method. A23282A is to be applied to cereals using tractor mounted field crop (boom) sprayers. A critical GAP has been defined for this application method based on the highest amount of active substance applied.

The highest application rate for a single application to cereals is 2.0 L product/ha in 100-400 L water/ha.

Worker

Worker exposure is defined by the task being undertaken and the amount of active substance that is available to be dislodged. An exposure assessment has been carried out for crop inspection in cereal crops at the maximum application rate and assuming as a worst case that re-entry occurs soon after spray deposits are dry.

The highest application rate for a single application to cereals is 2.0 L product/ha in 100-400 L water/ha

Bystanders/residents

The critical GAP for bystanders and residents depends on the method of application, the amount of active substance applied, the spray volume, the number of applications and the interval between applications. The method of application is by tractor mounted field crop (boom) sprayers.

The highest application rate for a single application to cereals is 2.0 L product/ha in 100-400 L water/ha. Levels of exposure have been predicted for cyprodinil, prothioconazole and prothioconazole-desthio assuming applications are made using the minimum and maximum water volumes. As different dermal absorption values are available for the different spray dilutions, the values used for the risk assessment are summarised as follows;

| | **Dermal absorption value (%)** | | |
|---|---|---|---|
| | Cyprodinil | Prothioconazole | Prothioconazole-desthio |
| **Water volume** | | | |
| 100 L water/ha | 10 | 16 | 14 |
| 400 L water/ha | 13 | 11 | 16 |

### 6.6.2 Operator exposure (KCP 7.2.1)

#### 6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of A23282A according to the critical use is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in 0.

At this time, no acute AOELs have been set for cyprodinil, prothioconazole and prothioconazole-desthio. Consequently, no acute risk assessment has been provided for these active substances.

**Table 6.6-2: Exposure models for intended uses**

| | |
|---|---|
| Critical use | Winter wheat (max. 2 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<br>calculator version: 30/03/2015 |

**Table 6.6-3: Estimated operator exposure (longer term exposure)**

| | | **Cyprodinil** | |
|---|---|---|---|
| **Model data** | **Level of PPE** | **Total absorbed dose (mg/kg/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops | | | |
| Application rate | | 0.45 kg a.s./ha (cereals) | |
| **Spray application** (AOEM**;** 75th percentile) Body weight: 60 kg | Work wear (arms, body and legs covered) M/L and A | 0.0215 | 71.66 |
| | Work wear (arms, body and legs covered) M/L and A + gloves ML | 0.0082 | 27.41 |

| | | **Prothioconazole** | | **Prothioconazole-desthio*** | |
|---|---|---|---|---|---|
| **Model data** | **Level of PPE** | **Total absorbed dose (mg/kg/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops | | | | | |
| Application rate | | 0.15 kg a.s./ha (cereals) | | 0.136 kg a.s./ha (cereals) | |
| **Spray application** (AOEM**;** 75th percentile) Body weight: 60 kg | Work wear (arms, body and legs covered) M/L and A | 0.0142 | 7.09 | - | - |
| | Work wear (arms, body and legs covered) M/L and A + gloves ML | 0.0036 | 1.78 | - | - |
| | Work wear (arms, body and legs covered) A* | - | - | 0.0028 | 28.47 |

*First tier estimates of exposure assume as a theoretical worst case that there is 100% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio. For this conversion 1 kg prothioconazole yields 0.907 kg prothioconazole-desthio. This conversion can only occur after a drying process so for spray operators the exposure assessment only considers exposure from application of the spray solution and not mixing and loading

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

| | | Prothioconazole-desthio* | |
|---|---|---|---|
| **Model data** | **Level of PPE** | **Total absorbed dose (mg/kg/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops | | | |
| Application rate | | 0.068 kg a.s./ha (cereals) | |
| **Spray application** (AOEM**;** 75th percentile) Body weight: 60 kg | Work wear (arms, body and legs covered) M/L and A | 0.0514 | 514,12 |
| | Work wear (arms, body and legs covered) M/L and A + gloves ML | 0.002275 | 22.75 |

*It this approach the exposure to Prothioconazole-desthio was estimated assuming as proposed by DE that there is 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio and this conversion already occurs during mixing with water during mixing and loading. For this conversion 1 kg prothioconazole yields 0.454 kg prothioconazole-desthio. Dermal absorption during mixing and loading was assumed to be 14% ( as for dilution 1:50 1.5 g/L prothioconazole-desthio) and during application 16% ( as for dilution 1/200 (0.375g/L)
the dilution 1:50 (1.5g/L) L)

### 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.

**zRMS**:
The exposure to Cyprodinil of operator wearing a work clothing (long sleeved shirt, long trousers) but no PPE and applying Kayak Era ( A23282A) on cereals at maximal dose of 2.0 L product/ha (0.450 kg a.s./ha) using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM amounted to 71.66% of AOEL. In case the operator is using protective gloves during mixing and loading the exposure to Cyprodinil is reduced to 27.41% of AOEL.

The exposure to Prothioconazole of operator wearing a work clothing (long sleeved shirt, long trousers) but no PPE and applying Kayak Era ( A23282A) on cereals at maximal dose of 2.0 L product/ha (0.150 kg a.s./ha) using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM amounted to 7.09 % of AOEL. In case the operator is using protective gloves during mixing and loading the exposure to Prothioconazole is reduced to 1.78 % of AOEL.

The maximal exposure during application of the Kayak Era to Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) of operator wearing a work clothing (long sleeved shirt, long trousers) but no PPE and applying Kayak Era ( A23282A) on cereals at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole/ha) using tractor-mounted/trailed boom sprayer, calculated with the EFSA AOEM amounted to 28.47% of AOEL.

~~The sum of exposures of operator wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading and application to both active substances or to Cyprodinil and Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) expressed as percentage of their AOELs is also below 100%, therefore the application of product Kayak Era ( A23282A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of operator .~~

The sum of exposures of operator wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading and application, but no other PPE, to Cyprodinil and Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) expressed as percentage of their AOELs is 100.13% of AOEL (71.66% + 28.47% ), therefore the application of product Kayak Era ( A23282A) according to its intended use within good agricultural practice pose an unacceptable risk to the health of operator .
The sum of exposures of operator wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading and application and protective gloves during mixing and loading to Cyprodinil and Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) expressed as percentage of their AOELs is 55.88 % of AOEL (27.41% + 28.47% ), therefore the application of product Kayak Era ( A23282A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of operator .

Assuming that there is 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio and this conversion already occurs during mixing with water during mixing and loading and that dermal absorption during mixing and loading is 14% ( as for dilution 1:50, 1.5 g/L prothioconazole-desthio) and during application 16% ( as for dilution 1/200 (0.375g/L) the exposure of operator wearing wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading, but not protective gloves is above AOEL for prothioconazole-desthio, thus is not acceptable. However if operator is wearing a work clothing (long sleeved shirt, long trousers) during mixing/loading and application and protective gloves during mixing and loading the exposure is 22.75% of AOEL and is acceptable.

Summing up, the application of product Kayak Era ( A23282A) does not pose an unacceptable risk to the health of operator during its intended use within good agricultural practice providing that operator is wearing work wear covering arms, body and legs during mixing/loading and application and protective gloves during mixing/loading. Since the product classified as Eye Dam. 1, Skin Irrit.2 and Skin Sens. 1 the operator should wear protective gloves, eye protection/face protection during mixing/loading operations or when directly contacting surface of equipment contaminated with concentrated product.

### 6.6.3 Worker exposure (KCP 7.2.3)

#### 6.6.3.1 Estimation of worker exposure

Table 6.6-5 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with A23282A according to the critical use. Outcome of the estimation is presented in Table 6.6-6 (longer term exposure). Detailed calculations are in 0.

At this time, no acute AOELs have been set for cyprodinil, prothioconazole and prothioconazole-desthio. and there is no guidance on acute exposure assessment for the worker. Consequently, no acute risk assessment has been provided for these active substances.

**Table 6.6-5: Exposure models for intended uses**

| | |
|---|---|
| Critical use | Winter wheat (max. 1 x 2 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<br>calculator version: 30/03/2015 |

**Table 6.6-6: Estimated worker exposure (longer term exposure)**

| | | **Cyprodinil** | |
|---|---|---|---|
| **Model data** | **Level of PPE** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Crop Inspection (cereals are mechanically harvested)<br>Outdoor<br>Work rate: 2 hours/day,<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | |
| Number of applications and application rate | | Low water volume 1 x 0.45 kg a.s./ha in 100 L water/ha | |
| Body weight: 60 kg | Work wear (arms, body and legs covered)<br>TC: 1400 cm$^2$/person/h | 0.0063 | 21.00 |
| Number of applications and application rate | | High water volume 1 x 0.45 kg a.s./ha in 400 L water/ha | |
| Body weight: 60 kg | Work wear (arms, body and legs covered)<br>TC: 1400 cm$^2$/person/h | 0.0082 | 27.30 |

| | | 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** |
| Crop Inspection (cereals mechanically harvested)<br>Outdoor<br>Work rate: 2 hours/day,<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| | | Low water volume - 100 L water/ha | | | |
| Number of applications and application rate | | 1 x 0.150 kg a.s./ha | | 1 x 0.13605 kg a.s./ha | |
| Body weight: 60 kg | Work wear (arms, body and legs covered)<br>TC: 1400 cm$^2$/person/h | 0.0034 | 1.68 | 0.0027 | 26.66 |
| | | High water volume - 400 L water/ha | | | |
| Number of applications and application rate | | 1 x 0.099 kg a.s./ha | | 1 x 0.13605 kg a.s./ha | |
| Body weight: 60 kg | Work wear (arms, body and legs covered)<br>TC: 1400 cm$^2$/person/h | 0.0023 | 1.16 | 0.0030 | 30.46 |

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

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 dislodgeable foliar residues for cyprodinil, prothioconazole or the metabolite prothioconazole-desthio was not necessary.

### 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.

**zRMS evaluation of worker exposure**

The exposure to Cyprodinil, an active substance of a product Kayak Era ( A23282A) of worker not wearing PPE (gloves) but wearing a work clothing (long sleeved shirt, long trousers) and entering for 2 hours for inspection a field of cereals treated with a product Kayak Era ( A23282A) at maximal dose of 2.0 L product/ha (0.450 kg a.s./ha) as foreseen in GAP, calculated with the EFSA AOEM amounted 21 - 27.30% of respective AOEL depending upon a volume of water used (100-400L/ha) .

The exposure to Prothioconazole, an active substance of a product Kayak Era ( A23282A), of worker not wearing PPE (gloves) but wearing a work clothing (long sleeved shirt, long trousers) and entering for 2 hours for inspection a field of cereals treated with a product Kayak Era ( A23282A) at maximal dose of

2.0 L product/ha (0.150 kg a.s./ha) as foreseen in GAP, calculated with the EFSA AOEM amounted 1.68 % - 1.16 % of respective AOEL depending upon a volume of water used (100-400L/ha) .

The exposure to Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) of worker not wearing PPE (gloves) but wearing a work clothing (long sleeved shirt, long trousers) and entering for 2 hours for inspection a field of cereals treated with a product Kayak Era ( A23282A) at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole /ha) as foreseen in GAP, calculated with the EFSA AOEM amounted 26.66 % - 30.46 % of respective AOEL depending upon a volume of water used (100-400L/ha).
The exposure to Prothioconazole-desthio (assuming 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio) of worker not wearing PPE (gloves) but wearing a work clothing (long sleeved shirt, long trousers) and entering for 2 hours for inspection a field of cereals treated with a product Kayak Era ( A23282A) at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole /ha) as foreseen in GAP, calculated with the EFSA AOEM amounted 15.23 % of respective AOEL, thus it does not pose an unacceptable health risk.

The sum of exposures of worker wearing a work clothing (long sleeved shirt, long trousers) to both active substance or to Cyprodinil and Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying) expressed as percentage of their AOELs is below 100%, therefore the application of product Kayak Era ( A23282A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of worker.

Thus, it is concluded that the application of a product Kayak Era ( A23282A) does not pose an unacceptable risk to the health of worker due to its intended use within good agricultural practice providing that the worker is wearing a work clothing (long sleeved shirt, long trousers).

### 6.6.4 Resident and bystander exposure (KCP 7.2.2)

#### 6.6.4.1 Estimation of resident and bystander exposure

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

Table 6.6-7 shows the exposure model used for estimation of resident exposure to cyprodinil, prothioconazole and the metabolite prothioconazole-desthio. The outcome of the estimations is presented in Table 6.6-8 (longer term resident exposure). Detailed calculations are in 0.

At this time, no acute AOELs have been set for cyprodinil, prothioconazole or the metabolite prothioconazole-desthio. Consequently, no acute risk assessment has been provided for these active substances.

**Table 6.6-7: Exposure models for intended uses**

| | |
|---|---|
| Critical use | Winter wheat (max. 1 x 2 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<br>calculator version: 30/03/2015 |

**Table 6.6-8: Estimated resident exposure (longer term exposure) without mitigation measures**

| NO RISK MITIATION MEASURES | | Cyprodinil | | | |
|---|---|---|---|---|---|
| | | Low water volume (100 L water/ha) | | High water volume (400 L water/ha) | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.45 kg a.s./ha | | 1 x 0.45 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0122 | 40.55 | 0.0039 | 13.15 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 3.57 | 0.0011 | 3.57 |
| | Deposits (75$^{th}$ perc.) | 0.0010 | 3.40 | 0.0012 | 4.06 |
| | Re-entry (75$^{th}$ perc.) | 0.0076 | 25.31 | 0.0099 | 32.91 |
| | **Sum (mean)** | 0.0146 | 48.63 | 0.0120 | 40.03 |
| Resident adult<br>Body weight: 60 kg | Drift (75$^{th}$ perc.) | 0.0029 | 9.66 | 0.0009 | 3.14 |
| | Vapour (75$^{th}$ perc.) | 0.0002 | 0.77 | 0.0002 | 0.77 |
| | Deposits (75$^{th}$ perc.) | 0.0003 | 1.02 | 0.0004 | 1.33 |
| | Re-entry (75$^{th}$ perc.) | 0.0042 | 14.06 | 0.0055 | 18.28 |
| | **Sum (mean)** | 0.0052 | 17.33 | 0.0053 | 17.81 |

| NO RISK MITIATION MEASURES | | Prothioconazole | | | |
|---|---|---|---|---|---|
| | | Low water volume (100 L water/ha) | | High water volume (400 L water/ha) | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.15 kg a.s./ha | | 1 x 0.15 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0065 | 3.23 | 0.0011 | 0.56 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 0.54 | 0.0011 | 0.54 |
| | Deposits (75$^{th}$ perc.) | 0.0005 | 0.24 | 0.0004 | 0.18 |

| | | | | | |
|---|---|---|---|---|---|
| | Re-entry (75th perc.) | 0.0041 | 2.03 | 0.0028 | 1.39 |
| | **Sum (mean)** | 0.0082 | 4.11 | 0.0042 | 2.09 |
| Resident adult<br>Body weight: 60 kg | Drift (75th perc.) | 0.0015 | 0.77 | 0.0003 | 0.13 |
| | Vapour (75th perc.) | 0.0002 | 0.12 | 0.0002 | 0.12 |
| | Deposits (75th perc.) | 0.0002 | 0.08 | 0.0001 | 0.06 |
| | Re-entry (75th perc.) | 0.0023 | 1.13 | 0.0015 | 0.77 |
| | **Sum (mean)** | 0.0029 | 1.44 | 0.0017 | 0.84 |
| **NO RISK MITIATION MEASURES** | | **Prothioconazole-desthio** | | | |
| | | **Low water volume (100 L water/ha)** | | **High water volume (400 L water/ha)** | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm²/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.13605 kg a.s./ha | | 1 x 0.13605 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75th perc.) | 0.0051 | 51.35 | 0.0015 | 14.66 |
| | Vapour (75th perc.) | 0.0011 | 10.70 | 0.0011 | 10.70 |
| | Deposits (75th perc.) | 0.0004 | 3.88 | 0.0004 | 4.27 |
| | Re-entry (75th perc.) | 0.0032 | 32.13 | 0.0037 | 36.72 |
| | **Sum (mean)** | 0.0067 | 67.49 | 0.0051 | 51.19 |
| Resident adult<br>Body weight: 60 kg | Drift (75th perc.) | 0.0012 | 12.25 | 0.0003 | 3.50 |
| | Vapour (75th perc.) | 0.0002 | 2.30 | 0.0002 | 2.30 |
| | Deposits (75th perc.) | 0.0001 | 1.30 | 0.0001 | 1.48 |
| | Re-entry (75th perc.) | 0.0018 | 17.85 | 0.0020 | 20.40 |
| | **Sum (mean)** | 0.0023 | 23.31 | 0.0021 | 21.32 |

**Table 6.6-9: Estimated resident exposure (longer term exposure) with mitigation measures**

| **WITH LOW DRIFT NOZZLES** | | **Cyprodinil** | | | |
|---|---|---|---|---|---|
| | | **Low water volume (100 L water/ha)** | | **High water volume (400 L water/ha)** | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: **Yes** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| $DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.45 kg a.s./ha | | 1 x 0.45 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0061 | 20.28 | 0.0020 | 6.58 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 3.57 | 0.0011 | 3.57 |
| | Deposits (75$^{th}$ perc.) | 0.0005 | 1.70 | 0.0006 | 2.03 |
| | Re-entry (75$^{th}$ perc.) | 0.0076 | 25.31 | 0.0099 | 32.91 |
| | **Sum (mean)** | 0.0109 | 36.19 | 0.0105 | 34.92 |
| Resident adult<br>Body weight: 60 kg | Drift (75$^{th}$ perc.) | 0.0014 | 4.83 | 0.0005 | 1.57 |
| | Vapour (75$^{th}$ perc.) | 0.0002 | 0.77 | 0.0002 | 0.77 |
| | Deposits (75$^{th}$ perc.) | 0.0002 | 0.51 | 0.0002 | 0.66 |
| | Re-entry (75$^{th}$ perc.) | 0.0042 | 14.06 | 0.0055 | 18.28 |
| | **Sum (mean)** | 0.0044 | 14.65 | 0.0050 | 16.58 |
| **WITH LOW DRIFT NOZZLES** | | **Prothioconazole** | | | |
| | | **Low water volume (100 L water/ha)** | | **High water volume (400 L water/ha)** | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: **Yes**<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.15 kg a.s./ha | | 1 x 0.15 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0032 | 1.62 | 0.0006 | 0.28 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 0.54 | 0.0011 | 0.54 |
| | Deposits (75$^{th}$ perc.) | 0.0002 | 0.12 | 0.0002 | 0.09 |
| | Re-entry (75$^{th}$ perc.) | 0.0041 | 2.03 | 0.0028 | 1.39 |
| | **Sum (mean)** | 0.0063 | 3.13 | 0.0037 | 1.87 |
| Resident adult<br>Body weight: 60 kg | Drift (75$^{th}$ perc.) | 0.0008 | 0.39 | 0.0001 | 0.07 |
| | Vapour (75$^{th}$ perc.) | 0.0002 | 0.12 | 0.0002 | 0.12 |
| | Deposits (75$^{th}$ perc.) | 0.0001 | 0.04 | 0.0001 | 0.03 |
| | Re-entry (75$^{th}$ perc.) | 0.0023 | 1.13 | 0.0015 | 0.77 |
| | **Sum (mean)** | 0.0025 | 1.23 | 0.0016 | 0.78 |

| WITH LOW DRIFT NOZZLES | | Prothioconazole-desthio | | | |
|---|---|---|---|---|---|
| | | Low water volume (100 L water/ha) | | High water volume (400 L water/ha) | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 2,3 (m)<br>Drift reduction technology: **Yes**<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.13605 kg a.s./ha | | 1 x 0.13605 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0026 | 25.68 | 0.0007 | 7.33 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 10.70 | 0.0011 | 10.70 |
| | Deposits (75$^{th}$ perc.) | 0.0002 | 1.94 | 0.0002 | 2.14 |
| | Re-entry (75$^{th}$ perc.) | 0.0032 | 32.13 | 0.0037 | 36.72 |
| | **Sum (mean)** | 0.0052 | 51.90 | 0.0046 | 45.59 |
| Resident adult<br>Body weight: 60 kg | Drift (75$^{th}$ perc.) | 0.0006 | 6.13 | 0.0002 | 1.75 |
| | Vapour (75$^{th}$ perc.) | 0.0002 | 2.30 | 0.0002 | 2.30 |
| | Deposits (75$^{th}$ perc.) | 0.0001 | 0.65 | 0.0001 | 0.74 |
| | Re-entry (75$^{th}$ perc.) | 0.0018 | 17.85 | 0.0020 | 20.40 |
| | **Sum (mean)** | 0.0020 | 19.92 | 0.0020 | 19.94 |

| WITH 5M BUFFER ZONE | | Cyprodinil | | | |
|---|---|---|---|---|---|
| | | Low water volume (100 L water/ha) | | High water volume (400 L water/ha) | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: **5 (m)**<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm$^2$/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.45 kg a.s./ha | | 1 x 0.45 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75$^{th}$ perc.) | 0.0081 | 27.01 | 0.0026 | 8.76 |
| | Vapour (75$^{th}$ perc.) | 0.0011 | 3.57 | 0.0011 | 3.57 |
| | Deposits (75$^{th}$ perc.) | 0.0004 | 1.40 | 0.0005 | 1.67 |
| | Re-entry (75$^{th}$ perc.) | 0.0076 | 25.31 | 0.0099 | 32.91 |
| | **Sum (mean)** | 0.0119 | 39.81 | 0.0108 | 35.96 |
| Resident adult | Drift (75$^{th}$ perc.) | 0.0015 | 4.90 | 0.0005 | 1.59 |

| | | | | | |
|---|---|---|---|---|---|
| Body weight: 60 kg | Vapour (75th perc.) | 0.0002 | 0.77 | 0.0002 | 0.77 |
| | Deposits (75th perc.) | 0.0001 | 0.42 | 0.0002 | 0.55 |
| | Re-entry (75th perc.) | 0.0042 | 14.06 | 0.0055 | 18.28 |
| | **Sum (mean)** | 0.0045 | 14.84 | 0.0050 | 16.59 |
| **WITH 5M BUFFER ZONE** | | **Prothioconazole** | | | |
| | | **Low water volume (100 L water/ha)** | | **High water volume (400 L water/ha)** | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: **5 (m)**<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm²/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.15 kg a.s./ha | | 1 x 0.15 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75th perc.) | 0.0043 | 2.15 | 0.0007 | 0.37 |
| | Vapour (75th perc.) | 0.0011 | 0.54 | 0.0011 | 0.54 |
| | Deposits (75th perc.) | 0.0002 | 0.10 | 0.0001 | 0.07 |
| | Re-entry (75th perc.) | 0.0041 | 2.03 | 0.0028 | 1.39 |
| | **Sum (mean)** | 0.0068 | 3.42 | 0.0038 | 1.91 |
| Resident adult<br>Body weight: 60 kg | Drift (75th perc.) | 0.0008 | 0.39 | 0.0001 | 0.07 |
| | Vapour (75th perc.) | 0.0002 | 0.12 | 0.0002 | 0.12 |
| | Deposits (75th perc.) | 0.0001 | 0.03 | 0.0000 | 0.02 |
| | Re-entry (75th perc.) | 0.0023 | 1.13 | 0.0015 | 0.77 |
| | **Sum (mean)** | 0.0025 | 1.24 | 0.0016 | 0.78 |
| **WITH 5M BUFFER ZONE** | | **Prothioconazole-desthio** | | | |
| | | **Low water volume (100 L water/ha)** | | **High water volume (400 L water/ha)** | |
| **Model data** | | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** | **Total absorbed dose (mg/kg bw/day)** | **% of systemic AOEL** |
| Tractor mounted boom spray application outdoors to low crops<br>Buffer zone: 5 (m)<br>Drift reduction technology: no<br>$DT_{50}$: 30 days<br>DFR: 3 µg/cm²/kg a.s./ha<br>Interval between treatments: Not applicable | | | | | |
| Number of applications and application rate | | 1 x 0.13605 kg a.s./ha | | 1 x 0.13605 kg a.s./ha | |
| Resident child<br>Body weight: 10 kg | Drift (75th perc.) | 0.0034 | 34.19 | 0.0010 | 9.76 |
| | Vapour (75th perc.) | 0.0011 | 10.70 | 0.0011 | 10.70 |

| | | | | | |
|---|---|---|---|---|---|
| | Deposits (75th perc.) | 0.0002 | 1.59 | 0.0002 | 1.75 |
| | Re-entry (75th perc.) | 0.0032 | 32.13 | 0.0037 | 36.72 |
| | **Sum (mean)** | 0.0056 | 56.49 | 0.0047 | 46.75 |
| Resident adult Body weight: 60 kg | Drift (75th perc.) | 0.0006 | 6.21 | 0.0002 | 1.77 |
| | Vapour (75th perc.) | 0.0002 | 2.30 | 0.0002 | 2.30 |
| | Deposits (75th perc.) | 0.0001 | 0.53 | 0.0001 | 0.61 |
| | Re-entry (75th perc.) | 0.0018 | 17.85 | 0.0020 | 20.40 |
| | **Sum (mean)** | 0.0020 | 20.16 | 0.0020 | 19.96 |

### 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 cyprodinil, prothioconazole or the metabolite prothioconazole-desthio will not be exceeded under conditions of intended uses as modelled by tier-1 risk assessment (no risk mitigation measures required, see Table 6.6-8), a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

Reductions in exposure are included using risk mitigation measures (DRT or buffer zone, see Table 6.6-9) to better represent the actual agricultural practices conducted using A23282A in individual countries and therefore, more accurate reflects any potential resident/bystander exposure to the active substances from boom application on cereals.

**zRMS:**

**No additional mitigation measures used**

The exposure estimation of resident (adult and child) to Cyprodinil, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.450 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, without any additional mitigation measures, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 17.33 -17.81 % of AOEL and for child resident in the range of 48.63 - 40.03 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, without any additional mitigation measures, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 1.44 - 0.84 % of AOEL and for child resident in the range of 4.11– 2.09 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying), after application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, without any additional mitigation measures, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 23.31 - 21.32 % of AOEL and for child resident in the range of 67.49– 51.19 % of AOEL, depending upon a volume of water used (100-400L/ha).

The sum of exposures of residents (adult and child) to both active substance ( Cyprodinil and Prothioconazole) expressed as percentage of their AOELs is below 100%, however the sum of exposures of child

residents to Cyprodinil (48.63 of AOEL) and Prothioconazole-desthio (67.49 % of AOEL) expressed as percentage of their AOELs is above 100%, thus the risk is not acceptable.

The exposure estimation of resident (adult and child) to Prothioconazole-desthio (assuming 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio), after application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, without any additional mitigation measures, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 14.30 % of AOEL and for child resident in the range of 43.08 % of AOEL, depending upon a volume of water used (100-400L/ha).
In case of 50% conversion of prothioconazole to prothioconazole-desthio, the sum of exposures of residents (adult and child) to Cyprodinil (48.63 of AOEL) and Prothioconazole-desthio (14.3% or 43.08% of AOEL) expressed as percentage of their AOELs is below 100%, thus the risk is acceptable.

**Additional mitigation measures used**

**Drift reduction technology**
The exposure estimation of resident (adult and child) to Cyprodinil, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.450 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, with drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 14.65 -16.58% of AOEL and for child resident in the range of 36.19 - 34.92 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, with drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 1.23 - 0.78 % of AOEL and for child resident in the range of 3.13 - 1.87 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying), after application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, with drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 19.92 - 19.94 % of AOEL and for child resident in the range of 51.90 – 45.59 % of AOEL, depending upon a volume of water used (100-400L/ha).

The sum of exposures of residents (adult and child) to both active substance ( Cyprodinil and Prothioconazole) expressed as percentage of their AOELs is below 100%, however as a result of using drift reduction technology the sum of exposures of child residents to Cyprodinil (36.19 of AOEL) and Prothioconazole-desthio (51.90 % of AOEL) expressed as percentage of their AOELs is below 100%, thus the risk is acceptable .

**Use of Buffer zone: 5 (m)**
The exposure estimation of resident (adult and child) to Cyprodinil, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.450 kg a.s./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer with buffer zone of 5 m, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 14.84 -16.59 % of AOEL and for child resident in the range of 39.81- 35.96 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole, an active substance of a product Kayak Era ( A23282A) applied on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg a.s./ha)

as foreseen in GAP, using tractor-mounted/trailed boom sprayer, with buffer zone of 5 m, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 1.24 - 0.78 % of AOEL and for child resident in the range of 3.42 - 1.91 % of AOEL, depending upon a volume of water used (100-400L/ha).

The exposure estimation of resident (adult and child) to Prothioconazole-desthio (assuming total conversion of Prothioconazole to Prothioconazole-desthio during drying), after application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha (0.150 kg Prothioconazole./ha) as foreseen in GAP, using tractor-mounted/trailed boom sprayer, with buffer zone of 5 m, calculated with the EFSA AOEM demonstrates that such a exposure for adult resident is in the range of 20.16 - 19.96 % of AOEL and for child resident in the range of 56.49– 46.75 % of AOEL, depending upon a volume of water used (100-400L/ha).

The sum of exposures of residents (adult and child) to both active substance ( Cyprodinil and Prothioconazole) expressed as percentage of their AOELs is below 100%, however as a result of using a buffer zone of 5 m, the sum of exposures of child residents to Cyprodinil (39.81 of AOEL) and Prothioconazole-desthio (56.49 % of AOEL) expressed as percentage of their AOELs is below 100%, thus the risk is acceptable .

Thus based on these estimations it is concluded that the health risk of residents ( adult and child) caused by the application of a product Kayak Era ( A23282A) on a field of cereals at maximal dose of 2.0 L product/ha is acceptable when risk mitigation measures are used such as drift reduction technology or a buffer zone of 5 m.

No bystander acute exposure estimation for Cyprodinil, Prothioconazole or Prothioconazole-desthio is required since no acute acceptable operator exposure value (AAOEL) has be set for any of these substances. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for bystanders due to short-term single exposure to Cyprodinil, Prothioconazole or Prothioconazole-desthio as a result of application of a product Kayak Era ( A23282A) with accordance with intended use within good agricultural practice.

Summing up application of a product Kayak Era ( A23282A) in line with GAP on low crops at maximal dose of 2.0 L product/ha, using tractor-mounted/trailed boom sprayer does not pose an unacceptable health risk for residents and bystanders, providing that risk mitigation measures are used, either buffer zone of 5 m or drift reduction technology.

### 6.6.5 Combined exposure

~~The hazard endpoints of cyprodinil, prothioconazole and prothioconazole-desthio are based on different target organs. The AOEL of cyprodinil is derived from a NOAEL based on liver effects. The prothioconazole and prothioconazole-desthio AOELs are derived from NOAELs based on developmental effects. Therefore, a combined risk assessment is not necessary.~~

**zRMS**:

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

In the first tier of combined health risk assessment the summation of effects of all substances is assumed, thus the additive effect is proportional to the combined dose of all substances. In this approach 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 6.6.5-1: Long-term risk assessment from combined exposure**

| Application scenario | Active Ingredient | Estimated exposure / AOEL (HQ) |
|---|---|---|
| Operators (AOEM model) Work wear (arms, body and legs covered) M/land A + gloves M/L | Cyprodinil | 0.27 |
| | Protioconazole | 0.02 |
| | **Cumulative risk Operators (HI)** | **0.29** |
| Operators (AOEM model) Work wear (arms, body and legs covered) M/land A + gloves M/L | Cyprodinil | 0.27 |
| | Protioconazole - desthio | **0.28*/0.23**** |
| | **Cumulative risk Operators (HI)** | **0.55*/0.50**** |
| | | |
| Workers (AOEM model) Work wear (arms, body and legs covered) M/l and A | Cyprodinil | 0.27 |
| | Protioconazole | 0.02 |
| | **Cumulative risk Operators (HI)** | **0.29** |
| | Cyprodinil | 0.27 |
| | Protioconazole - desthio | **0.30*/0.15**** |
| | **Cumulative risk Operators (HI)** | **0.57*/0.42**** |
| | | |
| Resident - Adult | Cyprodinil | 0.18 |
| | Protioconazole | 0.01 |
| | **Cumulative risk Operators (HI)** | **0.19** |
| | | |
| Resident - Adult | Cyprodinil | 0.18 |
| | Protioconazole - desthio | **0.23*/0.14**** |
| | **Cumulative risk Operators (HI)** | **0.41*/0.32**** |
| | | |
| Resident - Child | Cyprodinil | 0.49 |
| | Protioconazole | 0.04 |
| | **Cumulative risk Operators (HI)** | **0.53** |
| | | |
| Resident - Child | Cyprodinil | 0.49 |
| | Protioconazole - desthio | **0.67*/0.43**** |
| | **Cumulative risk Operators (HI)** | **1.16*/0.92**** |
| | | |

*****Assuming 100% conversion of Protioconazole to its metabolite Protioconazole - desthio
****** Assuming 50% conversion of Protioconazole to its metabolite Protioconazole - desthio

Regardless of the assumption of the 100% or 50 % conversion of Protioconazole to its metabolite Protioconazole - desthio the Hazard Index for operators, workers and adult resident is below 1, therefore the

combined exposure to Cyprodinil and Protioconazole, active substances in Kayak Era and metabolite Protioconazole - desthio is not expected to present a risk for operators, workers and adult residents in this the first tier assessment of combined risk. No further refinement of the assessment is required.

The hazard index for child residents is only below 1 when it is assumed that conversion of Protioconazole to its metabolite Protioconazole – desthio is equal 50%, in such case the exposure of child residents is also acceptable.

However, in case of the assumption of 100% conversion of Protioconazole to its metabolite Protioconazole - desthio the Hazard Index for child residents is above 1 and further refinement of risk is necessary.

It is possible that there is no additive interaction between Cyprodinil and Protioconazole – desthio, their toxic effect do not sum up, thus their cumulative risk assessment is overestimated when using hazard quotient and hazard index, and in reality the combined exposure to these substance does not pose a health risk to child residents. However there are no sufficient data on mode of action and target organs for both substances to evaluate this option, thus the assumption of addition of the effects of both substances should be used.

One way of risk refinement would be use of additional risk mitigation measures such as such as drift reduction technology or a buffer zone of 5 m the sum of exposures of residents (adult and child) to reduce the combined exposure to both substances.

**Table 6.6.5-2: Long-term risk assessment of child residents from combined exposure assuming 100% conversion of Protioconazole to its metabolite Protioconazole - desthio**

| | | |
|---|---|---|
| Resident – Child<br>Drift reduction technology | Cyprodinil | 0.36 |
| | Protioconazole | 0.03 |
| | **Cumulative risk Operators (HI)** | **0.39** |
| | | |
| Resident – Child<br>Drift reduction technology | Cyprodinil | 0.36 |
| | Protioconazole - desthio | **0.52*** |
| | **Cumulative risk Operators (HI)** | **0.86*** |
| | | |
| Resident – Child<br>5 M Buffer Zone | **Cyprodinil** | **0.40** |
| | **Protioconazole** | **0.03** |
| | **Cumulative risk Operators (HI)** | **0.39** |
| | | |
| Resident – Child<br>5 M Buffer Zone | **Cyprodinil** | **0.40** |
| | **Protioconazole - desthio** | **0.56*** |
| | **Cumulative risk Operators (HI)** | **0.96*** |
| | | |

***Assuming 100% conversion of Protioconazole to its metabolite Protioconazole - desthio

When risk mitigation measures are used such as drift reduction technology or a buffer zone of 5 m the hazard index for child residents due to combined exposure to both active substance ( Cyprodinil and Prothioconazole) or to Cyprodinil and Prothioconazole-desthio (assuming total conversion of Prothioconazole

to Prothioconazole-desthio during drying) is below 1. Thus the application of product Kayak Era ( A23282A) according to its intended use within good agricultural practice does not pose an unacceptable risk to the health of child residents due to combined exposure to these substances providing that risk mitigation measures are used such as drift reduction technology or a buffer zone of 5 m.

No bystander acute exposure estimation for Cyprodinil, Prothioconazole or Prothioconazole-desthio is required since no acute acceptable operator exposure value (AAOEL) has be set for any of these substances. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for bystanders due to short-term single exposure to Cyprodinil, Prothioconazole or Prothioconazole-desthio as a result of application of a product Kayak Era ( A23282A) with accordance with intended use within good agricultural practice.

# Appendix 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<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Verte-brate study Y/N | Owner |
|---|---|---|---|---|---|
| KCP 7.3 | Stephen, C.<br>Kerr, M. | 20/09/2021 | Cyprodinil/Prothioconazole/Desthio EC (A23282A) - The In Vitro Percutaneous Absorption of Radiolabelled Cyprodinil, Radiolabelled Prothioconazole and Radiolabelled Desthio in Concentrate Formulation and/ or Two In-Use Dilutions Through Human Split-Thickness Skin<br>Report No. 787699<br>Document No. VV-920226<br>Test Facility Charles River Laboratories Edinburgh, Ltd.<br>GLP<br>Unpublished | No | SYN |

**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<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Verte-brate study Y/N | Owner |
|---|---|---|---|---|---|
| none | | | | | |

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<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not | Verte-brate study Y/N | Owner |
|---|---|---|---|---|---|
| | | | | | |

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

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

# Appendix 2 Detailed evaluation of the studies relied upon

## A 2.1 Statement on ATE and Additivity calculations

Acute Toxicity Estimate (ATE) and Additivity calculations have been conducted and are provided in the Part C document. As acute toxicity studies have not been conducted, the calculations have been relied upon for classification of the product.

## A 2.2 Acute oral toxicity (KCP 7.1.1)

| | |
|---|---|
| Comments of zRMS: | The evaluation of acute oral toxicity of a product Kayak Era (A23282A) has been done based on known classification of its ingredients using rules given in Regulation 1272/2008, point 3.1.3.6.<br><br>The product Kayak Era (A23282A) does not require classification for acute oral toxicity (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

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

| | |
|---|---|
| Comments of zRMS: | The evaluation of acute dermal toxicity of a product Kayak Era (A23282A) has been done based on known classification of its ingredients using rules given in Regulation 1272/2008, point 3.1.3.6.<br><br>The product Kayak Era (A23282A) does not require classification for acute dermal toxicity (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

## A 2.4 Acute inhalation toxicity (KCP 7.1.3)

| | |
|---|---|
| Comments of zRMS: | The evaluation of acute inhalation toxicity of a product Kayak Era (A23282A) has been done based on known classification of its ingredients using rules given in Regulation 1272/2008, point 3.1.3.6.<br><br>The product Kayak Era (A23282A) does not require classification for acute inhalation toxicity. (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

## A 2.5 Skin irritation (KCP 7.1.4)

| | |
|---|---|
| Comments of zRMS: | Since the combined concentration of the ingredients classified as Skin Irrit. 2; H315 is well above 10%, the generic concentration limit of ingredients classified for skin |

| | |
|---|---|
| | irritant hazard (Category 2) given in Table 3.2.3 of Regulation 1272/2008 that trigger classification of the mixture as irritant to skin the product Kayak Era (A23282A) requires classification as Skin Irrit. 2; H315 (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

## A 2.6 Eye irritation (KCP 7.1.5)

| | |
|---|---|
| Comments of zRMS: | Since the combined concentration of the ingredients classified as Eye Dam. 1, H318 is well above 3%, the generic concentration limit of ingredients classified for serious eye damage (Category 1) given in Table 3.3.3 of Regulation 1272/2008 that trigger classification of the mixture as serious eye damage where the additivity approach applies, the product Kayak Era (A23282A) requires classification as Eye Dam. 1, H318 Causes serious eye damage (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

## A 2.7 Skin sensitisation (KCP 7.1.6)

| | |
|---|---|
| Comments of zRMS: | Since the concentration of Cyprodinil classified as Skin Sens. 1 is well above 1%, the generic concentration limit of ingredients classified for skin sensitization (Category 1) given in Table 3.4.5 of Regulation 1272/2008 that trigger classification of the mixture as skin sensitiser, the product Kayak Era (A23282A) requires classification as Skin Sens. 1; H317 May cause an allergic skin reaction. (please refer to Part C) |

Please refer to Acute Toxicity Estimate (ATE) available in Part C

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

None

## A 2.9 Data on co-formulants (KCP 7.4)

### A 2.9.1 Material safety data sheet for each co-formulant

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

### A 2.9.2 Available toxicological data for each co-formulant

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

## A 2.10 Studies on dermal absorption (KCP 7.3)

## A 2.10.1 Study 1 – Cyprodinil/ Prothioconazole/ Desthio in A23282A/KAYAK ERA

**Comparative dermal absorption, in vitro using rat and human skin**

| | |
|---|---|
| Comments of zRMS: | The study performed on formulation A23282A (Kayak Era) according to relevant OECD method and in GLP conditions is acceptable<br><br>The final dermal absorption rates were derived according to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873 ) using for calculation of the dermal absorption of each substance a formula: mean value for a given concentrate or dilution + ks, where k is multiplication factor and s is the sample standard deviation. Since permeation (in vitro) was essentially not complete at the end of the study, all tape stripped skin material was included in the calculation of the absorbable dose fraction, except for Prothioconazole-Desthio: dilution 1/200 (0.375g/L).<br><br>Thus, the dermal penetration estimates to be used for risk assessment due to exposure to Cyprodinil is 1.5 % for the concentrated formulation (225 g/L), 10 % for the dilution 1:50 (4.5g/L) and 13% for spray dilution 1/200 (1.125g/L.) based on the EFSA guidance criteria<br><br>The dermal penetration estimates to be used for risk assessment due to exposure to Prothioconazole is 2.8 % for the concentrated formulation (75 g/L), 16 % for the dilution 1:50 (1.5g/L) and 11% for spray dilution 1/200 (0.375g/L) based on the EFSA guidance criteria<br><br>The dermal penetration estimates to be used for risk assessment due to exposure to Prothioconazole-Desthio is 14 % for the dilution 1:50 (1.5g/L) and 16% for spray dilution 1/200 (0.375g/L) based on the EFSA guidance criteria.<br><br>Please note that applicant followed a conservative approach for dilution 1/200 (0.375g/L) of Prothioconazole-Desthio and all tape strips were added to the dermal absorption estimate. See asterisk in footnote of table A 4. Please consider to rephrase the zRMS comment. |

| | |
|---|---|
| **Reference:** | KCP 7.3 |
| **Report** | Cyprodinil/Prothioconazole/Desthio EC (A23282A) - The *In Vitro* Percutaneous Absorption of Radiolabelled Cyprodinil, Radiolabelled Prothioconazole and Radiolabelled Desthio in Concentrate Formulation and/ or Two In-Use Dilutions Through Human Split-Thickness Skin. Stephen, C., 2021. 787699 VV-920226 |
| **Guideline(s):** | Yes.<br>OECD Guideline for Testing of Chemicals, Guideline 428: Skin Absorption: In Vitro Method (2004).<br>OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 28. Guidance Document for the Conduct of Skin Absorption Studies (2004).<br>European Commission Guidance Document on Dermal Absorption – Sanco/222/2000/Rev. 7 (19 March 2004).<br>Guidance on Dermal Absorption (EFSA Journal, 2017, 15(6): 4873). |

| | |
|---|---|
| **Deviations:** | None. |
| **GLP:** | Yes. |
| **Acceptability:** | Yes |

**EXECUTIVE SUMMARY**

The rate and extent of absorption of [$^{14}$C]-Cyprodinil, [$^{14}$C]-Prothioconazole and [$^{14}$C]-Desthio following topical application as an emulsifiable concentrate (EC) formulation was measured *in vitro* through human split-thickness skin. The concentration of cyprodinil in the formulation concentrate, spray dilution 1 and spray dilution 2 was *ca* 225 g/L, *ca* 4.5 g/L and *ca* 1.125 g/L, respectively. The concentration of prothioconazole in the formulation concentrate, spray dilution 1 and spray dilution 2 was *ca* 75 g/L, *ca* 1.5 g/L and *ca* 0.375 g/L, respectively. The concentration of desthio in the spray dilution 1 and spray dilution 2 was *ca* 1.5 g/L and *ca* 0.375 g/L, respectively.

The doses were applied at 10 µL/cm$^2$ and left unoccluded for an experimental period of 24 h, with an interim wash at 6 h post-application.

The absorption process was followed by taking samples of the receptor fluid, phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, *ca* 6%, w/v), sodium azide (*ca* 0.01%, w/v), streptomycin (*ca* 0.1 mg/mL) and penicillin (*ca* 100 units/mL), pH 7.4 ± 0.1, at recorded intervals throughout the experimental period.

The distribution of cyprodinil, prothioconazole and desthio within the test system and a 24 h absorption profile was determined using liquid scintillation counting. Before conducting the main study, stability and solubility assessments were carried out. No stability assessment for desthio was conducted due to delays in shipment of the radiolabelled test item.

**The study demonstrated that the amount of cyprodinil absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (225 g/L) and the intended in-use dilutions (4.5 g/L and 1.125 g/L) was 0.27%, 2.63% and 4.27% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.**

**The study demonstrated that the amount of prothioconazole absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (75 g/L) and the intended in-use dilutions (1.5 g/L and 0.375 g/L) was 0.20%, 2.06% and 2.43% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.**

**The study demonstrated that the amount of desthio absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the intended in-use dilutions (1.5 g/L and 0.375 g/L) was 5.69% and 9.63% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.**

Interpreting the study in compliance with the EFSA Guidance on Dermal Absorption (2017) results in absorption values to be used for human risk assessment of 1.5%, 10% and 13% for the formulation concentrate (225g/L), spray dilution 1 (4.5g/L) and spray dilution 2 (1.125g/L), respectively for Cyprodinil. Interpreting the study in compliance with the EFSA Guidance on Dermal Absorption (2017) results in absorption values to be used for human risk assessment of 2.8%, 16% and 11% for the formulation concentrate (75g/L), spray dilution 1 (1.5g/L) and spray dilution 2 (0.375g/L), respectively for Prothioconazole.
Interpreting the study in compliance with the EFSA Guidance on Dermal Absorption (2017) results in absorption values to be used for human risk assessment of 14% and 16% for the spray dilution 1 (1.5g/L) and spray dilution 2 (0.375g/L), respectively for Desthio.

**MATERIALS AND METHODS**

**Materials:**

| | |
|---|---|
| **Test Material:** | Cyprodinil tech. |
| **Batch Number:** | P.012011 |
| **Product Code:** | CGA219417 tech. |
| **Physical Appearance:** | Light beige crumbs |
| **Purity:** | 99.2% w/w |
| **Re-certification date:** | 31 August 2024 |
| **Storage Conditions:** | <30°C |
| **Test Material:** | Prothioconazole tech. |
| **Batch Number:** | AE 1344248-03-08 |
| **Alternative Name** | JAU6476 (Prothioconazole / AE 1344248) |
| **Physical Appearance:** | Light beige solid |
| **Purity:** | 97.3% w/w |
| **Re-certification date:** | 09 March 2022 |
| **Storage Conditions:** | +10 to +30°C |
| **Test Material:** | Prothioconazole Desthio tech. |
| **Batch Number:** | AE 1194888-PU-04 |
| **Alternative Name** | JAU6476 (Prothioconazole / AE 1344248) |
| **Physical Appearance:** | White powder |
| **Purity:** | 98.3% w/w |
| **Re-certification date:** | 11 May 2023 |
| **Storage Conditions:** | +5 ± 5°C |
| **Radiolabelled Test Material:** | [$^{14}$C]-Cyprodinil |
| **Alternative Names:** | [Pyrimidinyl-2-$^{14}$C]-CGA219417 |
| **Synonyms:** | [Pyrimidinyl-2-$^{14}$C]-CSAA206295 |
| **Batch Number:** | CDC-20-50710-1 |
| **Radiochemical Purity:** | 97.5% |
| **Specific Activity:** | 71.3 µCi/mg |
| **Storage Conditions:** | Refrigerator |
| **Radiolabelled Test Material:** | [$^{14}$C]-Prothioconazole |
| **Alternative Names:** | [triazole-U-$^{14}$C]-Prothioconazole |
| **Batch Number:** | 11554CEO001-1 |
| **Radiochemical Purity:** | 96.0% |
| **Specific Activity:** | 65.1 µCi/mg |
| **Storage Conditions:** | Glass bottle, below -70°C |
| **Radiolabelled Test Material:** | [$^{14}$C]-Desthio |
| **Alternative Names:** | [triazole-UL-$^{14}$C]-SXX 0665 |
| **Batch Number:** | MXM 20171 |
| **Radiochemical Purity:** | >99% |
| **Specific Activity:** | 115.95 µCi/mg |
| **Storage Conditions:** | Glass bottle, bellow -70°C |
| **Commercial Formulation** | A23282A |
| **Batch Number:** | LCR001-021-001 |
| **Other Batch ID:** | 1160912 |
| **Physical Appearance:** | Yellow liquid |
| **Density:** | 993 kg/m$^3$ |
| **Re-certification date:** | 30 September 2023 |
| **Storage Conditions:** | <30°C |

| | |
|---|---|
| **Blank Formulation** | EXF22129A |
| **Batch Number:** | LCR001-004-003 |
| **Physical Appearance:** | Liquid |
| **Expiry date:** | 30 September 2022 |
| **Storage Conditions:** | Ambient |
| **Blank Formulation** | EXF23411A |
| **Batch Number:** | LCR001-029-002 |
| **Physical Appearance:** | Liquid |
| **Expiry date:** | 25 February 2023 |
| **Storage Conditions:** | Ambient |
| **Blank Formulation** | EXF23411A |
| **Batch Number:** | LCR001-029-003 |
| **Physical Appearance:** | Liquid |
| **Expiry date:** | 25 February 2023 |
| **Storage Conditions:** | Ambient |

**Study Design and Methods:**

**In-life (experimental) dates:** Start: 25 March 2021 End: 13 May 2021
**Diffusion cell:** An automated flow-through diffusion system (McGregor/Toner) was used. The flow-through diffusion cells were placed in a steel manifold heated *via* a circulating water bath set to maintain the skin surface temperature at 32°C ± 1°C. The cells were connected to multi-channel peristaltic pumps from their afferent ports with the receptor fluid effluent dropping *via* fine bore tubing into scintillation vials on a fraction collector. The surface area of exposed skin within the cells was 0.64 $cm^2$. The receptor chamber volume was 0.25 mL. The peristaltic pumps were adjusted to maintain a flow-rate of 1.5 mL/h ± 0.15 mL/h.

**Receptor fluid:** The receptor fluid chosen for use in this study was phosphate buffered saline containing polyoxyethylene 20 oleyl ether (PEG, ca 6%, w/v), sodium azide (ca 0.01%, w/v), streptomycin (ca 0.1 mg/mL) and penicillin (ca 100 units/mL). The pH of the receptor fluid was checked and adjusted to and/ or confirmed to be pH 7.30-7.44.

Solubility of [$^{14}$C]-Cyprodinil in the chosen receptor fluid was determined based on a 25% default absorption value for EC formulations, as recommended in EFSA Journal, 2017, 15 (6): 4873. The results are presented in the table below:

| Sample Type | Concentration of [$^{14}$C]-Cyprodinil in Solution (g/L) | % of Target [$^{14}$C]-Cyprodinil Concentration |
|---|---|---|
| Receptor Fluid | 1.58 | 65.68 |
| Ethanol | 2.46 | 102.66 |

The target concentration (*ca* 2.4 g/L) represented 10 times the default value (25% absorption for a EC formulation as defined by EFSA Journal (2017). As 65.68% of the target concentration was accepted into the receptor fluid, the receptor fluid was deemed not to be rate limiting to absorption.

Solubility of [$^{14}$C]-Prothioconazole in the chosen receptor fluid was determined based on a 25% default absorption value for EC formulations, as recommended in EFSA Journal, 2017, 15 (6): 4873. The results are presented in the table below:

| Sample Type | Concentration of [$^{14}$C]-Prothioconazole in Solution (g/L) | % of Target [$^{14}$C]-Prothioconazole Concentration |
|---|---|---|
| Receptor Fluid | 0.74 | 92.39 |
| Acetone | 0.83 | 104.02 |

The target concentration (*ca* 0.8 g/L) represented 10 times the default value (25% absorption for a EC formulation as defined by EFSA Journal (2017). As 92.39% of the target concentration was accepted into the receptor fluid, the receptor fluid was deemed not to be rate limiting to absorption.

Solubility of [$^{14}$C]-Desthio in the chosen receptor fluid was determined based on a 70% default absorption value for dilutions of EC formulations, as recommended in EFSA Journal, 2017, 15 (6): 4873. The results are presented in the table below:

| Sample Type | Concentration of [$^{14}$C]-Desthio in Solution (g/L) | % of Target [$^{14}$C]-Desthio Concentration |
|---|---|---|
| Receptor Fluid | 0.0464 | 103.57 |
| Acetone | 0.0469 | 104.66 |

The target concentration (*ca* 0.0448 g/L) represented 10 times the default value (70% absorption for an EC dilution as defined by EFSA Journal (2017). As 103.57% of the target concentration was accepted into the receptor fluid, the receptor fluid was deemed not to be rate limiting to absorption.

**Skin preparations:** Samples of full-thickness human skin (abdomen and thigh) were obtained from 8 male and female donors aged 28 to 57 years old. Skin samples were received from Tissue Solutions, Glasgow. The samples arrived at Charles River deep frozen on dry ice and were stored in a freezer set to maintain a temperature of -20°C until used in the study. The age and sex of the donor and site from which the skin was taken were recorded centrally and in the study records.
All skin samples were removed from storage and allowed to thaw at ambient temperature. The thickness of the uncut skin membranes was measured using a micrometer. Split-thickness membranes were prepared by pinning the full-thickness skin, *stratum corneum* uppermost, onto a raised cork board and cutting at a setting equivalent to 200-400 µm depth using a Zimmer® electric dermatome. The thickness of the membranes was measured using a micrometer. The membranes were then wrapped in aluminium foil and stored in a freezer set to maintain a temperature of -20°C and used within two months.

**Skin preparation integrity:** Phosphate buffered saline (1 mL) was added to the donor chamber and the skin samples were allowed to equilibrate for a minimum of 30 min. The electrical resistance was then measured using a Tinsley Databridge (Model: 6401) set at low voltage alternating current, 1000 Hz with a maximum voltage of 300 mV root-mean-squared in the parallel equivalent circuit mode. Any skin sample exhibiting a resistance less than 7.7 kΩ was excluded from subsequent absorption measurements. The phosphate buffered saline was removed from the skin surface and then the skin was rinsed with water and dried with tissue paper.

**Test substance:**

**Table A 1: Details on dosing**

| Test Preparation | Dose Level (g/L) | Amount compound in dosing solution | | Specific Activity (µCi/mg) | Nominal Dose (µL/cm²) | Actual Dose (µg ai/cm²) | Acheived Concentration (g/L) |
|---|---|---|---|---|---|---|---|
| | | Radiolabelled | Non-labelled | | | | |
| [14C]-Cyprodinil Formulation Concentrate | 225 | 245 µL | N/A | 71.3 | 10 | 2213 | 221 |
| [14C]-Cyprodinil Spray Dilution 1 | 4.5 | 1089 µL [a] | 10.46 [a] | 33.7 | 10 | 49.04 | 4.90 |
| [14C]-Cyprodinil Spray Dilution 2 | 1.125 | 1089 µL [a] | 10.46 [a] | 33.7 | 10 | 12.44 | 1.24 |
| [14C]-Prothioconazole Formulation Concentrate | 75 | 160 µL | N/A | 65.1 | 10 | 761.3 | 76.1 |
| [14C]-Prothioconazole Spray Dilution 1 | 1.5 | 100 µL | N/A | 65.1 | 10 | 16.16 | 1.62 |
| [14C]-Prothioconazole Spray Dilution 2 | 0.375 | N/A [b] | N/A | 65.1 | 10 | 4.131 | 0.41 |
| [14C]-Desthio Spray Dilution 1 | 1.5 | 226 µL | N/A | 115.95 | 10 | 15.55 | 1.56 |
| [14C]-Desthio Spray Dilution 2 | 0.375 | N/A [b] | N/A | 115.95 | 10 | 3.954 | 0.40 |

[a] = Test preparation was prepared from a solution containing these quantities of radiolabelled and non-radiolabelled test item.
[b] = Test preparation made from mixture of spray dilution 1 (250 µL) and water D solution (750 µL)

**Dose preparation, administration and quantification:**

**Preparation of [14C]-Cyprodinil Test Preparations:**

For the stability experiment to prepare the formulation concentrate, [14C]-Cyprodinil (245 µL, S.A. 71.3 µCi/mg) was dispensed into a glass vial and the solvent was removed under a gentle stream of nitrogen gas. A23282A (1000 µL) was shaken prior to use and added to the glass vial. A magnetic stirring bar was added and the contents were mixed by vortex and placed on a magnetic stirring plate to stir continuously. The glass vial was then sonicated for *ca* 1 min and placed on the magnetic stirring plate. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

To prepare spray dilution 1, [14C]-Cyprodinil (1089 µL; S.A. 71.3 µCi/mg) was transferred into a 1 mL volumetric flask and the solvent was removed under a gentle stream of nitrogen gas. Cyprodinil tech. (10.46 mg) was added to the volumetric flask and the 1 mL calibration line was made up with ethanol. The contents were mixed by vortex until fully dissolved. Three aliquots (10 µL) were collected into vials and mixed with ethanol (10 mL). Duplicate aliquots (1 mL) were removed, mixed with scintillation fluid and analysed by liquid scintillation counting.

By radioactivity, the concentration of [14C]-Cyprodinil was determined to be 19.7 g/L, taking into account purity. [14C]-Cyprodinil was distributed within the solution with a CV of 0.60% and the specific activity was determined to be 33.7 µCi/mg.

A premix was created as follows. EXF22129A blank formulation (691.41 mg) and prothioconazole technical (76.78 mg) were weighed into a glass vial. The contents were mixed by vortex.

[14C]-Cyprodinil (227.4 µL, S.A. 33.7 µCi/mg) was added to a small glass vial and the solvent was removed under a gentle stream of nitrogen gas. The premix was mixed by vortex. Premix (15.80 mg) was added to the small glass vial along with water D solution (1080 µL) which was added in small aliquots with

the contents being mixed by vortex between each addition. A magnetic stirring bar was added and the vial was placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

By radioactivity, the concentration of [14C]-Cyprodinil was determined to be 4.01 g/L, taking into account purity. [14C]-Cyprodinil was distributed within the solution with a CV of 4.21%. This low concentration was caused by adding 1080 µL of water D solution instead of the intended 980 µL in error. This process was corrected as follows.

[14C]-Cyprodinil (40 µL, S.A. 33.7 µCi/mg) was added to a new glass vial and the solvent was removed under a gentle stream of nitrogen gas. The contents of the above glass vial were then transferred into the new glass vial and the contents were mixed by vortex. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting

To prepare spray dilution 2, [$^{14}$C]-Cyprodinil in spray dilution 1 (255 µL) was added to a small glass vial. Water D solution (750 µL) and a magnetic stirring bar were added to the glass vial. The contents were then mixed by vortex and placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

For the absorption experiment, the [$^{14}$C]-Cyprodinil in the formulation concentrate, spray dilution 1 and spray dilution 2 were prepared in a similar manner to that described above. The formulation concentrate was prepared one day before the day of dosing and the spray dilutions were prepared on the day of dosing A summary of the preparation of [$^{14}$C]-Cyprodinil in the formulation concentrate, spray dilution 1 and spray dilution 2 is provided in the following table.

| | [$^{14}$C]-Cyprodinil | | |
|---|---|---|---|
| | Formulation Concentrate | Spray Dilution 1 | Spray Dilution 2 |
| Volume of [$^{14}$C]-Cyprodinil (71.3 µCi/mg, µL) | 245 | N/A | N/A |
| Volume of [$^{14}$C]-Cyprodinil (33.71 µCi/m, µL) | N/A | 227.4 | N/A |
| Mass of premix (mg) | N/A | 15.84 | N/A |
| Volume of A23282A (µL) | 1000 | N/A | N/A |
| Volume of Spray Dilution 1 (µL) | N/A | N/A | 250 |
| Volume of water D solution (µL) | N/A | 980 | 750 |
| Concentration of [$^{14}$C]-Cyprodinil by radioactivity (g/L) | 221 | 4.60 | 1.18 |
| Target concentration of [$^{14}$C]-Cyprodinil (g/L) | 225 | 4.5 | 1.125 |
| Percentage of target (%) | 98.33 | 102.19 | 105.27 |
| CV (%) | 1.77 | 0.59 | 1.30 |

N/A = Not Applicable

**Preparation of [$^{14}$C]-Prothioconazole Test Preparations**

For the stability experiment to prepare the formulation concentrate, [$^{14}$C]-Prothioconazole (160 µL, S.A. 65.1 µCi/mg) was added to a small glass vial and the solvent was removed under a gentle stream of nitrogen gas. A23282A (1000 µL) and a magnetic stirring bar were added to the glass vial. The contents were then mixed by vortex and placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

To prepare spray dilution 1, [14C]-Prothioconazole (100 µL; S.A. 65.1 µCi/mg) was added to a small glass vial and the solvent was removed under a gentle stream of nitrogen gas. EXF23411A blank formulation (18.04 mg) was added to the glass vial. Water D solution (980 µL) was added in small aliquots with the contents being vortex mixed in between each aliquot addition. A magnetic stirring bar was added and the vial was placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

By radioactivity, the concentration of [14C]-Prothioconazole was below the accepted range, therefore the contents of the small glass vial were sonicated for ca 5 min, mixed by vortex and placed on a magnetic

stirring plate. A further four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

To prepare spray dilution 2, [14C]-Prothioconazole in spray dilution 1 (235 µL) and water D solution (750 µL) was added to a small glass vial. A magnetic stirring bar was then added. The contents of the vial were then sonicated for ca 5 min, vortex mixed and placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

For the absorption experiment, the [14C]-Prothioconazole in the formulation concentrate, spray dilution 1 and spray dilution 2 were prepared in a similar manner to that described above. The test preparations were prepared one day before the day of dosing. A summary of the preparation of [14C]-Prothioconazole in the formulation concentrate, spray dilution 1 and spray dilution 2 is provided in the following table.

| | [$^{14}$C]-Prothioconazole | | |
|---|---|---|---|
| | Formulation Concentrate | Spray Dilution 1 | Spray Dilution 2 |
| Volume of [$^{14}$C]-Prothioconazole (65.1 µCi/mg, µL) | 160 | 100 | N/A |
| Mass of EXF23411A (µL) | N/A | 17.68 | N/A |
| Volume of A23282A (µL) | 1000 | N/A | N/A |
| Volume of Spray Dilution 1 (µL) | N/A | N/A | 250 |
| Volume of water D solution (µL) | N/A | 980 | 750 |
| Concentration of [$^{14}$C]-Prothioconazole by radioactivity (g/L) | 76.1 | 1.56 | 0.405 |
| Target concentration of [$^{14}$C]-Prothioconazole (g/L) | 75 | 1.5 | 0.375 |
| Percentage of target (%) | 101.42 | 103.69 | 108.13 |
| CV (%) | 2.27 | 0.85 | 0.05 |

N/A = Not Applicable

**Preparation of [$^{14}$C]-Desthio Test Preparations:**

A stability assessment for [$^{14}$C]-Desthio was not performed due to a delay in shipment of the radiolabelled test item and therefore arrival at the Test Facility. It was not suspected that this would have any impact on the study as desthio is effectively a degradation product of prothioconazole-desthio. This omission of a stability assessment for the two in-use dilutions was discussed and approved by the Sponsor.

For the absorption experiment to prepare spray dilution 1, [$^{14}$C]-Desthio (226 µL; S.A. 115.95 µCi/mg) was added to a small glass vial and the solvent was removed under a gentle stream of nitrogen gas. EXF23411A (17.48 mg) was added to the glass vial and the contents were mixed by vortex. Water D solution (800 µL) was added in small aliquots with vortex mixing in between each aliquot addition. The glass vial was then sonicated for *ca* 5 min. A magnetic stirring bar was then added and the vial was placed on a magnetic stirring plate to stir continuously. Four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

Water D solution (100 µL) was further added to the glass vial and the contents were mixed by vortex and sonicated for *ca* 10 min. A further four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting. The contents of the glass vial were vortex mixed in between each aliquot

Water D solution (100 µL) was further added to the glass vial and the contents were mixed by vortex and sonicated for *ca* 10 min. A further four aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting. The contents of the glass vial were vortex mixed in between each aliquot.

To prepare spray dilution 2, [$^{14}$C]-Desthio in spray dilution 1 (250 µL) and water D solution (750 µL) were added to a small glass vial. A magnetic stirring bar was then added. The contents of the vial were then mixed by vortex, sonicated for *ca* 5 min and placed on a magnetic stirring plate to stir continuously. Four

aliquots (6.4 µL) were collected, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

The test preparations were prepared on the day of dosing. A summary of the preparation of [$^{14}$C]-Desthio in the spray dilution 1 and spray dilution 2 is provided in the following table.

| | [$^{14}$C]-Desthio | |
|---|---|---|
| | Spray Dilution 1 | Spray Dilution 2 |
| Volume of [$^{14}$C]-Desthio (115.95 µCi/mg, µL) | 226 | N/A |
| Mass of EXF23411A (mg) | 17.48 | N/A |
| Volume of Spray Dilution 1 (µL) | N/A | 250 |
| Volume of water D solution (µL) | 1000 | 750 |
| Concentration of [$^{14}$C]-Desthio by radioactivity (g/L) | 1.50 | 0.39 |
| Target concentration of [$^{14}$C]-Desthio (g/L) | 1.5 | 0.375 |
| Percentage of target (%) | 100.30 | 104.09 |
| CV (%) | 1.82 | 1.03 |

N/A = Not Applicable

**Application to the skin:** The test preparations for [$^{14}$C]-Cyprodinil were applied evenly over the surface of the exposed skin of 8 split-thickness samples for the formulation concentrate and 16 split-thickness samples for the two in-use dilutions using a positive displacement pipette set to deliver 6.4 µL (10 µL/cm$^2$). The donor chambers of the cells were not occluded. Seven representative aliquots of the test preparation were dispensed into vials at the time of dosing, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting. The test preparations for [$^{14}$C]-Prothioconazole and [$^{14}$C]-Desthio were processed as described above, however all test preparations were applied to 8 split-thickness samples. The results of the representative aliquots are provided in the following table.

| Test Preparation | Target Concentration (g/L) | Test Item Concentration | |
|---|---|---|---|
| | | Mean (g/L) | CV (%) |
| [$^{14}$C]-Cyprodinil in Formulation Concentrate | 225 | 221 | 2.25 |
| [$^{14}$C]-Cyprodinil in Spray Dilution 1 | 4.5 | 4.90 | 1.88 |
| [$^{14}$C]-Cyprodinil in Spray Dilution 2 | 1.125 | 1.24 | 0.96 |
| [$^{14}$C]-Prothioconazole in Formulation Concentrate | 75 | 76.1 | 1.45 |
| [$^{14}$C]-Prothioconazole in Spray Dilution 1 | 1.5 | 1.62 | 0.94 |
| [$^{14}$C]-Prothioconazole in Spray Dilution 2 | 0.375 | 0.41 | 0.81 |
| [$^{14}$C]-Desthio in Spray Dilution 1 | 1.5 | 1.56 | 1.92 |
| [$^{14}$C]-Desthio in Spray Dilution 2 | 0.375 | 0.40 | 0.71 |

Immediately after dosing, an aliquot was removed from each of the test preparations to analysis the radiochemical purity. The results of this analysis are provided in the table below.

| Sample Description | Radiochemical Purity (%) |
|---|---|
| Post dose [$^{14}$C]-Cyprodinil in Formulation Concentrate | 95.8 |
| Post dose [$^{14}$C]-Cyprodinil in Spray Dilution 1 | 96.5 |
| Post dose [$^{14}$C]-Cyprodinil in Spray Dilution 2 | 95.4 |
| Post dose [$^{14}$C]-Prothioconazole in Formulation Concentrate | 96.3 |
| Post dose [$^{14}$C]-Prothioconazole in Spray Dilution 1 | 98.1 |
| Post dose [$^{14}$C]-Prothioconazole in Spray Dilution 2 | 97.0 |
| Post dose [$^{14}$C]-Desthio in Spray Dilution 1 | 99.8 |
| Post dose [$^{14}$C]-Desthio in Spray Dilution 2 | 99.1 |

The results of the radiochemical purity assessment confirmed that the test items were stable over the dosing period in all test preparations.

**Duration of exposure and sampling:** The skin was exposed to the test preparations for 6 hours and receptor fluid samples were collected in hourly fractions from 0 to 6 h post dose and then 2-hourly fractions from 6 to 24 h post dose.

**Terminal exposure (6 h Post Dose)**: The exposure period was terminated at 6 h post dose. Commercial hand wash soap (*ca* 50 µL) was applied to the skin and the soap gently rubbed on the skin with a tissue

swab. The skin was then rinsed with *ca* 5 mL of a *ca* 2% (v/v) commercial soap solution. The soap solution was applied in aliquots (0.5 mL) and each aliquot was aspirated three times with a pipette. The skin was dried with a tissue swab. The process was repeated and the skin was dried with an additional tissue swab.

The soap solution (skin wash) was pooled into a single vial for each cell. This bulk sample was split, the samples mixed with scintillation fluid and analysed by liquid scintillation counting. The tissue swabs were retained separately for analysis in order to investigate the efficacy of the wash procedure. The pipette tip was cut in half and retained. Methanol: scintillation fluid was added to the tissue swabs and pipette tips and samples analysed by liquid scintillation counting. The tissue swab samples were sonicated for *ca* 10 min prior to analysis.

**Terminal post exposure procedure (24 h Post Dose**): After an 18 h monitoring period, *i.e*. at 24 h post dose, the diffusion cells were disconnected from the receptor fluid inlet pump lines and the underside of the skin was rinsed (receptor rinse) with receptor fluid (*ca* 1-2 mL) which was then mixed with scintillation fluid. The receptor rinse represented the absorbed test item, which was in the receptor chamber, but had not been collected into the final receptor fluid fraction. The skin was washed, dried and samples analysed as described above with the exception that the tissue swabs were pooled into a single vial for each cell.
The donor chambers were transferred to a pot containing ethanol (*ca* 15 mL) for the cyprodinil samples and acetone (*ca* 15 mL) for the prothioconazole and desthio samples. Equipment was extracted in solvent for >30 min, before sonication for *ca* 10 min. The equipment was removed from each pot, solvent samples were split into a total of five vials and mixed with scintillation fluid (10 mL for all samples except Cell 55 donor wash aliquot 2 vial, which had 20 mL scintillation fluid added in error. This particular sample was therefore spilt into 2 vials prior to analysis). The skin was removed from each cell and placed on a piece of tissue to remove any remaining receptor fluid from the underside of the skin. This tissue was placed into the receptor chamber wash vial for that particular cell.
The *stratum corneum* was removed with 20 successive tape strips using D-squame® disks. The skin sample was rotated 90° after each tape strip. If any epidermis was removed or if the epidermis/dermis junction became fragile, the rotation of the skin between each tape strip was stopped. Each tape strip was placed into an individual vial containing methanol: scintillation fluid and then analysed by liquid scintillation counting. The skin under the cell flange (unexposed skin) was cut away from the exposed skin. The exposed and unexposed skin samples were placed into separate vials containing Solvable™ (2 mL). The skin samples were placed into a waterbath set to *ca* 60°C to aid solubilisation. Stannous chloride solution (0.2 g/mL in ethanol; 500 µL) and scintillation fluid were added to each skin sample.
The receptor chambers were transferred to a pre-weighed pot containing ethanol (*ca* 40 mL) for the cyprodinil samples and acetone (*ca* 40 mL) for the prothioconazole and desthio samples. Equipment was extracted in the solvent for >30 min, before sonication for *ca* 10 min. The equipment was removed from each pot. Duplicate weighed aliquots (*ca* 1 mL) were collected and mixed with scintillation fluid.
**Analysis:** All components of the test system (e.g. receptor fluid, skin wash, tissue swabs *etc*) were analysed by liquid scintillation counting and the recovery determined.
**Data:** Results of the analysis of the samples of receptor fluid collected in the study were expressed as amounts of [$^{14}$C]-Cyprodinil, [$^{14}$C]-Prothioconazole and [$^{14}$C]-Desthio in the receptor solution in terms of µg equiv./cm$^2$ or ng equiv./cm$^2$, 'percentage of dose absorbed' and rates of absorption (µg equiv./cm$^2$/h or ng equiv./cm$^2$/h). The results of the mass balance and distribution determinations are expressed in terms of amount (µg equiv./cm$^2$ or ng equiv./cm$^2$) and 'percentage of applied dose'.
**Definition of absorbed test material:** The absorbed (systemically available) dose is considered to be the test material detected in the receptor fluid, receptor rinse and receptor chamber wash. Material removed from the surface of the skin by the washing procedure is regarded as unabsorbed. The test material recovered from the skin at the end of the exposure is also considered to be unabsorbed, although it is recognised that a proportion of this material may be absorbed beyond the duration of the exposure investigated in this study.

**RESULTS**

**[$^{14}$C]-Cyprodinil**

**Formulation concentrate:** A total of 6 of the 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Cyprodinil formulation concentrate (225 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples except Cell 3, with the absorption of [$^{14}$C]-Cyprodinil increasing to 24 h. Cell 3 has been excluded from the dataset due to an abnormal receptor fluid profile caused by a suspected leakage. Cell 6 has also been excluded from the dataset due to a potential leakage leading to outlier values for the donor wash, receptor wash and skin samples. Mean mass balance was 100.41% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Cyprodinil from the formulation concentrate through human split-thickness skin was 0.16 µg equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 6-24 h with 0.20 µg equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 3.74 µg equiv./cm$^2$ (0.17% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Spray dilution 1:** A total of 15 of the 16 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Cyprodinil spray dilution 1 (4.5 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Cyrpodinil increasing to 24 h. Cell 15 has been excluded from the dataset due to an outlying unexposed skin value suggesting a potential leakage. Mean mass balance was 100.27% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Cyprodinil from spray dilution 1 through human split-thickness skin was 40.9 ng equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 6-24 h with 44.2 ng equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 981 ng equiv./cm$^2$ (2.00% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Spray Dilution 2:** A total of 15 of the 16 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Cyprodinil spray dilution 2 (1.125 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples except for Cell 28, with the absorption of [$^{14}$C]-Cyprodinil increasing to 24 h. Cell 28 has been excluded from the dataset due to an abnormal receptor fluid profile caused by a suspected leak. Mean mass balance was 97.93% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Cyprodinil from spray dilution 2 through human split-thickness skin was 17.9 ng equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 2-6 h with 20.4 ng equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 429 ng equiv./cm$^2$ (3.45% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**[$^{14}$C]-Prothioconazole**

**Formulation Concentrate:** A total of 5 of the 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Prothioconazole formulation concentrate (75 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Prothioconazole increasing to 24 h. Cells 44 and 46 have been excluded from the dataset due to outlier values for donor chamber wash and unexposed skin samples, resulting from potential contamination. Cell 47 was also excluded from the dataset as an outlier due to suspected leakage. Mean mass balance was 102.01% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Prothioconazole from the formulation concentrate through human split-thickness skin was 0.01 µg equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 6-24 h with 0.015 µg equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 0.31 µg equiv./cm$^2$ (0.04% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Spray Dilution 1:** A total of 7 of the 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Prothioconazole spray dilution 1 (1.5 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Prothi-

oconazole increasing to 24 h. Cell 55 has been excluded from the dataset as a statistical outlier for unexposed skin. Mean mass balance was 99.47% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Prothioconazole from spray dilution 1 through human split-thickness skin was 0.01 µg equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 6-24 h with 0.010 µg equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 0.17 µg equiv./cm$^2$ (1.05% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Spray Dilution 2:** All 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Prothioconazole spray dilution 2 (0.375 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Prothioconazole increasing to 24 h. Mean mass balance was 102.50% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Prothioconazole from spray dilution 2 through human split-thickness skin was 3.47 ng equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 2-6 h with 7.78 ng equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 83.3 ng equiv./cm$^2$ (2.02% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**[$^{14}$C]-Desthio**

**Spray Dilution 1:** All 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Desthio spray dilution 1 (1.5 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Desthio increasing to 24 h. Mean mass balance was 101.60% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Desthio from spray dilution 1 through human split-thickness skin was 0.03 µg equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 2-6 h with 0.06 µg equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 0.72 µg equiv./cm$^2$ (4.64% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Spray Dilution 2:** All 8 samples of human split-thickness skin membranes obtained from 4 different donors dosed topically with [$^{14}$C]-Desthio spray dilution 2 (0.375 g/L) were considered acceptable. Overall, the absorption profiles looked similar for all samples, with the absorption of [$^{14}$C]-Desthio increasing to 24 h. Mean mass balance was 96.51% (Table 7.3-3).
The mean absorption rate of [$^{14}$C]-Desthio from spray dilution 2 through human split-thickness skin was 13.2 ng equiv./cm$^2$/h during the 24 h experimental period; maximum absorption rate was seen at 2-6 h with 33.02 ng equiv./cm$^2$/h (Table 7.3-4). The amount penetrated at 24 h, as measured in the receptor fluid corresponded to 316 ng equiv./cm$^2$ (7.98% of the applied dose). The majority of applied dose were removed with the 6 h and 24 h skin washes. Small amounts remained associated with the skin.

**Table A 2: Dermal absorption of [$^{14}$C]-Cyprodinil, [$^{14}$C]-Prothioconazole and [$^{14}$C]-Desthio as A23282A through human split thickness skin**

| | [$^{14}$C]-Cyprodinil | | | [$^{14}$C]-Prothioconazole | | | [$^{14}$C]-Desthio | |
|---|---|---|---|---|---|---|---|---|
| **Dose group** | **FC** | **SD1** | **SD2** | **FC** | **SD1** | **SD2** | **SD1** | **SD2** |
| Target concentration [g/L] | 225 | 4.5 | 1.125 | 75 | 1.5 | 0.375 | 1.5 | 0.375 |
| Achieved concentration [g/L] | 221 | 4.90 | 1.24 | 76.1 | 1.62 | 0.41 | 1.56 | 0.40 |
| No of cells evaluated | 6 | 15 | 15 | 5 | 7 | 8 | 8 | 8 |
| | **% Applied Dose** | | | | | | | |
| Skin washing after 6 h | 97.94 | 83.26 | 75.12 | 97.87 | 74.83 | 81.54 | 84.25 | 78.29 |
| Skin washing after 24 h | 0.95 | 6.54 | 9.39 | 1.15 | 9.44 | 8.60 | 4.14 | 3.54 |
| Donor chamber wash | 0.19 | 0.71 | 0.77 | 0.52 | 1.17 | 0.77 | 0.70 | 0.48 |
| **Dislodgeable dose** | 99.09 | 90.51 | 85.28 | 99.54 | 85.43 | 90.91 | 89.10 | 82.32 |
| Unexposed skin | 0.03 | 0.10 | 0.38 | 0.42 | 0.56 | 0.28 | 0.96 | 0.56 |
| **Dose associated with exposed skin** | 1.02 | 7.03 | 8.00 | 1.85 | 11.42 | 8.88 | 5.86 | 4.01 |
| Tape strips: 1 – 2 | 0.21 | 0.86 | 1.05 | 0.27 | 1.42 | 1.30 | 0.52 | 0.30 |
| Tape strips: 3 - 20 | 0.33 | 2.00 | 2.44 | 0.92 | 6.70 | 4.93 | 0.83 | 0.70 |
| Exposed skin | 0.48 | 4.17 | 4.52 | 0.67 | 3.30 | 2.64 | 4.50 | 3.01 |
| Receptor fluid | 0.17 | 2.00 | 3.45 | 0.04 | 1.05 | 2.02 | 4.64 | 7.98 |
| Receptor rinse | 0.01 | 0.14 | 0.21 | <0.01 | 0.04 | 0.04 | 0.19 | 0.16 |
| Receptor chamber wash | 0.09 | 0.49 | 0.61 | 0.16 | 0.97 | 0.37 | 0.86 | 1.49 |
| **Absorbed dose** | 0.27 | 2.63 | 4.27 | 0.20 | 2.06 | 2.43 | 5.69 | 9.63 |
| **Total recovery** | 100.41 | 100.27 | 97.93 | 102.01 | 99.47 | 102.50 | 101.60 | 96.51 |

**Table A 3: Absorption rate of [$^{14}$C]-Cyprodinil, [$^{14}$C]-Prothioconazole and [$^{14}$C]-Desthio as A23282A in human split thickness skin**

| Time Period [h] | Absorption Rate [ng or µg equiv./cm$^2$/h] ± SEM | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | [$^{14}$C]-Cyprodinil | | | [$^{14}$C]-Prothioconazole | | | [$^{14}$C]-Desthio | |
| | **FC (µg)** | **SD1 (ng)** | **SD2 (ng)** | **FC (µg)** | **SD1 (µg)** | **SD2 (ng)** | **SD1 (µg)** | **SD2 (ng)** |
| 0-2 | 0.01 ± 0.01 | 8.81 ± 1.96 | 3.34 ± 0.45 | 0.00 ± 0.00 | 0.00 ± 0.00 | 2.51 ± 0.55 | 0.05 ± 0.01 | 17.5 ± 3.64 |
| 2-6 | 0.07 ± 0.05 | 41.7 ± 7.57 | 20.4 ± 3.31 | 0.01 ± 0.00 | 0.01 ± 0.00 | 7.78 ± 1.59 | 0.06 ± 0.01 | 33.0 ± 5.46 |
| 6-24 | 0.20 ± 0.09 | 44.2 ± 3.91 | 18.9 ± 1.04 | 0.01 ± 0.00 | 0.01 ± 0.00 | 2.62 ± 0.54 | 0.02 ± 0.00 | 8.25 ± 1.21 |
| 0-24 | 0.16 ± 0.07 | 40.9 ± 3.89 | 17.9 ± 1.18 | 0.01 ± 0.00 | 0.01 ± 0.00 | 3.47 ± 0.65 | 0.03 ± 0.01 | 13.2 ± 2.04 |

Interpreting the study in compliance with the 2017 EFSA Guidance on Dermal Absorption (EFSA 2017; 15(6):4873)) results in absorption values to be used for human risk assessment of 1.5%, 10% and 13% for the formulation concentrate (225g/L), spray dilution 1 (4.5g/L) and spray dilution 2 (1.125g/L), respectively for Cyprodinil

Interpreting the study in compliance with the EFSA Guidance on Dermal Absorption (2017) results in absorption values to be used for human risk assessment of 2.8%, 16% and 11% for the formulation concentrate (75g/L), spray dilution 1 (1.5g/L) and spray dilution 2 (0.375g/L), respectively for Prothioconazole.

Interpreting the study in compliance with the EFSA Guidance on Dermal Absorption (2017) results in absorption values to be used for human risk assessment of 14% and 16% for the spray dilution 1 (1.5g/L) and spray dilution 2 (0.375g/L), respectively for Desthio.

**Table A 4: Interpretation according to 2017 EFSA Guidance on Dermal Absorption[1]**

| Dose group | [$^{14}$C]-Cyprodinil | | | [$^{14}$C]-Prothioconazole | | | [14C]-Desthio | |
|---|---|---|---|---|---|---|---|---|
| | **FC** | **SD1** | **SD2** | **FC** | **SD1** | **SD2** | **SD1** | **SD2** |
| Target concentration [g/L] | 225 | 4.5 | 1.125 | 75 | 1.5 | 0.375 | 1.5 | 0.375 |
| Achieved concentration [g/L] | 221 | 4.90 | 1.24 | 76.1 | 1.62 | 0.41 | 1.56 | 0.40 |
| No of cells evaluated | 6 | 15 | 15 | 5 | 7 | 8 | 8 | 8 |
| Meets EFSA criteria for exclusion of all tape strips (% absorbed in first 12 h) | N 34.19 | N 49.27 | N 52.30 | N 44.83 | N 56.41 | N 73.18 | N 71.48 | Y* 78.11 |
| Meets EFSA criteria for mass balance (Recovery (%) of applied dose) | Y 100.41 | Y 100.27 | Y 97.93 | Y 102.01 | Y 99.47 | Y 102.50 | Y 101.60 | Y 96.51 |
| Tape strips 3-20 | 0.33 | 2.00 | 2.44 | 0.92 | 6.70 | 4.93 | 0.83 | 0.70* |
| Exposed skin | 0.48 | 4.17 | 4.52 | 0.67 | 3.30 | 2.64 | 4.50 | 3.01 |
| Receptor fluid | 0.17 | 2.00 | 3.45 | 0.04 | 1.05 | 2.02 | 4.64 | 7.98 |
| Receptor rinse | 0.01 | 0.14 | 0.21 | <0.01 | 0.04 | 0.04 | 0.19 | 0.16 |
| Receptor Chamber wash | 0.09 | 0.49 | 0.61 | 0.16 | 0.97 | 0.37 | 0.86 | 1.49 |
| Absorption estimate: mean +/- SD[1] | 1.08 ± 0.45 | 8.80 ± 2.25 | 11.23 ± 2.77 | 1.79 ± 0.86 | 12.07 ± 3.90 | 10.01 ± 1.53 | 11.02 ± 3.01 | 13.34 ± 2.97 |
| k | 1.0 | 0.55 | 0.55 | 1.2 | 0.92 | 0.84 | 0.84 | 0.84 |
| Mean + k*SD | **1.53** | **10.04** | **12.75** | **2.82** | **15.65** | **11.29** | **13.55** | **15.84** |
| **Absorption estimates used for risk assessment[3]** | 1.5 | 10 | 13 | 2.8 | 16 | 11 | 14 | 16 |

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

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

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

* Mean cumulative absorption at t0.5 close to 75%. As a conservative approach, Tape Strips 3-20 were added to the Dermal Absorption calculation and for use in the risk assessment.

Y = Yes, N = No, N/A = not applicable

## CONCLUSION

The study demonstrated that the amount of cyprodinil absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (225 g/L) and the intended in-use dilutions (4.5 g/L and 1.125 g/L) was 0.27%, 2.63%, and 4.27% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.

The study demonstrated that the amount of prothioconazole absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the formulation concentrate (75 g/L) and the intended in-use dilutions (1.5 g/L and 0.375 g/L) was 0.20%, 2.06%, and 2.43% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.

The study demonstrated that the amount of desthio absorbed through human split-thickness skin membranes over 24 h (following a 6 h exposure) from the intended in-use dilutions (1.5 g/L and 0.375 g/L) was 5.69%, and 9.63% of the applied dose, respectively, as measured in the receptor fluid, receptor rinse and receptor chamber wash.

**zRMS**:
Since permeation (in vitro) was essentially not complete at the end of the study, all tape stripped skin material and that in exposed skin, receptor fluid, receptor rinse and receptor Chamber wash was included in the calculation of the absorbable dose fraction, except for Prothioconazole-Desthio: dilution 1/200 (0.375g/L).

Thus, the dermal penetration estimates to be used for risk assessment due to exposure to Cyprodinil is 1.5 % for the concentrated formulation (225 g/L), 10 % for the dilution 1:50 (4.5g/L) and 13% for spray dilution 1/200 (1.125g/L.) based on the EFSA guidance criteria

The dermal penetration estimates to be used for risk assessment due to exposure to Prothioconazole is 2.8 % for the concentrated formulation (75 g/L), 16 % for the dilution 1:50 (1.5g/L) and 11% for spray dilution 1/200 (0.375g/L) based on the EFSA guidance criteria

The dermal penetration estimates to be used for risk assessment due to exposure to Prothioconazole-Desthio is 14 % for the dilution 1:50 (1.5g/L) and 16% for spray dilution 1/200 (0.375g/L) based on the EFSA guidance criteria. The applicant followed a conservative approach for dilution 1/200 (0.375g/L) of Prothioconazole-Desthio and all tape strips were added to the dermal absorption estimate.

## A 2.11 Other/Special Studies

No other studies are submitted with this application.

# Appendix 3 Exposure calculations

## A 3.1 Operator exposure calculations (KCP 7.2.1.1)

### A 3.1.1 Calculations for Cyprodinil

**Table A 5: Input parameters considered for the estimation of operator exposure -cereals**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0.45 kg a.s. /ha | Spray dilution = 1.125 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 1.5 | Dermal for in use dilution = 13 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.03 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./cm$^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 6: Estimation of longer term operator exposure towards cyprodinil according to EFSA guidance – cereals**

**No PPE**

| **Operator Model** | Mixing, loading and application AOEM | | | |
|---|---|---|---|---|
| Potential exposure | Longer term systemic exposure mg/kg bw/day | 0.0333 | % of RVNAS | 110.98% |
| | Acute systemic exposure mg/kg bw/day | 0.1671 | % of RVAAS | Not Applicable |
| Mixing and Loading | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | 0.0215 | % of RVNAS | 71.66% |
| | Acute systemic exposure mg/kg bw/day | 0.1029 | % of RVAAS | Not Applicable |

**Gloves worn for mixing and loading**

| **Operator Model** | | Mixing, loading and application AOEM | | |
|---|---|---|---|---|
| Potential exposure | Longer term systemic exposure mg/kg bw/day | 0.0333 | % of RVNAS | 110.98% |
| | Acute systemic exposure mg/kg bw/day | 0.1671 | % of RVAAS | Not Applicable |
| Mixing and Loading | Gloves = Yes | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | 0.0082 | % of RVNAS | 27.41% |
| | Acute systemic exposure mg/kg bw/day | 0.0538 | % of RVAAS | Not Applicable |

# zRMS calculation of exposure of operator, worker and residents to cyprodinil

| | | | | | |
|---|---|---|---|---|---|
| Substance | cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0,45 kg a.s. /ha | Spray dilution = 1,125 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absoprtion | Dermal for product = 1,5 | Dermal for in use diluation = 13 | Oral = 90 | Inhalation = 100 | |
| RVNAS | 0,03 mg/kg bw/day | | RVAAS | mg/kg bw/day | |
| DFR | 3 µg a.s./cm2 per kg a.s./ha | | DT50 | 30 days | |

| | | | | | |
|---|---|---|---|---|---|
| **Operator Model** | | Mixing, loading and application AOEM | | | |
| Potential exposure | Longer term systemic exposure mg/kg bw/day | | 0,0333 | % of RVNAS | 110,98% |
| | Acute systemic exposure mg/kg bw/day | | 0,1671 | % of RVAAS | |
| Mixing and Loading | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | | 0,0215 | % of RVNAS | 71,66% |
| | Acute systemic exposure mg/kg bw/day | | 0,1029 | % of RVAAS | |

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0,0731 | % of RVNAS | 243,75% |
| | Working clothing mg/kg bw/day | 0,0082 | % of RVNAS | 27,30% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0,0039 | % of RVNAS | 13,15% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0011 | % of RVNAS | 3,57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0012 | % of RVNAS | 3,94% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0099 | % of RVNAS | 32,91% |
| | All pathways (mean) mg/kg bw/day | 0,0120 | % of RVNAS | 39,94% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0,0009 | % of RVNAS | 3,14% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0002 | % of RVNAS | 0,77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0004 | % of RVNAS | 1,33% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0055 | % of RVNAS | 18,28% |
| | All pathways (mean) mg/kg bw/day | 0,0053 | % of RVNAS | 17,81% |

| | | | | | |
|---|---|---|---|---|---|
| Substance | cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0,45 kg a.s. /ha | Spray dilution = 4,5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absoprtion | Dermal for product = 1,5 | Dermal for in use diluation = 10 | Oral = 90 | Inhalation = 100 | |
| RVNAS | 0,03 mg/kg bw/day | | RVAAS | mg/kg bw/day | |
| DFR | 3 µg a.s./cm2 per kg a.s./ha | | DT50 | 30 days | |

| | | | | | |
|---|---|---|---|---|---|
| **Operator Model** | | Mixing, loading and application AOEM | | | |
| Potential exposure | Longer term systemic exposure mg/kg bw/day | | 0,0306 | % of RVNAS | 102,16% |
| | Acute systemic exposure mg/kg bw/day | | 0,1510 | % of RVAAS | |
| Mixing and Loading | | Gloves = Yes | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | | 0,0065 | % of RVNAS | 21,61% |
| | Acute systemic exposure mg/kg bw/day | | 0,0424 | % of RVAAS | |

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0,0563 | % of RVNAS | 187,50% |
| | Working clothing mg/kg bw/day | 0,0063 | % of RVNAS | 21,00% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0,0122 | % of RVNAS | 40,55% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0011 | % of RVNAS | 3,57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0010 | % of RVNAS | 3,28% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0076 | % of RVNAS | 25,31% |
| | All pathways (mean) mg/kg bw/day | 0,0146 | % of RVNAS | 48,55% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0,0029 | % of RVNAS | 9,66% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0002 | % of RVNAS | 0,77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0003 | % of RVNAS | 1,02% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0042 | % of RVNAS | 14,06% |
| | All pathways (mean) mg/kg bw/day | 0,0052 | % of RVNAS | 17,33% |

### A 3.1.2 Calculations for Prothioconazole

**Table A 7: Input parameters considered for the estimation of operator exposure - cereals**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothiocona-zole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0.15 kg a.s. /ha | Spray dilution = 1.5 g a.s./l | Vapour pres-sure = low vol-atile substances having a va-pour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number appli-cations = 1, Application in-terval = 365 days |
| Percentage Absorp-tion | Dermal for product = 2.8 | Dermal for in use dilu-tion = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.2 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

## zRMS calculation of exposure of operator, worker and residents to Prothioconazole

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0,15 kg a.s. /ha | Spray dilution = 1,5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absoprtion | Dermal for product = 2,8 | Dermal for in use diluation = 16 | Oral = 90 | Inhalation = 100 | |
| RVNAS | 0,2 mg/kg bw/day | | RVAAS | mg/kg bw/day | |
| DFR | 3 µg a.s./cm2 per kg a.s./ha | | DT50 | 30 days | |
| | | | | | |
| **Operator Model** | | Mixing, loading and application AOEM | | | |
| Potential exposure | Longer term systemic exposure mg/kg bw/day | | 0,0226 | % of RVNAS | 11,30% |
| | Acute systemic exposure mg/kg bw/day | | 0,1374 | % of RVAAS | |
| Mixing and Loading | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | | 0,0142 | % of RVNAS | 7,09% |
| | Acute systemic exposure mg/kg bw/day | | 0,0691 | % of RVAAS | |
| | | | | | |
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | | 0,0300 | % of RVNAS | 15,00% |
| | Working clothing mg/kg bw/day | | 0,0034 | % of RVNAS | 1,68% |
| | Working clothing and gloves mg/kg bw/day | | | % of RVNAS | |
| | | | | | |
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | | 0,0065 | % of RVNAS | 3,23% |
| | Vapour (75th percentile) mg/kg bw/day | | 0,0011 | % of RVNAS | 0,54% |
| | Surface deposits (75th percentile) mg/kg bw/day | | 0,0005 | % of RVNAS | 0,23% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | | 0,0041 | % of RVNAS | 2,03% |
| | All pathways (mean) mg/kg bw/day | | 0,0082 | % of RVNAS | 4,10% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | | 0,0015 | % of RVNAS | 0,77% |
| | Vapour (75th percentile) mg/kg bw/day | | 0,0002 | % of RVNAS | 0,12% |
| | Surface deposits (75th percentile) mg/kg bw/day | | 0,0002 | % of RVNAS | 0,08% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | | 0,0023 | % of RVNAS | 1,13% |
| | All pathways (mean) mg/kg bw/day | | 0,0029 | % of RVNAS | 1,44% |

**Table A 8: Estimation of longer term operator exposure towards prothioconazole according to EFSA guidance – cereals**

**No PPE**

| **Operator Model** | | Mixing, loading and application AOEM | | |
|---|---|---|---|---|
| Potential exposure | Longer term systemic exposure mg/kg bw/day | 0.0226 | % of RVNAS | 11.30% |
| | Acute systemic exposure mg/kg bw/day | 0.1374 | % of RVAAS | Not Applicable |
| Mixing and Loading | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | 0.0142 | % of RVNAS | 7.09% |
| | Acute systemic exposure mg/kg bw/day | 0.0691 | % of RVAAS | Not Applicable |

**Gloves worn for mixing and loading**

| **Operator Model** | | Mixing, loading and application AOEM | | |
|---|---|---|---|---|
| Potential exposure | Longer term systemic exposure mg/kg bw/day | 0.0226 | % of RVNAS | 11.30% |
| | Acute systemic exposure mg/kg bw/day | 0.1374 | % of RVAAS | Not Applicable |
| Mixing and Loading | Gloves = Yes | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | 0.0036 | % of RVNAS | 1.78% |
| | Acute systemic exposure mg/kg bw/day | 0.0299 | % of RVAAS | Not Applicable |

### A 3.1.3 Calculations for Prothioconazole-desthio

zRMS calculation of exposure of operator, worker and residents to Prothioconazole-desthio assuming 100 % conversion from the parent prothioconazole to the metabolite prothioconazole-desthio. Dermal absorption during mixing and loading was assumed to be 0.0% and during application 16% ( as for dilution 1/200 (0.375g/L)

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole-Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0,136 kg a.s. /ha | Spray dilution = 1,36 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absoprtion | Dermal for product = 0 | Dermal for in use diluation = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0,01 mg/kg bw/day | | RVAAS | mg/kg bw/day | |
| DFR | 3 µg a.s./cm2 per kg a.s./ha | | DT50 | 30 days | |

| | | | | | |
|---|---|---|---|---|---|
| **Operator Model** | | Mixing, loading and application AOEM | | | |
| Potential exposure | Longer term systemic exposure mg/kg bw/day | | 0,0044 | % of RVNAS | 44,19% |
| | Acute systemic exposure mg/kg bw/day | | 0,0335 | % of RVAAS | |
| Mixing and Loading | | Gloves = Yes | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | | 0,0030 | % of RVNAS | 29,56% |
| | Acute systemic exposure mg/kg bw/day | | 0,0258 | % of RVAAS | |

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0,0272 | % of RVNAS | 272,00% |
| | Working clothing mg/kg bw/day | 0,0030 | % of RVNAS | 30,46% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0,0059 | % of RVNAS | 58,65% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0011 | % of RVNAS | 10,70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0004 | % of RVNAS | 4,27% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0037 | % of RVNAS | 36,72% |
| | All pathways (mean) mg/kg bw/day | 0,0075 | % of RVNAS | 75,46% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0,0014 | % of RVNAS | 14,00% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0002 | % of RVNAS | 2,30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0001 | % of RVNAS | 1,48% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0020 | % of RVNAS | 20,40% |
| | All pathways (mean) mg/kg bw/day | 0,0026 | % of RVNAS | 26,31% |

zRMS calculation of exposure of operator, worker and residents to Prothioconazole-desthio assuming, as suggested by some cMSs that there is 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio and this conversion already occurs during mixing with water during mixing and loading. For this conversion 1 kg prothioconazole yields 0.454 kg prothioconazole-desthio. Dermal absorption during mixing and loading was assumed to be 14% ( as for dilution 1:50 1.5 g/L prothioconazole-desthio) and during application 16% ( as for dilution 1/200 (0.375g/L)

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole-Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0,068 kg a.s. /ha | Spray dilution = 0,68 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absoprtion | Dermal for product = 14 | Dermal for in use diluation = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0,01 mg/kg bw/day | | RVAAS | mg/kg bw/day | |
| DFR | 3 µg a.s./cm2 per kg a.s./ha | | DT50 | 30 days | |

| | | | | | |
|---|---|---|---|---|---|
| **Operator Model** | | Mixing, loading and application AOEM | | | |
| Potential exposure | Longer term systemic exposure mg/kg bw/day | | 0,0514 | % of RVNAS | 514,12% |
| | Acute systemic exposure mg/kg bw/day | | 0,3693 | % of RVAAS | |
| Mixing and Loading | | Gloves = Yes | Clothing = Work wear - arms, body and legs covered | RPE = None | Soluble bags = No |
| Application | | Gloves = No | Clothing = Work wear - arms, body and legs covered | RPE = None | Closed cabin = No |
| Exposure (including PPE options above) | Longer term systemic exposure mg/kg bw/day | | 0,0023 | % of RVNAS | 22,75% |
| | Acute systemic exposure mg/kg bw/day | | 0,0207 | % of RVAAS | |

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0,0136 | % of RVNAS | 136,00% |
| | Working clothing mg/kg bw/day | 0,0015 | % of RVNAS | 15,23% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0,0029 | % of RVNAS | 29,32% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0011 | % of RVNAS | 10,70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0002 | % of RVNAS | 2,14% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0018 | % of RVNAS | 18,36% |
| | All pathways (mean) mg/kg bw/day | 0,0043 | % of RVNAS | 43,08% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0,0007 | % of RVNAS | 7,00% |
| | Vapour (75th percentile) mg/kg bw/day | 0,0002 | % of RVNAS | 2,30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0,0001 | % of RVNAS | 0,74% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0,0010 | % of RVNAS | 10,20% |
| | All pathways (mean) mg/kg bw/day | 0,0014 | % of RVNAS | 14,30% |

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

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.13605 kg a.s. /ha | Spray dilution = 0.34 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = NA | Dermal for in use dilution = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.01 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 10: Estimation of longer term operator exposure towards prothioconazole-desthio according to EFSA guidance – cereals**

| Spray Application | Systemic exposure [µg a.s./kg bw/day] |
|---|---|
| **Clothing = Work wear - arms, body and legs covered** | |
| Hands | 2.6895973 |
| Body | 0.0412530 |
| Head | 0.0710769 |
| Inhalation | 0.0450949 |
| Sum | 2.8470221 |

First tier estimates of exposure assume as a theoretical worst case that there is 100% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio. For this conversion 1 kg prothioconazole yields 0.907 kg prothioconazole-desthio. This conversion can only occur after a drying process so for spray operators the exposure assessment only considers exposure from application of the spray solution and not mixing and loading

## A 3.2 Worker exposure calculations (KCP 7.2.3.1)

### A 3.2.1 Calculations for Cyprodinil

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

| | | | | | |
|---|---|---|---|---|---|
| Substance | Cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.45 kg a.s. /ha | Spray dilution = 4.5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 1.5 | Dermal for in use dilution = 10 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.03 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 12: Estimation of longer term worker exposure towards cyprodinil according to EFSA guidance when the minimum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0563 | % of RVNAS | 187.50% |
| | Working clothing mg/kg bw/day | 0.0063 | % of RVNAS | 21.00% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

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

| | | | | | |
|---|---|---|---|---|---|
| Substance | Cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.45 kg a.s. /ha | Spray dilution = 1.125 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 1.5 | Dermal for in use dilution = 13 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.03 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 14: Estimation of longer term worker exposure towards cyprodinil according to EFSA guidance when the maximum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0731 | % of RVNAS | 243.75% |
| | Working clothing mg/kg bw/day | 0.0082 | % of RVNAS | 27.30% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

### A 3.2.2 Calculations for Prothioconazole

**Table A 15: Input parameters considered for the estimation of worker exposure**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.15 kg a.s. /ha | Spray dilution = 1.5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 2.8 | Dermal for in use dilution = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.2 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 16: Estimation of longer term worker exposure towards prothioconazole according to EFSA guidance when the minimum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0300 | % of RVNAS | 15.00% |
| | Working clothing mg/kg bw/day | 0.0034 | % of RVNAS | 1.68% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

**Table A 17: Input parameters considered for the estimation of worker exposure**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.15 kg a.s. /ha | Spray dilution = 0.375 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 2.8 | Dermal for in use dilution = 11 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.2 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 18: Estimation of longer term worker exposure towards prothioconazole according to EFSA guidance when the maximum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0206 | % of RVNAS | 10.31% |
| | Working clothing mg/kg bw/day | 0.0023 | % of RVNAS | 1.16% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

### A 3.2.3 Calculations for Prothioconazole-desthio

**Table A 19: Input parameters considered for the estimation of worker exposure**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.13605 kg a.s. /ha | Spray dilution = 1.36 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = NA | Dermal for in use dilution = 14 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.01 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 20: Estimation of longer term worker exposure towards prothioconazole-desthio according to EFSA guidance when the minimum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0238 | % of RVNAS | 238.00% |
| | Working clothing mg/kg bw/day | 0.0027 | % of RVNAS | 26.66% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

**Table A 21: Input parameters considered for the estimation of worker exposure**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.13605 kg a.s. /ha | Spray dilution = 0.34 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = NA | Dermal for in use dilution = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.01 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 22: Estimation of longer term worker exposure towards prothioconazole-desthio according to EFSA guidance when the maximum water volume is applied**

| | | | | |
|---|---|---|---|---|
| **Worker - Inspection, irrigation** | Potential exposure mg/kg bw/day | 0.0272 | % of RVNAS | 272.00% |
| | Working clothing mg/kg bw/day | 0.0030 | % of RVNAS | 30.46% |
| | Working clothing and gloves mg/kg bw/day | | % of RVNAS | |

## A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

### A 3.3.1 Calculations for Cyprodinil

**Table A 23: Input parameters considered for the estimation of longer term resident exposure when the minimum water volume is applied**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate-0.45 kg a.s. /ha | Spray dilution = 4.5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 1.5 | Dermal for in use dilution = 10 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.03 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not required |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 24: Estimation of longer term resident exposure towards cyprodinil according to EFSA guidance when the minimum water volume is applied**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0122 | % of RVNAS | 40.55% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0010 | % of RVNAS | 3.40% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0076 | % of RVNAS | 25.31% |
| | All pathways (mean) mg/kg bw/day | 0.0146 | % of RVNAS | 48.63% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0029 | % of RVNAS | 9.66% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0003 | % of RVNAS | 1.02% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0042 | % of RVNAS | 14.06% |
| | All pathways (mean) mg/kg bw/day | 0.0052 | % of RVNAS | 17.33% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0061 | % of RVNAS | 20.28% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0005 | % of RVNAS | 1.70% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0076 | % of RVNAS | 25.31% |
| | All pathways (mean) mg/kg bw/day | 0.0109 | % of RVNAS | 36.19% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0014 | % of RVNAS | 4.83% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.51% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0042 | % of RVNAS | 14.06% |
| | All pathways (mean) mg/kg bw/day | 0.0044 | % of RVNAS | 14.65% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0081 | % of RVNAS | 27.01% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0004 | % of RVNAS | 1.40% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0076 | % of RVNAS | 25.31% |
| | All pathways (mean) mg/kg bw/day | 0.0119 | % of RVNAS | 39.81% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 4.90% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.42% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0042 | % of RVNAS | 14.06% |
| | All pathways (mean) mg/kg bw/day | 0.0045 | % of RVNAS | 14.84% |

**Table A 25: Input parameters considered for the estimation of longer term resident exposure when the maximum water volume is applied**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Cyprodinil | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.45 kg a.s. /ha | Spray dilution = 1.125 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 1.5 | Dermal for in use dilution = 13 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.03 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 26: Estimation of longer term resident exposure towards cyprodinil according to EFSA guidance when the maximum water volume is applied**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0039 | % of RVNAS | 13.15% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0012 | % of RVNAS | 4.06% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0099 | % of RVNAS | 32.91% |
| | All pathways (mean) mg/kg bw/day | 0.0120 | % of RVNAS | 40.03% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0009 | % of RVNAS | 3.14% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0004 | % of RVNAS | 1.33% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0055 | % of RVNAS | 18.28% |
| | All pathways (mean) mg/kg bw/day | 0.0053 | % of RVNAS | 17.81% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0020 | % of RVNAS | 6.58% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0006 | % of RVNAS | 2.03% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0099 | % of RVNAS | 32.91% |
| | All pathways (mean) mg/kg bw/day | 0.0105 | % of RVNAS | 34.92% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0005 | % of RVNAS | 1.57% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.66% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0055 | % of RVNAS | 18.28% |
| | All pathways (mean) mg/kg bw/day | 0.0050 | % of RVNAS | 16.58% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0026 | % of RVNAS | 8.76% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 3.57% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0005 | % of RVNAS | 1.67% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0099 | % of RVNAS | 32.91% |
| | All pathways (mean) mg/kg bw/day | 0.0108 | % of RVNAS | 35.96% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0005 | % of RVNAS | 1.59% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.77% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.55% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0055 | % of RVNAS | 18.28% |
| | All pathways (mean) mg/kg bw/day | 0.0050 | % of RVNAS | 16.59% |

### A 3.3.2 Calculations for Prothioconazole

**Table A 27: Input parameters considered for the estimation of longer term resident exposure when the minimum water volume is applied**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.15 kg a.s. /ha | Spray dilution = 1.5 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 2.8 | Dermal for in use dilution = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.2 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 28: Estimation of longer term resident exposure towards prothioconazole according to EFSA guidance when the minimum water volume is applied**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0065 | % of RVNAS | 3.23% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0005 | % of RVNAS | 0.24% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0041 | % of RVNAS | 2.03% |
| | All pathways (mean) mg/kg bw/day | 0.0082 | % of RVNAS | 4.11% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 0.77% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.08% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0023 | % of RVNAS | 1.13% |
| | All pathways (mean) mg/kg bw/day | 0.0029 | % of RVNAS | 1.44% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0032 | % of RVNAS | 1.62% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0041 | % of RVNAS | 2.03% |
| | All pathways (mean) mg/kg bw/day | 0.0063 | % of RVNAS | 3.13% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0008 | % of RVNAS | 0.39% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.04% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0023 | % of RVNAS | 1.13% |
| | All pathways (mean) mg/kg bw/day | 0.0025 | % of RVNAS | 1.23% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0043 | % of RVNAS | 2.15% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.10% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0041 | % of RVNAS | 2.03% |
| | All pathways (mean) mg/kg bw/day | 0.0068 | % of RVNAS | 3.42% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0008 | % of RVNAS | 0.39% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.03% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0023 | % of RVNAS | 1.13% |
| | All pathways (mean) mg/kg bw/day | 0.0025 | % of RVNAS | 1.24% |

**Table A 29: Input parameters considered for the estimation of longer term resident exposure when the maximum water volume is applied**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.15 kg a.s. /ha | Spray dilution = 0.375 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = 2.8 | Dermal for in use dilution = 11 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.2 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not Applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 30: Estimation of longer term resident exposure towards prothioconazole according to EFSA guidance when the maximum water volume is applied**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.56% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0004 | % of RVNAS | 0.18% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0028 | % of RVNAS | 1.39% |
| | All pathways (mean) mg/kg bw/day | 0.0042 | % of RVNAS | 2.09% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0003 | % of RVNAS | 0.13% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.06% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 0.77% |
| | All pathways (mean) mg/kg bw/day | 0.0017 | % of RVNAS | 0.84% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0006 | % of RVNAS | 0.28% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.09% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0028 | % of RVNAS | 1.39% |
| | All pathways (mean) mg/kg bw/day | 0.0037 | % of RVNAS | 1.87% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.07% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.03% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 0.77% |
| | All pathways (mean) mg/kg bw/day | 0.0016 | % of RVNAS | 0.78% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0007 | % of RVNAS | 0.37% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 0.54% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.07% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0028 | % of RVNAS | 1.39% |
| | All pathways (mean) mg/kg bw/day | 0.0038 | % of RVNAS | 1.91% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.07% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 0.12% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0000 | % of RVNAS | 0.02% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 0.77% |
| | All pathways (mean) mg/kg bw/day | 0.0016 | % of RVNAS | 0.78% |

### A 3.3.3 Calculations for Prothioconazole-desthio

**Table A 31: Input parameters considered for the estimation of longer term resident exposure when the minimum water volume is applied**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.13605 kg a.s. /ha | Spray dilution = 1.36 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = NA | Dermal for in use dilution = 14 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.01 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 32: Estimation of longer term resident exposure towards prothioconazole-desthio according to EFSA guidance when the minimum water volume is applied**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0051 | % of RVNAS | 51.35% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0004 | % of RVNAS | 3.88% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0032 | % of RVNAS | 32.13% |
| | All pathways (mean) mg/kg bw/day | 0.0067 | % of RVNAS | 67.49% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0012 | % of RVNAS | 12.25% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 1.30% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0018 | % of RVNAS | 17.85% |
| | All pathways (mean) mg/kg bw/day | 0.0023 | % of RVNAS | 23.31% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0026 | % of RVNAS | 25.68% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 1.94% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0032 | % of RVNAS | 32.13% |
| | All pathways (mean) mg/kg bw/day | 0.0052 | % of RVNAS | 51.90% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0006 | % of RVNAS | 6.13% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.65% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0018 | % of RVNAS | 17.85% |
| | All pathways (mean) mg/kg bw/day | 0.0020 | % of RVNAS | 19.92% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0034 | % of RVNAS | 34.19% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 1.59% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0032 | % of RVNAS | 32.13% |
| | All pathways (mean) mg/kg bw/day | 0.0056 | % of RVNAS | 56.49% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0006 | % of RVNAS | 6.21% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.53% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0018 | % of RVNAS | 17.85% |
| | All pathways (mean) mg/kg bw/day | 0.0020 | % of RVNAS | 20.16% |

**Table A 33: Input parameters considered for the estimation of longer term resident exposure when the maximum water volume is applied - cereals**

| | | | | | |
|---|---|---|---|---|---|
| Substance | Prothioconazole Desthio | Formulation = Soluble concentrates, emulsifiable concentrate, etc. | Application rate- 0.13605 kg a.s. /ha | Spray dilution = 0.34 g a.s./l | Vapour pressure = low volatile substances having a vapour pressure of $<5*10^{-3}$Pa |
| Scenario | Cereals / Outdoor / Downward spraying / Vehicle-mounted | | | Buffer = 2-3 or 5m | Number applications = 1, Application interval = 365 days |
| Percentage Absorption | Dermal for product = NA | Dermal for in use dilution = 16 | Oral = 100 | Inhalation = 100 | |
| RVNAS | 0.01 mg/kg bw/day | | RVAAS | mg/kg bw/day | Not applicable |
| DFR | 3 µg a.s./$cm^2$ per kg a.s./ha | | DT50 | 30 days | |

**Table A 34: Estimation of longer term resident exposure towards prothioconazole-desthio according to EFSA guidance when the maximum water volume is applied - cereals**

**I. No risk mitigation**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0015 | % of RVNAS | 14.66% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0004 | % of RVNAS | 4.27% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0037 | % of RVNAS | 36.72% |
| | All pathways (mean) mg/kg bw/day | 0.0051 | % of RVNAS | 51.19% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0003 | % of RVNAS | 3.50% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 1.48% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0020 | % of RVNAS | 20.40% |
| | All pathways (mean) mg/kg bw/day | 0.0021 | % of RVNAS | 21.32% |

**II. With low drift nozzles**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0007 | % of RVNAS | 7.33% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.14% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0037 | % of RVNAS | 36.72% |
| | All pathways (mean) mg/kg bw/day | 0.0046 | % of RVNAS | 45.59% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 1.75% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.74% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0020 | % of RVNAS | 20.40% |
| | All pathways (mean) mg/kg bw/day | 0.0020 | % of RVNAS | 19.94% |

**III. With 5m buffer zone**

| | | | | |
|---|---|---|---|---|
| **Resident - child** | Spray drift (75th percentile) mg/kg bw/day | 0.0010 | % of RVNAS | 9.76% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0011 | % of RVNAS | 10.70% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 1.75% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0037 | % of RVNAS | 36.72% |
| | All pathways (mean) mg/kg bw/day | 0.0047 | % of RVNAS | 46.75% |
| **Resident - adult** | Spray drift (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 1.77% |
| | Vapour (75th percentile) mg/kg bw/day | 0.0002 | % of RVNAS | 2.30% |
| | Surface deposits (75th percentile) mg/kg bw/day | 0.0001 | % of RVNAS | 0.61% |
| | Entry into treated crops (75th percentile) mg/kg bw/day | 0.0020 | % of RVNAS | 20.40% |
| | All pathways (mean) mg/kg bw/day | 0.0020 | % of RVNAS | 19.96% |

# 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)

None