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| REGISTRATION REPORT  **Part B**  Section 6  Mammalian Toxicology Detailed summary of the risk assessment |
| Product code: IN233C1560  Product name(s): **AVTAR**  Chemical active substances:  Prothioconazole, 250 g/L  Difenoconazole, 130 g/L |
| Central Zone  Zonal Rapporteur Member State: Poland |
| CORE ASSESSMENT  (Authorisation – Article 33) |
| Applicant: XXXX  Submission date: January 2022  Evaluation date: June 2023  MS Finalisation date: February 2024 |

Version history

|  |  |
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| When | What |
| January 2022 | First version of the document |
| June 2023 | Version evaluated by zRMS PL |
| February 2024 | Version revised to take into account comments of cMSs and the applicant |
|  |  |

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# Mammalian Toxicology (KCP 7)

Preliminary remark: According to the EFSA peer review of prothioconazole (EFSA Scientific Report (2007) 106, 1-98), prothioconazole-desthio is considered as a relevant metabolite with toxicity effects which is formed after foliar spray application of prothioconazole containing products. Diluted prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Accordingly, although prothioconazole-desthio is not part of the formulation per se, non-dietary risk assessments are always performed for prothioconazole-desthio due to its toxicological properties.

Since the conversion rate of prothioconazole to prothioconazole-desthio is not known, a conservative approach was applied in the framework of this dossier. For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio was assumed. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio).

## Summary

Table 6.1‑1: Information on IN233C1560/ AVTAR \*

|  |  |
| --- | --- |
| Product name and code | IN233C1560/ AVTAR |
| Formulation type | Emilsifiable concentrate EC |
| Active substance(s) (incl. content) | Prothioconazole, 250 g/L  Difenoconazole, 130 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 IN233C1560/ AVTAR 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 IN233C1560 / AVTAR according to Regulation (EC) No 1272/2008

|  |  |
| --- | --- |
| Hazard class(es), categories | Eye irritation (Category 2)  Skin irritation ( Category 2)  Carcinogenicity (category 2)  Aquatic Chronic (Category 3) |
| Hazard pictograms or Code(s) for hazard pictogram(s) | GHS 07 GHS 08 |
| Signal word | Warning |
| Hazard statement(s) | **H315:** Causes skin irritation  **H319:** Causes serious eye irritation.  **H351:** Suspected of causing cancer  **H412:** Harmful to aquatic life with long lasting effects |
| Precautionary statement(s) | **P201:** Obtain special instructions before use.  **P202:** Do not handle until all safety precautions have been read and understood  **~~P261:~~** ~~Avoid breathing mist/vapours~~  **~~P271:~~** ~~Use only outdoors or in a well-ventilated area~~.  **P273:** Avoid release to the environment, if this is not the intended use  **P264:** Wash face and hands thoroughly after handling.  **P280:** Wear protective gloves/protective clothing/eye protection/face protection.  **~~P304 + P340: IF INHALED:~~** ~~Remove person to fresh air and keep comfortable for breathing~~.  **~~P311~~**~~: Call a POISON CENTER/doctor/...~~  **~~P321:~~** ~~Specific treatment (see … on this label~~)  **P302 + P352:** IF ON SKIN: Wash with plenty of water  **P332 + P313:** If skin irritation occurs: Get medical advice/attention  **P362 + P364:** Take off contaminated clothing and wash it before reuse  **P308 + P313:** IF exposed or concerned: Get medical advice /attention.  **~~P321:~~** ~~Specific treatment (see … on this label)~~  **P305+P351+P338:** IF IN EYES: Rinse cautiously with water for several minutes. Rem contact lenses, if present and easy to do. Continue rinsing. **P337+P313:** If eye irritation persists: Get medical advice/attention.  **P405:** Store locked up.  **P501:** Dispose of contents/ container in accordance with local/ regional/ national/international regulation |
| Additional labelling phrases | To avoid risks to human health and the environment, comply with the instructions for use. [EUH401] |

Table 6.1‑3: Summary of risk assessment for operators, workers, residents and bystanders for product IN233C1560/ AVTAR

|  | Result | PPE / Risk mitigation measures |
| --- | --- | --- |
| Operators | Acceptable | Vehicle-mounted application ~~with a drift reduction nozzle~~.  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 | Acceptable | None |
| Residents | Acceptable | None |
| Bystanders | Acceptable | None |

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

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table. These critical uses cover the other intended uses on barley, triticale, rye and oats ( see partB0) since rate and method of application are the same.

**zRMS**:

***Assuming 50% conversion from the parent prothioconazole to the metabolite prothioconazole-desthio:***

**Operators.** The application of a product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator using tractor-mounted/trailed boom sprayer without drift reduction technology for application of the product in line with its intended use within good agricultural practice providing that he is wearing a work wear (with arms, body and legs covered) and protective gloves during M/L. It is noted that the product is classified as Skin Irrit. 2 and Eye Irrit 2 thus the operator should wear a 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 IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology in line with GAP does not pose an unacceptable health risk for worker wearing a work wear (with arms, body and legs covered) and entering a treated field for 2hrs inspection after a spray has dried up.

**Residents:**

The application of application of a product IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology in line with GAP does not pose an unacceptable health risk for residents and bystanders.

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) a.s. 1 b) a.s. 2 | Water L/ha  min / max | Operator | Worker | Residents | Bystander |
| 1 | Wheat  Cereals  BBCH 25-69 | F | foliar spray | 2 (14 ) | a) Prothioconazole 0.175 b) Difenoconazole 0.091 | 100-400 | NA | 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 |  |  |  |  |
| 8 | Oilseed rape  Spring: just before mid-flowering (anticipating any significant petal fall)  Autumn: At the first sign of disease  [ Until BBCH 69.or BBCH 14 - 69 ] | F | foliar spray | 2 (14 ) | a) Prothioconazole 0.150 +  b) Difenoconazole 0.078 | 100-500 | NA |  |  |  |  |

\* 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:

* No data gap

## Toxicological Information on Active Substance(s)

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

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

|  | Prothioconazole | Difenoconazole |
| --- | --- | --- |
| Common Name | Prothioconazole | Difenoconazole |
| CAS-No. | 178928-70-6 | 119446-68-3 |
| Classification and proposed labelling | | |
| With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended) | Hazard classes (s), categories: -  Code(s) for hazard pictogram(s): -  Signal word: -  Hazard statement(s): -  Precautionary statement(s): - | Hazard classes (s), categories:  - Acute Toxicity (Category 4)  - Eye irritation (Category 2)  - Carcinogenicity (category 2);  Code(s) for hazard pictogram(s):  - GHS07, GHS08  Signal word:  - Warning  Hazard statement(s):  - H302: Harmful if swallowed  - H319: Causes serious eye irritation  - H351: Suspected of causing cancer    Precautionary statement(s):  - P201: Obtain special instructions before use.  - P202: Do not handle until all safety precautions have been read and understood  - P270: Do not eat, drink or smoke when using this product.  - P280: Wear protective gloves/protective clothing/eye protection/face protection.  - P301+P312: IF SWALLOWED: Call a POISON Center or doctor/physician if you fee unwell.  - P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Rem contact lenses, if present and easy to do. Continue rinsing.  - P308 + P313: IF exposed or concerned: Get medical advice /attention.  - P337+P313: If eye irritation persists: Get medical advice/attention.  - P405: Store locked up.  - P501: Dispose of contents/ container in accordance with local/ regional/ national/international regulation |
| Additional C&L proposal | None | None |
| Agreed EU endpoints | | |
| AOEL systemic | 0.2 mg/kg bw/d | 0.16 mg/kg bw/d |
| ARfD | 0.01 mg/kg bw/d | 0.16 mg/kg bw/d |
| Reference | Review report (SANCO/3923/07/  26 January 2021)  RAC ECHA opinion adopted on 15 March 2019 | Review report (SANCO/830/08/  18 May 2020)  RAC ECHA opinion adopted on 10 June 2021 |
| Conditions to take into account/critical areas of concern with regard to toxicology | | |
| According to Review Report for active substance | * The operator safety in spray applications. Conditions of use should include adequate protective measures; * The protection of aquatic organisms. Risk mitigation measures such as buffer zones should be applied, where appropriate; * The protection of birds and small mammals. Risk mitigation measures should be applied, where appropriate. | Member States must pay particular attention to the protection of aquatic organisms. Conditions of use shall include adequate risk mitigation measures, where appropriate. |

## Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for AVTAR 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 AVTAR

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Type of test, species, model system (Guideline) | Result | Acceptability | Classification  (acc. to the criteria in Reg. 1272/2008) | Reference |
| LD50 oral | N/A | Yes | None | Classification by calculation |
| LD50 dermal | N/A | Yes | None | Classification by calculation |
| LC50 inhalation | N/A | Yes | None  ~~Acute Tox. Inhalation Category 3 (H331)~~ | Classification by calculation |
| Skin irritation, Reconstructed Human Epidermis  (OECD 439) | Irritant | Yes | Skin Irrit. 2; H315 | Cattaneo A., 2021  KCP 7.1.4/01 |
| Skin corrosion, Reconstructed Human Epidermis  (OECD 431) | Non corrosive | Yes | None | Cattaneo A., 2021  KCP 7.1.4/02 |
| Eye irritation, Bovine  (OECD 437) | Irritant | Yes | Eye Irrt. 2; H319 | Cattaneo A., 2021  KCP 7.1.5/01 |
| Eye irritation & corrosion | None | Yes | None | Cattaneo A., 2021  KCP 7.1.5/02 |
| Skin sensitisation | N/A | Yes | None | Classification by calculation |
| Supplementary studies for combinations of plant protection products | Not required |  |  |  |

N/A = not applicable

Table 6.3‑2: Additional toxicological information relevant for classification/labelling of AVTAR

|  | 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) | Difenoconazole  (CAS No. 119446-68-3, ≈11.40% (w/w)) | H302 Acute Tox. 4  H319 Eye Irritation 2 | MSDS\*\* | H319 Eye Irrit. 2  ~~H302 Acute tox. 4~~ |
| Difenoconazole  (CAS No. 119446-68-3, ≈11.40% (w/w)) | Carc. 2, H351  Acute Tox. 4; H302  Eye Irrit. 2, H319 | RAC opinion adopted on  10 June 2021 | Eye Irrit. 2, H319  Carc. 2; H351 Suspected of causing cancer |
| Prothioconazole  (CAS No. 178928-70-6, ≈ 21.94%(w/w)) | None | MSDS\*\* | None |
| Toxicological properties of non-active substance(s) (relevant for classification of product) | Geronol TE 777  (20-30% (w/w)) | H315: Causes skin irritation. | MSDS\*\* | H315: Causes skin irritation according to in vitro studies performed on the product |
| H318: Causes serious eye damage. | MSDS\*\* | ~~H318: Causes serious eye damage according to in vitro studies performed on the product~~  Eye Irrit. 2, H319 Causes serious eye irritation -  based on calculation and in vitro studies |
| Further toxicological information | No data – not required | / | / | / |

\*\*Material safety data sheet by the applicant

## Toxicological Evaluation of Groundwater Metabolites

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

## Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in AVTAR is presented in the following table. According to the EFSA peer review of prothioconazole (EFSA Scientific Report (2007) 106, 1-98), the main metabolite prothioconazole-desthio (also named M04) is considered as toxicologically relevant. Therefore, the dermal absorption rate of this molecule has also been determined and is presented in the following table.

Table 6.5‑1: Dermal absorption rates for active substances in AVTAR

|  | Prothioconazole | | Prothioconazole-desthio | | Difenoconazole | |
| --- | --- | --- | --- | --- | --- | --- |
|  | Value | Reference | Value | Reference | Value | Reference |
| Concentrate | ~~0.28%~~  0.3% | Nagane, 2021a | 0 % | Nagane, 2021b | 3.1% | Nagane, 2021c |
| Dilution | ~~14%~~  15% | Nagane, 2021a | Dilution-1: ~~11%~~ 12%  Dilution-2: 13% | Nagane, 2021b | 22% | Nagane, 2021c |

**Remark:**

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

* For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio was assumed. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 was applied (based on a molecular weight of 344.254 g/mol for prothioconazole and 312.194 g/mol for prothioconazole-desthio).
* Formation of prothioconazole-desthio is not expected in the concentrate, thus during the mixing and loading task dermal absorption of prothioconazole-desthio was not considered and a dermal absorption value of 0% was applied to remove this from calculation.
* No conversion of prothioconazole to prothioconazole-desthio was considered for the exposure assessment of prothioconazole.

Therefore, to assess dermal absorption of prothioconazole-desthio, two concentrations have been tested:

1. Test preparation I - as an aqueous spray dilution-1 [0.7 L of AVTAR mixed with 100 L of water (1:143)] i.e., 159 g prothioconazole-desthio in 100 L of water gives 1.59 g prothioconazole-desthio/L and
2. Test preparation II - as an aqueous spray dilution-2 [0.7 L of AVTAR mixed with 400 L of water (1:571)] i.e., 159 g prothioconazole-desthio in 400 L of water gives 0.40 g prothioconazole-desthio/L.

### Justification for proposed values – Prothioconazole

Proposed dermal absorption rates for prothioconazole are based on dermal absorption studies on a formulation identical to AVTAR. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of formulation that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5‑2: Summary of the results of submitted dermal absorption studies for prothioconazole

| Test | Concentrate  (250 g /L) | Spray dilution  (0.44 g/L) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| In-vivo (human) | ~~0.28%~~  0.3% | ~~14%~~  15% | IN233C1560/ AVTAR | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product. | Nagane, 2021a |

### Justification for proposed values – Prothioconazole-desthio

Proposed dermal absorption rates for prothioconazole-desthio are based on dermal absorption studies on a formulation identical to AVTAR. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of formulation that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5‑3: Summary of the results of submitted dermal absorption studies for prothioconazole-desthio

| Test | Concentrate | Spray dilution | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| In-vivo (human) | 0% | Dilution-1(1:143)]: ~~11%~~ 12%  Dilution-2 (1:571): 13% | IN233C1560/ AVTAR | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product. | Nagane, 2021b |

### Justification for proposed values - difenoconazole

Proposed dermal absorption rates for difenoconazole are based on dermal absorption studies on a formulation identical to AVTAR. The study results are summarised in the following table. Full summaries of studies on the dermal absorption of formulation that have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5‑3: Summary of the results of submitted dermal absorption studies for difenoconazole

| Test | Concentrate | Spray dilution  (0.23 g/L) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| In-vivo (human) | 3.1% | 22 % | IN233C1560/ AVTAR | Yes | Yes (see Appendix A 2.10) | Justification accepted. Endpoint can be used for current product | Nagane, 2021c |

## Exposure Assessment of Plant Protection Product (KCP 7.2)

According to the EFSA peer review of prothioconazole (EFSA Scientific Report (2007) 106, 1-98), the main metabolite prothioconazole-desthio (also named M04) is considered as toxicologically relevant. Indeed, diluted prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Accordingly, although prothioconazole-desthio is not part of the formulation per se, non-dietary risk assessments are always performed for prothioconazole-desthio due to its toxicological properties. For this risk assessment the worst-case dermal absorption (13% corresponding to the dilution-2) is used.

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

|  |  |  |  |
| --- | --- | --- | --- |
| Product name and code | IN233C1560 / AVTAR | | |
| Formulation type | EC | | |
| Category | Fungicide | | |
| Active substance(s) (incl. content) | **Prothioconazole**  250 g/L | **Prothioconazole-desthio**  226.75 g/L | **Difenoconazole**  130 g/L |
| AOEL systemic | 0.2 mg/kg bw/d | **~~ARfD for Prothioconazole~~**  EFSA Scientific Report (2007) 106, 1-98  0.01 mg/kg bw/d | 0.16 mg/kg bw/d |
| ~~AAOEL~~ | ~~0.01 mg/kg bw/d~~ | ~~0.01 mg/kg bw/d~~ | ~~0.16 mg/kg bw/d~~ |
| Inhalation absorption | 100% | 100% | 100% |
| Oral absorption | 100% | 100% | 100% |
| Dermal absorption | Concentrate: ~~0.28%~~ 0.3%  Dilution: ~~14%~~ 15% | Concentrate: 0%  Dilution-1: ~~11%~~  12%  Dilution-2: 13%\* | Concentrate: 3.1%  Dilution: 22% |

\* Dilution-2 will be used in the risk assessment as a worst-case

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

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

Justification

The risk for the uses barley, triticale, rye and oats is covered by the risk assessment conducted on wheat. Only the risk assessment on wheat and oilseed rape is therefore provided.

#### Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of AVTAR according to the critical uses is presented in Table 6.6‑2. The outcome of the estimation is presented in Table 6.6‑3 (acute exposure) and NR = not required

Table 6.6‑4 (longer term exposure). Detailed calculations are in Appendix 3.

On the request of cMS additional

Table 6.6‑2: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Cereal (max 0.7 L of AVTAR/ha per application)  Oilseed rape (max 0.6 L of AVTAR/ha per application) |
| Model(s) | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874  calculator version: 30/03/2015 |

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ~~Difenoconazole~~ | | ~~Prothioconazole~~ | | ~~Prothioconazole-desthio~~ | |
| ~~Model data~~ | ~~Level of PPE~~ | ~~Total absorbed dose  (mg/kg/day)~~ | ~~% of systemic AAOEL~~ | ~~Total absorbed dose  (mg/kg/day)~~ | ~~% of systemic AAOEL~~ | ~~Total absorbed dose  (mg/kg/day)~~ | ~~% of systemic AAOEL~~ |
| ~~Tractor mounted with drift reduction boom spray application outdoors to low crops~~ | | | | | | | |
| ~~Cereals~~ | | | | | | | |
| ~~Application rate~~ | | ~~0.091 kg a.s./ha~~ | | ~~0.175 kg a.s./ha~~ | | ~~0.159 kg a.s./ha~~ | |
| **~~Spray application outdoor~~** ~~(AOEM~~**~~;~~** ~~95~~~~th~~ ~~percentile)~~  ~~Body weight: 60 kg~~ | ~~Potential exposure~~ | ~~0.0954~~ | ~~59.63~~ | ~~0.0182~~ | **~~182.06~~** | ~~0.0064~~ | ~~63.69~~ |
| ~~Work wear (arms, body and legs covered) M/L and A~~ | ~~0.0377~~ | ~~23.59~~ | ~~0.0117~~ | **~~116.96~~** | ~~0.0061~~ | ~~61.52~~ |
| ~~Work wear (arms, body and legs covered) M/L and A + gloves during M/L~~ | ~~0.0083~~ | ~~5.18~~ | ~~0.0073~~ | ~~72.81~~ | ~~0.0061~~ | ~~61.52~~ |
| ~~Oilseed rape~~ | | | | | | | |
| ~~Application rate~~ | | ~~0.078 kg a.s./ha~~ | | ~~0.150 kg a.s./ha~~ | | ~~0.136 kg a.s./ha~~ | |
| **~~Spray application outdoor~~** ~~(AOEM~~**~~;~~** ~~95~~~~th~~ ~~percentile)~~  ~~Body weight: 60 kg~~ | ~~Potential exposure~~ | ~~0.0887~~ | ~~55.43~~ | ~~0.0167~~ | **~~166.70~~** | ~~0.0057~~ | ~~57.26~~ |
| ~~Work wear (arms, body and legs covered) M/L and A~~ | ~~0.0335~~ | ~~20.96~~ | ~~0.0105~~ | **~~104.65~~** | ~~0.0055~~ | ~~55.40~~ |
| ~~Work wear (arms, body and legs covered) M/L and A + gloves during M/L~~ | ~~0.0074~~ | ~~4.63~~ | ~~0.0065~~ | ~~65.47~~ | ~~0.0055~~ | ~~55.40~~ |

NR = not required

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | 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 | Total absorbed dose  (mg/kg/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to low crops with drift reduction technology | | | | | | | |
| Cereals | | | | | | | |
| Application rate | | 0.091 kg a.s./ha | | 0.175 kg a.s./ha | | 0.159 kg a.s./ha | |
| **Spray application** (AOEM**;** 75th percentile)  Body weight: 60 kg | Potential exposure | 0.0149 | 9.33 | 0.0037 | 1.86 | 0.0015 | 14.74 |
| Work wear (arms, body and legs covered) M/L and A | 0.0094 | 5.89 | 0.0027 | 1.35 | 0.0013 | 12.60 |
| Work wear (arms, body and legs covered) M/L and A + gloves during M/L | 0.0014 | 0.88 | 0.0015 | 0.75 | 0.0013 | 12.60 |
| **Spray application** (AOEM**;** 75th percentile)  Body weight: 60 kg | Potential exposure taking dermal absorption of prothioconazole from the concentrate 0.3% and from dilution 15% | - | - | 0.0039 | 1.98 |  |  |
|  | Work wear (arms, body and legs covered) M/L and A + gloves during M/L |  |  | 0.0016 | 0.80 |  |  |
|  |  |  |  |  |  |  |  |
| Oilseed rape | | | | | | | |
| Application rate | | 0.078 kg a.s./ha | | 0.150 kg a.s./ha | | 0.136 kg a.s./ha | |
| **Spray application outdoor** (AOEM**;** 95th percentile)  Body weight: 60 kg | Potential exposure | 0.1327 | 8.30 | 0.0033 | 1.63 | 0.0013 | 12.76 |
| Work wear (arms, body and legs covered) M/L and A | 0.0083 | 5.21 | 0.0024 | 1.18 | 0.0011 | 10.92 |
| Work wear (arms, body and legs covered) M/L and A + gloves during M/L | 0.0012 | 0.77 | 0.0013 | 0.65 | 0.0011 | 10.92 |
| Potential exposure taking dermal absorption of prothioconazole from the concnetrate 0.3% and from dilution 15% |  |  | 0.0035 | 1.74% |  |  |
| Work wear (arms, body and legs covered) M/L and A + gloves during M/L |  |  | 0.0014 | 0.69 |  |  |

NR = not required

**zRMS**:

The estimation of potential exposure of operator and of operator wearing a work wear (with arms, body and legs covered) and protective gloves to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of operator and an exposure of operator wearing a work wear (with arms, body and legs covered) and gloves is equal respectively to 9.33% and to 0.88% of AOEL for Difenconazole, and to 1.98% and to 0.80 % of AOEL for Prothioconazole, and to 14.74 % and 12.60 % of ARfD for Prothioconazole used as AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of potential exposure of operator and exposure of operator wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator applying a product IN233C1560 / AVTAR on a field of cereals according to its intended use on cereals within good agricultural practice.

The estimation of potential exposure of operator and of operator wearing a work wear (with arms, body and legs covered) and protective gloves to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of operator and an exposure of operator wearing a work wear (with arms, body and legs covered) and gloves is equal respectively to 8.30% and to 0.0012% of AOEL for Difenconazole, and to 1.74% and to 0.69 % of AOEL for Prothioconazole, and to 12.76 % and 10.92 % of ARfD for Prothioconazole used as surrogate AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of potential exposure of operator and exposure of operator wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator applying a product IN233C1560 / AVTAR on a field of oilseed rape according to its intended use on cereals within good agricultural practice.

No operator acute exposure estimation for Difenconazole and for Prothioconazole is required since no acute acceptable operator exposure value (AAOEL) has be set for any of this active substance nor for metabolite Prothioconazole-desthio. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for operator due to short-term single exposure to Difenconazole and to Prothioconazole, and to metabolite Prothioconazole-desthio as a result of application of a product IN233C1560 / AVTAR with accordance with intended use within good agricultural practice.

Summing up the application of a product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator using tractor-mounted/trailed boom sprayer with drift reduction technology for application of the product in line with its intended use within good agricultural practice. Since the product classified as Skin Irrit. 2 and Eye Irrit 2 the operator should wear a 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.

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

On the request of commenting Member States the additional calculations of operator, worker and resident was provided assuming application of the product for cereals and oilseed rape without vehicle-mounted-drift reduction, assuming use of 100 L of water, a minimal volume of water proposed by the applicant. 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 during mixing with water during mixing and loading. For this conversion 1 kg prothioconazole yields 0.454 kg prothioconazole-desthio. Dermal absorption of prothioconazole-desthio during mixing and loading was assumed to be 12%) and during application 13 %.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | 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 | Total absorbed dose  (mg/kg/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to low crops **without d**rift reduction technology | | | | | | | |
| **Cereals** | | | | | | | |
| Application rate | | 0.091 kg a.s./ha | | 0.00875 kg a.s./ha  (0.175 kg a.s./ha x 0.5= 0.00875 kg a.s./ha) | | 0.0795 kg a.s./ha  ( 0.159 kg a.s./ha x 0.5 = 0.0795 kg a.s./ha | |
| **Spray application** (AOEM**;** 75th percentile)  Body weight: 60 kg | Potential exposure | 0.01756 | 10.99 | 0.00397 | 1.99 | 0.04949 | **494.91** |
| Work wear (arms, body and legs covered) M/L and A | 0.01094 | 6.84 | 0.00259 | 1.30 | 0.03013 | **301.37%** |
| Work wear (arms, body and legs covered) M/L and A + gloves during M/L | 0.00293 | 1.83 | 0.001842 | 0.92 | 0.00220 | 22.01% |
| **Oilseed rape** | | | | | | | |
| Application rate | | 0.078 kg a.s./ha | | 0.075 kg a.s./ha  (0.150 kg a.s./ha x 0.5= 0.075 kg a.s./ha) | | 0.068 kg a.s./ha  (0.136 kg a.s./ha x 0.5= 0.068 kg a.s./ha) | |
| **Spray application outdoor** (AOEM**;** 95th percentile)  Body weight: 60 kg | Potential exposure | 0.01555 | 9.72 | 0.00346 | 1.73 | 0.04398 | **439.89** |
| Work wear (arms, body and legs covered) M/L and A | 0.00964 | 6.02 | 0.00225 | 1.13 | 0.02667 | **266.72** |
| Work wear (arms, body and legs covered) M/L and A + gloves during M/L | 0.00252 | 1.58 | 0.00159 | 0.80 | 0.001905 | 19.05 |

**zRMS**:

The estimation of potential exposure of operator and of operator wearing a work wear (with arms, body and legs covered) and protective gloves to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of operator and an exposure of operator wearing a work wear (with arms, body and legs covered) and gloves is equal respectively to 10.99% and to 1.83% of AOEL for Difenconazole, and to 1.99% and to 0.92 % of AOEL for Prothioconazole, and to 494,91 % and 22.01 % of AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures ( 1.83% + 0.92 % + 22.01%) of operator wearing a work wear (with arms, body and legs covered) and protective gloves durng M/L to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator applying a product IN233C1560 / AVTAR on a field of cereals according to its intended use on cereals within good agricultural practice providing that they use these PPE.

The estimation of potential exposure of operator and of operator wearing a work wear (with arms, body and legs covered) and protective gloves to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of operator and an exposure of operator wearing a work wear (with arms, body and legs covered) and gloves is equal respectively to 9.72% and to 1.58 2% of AOEL for Difenconazole, and to 1.73% and to 0.80 % of AOEL for Prothioconazole, and to 439.89 % and 19.05 % of AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of operator (1.58% + 0.80% + 19.05%) wearing a work wear (with arms, body and legs covered) and protective gloves during M/L to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator applying a product IN233C1560 / AVTAR on a field of oilseed rape according to its intended use on cereals within good agricultural practice providing that they use these PPE.

No operator acute exposure estimation for Difenconazole and for Prothioconazole is required since no acute acceptable operator exposure value (AAOEL) has be set for any of this active substance nor for metabolite Prothioconazole-desthio. Therefore, as indicated in the EU guidance (SANTE-10832-2015 rev. 1.7; 24 January 2017), no unacceptable risk is expected for operator due to short-term single exposure to Difenconazole and to Prothioconazole, and to metabolite Prothioconazole-desthio as a result of application of a product IN233C1560 / AVTAR with accordance with intended use within good agricultural practice.

Summing up the application of a product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of operator using tractor-mounted/trailed boom sprayer for application of the product in line with its intended use within good agricultural practice providing that he is wearing a work wear (with arms, body and legs covered) and protective gloves during M/L. It is noted that the product is classified as Skin Irrit. 2 and Eye Irrit 2 the operator should wear a 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.

#### Measurement of operator exposure

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

### Worker exposure (KCP 7.2.3)

#### 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 AVTAR according to the critical use. Outcome of the estimation is presented in Table 6.6‑6. Detailed calculations are in Appendix 3.

Table 6.6‑5: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Cereal (max 0.7 L of AVTAR/ha per application)  Oilseed rape (max 0.6 L of AVTAR/ha per application) |
| Model | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874  calculator version: 30/03/2015 |

Table 6.6‑6: Estimated worker exposure

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | Prothioconazole | | Prothioconazole-desthio | |
| **Model data** | Level of PPE | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL |
| Inspection, Irrigation  Outdoor  Work rate: 2 hours/day  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha | | | | | | | |
| Cereals | | | | | | | |
| Application rate | | 0.091 kg a.s./ha | | 0.175 kg a.s./ha | | 0.159 kg a.s./ha | |
| Body weight: 60 kg | Potential  TC:12500cm2/person/h | 0.0431 | 26.96 | 0.0528 | 26.39 | 0.0445 | **445.34** |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.0048 | 3.02 | 0.0059 | 2.96 | 0.0050 | 49.88 |
| Potential  TC:12500cm2/person/h assuming dermal absorption of prothioconazole from concentrate 0.3% and from dilution 15% | - | - | 0.0565 | 28.28% |  |  |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h  assuming dermal absorption of prothioconazole from concentrate 0.3% and from dilution 15% | - | - | 0.0063 | 3.17% |  |  |
| Oilseed rape | | | | | | | |
| Application rate | | 0.078 kg a.s./ha | | 0.150 kg a.s./ha | | 0.136 kg a.s./ha | |
| Body weight: 60 kg | Potential  TC:12500cm2/person/h | 0.0370 | 23.11 | 0.0452 | 22.62 | 0.0381 | **380.92** |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.0041 | 2.59 | 0.0051 | 2.53 | 0.0043 | 42.66 |
| Potential  TC:12500cm2/person/h assuming dermal absorption of prothioconazole from concentrate 0.3% and from dilution 15% | - | - | 0.0485 | 24.24% |  |  |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h  assuming dermal absorption of prothioconazole from concentrate 0.3% and from dilution 15% | - | - | 0.0054 | 2.71% |  |  |

**zRMS**:

The estimation of potential exposure of worker and of worker wearing a work wear (with arms, body and legs covered) to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of worker and an exposure of worker wearing a work wear (with arms, body and legs covered) is equal respectively to 29.96% and to 3.02% of AOEL for Difenconazole, and to 28.28% and to 3.17 % of AOEL for Prothioconazole, and to 445.34% and 49.88% of ARfD for Prothioconazole used as AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of worker wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of worker entering for 2hrs inspection a field of cereals treated with a product IN233C1560 / AVTAR according to its intended use on cereals within good agricultural practice.

The estimation of potential exposure of worker and of worker wearing a work wear (with arms, body and legs covered) to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of worker and an exposure of worker wearing a work wear (with arms, body and legs covered) is equal respectively to 23.11% and to 2.59% of AOEL for Difenconazole, and to 24.24 % and to 2.71 % of AOEL for Prothioconazole, and to 380.92% and 42.66% of ARfD for Prothioconazole used as AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of worker wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of worker entering for 2hrs inspection a field of oilseed rape treated with a product IN233C1560 / AVTAR according to its intended use on oilseed rape within good agricultural practice.

Summing up application of a product IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology in line with GAP does not pose an unacceptable health risk for worker entering a treated field for 2hrs inspection after a spray has dried up.

Table 6.6‑6A: Estimated worker exposure

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | Prothioconazole | | Prothioconazole-desthio | |
| **Model data** | Level of PPE | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AAOEL |
| Inspection, Irrigation  Outdoor  Work rate: 2 hours/day  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha | | | | | | | |
| Cereals | | | | | | | |
| Application rate | | 0.091 kg a.s./ha | | 0.0875 kg a.s./ha  (0.175 kg a.s./ha x 0.5= 0.00875 kg a.s./ha) | | 0.0795 kg a.s./ha  ( 0.159 kg a.s./ha x 0.5 = 0.0795 kg a.s./ha | |
| Body weight: 60 kg | Potential  TC:12500cm2/person/h | 0.0431 | 26.96 | 0.0282 | 14.14 | 0.02226 | **222.67** |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.00048 | 3.02 | 0.0032 | 1.58 | 0.00249 | 24.94 |
| Oilseed rape | | | | | | | |
| Application rate | | 0.078 kg a.s./ha | | 0.075 kg a.s./ha  (0.150 kg a.s./ha x 0.5= 0.075 kg a.s./ha) | | 0.068 kg a.s./ha  (0.136 kg a.s./ha x 0.5= 0.068 kg a.s./ha) | |
| Body weight: 60 kg | Potential  TC:12500cm2/person/h | 0.0369 | 23.11 | 0.0242 | 12.12 | 0.019046 | **190.46** |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.00041 | 2.59 | 0.0027 | 1.36 | 0.002133 | 21.33% |

**zRMS**:

The estimation of potential exposure of worker and of worker wearing a work wear (with arms, body and legs covered) to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of worker and an exposure of worker wearing a work wear (with arms, body and legs covered) is equal respectively to 26.96% and to 3.02% of AOEL for Difenconazole, and to 14.14% and to 1.58 % of AOEL for Prothioconazole, and to 222.67% and 24.96% of AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of worker wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs (3.02 % + 1.58% + 24.96%) is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of worker wearing a work wear (with arms, body and legs covered) entering for 2hrs inspection a field of cereals treated with a product IN233C1560 / AVTAR according to its intended use on cereals within good agricultural practice.

The estimation of potential exposure of worker and of worker wearing a work wear (with arms, body and legs covered) to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that a potential exposure of worker and an exposure of worker wearing a work wear (with arms, body and legs covered) is equal respectively to 23.11% and to 2.59% of AOEL for Difenconazole, and to 12.12 % and to 1.36 % of AOEL for Prothioconazole, and to 190.46% and 21.33% of AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of worker wearing a work wear (with arms, body and legs covered) to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs (2.59% + 1.36% + 21.33%) is below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of worker entering for 2hrs inspection a field of oilseed rape treated with a product IN233C1560 / AVTAR according to its intended use on oilseed rape within good agricultural practice.

Summing up application of a product IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology in line with GAP does not pose an unacceptable health risk for worker wearing a work wear (with arms, body and legs covered) and entering a treated field for 2hrs inspection after a spray has dried up.

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

Not required.

#### Measurement of worker exposure

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

### Resident and bystander exposure (KCP 7.2.2)

#### Estimation of resident and bystander exposure

Table 6.6‑7 shows the exposure model used for estimation of resident and bystander exposure to difenoconazole, prothioconazole, and prothioconazole-desthio. The outcome of the estimation is presented in Table 6.6‑8

Detailed calculations are in Appendix 3.

Table 6.6‑7: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Cereal (max 0.7 L of AVTAR/ha per application)  Oilseed rape (max 0.6 L of AVTAR/ha per application) |
| Model | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874  calculator version: 30/03/2015 |

Table 6.6‑8: Estimated resident exposure (long term exposure)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | Prothioconazole | | **Prothioconazole-desthio** | |
| Model data |  | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to low crops  Buffer zone: 2-3 (m)  Drift reduction technology: yes  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha  Interval between treatments: 14 days | | | | | | | |
| Cereals | | | | | | | |
| Number of applications and application rate | | 2 x 0.091kg a.s./ha | | 2 x 0.175 kg a.s./ha | | 2 x 0.159 kg a.s./ha | |
| Resident child  Body weight: 10 kg | Drift (75th perc.) | 0.0027 | 1.68 | 0.0033 | 1.65 | 0.0007 | 6.97 |
| Vapour (75th perc.) | 0.0010 | 0.67 | 0.0011 | 0.54 | 0.0011 | 10.70 |
| Deposits (75th perc.) | 0.0003 | 0.20 | 0.0004 | 0.21 | 0.0004 | 3.71 |
| Re-entry (75th perc.) | 0.0058 | 3.64 | 0.0071 | 3.56 | 0.0060 | 60.12 |
| **Sum (mean)** | 0.0074 | 4.64 | 0.0089 | 4.44 | 0.0065 | 65.20 |
| **Sum (mean) taking dermal absorption of prothioconazole 0.3% for concentrate and 15% for dilution** |  |  | 0.0079 | 3.99% |  |  |
| Resident adult  Body weight: 60 kg | Drift (75th perc.) | 0.0006 | 0.40 | 0.0008 | 0.39 | 0.0002 | 1.66 |
| Vapour (75th perc.) | 0.0002 | 0.14 | 0.0002 | 0.12 | 0.0002 | 2.30 |
| Deposits (75th perc.) | 0.0001 | 0.07 | 0.0001 | 0.07 | 0.0001 | 1.21 |
| Re-entry (75th perc.) | 0.0032 | 2.02 | 0.0040 | 1.98 | 0.0033 | 33.40 |
| **Sum (mean)** | 0.0032 | 2.00 | 0.0039 | 1.93 | 0.0031 | 30.61 |
| **Sum (mean) taking dermal absorption of prothioconazole 0.3% for concentrate and 15% for dilution** |  |  | 0.0038 | 1.91% |  |  |
| Oilseed rape | | | | | | | |
| Number of applications and application rate | | 2 x 0.078 kg a.s./ha | | 2 x 0.150 kg a.s./ha | | 2 x 0.136 kg a.s./ha | |
| Resident child  Body weight: 10 kg | Drift (75th perc.) | 0.0023 | 1.44 | 0.0028 | 1.42 | 0.0006 | 5.96 |
| Vapour (75th perc.) | 0.0011 | 0.67 | 0.0011 | 0.54 | 0.0011 | 10.70 |
| Deposits (75th perc.) | 0.0003 | 0.17 | 0.0004 | 0.18 | 0.0003 | 3.17 |
| Re-entry (75th perc.) | 0.005 | 3.12 | 0.0061 | 3.05 | 0.0051 | 51.42 |
| **Sum (mean)** | 0.0065 | 4.08 | 0.0078 | 3.89 | 0.0057 | 57.31 |
|  | **Sum (mean) taking dermal absorption of prothioconazole 0.3% for concentrate and 15% for dilution** |  |  | 0.0069 | 3.45 |  |  |
| Resident adult  Body weight: 60 kg | Drift (75th perc.) | 0.0006 | 0.34 | 0.0007 | 0.34 | 0.0001 | 1.42 |
| Vapour (75th perc.) | 0.00023 | 0.14 | 0.0002 | 0.12 | 0.0002 | 2.30 |
| Deposits (75th perc.) | 0.0001 | 0.06 | 0.0001 | 0.06 | 0.0001 | 1.04 |
| Re-entry (75th perc.) | 0.0027 | 1.73 | 0.0034 | 1.70 | 0.0029 | 28.57 |
| **Sum (mean)** | 0.0028 | 1.74 | 0.0033 | 1.67 | 0.0027 | 26.52 |
|  | **Sum (mean) taking dermal absorption of prothioconazole 0.3% for concentrate and 15% for dilution** |  |  | 0.0033 | 1.65 |  |  |

**zRMS**:

The exposure estimation of resident (adult and child) to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult and child resident is equal respectively to 2.00% and to 4.64% of AOEL for Difenconazole, and to 1.91% and to 3.99% of AOEL for Prothioconazole, and to 30.61% and 65.2% of ARfD for Prothioconazole used as AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of adult or child resident to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is also below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of adult and child resident for its intended use on cereals within good agricultural practice.

The exposure estimation of resident (adult and child) to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult and child resident is equal respectively to 1.74% and to 4.08% of AOEL for Difenconazole, and to 1.65% and to 3.45% of AOEL for Prothioconazole, and to 26.52% and 57.31% of ARfD for Prothioconazole used as AOEL for Prothioconazole-desthio, an environmental metabolite of Prothioconazole. The sum of exposures of adult or child resident to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is also below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of adult and child resident for its intended use on oilseed rape within good agricultural practice.

No bystander acute exposure estimation for Difenconazole and for Prothioconazole is required since no acute acceptable operator exposure value (AAOEL) has be set for any of this active substance nor for metabolite Prothioconazole-desthio. 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 Difenconazole and to Prothioconazole, and to metabolite Prothioconazole-desthio as a result of application of a product IN233C1560 / AVTAR with accordance with intended use within good agricultural practice.

Summing up application of a product IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer with drift reduction technology in line with GAP does not pose an unacceptable health risk for residents and bystanders.

Table 6.6‑9: Estimated bystander exposure (acute exposure)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ~~Difenoconazole~~ | | ~~Prothioconazole~~ | | ~~Prothioconazole-desthio~~ | |
| ~~Model data~~ |  | ~~Total absorbed dose (mg/kg bw/day)~~ | ~~% of systemic AAOEL~~ | ~~Total absorbed dose (mg/kg bw/day)~~ | ~~% of systemic AAOEL~~ | ~~Total absorbed dose (mg/kg bw/day)~~ | ~~% of systemic AAOEL~~ |
| ~~Tractor mounted boom spray application outdoors to low crops~~  ~~Buffer zone: 2-3(m)~~  ~~Drift reduction technology: yes~~  ~~DFR: 3 µg/cm~~~~2~~~~/kg a.s./ha~~ | | | | | | | |
| ~~Cereals~~ | | | | | | | |
| ~~Application rate:~~ | | ~~2 x 0.091 kg a.s./ha~~ | | ~~2 x 0.175 kg a.s./ha~~ | | ~~2 x 0.159 kg a.s./ha~~ | |
| ~~Bystander child~~  ~~Body weight: 10 kg~~ | ~~Drift (95~~~~th~~ ~~perc.)~~ | ~~0.0613~~ | ~~3.83~~ | ~~0.0075~~ | ~~75.31~~ | ~~0.0016~~ | ~~15.90~~ |
| ~~Vapour (95~~~~th~~ ~~perc.)~~ | ~~0.0011~~ | ~~0.67~~ | ~~0.0011~~ | ~~10.70~~ | ~~0.0011~~ | ~~10.70~~ |
| ~~Deposits (95~~~~th~~ ~~perc.)~~ | ~~0.0009~~ | ~~0.58~~ | ~~0.0011~~ | ~~12.54~~ | ~~0.0011~~ | ~~10.79~~ |
| ~~Re-entry (95~~~~th~~ ~~perc.)~~ | ~~0.0058~~ | ~~3.64~~ | ~~0.0071~~ | ~~71.26~~ | ~~0.0060~~ | ~~60.12~~ |
| ~~Bystander adult~~  ~~Body weight: 60 kg~~ | ~~Drift (95~~~~th~~ ~~perc.)~~ | ~~0.0017~~ | ~~1.04~~ | ~~0.0020~~ | ~~20.33~~ | ~~0.0004~~ | ~~4.29~~ |
| ~~Vapour (95~~~~th~~ ~~perc.)~~ | ~~0.0002~~ | ~~0.14~~ | ~~0.0002~~ | ~~2.30~~ | ~~0.0002~~ | ~~2.30~~ |
| ~~Deposits (95~~~~th~~ ~~perc.)~~ | ~~0.0003~~ | ~~0.22~~ | ~~0.0004~~ | ~~4.34~~ | ~~0.0004~~ | ~~3.66~~ |
| ~~Re-entry (95~~~~th~~ ~~perc.)~~ | ~~0.0032~~ | ~~2.02~~ | ~~0.0036~~ | ~~39.59~~ | ~~0.0033~~ | ~~33.40~~ |
| ~~Oilseed rape~~ | | | | | | | |
| ~~Application rate:~~ | | ~~2 x 0.078 kg a.s./ha~~ | | ~~2 x 0.150 kg a.s./ha~~ | | ~~2 x 0.136 kg a.s./ha~~ | |
| ~~Bystander child~~  ~~Body weight: 10 kg~~ | ~~Drift (95~~~~th~~ ~~perc.)~~ | ~~0.0052~~ | ~~3.28~~ | ~~0.0065~~ | ~~64.55~~ | ~~0.0014~~ | ~~13.60~~ |
| ~~Vapour (95~~~~th~~ ~~perc.)~~ | ~~0.0011~~ | ~~0.67~~ | ~~0.0011~~ | ~~10.70~~ | ~~0.0011~~ | ~~10.70~~ |
| ~~Deposits (95~~~~th~~ ~~perc.)~~ | ~~0.0008~~ | ~~0.50~~ | ~~0.0011~~ | ~~10.75~~ | ~~0.0009~~ | ~~9.23~~ |
| ~~Re-entry (95~~~~th~~ ~~perc.)~~ | ~~0.0050~~ | ~~3.12~~ | ~~0.0061~~ | ~~61.08~~ | ~~0.0051~~ | ~~51.42~~ |
| ~~Bystander adult~~  ~~Body weight: 60 kg~~ | ~~Drift (95~~~~th~~ ~~perc.)~~ | ~~0.0014~~ | ~~0.89~~ | ~~0.0017~~ | ~~17.43~~ | ~~0.0004~~ | ~~3.67~~ |
| ~~Vapour (95~~~~th~~ ~~perc.)~~ | ~~0.0002~~ | ~~0.14~~ | ~~0.0002~~ | ~~2.30~~ | ~~0.0002~~ | ~~2.30~~ |
| ~~Deposits (95~~~~th~~ ~~perc.)~~ | ~~0.0003~~ | ~~0.19~~ | ~~0.0004~~ | ~~3.72~~ | ~~0.0003~~ | ~~3.13~~ |
| ~~Re-entry (95~~~~th~~ ~~perc.)~~ | ~~0.0028~~ | ~~1.73~~ | ~~0.0034~~ | ~~33.93~~ | ~~0.0029~~ | ~~28.57~~ |

Table 6.6‑8A: Estimated resident exposure (long term exposure)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Difenoconazole | | Prothioconazole | | **Prothioconazole-desthio** | |
| Model data |  | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to low crops  Buffer zone: 2-3 (m)  Drift reduction technology: No  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha  Interval between treatments: 14 days | | | | | | | |
| Cereals | | | | | | | |
| Number of applications and application rate | | 2 x 0.091 kg a.s./ha | | 2 x 0.0875 kg a.s./ha  (0.175 kg a.s./ha x 0.5= 0.00875 kg a.s./ha) | | 2 x 0.0795 kg a.s./ha  ( 0.159 kg a.s./ha x 0.5 = 0.0795 kg a.s./ha | |
| Resident child  Body weight:  10 kg | **All pathways (mean)** | 0,00914 | 5.72 | 0.00639 | 3.20 | 0.00527 | 52.77 |
| Resident adult  Body weight: 60 kg | **All pathways (mean)** | 0.00359 | 2.25 | 0.00243 | 1.22 | 0.001966 | 19.67 |
| Oilseed rape | | | | | | | |
| Number of applications and application rate | | 2 x 0.078 kg a.s./ha | | 2 x 0.075 kg a.s./ha  (0.150 kg a.s./ha x 0.5= 0.075 kg a.s./ha) | | 2 x 0.068 kg a.s./ha  (0.136 kg a.s./ha x 0.5= 0.068 kg a.s./ha) | |
| Resident child  Body weight: 10 kg | **All pathways (mean)** | 0.00799 | 4.99 | 0.00563 | 2.82 | 0.00468 | 46.69 |
| Resident adult  Body weight: 60 kg | **All pathways (mean)** | 0.00311 | 1.95 | 0.00212 | 1.06 | 0.00171 | 17.16 |

**zRMS**:

The exposure estimation of resident (adult and child) to both active substances of a product IN233C1560 / AVTAR applied on a field of cereals at dose of 0.7 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult and child resident is equal respectively to 2.25% and to 5.72% of AOEL for Difenconazole, and to 1.22% and to 3.20% of AOEL for Prothioconazole, and to 19.67 % and 52.77% of AOEL for Prothioconazole-desthio an environmental metabolite of Prothioconazole. The sum of exposures of adult or child resident to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is also below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of adult and child resident for its intended use on cereals within good agricultural practice.

The exposure estimation of resident (adult and child) to both active substances of a product IN233C1560 / AVTAR applied on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology, calculated with the EFSA AOEM demonstrates that such a exposure for adult and child resident is equal respectively to 1.95% and to 4.99% of AOEL for Difenconazole, and to 1.06% and to 2.82 % of AOEL for Prothioconazole, and to 17.16 % and 46.69% of AOEL for Prothioconazole-desthio, an environmental metabolite of Prothioconazole. The sum of exposures of adult or child resident to both active substances and to metabolite Prothioconazole-desthio expressed as percentage of their AOELs is also below 100%, therefore the application of product IN233C1560 / AVTAR does not pose an unacceptable risk to the health of adult and child resident for its intended use on oilseed rape within good agricultural practice.

No bystander acute exposure estimation for Difenconazole and for Prothioconazole is required since no acute acceptable operator exposure value (AAOEL) has be set for any of this active substance nor for metabolite Prothioconazole-desthio. 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 Difenconazole and to Prothioconazole, and to metabolite Prothioconazole-desthio as a result of application of a product IN233C1560 / AVTAR with accordance with intended use within good agricultural practice.

Summing up application of a product IN233C1560 / AVTAR on a field of cereals at dose of 0.7 L product/ha or on a field of oilseed rape at dose of 0.6 L product/ha, using tractor-mounted/trailed boom sprayer without drift reduction technology in line with GAP does not pose an unacceptable health risk for residents and bystanders.

#### 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 active substance 1 and/or active substance 2 will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

### Combined exposure

The product is a mixture of two active substances.

#### Exposure assessment of difenoconazole and protioconazole in product IN233C1560/ AVTAR

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

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

For every scenario, the worst-case estimated exposure between the prothioconazole and the prothioconazole-desthio was considered in combination with the estimated exposure of difenoconazole to have the most conservative approach.

~~Table 6.6‑10: Risk assessment from combined exposure (acute exposure) – Cereals~~

| ~~Application scenario~~ | ~~Active ingredient~~ | ~~Estimated exposure / AAOEL (HQ)~~ |
| --- | --- | --- |
| ~~Operators –Vehicle-mounted-drift reduction~~ | ~~Difenoconazole~~ | ~~0.05~~ |
| ~~Prothioconazole~~ | ~~0.73~~ |
| **~~Cumulative risk operators (HI)~~** | **~~0.78~~** |
| ~~Workers – Inspection, Irrigation~~ | ~~Difenoconazole~~ | ~~0.03~~ |
| ~~Prothioconazole-desthio~~ | ~~0.50~~ |
| **~~Cumulative risk workers (HI)~~** | **~~0.53~~** |
| ~~Bystander - child~~ | ~~Difenoconazole~~ | |
| ~~Drift~~ | ~~0.04~~ |
| ~~Vapour~~ | ~~0.01~~ |
| ~~Deposits~~ | ~~0.01~~ |
| ~~Re-entry~~ | ~~0.04~~ |
| ~~Prothioconazole~~ | |
| ~~Difenoconazole~~ | ~~0.75~~ |
| ~~Vapour~~ | ~~0.11~~ |
| ~~Deposits~~ | ~~0.13~~ |
| ~~Re-entry~~ | ~~0.71~~ |
| **~~Cumulative risk bystander – child (HI)~~** | |
| ~~Drift~~ | **~~0.79~~** |
| ~~Vapour~~ | **~~0.11~~** |
| ~~Deposits~~ | **~~0.13~~** |
| ~~Re-entry~~ | **~~0.75~~** |
| ~~Bystander - adult~~ | ~~Difenconazole~~ | |
| ~~Drift~~ | ~~0.01~~ |
| ~~Vapour~~ | ~~0.00~~ |
| ~~Deposits~~ | ~~0.00~~ |
| ~~Re-entry~~ | ~~0.02~~ |
| ~~Prothioconazole~~ | |
| ~~Drift~~ | ~~0.20~~ |
| ~~Vapour~~ | ~~0.02~~ |
| ~~Deposits~~ | ~~0.04~~ |
| ~~Re-entry~~ | ~~0.40~~ |
| **~~Cumulative risk bystander – adult (HI)~~** | |
| ~~Drift~~ | **~~0.21~~** |
| ~~Vapour~~ | **~~0.02~~** |
| ~~Deposits~~ | **~~0.05~~** |
| ~~Re-entry~~ | **~~0.42~~** |

Table 6.6‑11: Risk assessment from combined exposure (longer term exposure) – Cereals assuming 100% conversion of prothioconazole to prothioconazole -desthio

| Application scenario | Active ingredient | Estimated exposure / AOEL (HQ) |
| --- | --- | --- |
| Operators –Vehicle-mounted-drift reduction | Difenoconazole | 0.01 |
| Prothioconazole-desthio | 0.13 |
| **Cumulative risk operators (HI)** | **0.14** |
| Workers – Inspection, Irrigation | Difenoconazole | 0.03 |
| Prothioconazole | 0.50 |
| **Cumulative risk workers (HI)** | **0.53** |
| Resident - child | Difenoconazole | |
| Drift | 0.02 |
| Vapour | 0.01 |
| Deposits | 0.00 |
| Re-entry | 0.04 |
| Sum of all pathways | 0.05 |
| Prothioconazole-desthio | |
| Drift | 0.07 |
| Vapour | 0.11 |
| Deposits | 0.04 |
| Re-entry | 0.60 |
| Sum of all pathways | 0.65 |
| **Cumulative risk resident – child (HI)** | |
| Drift | 0.09 |
| Vapour | 0.11 |
| Deposits | 0.04 |
| Re-entry | 0.64 |
| **Sum of all pathways** | **0.70** |
| Resident - adult | Difenoconazole | |
| Drift | 0.00 |
| Vapour | 0.00 |
| Deposits | 0.00 |
| Re-entry | 0.02 |
| Sum of all pathways | 0.02 |
| Prothioconazole-dethio | |
| Drift | 0.02 |
| Vapour | 0.02 |
| Deposits | 0.01 |
| Re-entry | 0.33 |
| Sum of all pathways | 0.31 |
| **Cumulative risk resident – adult (HI)** | |
| Drift | 0.02 |
| Vapour | 0.02 |
| Deposits | 0.01 |
| Re-entry | 0.35 |
| **Sum of all pathways** | **0.33** |

Table 6.6‑11A: Risk assessment from combined exposure (longer term exposure) – Cereals assuming 50% conversion of prothioconazole to prothioconazole -desthio

| Application scenario | Active ingredient | Estimated exposure / AOEL (HQ) |
| --- | --- | --- |
| Operators wearing a work wear (with arms, body and legs covered) and protective gloves –Vehicle-mounted without drift reduction technology | Difenoconazole | 0.0183 |
| Prothioconazole | 0.0092 |
| Prothioconazole-desthio | 0.22 |
| **Cumulative risk operators (HI)** | **0.24** |
| Workers – Inspection, Irrigation  Work wear (arms, body and legs covered) | Difenoconazole | 0.0302 |
| Prothioconazole | 0.016 |
| Prothioconazole-desthio | 0.2494 |
| **Cumulative risk workers (HI)** | **0.2956** |
| Resident - child |  | |
| Difenoconazole Sum of all pathways | 0.0572 |
| Prothioconazole Sum of all pathways | 0.032 |
| Prothioconazole-desthio Sum of all pathways | 0.5277 |
| **Cumulative risk resident – child (HI) 0.62** | |
| Resident - adult |  | |
| Difenoconazole Sum of all pathways | 0.0225 |
| Prothioconazole Sum of all pathways | 0.0122 |
| Prothioconazole-desthio Sum of all pathways | 0.1967 |
| **Cumulative risk resident – adult (HI)** | **0.23** |

Table 6.6‑12: Risk assessment from combined exposure (acute exposure) – Oilseeds

| ~~Application scenario~~ | ~~Active ingredient~~ | ~~Estimated exposure / AAOEL (HQ)~~ |
| --- | --- | --- |
| ~~Operators –Vehicle-mounted-drift reduction~~ | ~~Difenoconazole~~ | ~~0.05~~ |
| ~~Prothioconazole~~ | ~~0.65~~ |
| **~~Cumulative risk operators (HI)~~** | **~~0.70~~** |
| ~~Workers – Inspection, Irrigation~~ | ~~Difenoconazole~~ | ~~0.03~~ |
| ~~Prothioconazole-desthio~~ | ~~0.43~~ |
| **~~Cumulative risk workers (HI)~~** | **~~0.46~~** |
| ~~Bystander - child~~ | ~~Difenoconazole~~ | |
| ~~Drift~~ | ~~0.03~~ |
| ~~Vapour~~ | ~~0.01~~ |
| ~~Deposits~~ | ~~0.01~~ |
| ~~Re-entry~~ | ~~0.03~~ |
| ~~Prothioconazole~~ | |
| ~~Drift~~ | ~~0.65~~ |
| ~~Vapour~~ | ~~0.11~~ |
| ~~Deposits~~ | ~~0.11~~ |
| ~~Re-entry~~ | ~~0.61~~ |
| **~~Cumulative risk bystander – child (HI)~~** | |
| ~~Drift~~ | **~~0.68~~** |
| ~~Vapour~~ | **~~0.11~~** |
| ~~Deposits~~ | **~~0.11~~** |
| ~~Re-entry~~ | **~~0.64~~** |
| ~~Bystander - adult~~ | ~~Difenconazole~~ | |
| ~~Drift~~ | ~~0.01~~ |
| ~~Vapour~~ | ~~0.00~~ |
| ~~Deposits~~ | ~~0.00~~ |
| ~~Re-entry~~ | ~~0.02~~ |
| ~~Prothioconazole~~ | |
| ~~Drift~~ | ~~0.17~~ |
| ~~Vapour~~ | ~~0.02~~ |
| ~~Deposits~~ | ~~0.04~~ |
| ~~Re-entry~~ | ~~0.34~~ |
| **~~Cumulative risk bystander – adult (HI)~~** | |
| ~~Drift~~ | **~~0.18~~** |
| ~~Vapour~~ | **~~0.02~~** |
| ~~Deposits~~ | **~~0.04~~** |
| ~~Re-entry~~ | **~~0.36~~** |

Table 6.6‑13 : Risk assessment from combined exposure (longer term exposure) – Oilseeds assuming 100% conversion of prothioconazole to prothioconazole -desthio

| Application scenario | Active ingredient | Estimated exposure / AOEL (HQ) |
| --- | --- | --- |
| Operators –Vehicle-mounted-drift reduction | Difenoconazole | 0.01 |
| Prothioconazole-desthio | 0.11 |
| **Cumulative risk operators (HI)** | **0.12** |
| Workers – Inspection, Irrigation | Difenoconazole | 0.03 |
| Prothioconazole | 0.43 |
| **Cumulative risk workers (HI)** | **0.46** |
| Resident - child | Difenoconazole | |
| Drift | 0.01 |
| Vapour | 0.01 |
| Deposits | 0.00 |
| Re-entry | 0.03 |
| Sum of all pathways | 0.04 |
| Prothioconazole-desthio | |
| Drift | 0.06 |
| Vapour | 0.11 |
| Deposits | 0.03 |
| Re-entry | 0.51 |
| Sum of all pathways | 0.57 |
| **Cumulative risk resident – child (HI)** | |
| Drift | 0.07 |
| Vapour | 0.11 |
| Deposits | 0.03 |
| Re-entry | 0.55 |
| **Sum of all pathways** | **0.61** |
| Resident - adult | Difenoconazole | |
| Drift | 0.00 |
| Vapour | 0.00 |
| Deposits | 0.00 |
| Re-entry | 0.02 |
| Sum of all pathways | 0.02 |
| Prothioconazole-desthio | |
| Drift | 0.01 |
| Vapour | 0.02 |
| Deposits | 0.01 |
| Re-entry | 0.29 |
| Sum of all pathways | 0.27 |
| **Cumulative risk resident – adult (HI)** | |
| Drift | 0.02 |
| Vapour | 0.02 |
| Deposits | 0.01 |
| Re-entry | 0.30 |
| **Sum of all pathways** | **0.28** |

Table 6.6‑13A: Risk assessment from combined exposure (longer term exposure) – Oilseeds assuming 50% conversion of prothioconazole to prothioconazole -desthio

| Application scenario | Active ingredient | Estimated exposure / AOEL (HQ) |
| --- | --- | --- |
| Operators wearing a work wear (with arms, body and legs covered) and protective gloves –Vehicle-mounted without drift reduction technology | Difenoconazole | 0.0158 |
| Prothioconazole | 0.008 |
| Prothioconazole-desthio | 0.19 |
| **Cumulative risk operators (HI)** | **0.22** |
| Workers – Inspection, Irrigation  Work wear (arms, body and legs covered) | Difenoconazole | 0.0259 |
| Prothioconazole | 0.0136 |
| Prothioconazole-desthio | 0.2133 |
| **Cumulative risk workers (HI)** | **0.25** |
| Resident - child |  | |
| Difenoconazole Sum of all pathways | 0.0499 |
| Prothioconazole Sum of all pathways | 0.0282 |
| Prothioconazole-desthio Sum of all pathways | 0.4669 |
| **Cumulative risk resident – child (HI) 0.545** | |
| Resident - adult |  | |
| Difenoconazole Sum of all pathways | 0.0195 |
| Prothioconazole Sum of all pathways | 0.0106 |
| Prothioconazole-desthio Sum of all pathways | 0.1716 |
| **Cumulative risk resident – adult (HI)** | **0.2017** |

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

1. Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

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

List of data submitted by the applicant and relied on

| Data point | Author(s) | Year | Title Company Report No.  Source (where different from company) GLP or GEP status Published or not | Vertebrate study  Y/N | Owner |
| --- | --- | --- | --- | --- | --- |
| KCP 7.1.4/01 | Cattaneo A. | 2021 | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: *In vitro* Skin Irritation Test with the EpiDermTM Model  Final Report CH – 0245/2021ChemService S.r.l. Controlli e RicercheGLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.1.4/02 | Cattaneo A. | 2021 | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: *In vitro* Skin Corrosion Test with the EpiDermTM Model  Final Report CH – 0246/2021ChemService S.r.l. Controlli e RicercheGLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.1.5/01 | Cattaneo A. | 2021 | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: *In vitro* Ocular Irritation Test with the EpiOcularTM Model  Final Report CH – 0247/2021ChemService S.r.l. Controlli e RicercheGLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.1.5/02 | Cattaneo A. | 2021 | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: *In vitro* Eye Irritation and Corrosion with the BCOP Test  Final Report CH – 0248/2021ChemService S.r.l. Controlli e RicercheGLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.3/01 | Nagane, R. | 2022a | IN VITRO DERMAL ABSORPTION OF DIFENOCONAZOLE FROM DIFENOCONAZOLE 130 G/L + PROTHIOCONAZOLE 250 G/L EC - IN233C1560 USING HUMAN SPLIT-THICKNESS SKIN IN A FLOW THROUGH DIFFUSION SYSTEM  Report No.: 617-1-06-29169  JAI RESEARCH FOUNDATION  GLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.3/02 | Nagane, R. | 2022b | IN VITRO DERMAL ABSORPTION OF PROTHIOCONAZOLE FROM DIFENOCONAZOLE 130 G/L + PROTHIOCONAZOLE 250 G/L EC - IN233C1560 USING HUMAN SPLIT-THICKNESS SKIN IN A FLOW THROUGH DIFFUSION SYSTEM  Report No.: 617-1-06-29234  JAI RESEARCH FOUNDATION  GLP Unpublished | N | Indofil Industries (Netherlands) B.V. |
| KCP 7.3/03 | Nagane, R. | 2022c | IN VITRO DERMAL ABSORPTION OF PROTHIOCONAZOLE-DESTHIO FROM DIFENOCONAZOLE 130 G/L + PROTHIOCONAZOLE 250 G/L EC - IN233C1560 USING HUMAN SPLIT-THICKNESS SKIN IN A FLOW THROUGH DIFFUSION SYSTEM  Report No.: 617-1-06-29977  JAI RESEARCH FOUNDATION  GLP Unpublished | N | Indofil Industries (Netherlands) B.V. |

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

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

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

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

1. Detailed evaluation of the studies relied upon
   1. Statement on bridging possibilities

No bridging was necessary

|  |  |
| --- | --- |
| Comments of zRMS: | No statement on bridging possibilities is necessary |

* 1. Acute oral toxicity (KCP 7.1.1)

|  |  |
| --- | --- |
| Comments of zRMS: | The acute oral toxicity of the product IN233C1560/AVTAR was evaluated based on the toxic properties and content of all components in line with rules provided in Regulation 1272/2008 ( see part C). The product IN233C1560/AVTAR does not require classification for acute oral toxicity. |

An acute oral toxicity study for AVTAR is not provided. Instead, the acute oral toxicity classification of the product was determined using the calculation method as described in Regulation (EC) No. 1272/2008.

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

|  |  |
| --- | --- |
| Comments of zRMS: | The acute dermal toxicity of the product IN233C1560/AVTAR was evaluated based on the toxic properties and content of all components in line with rules provided in Regulation 1272/2008 ( see part C). The product IN233C1560/AVTAR does not require classification for acute dermal toxicity. |

An acute dermal toxicity study for AVTAR is not provided. Instead, the acute dermal toxicity classification of the product was determined using the calculation method as described in Regulation (EC) No. 1272/2008.

* 1. Acute inhalation toxicity (KCP 7.1.3)

|  |  |
| --- | --- |
| Comments of zRMS: | The acute inhalation toxicity of the product IN233C1560/AVTAR was evaluated based on the toxic properties and content of all components in line with rules provided in Regulation 1272/2008 ( see part C). The product IN233C1560/AVTAR does not require classification for acute inhalation toxicity. |

An acute inhalation toxicity study for AVTAR is not provided. Instead, the acute inhalation toxicity classification of the product was determined using the calculation method as described in Regulation (EC) No. 1272/2008.

* 1. Skin irritation (KCP 7.1.4)

The irritation potential of the test item was predicted by measurement of its cytotoxic effect, as reflected in the MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue tetrazolium bromide; CAS number 298-93-1] assay, on the reconstructed human epidermis model (RhE). The test is designed to predict and classify the skin irritant potential of chemicals according to chemical safety regulations, using the EpiDermTM Model and parameters related to skin irritation. This model closely mimics the histological, biochemical and physiological properties of the upper parts of the human skin, i.e. the epidermis. Its use for skin irritation testing involves topical application of test materials to the surface of the epidermis and the subsequent assessment of their effects on cell viability.

|  |  |
| --- | --- |
| Comments of zRMS: | Based on the content of skin irritant ingredients in the product IN233C1560/AVTAR and on the results of two acceptable in vitro studies the formulation IN233C1560 / AVTAR should be classified as Skin Irrit. 2; H315 (see also part C) . |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.4/01 |
| Report | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: In vitro Skin Irritation Test with the EpiDermTM Model, Cattaneo A., 2021 GLP Study No. CH – 0245/2021 |
| Guideline(s) | Yes  OECD Guideline No. 439 |
| Deviations | Yes  *Deviation No. 1:* Formazan extraction into 12-well plate (paragraph “11.5.2 Formazan extraction” at page 14).  *Reason of change:* During the rinsing phase, the test item didn’t wash completely from the tissues because the nylon mesh remained stick. To avoid contaminating the isopropanol the extraction was only from the bottom of the insert.  *Impact on the study:* None.  *Deviation No. 2:* Asterisk in “production date” was eliminated (paragraph “8.1 TEST ITEM at page 8)  *Reason of change:* The reference to the POS G20 has been removed only for “production date” because the production date was expressed as day/month/year in the TSDS.  *Impact on the study:* None. |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | IN233C1560 (Batch No IND\_F032\_0321\_1.) |
| **Species** | Reconstructed Human Epidermis (RhE) |
| **No. of Human skin model** | 34110- Killed tissues  34193 - Living tissues |
| **Initial test using one animal** | No |
| **Exposure** | 30µl (60minutes, 37°C, 5 % CO2, 95 % RH.) |
| **Negative control** | 30µl Phosphate buffered saline, DPBS |
| **Positive control** | 30µl SDS 5% aq. |
| **Vehicle/Dilution** | None |
| **Post exposure observation period** | 42 h |
| **Remarks** | None |

NUMBER OF REPLICATE WELLS: In this assay 3 replicates per test item, negative control and positive control were used, furthermore 2 replicates for Non Specific Colour (NSC), Non Specific Colour in killed tissues (NSCkilled), Killed control (KU) and Killed Treated (KT) were used.

* Reception procedure
* Day 0: Pre-incubation
* Day 1: Chemical exposure

1 Test item Application

2 Test Substance Exposure

3 Rinsing

* Day 2: Change Medium
* Day 3: MTT Test

1 Formazan extraction

2 Cell viability measurements

Results and discussions

Table A 1: Skin irritation of IN233C1560/ AVTAR: treated tissues results

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Code No.** | **Tissue** | **Raw data OD** | | **Blanc corrected data** | | **OD Mean of aliquots** | **Corrected mead OD** | **% of Viability** |
| N° | Aliq. 1 | Aliq. 2 | Aliq. 1 | Aliq. 2 |
| 2102121 -00114 | 1 | 0.115 | 0.112 | 0.079 | 0.076 | 0.078 | 0.025 | 1.4 |
| 2 | 0.177 | 0.171 | 0.141 | 0.135 | 0.138 | 0.086 | 4.7 |
| 3 | 0.284 | 0.256 | 0.248 | 0.220 | 0.234 | 0.182 | 9.9 |
| Mean Value: | | | | | | | **0.097** | **5.3** |

Test item does reduce strong cell viability in comparison to the negative control. The mean viability of test item’s three replicates was 5.3 % of the mean value of negative control. Positive and negative controls showed the expected cell viability values within acceptable limits. The experiment was considered to be valid.

In this in vitro skin irritation test with the EpiDermTM model on test item “Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/ AVTAR” results indicated that the test item is at least irritant to skin [Category 1/2 according to EU CLP and UN GHS].

Conclusion

Under the experimental conditions, IN233C1560/ AVTAR is a skin irritant. Thus, a classification is required according to Regulation (EC) No. 1272/2008.

|  |  |
| --- | --- |
| Comments of zRMS: | The skin irritancy of the product IN233C1560/ AVTAR was evaluated with a method OECD TG 439 “In Vitro Skin Irritation: Reconstructed Human Epidermis Test Methods” in GLP conditions. The study is acceptable. The mean viability of cells treated with the product was well below 50% thus the product should be considered as either skin irritant (Cat. 2) or skin corrosive Cat. 1), therefore further testing is required to decide on its final classification |

* + 1. Study 2

The corrosion potential of the test item was predicted by measurement of its cytotoxic effect, as reflected in the MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Thiazolyl blue tetrazolium bromide; CAS number 298-93-1] assay, on the reconstructed human epidermis model (RhE). Its use for skin corrosion testing involves topical application of test materials to the surface of the epidermis and the subsequent assessment of their effects on cell viability.

The present test is based on the experience that corrosive chemicals show cytotoxic effects following short-term exposure of the stratum corneum of the epidermis. It makes use of RhE which closely mimics the histological, morphological, biochemical and physiological properties of the upper parts of the human skin, i.e. the epidermis. The purpose of this study is to predict the skin corrosivity potential of a chemical by assessment of its effect on RhE.

The reconstructed human epidermal model EpiDermTM is a three-dimensional human epidermis model comprising the organized basal, spinous and granular layers and a multilayered stratum corneum. Its use for skin corrosion testing involves topical application of test materials to the surface of the epidermis and the subsequent assessment of their effects on cell viability. Cell viability determination is based on cellular mitochondrial dehydrogenase activity, measured by MTT reduction and conversion into a blue formazan salt that is quantitatively measured after extraction from tissues (Liebsch et al., 2002, Mosmann, 1983).

The reduction of cell viability in treated tissues is compared to negative controls and expressed as a %. The % reduction in viability is used to predict the corrosive potential.

|  |  |
| --- | --- |
| Reference | KCP 7.1.4/02 |
| Report | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/ AVTAR: In vitro Skin Corrosion Test with the EpiDermTM Model, Cattaneo A., 2021 GLP Study No. CH – 0246/2021 |
| Guideline(s) | Yes  OECD Guideline No. 431 |
| Deviations | Yes  Deviation No. 1   |  |  | | --- | --- | | Change No. 1 | Formazan extraction into 12-well plate (paragraph “11.4.5 Formazan extraction” at page 15). | | Reason of change: | During the rinsing phase, the test item didn’t wash completely from the tissues because the nylon mesh remained stick. To avoid contaminating the isopropanol the extraction was only from the bottom of the insert. | | Impact on the study: | None. |   Deviation No. 2   |  |  | | --- | --- | | Change No. 1 | Asterisk in “production date” was eliminated (paragraph “8.1 TEST ITEM at page 8) | | Reason of change: | The reference to the POS G20 has been removed only for “production date” because the production date was expressed as day/month/year in the TSDS. | | Impact on the study: | None. | |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | IN233C1560/ AVTAR (Batch No IND\_F032\_0321\_1.) |
| **Species** | Three-dimensional human epidermis model |
| **No. of Human skin model** | 34110 - Killed tissues  34193 - Living tissues |
| **Initial test using one animal** | No |
| **Exposure** | 50µl (60minutes, 37°C, 5 % CO2) |
| **Negative control** | 50µl sterile demineralized water |
| **Positive control** | 50µl KOH 8N |
| **Vehicle/Dilution** | None |
| **Remarks** | None |

**NUMBER OF REPLICATE WELLS:** In this assay 3 replicates per test item, negative control and positive control were used, furthermore 2 replicates for Non Specific Colour (NSC), Non Specific Colour in killed tissues (NSCkilled), Killed control (KU) and Killed Treated (KT) were used for each exposure time (3 minutes and 1 hour).

* Reception procedure
* Pre-incubation
* Chemical exposure (1 hour application time)

1 Test item Application

2 Test Substance Exposure

3 Rinsing

4. MTT Viability Test

* Chemical exposure (3 minutes application time)

1 Test Substance Application

2 Test Substance Exposure

3. Rising

4. MTT Viability Test

* Formazan extraction
* Cell viability measurements

Results and discussions

Table A 2: Skin irritation of IN233C1560/ AVTAR: Summary Results

|  |  |
| --- | --- |
| Evaluations: | For every application time (3 minutes and 1 hour) the cell viability based on cellular mitochondrial dehydrogenase activity, measured by MTT reduction and conversion into a blue formazan salt was quantitatively measured after extraction from tissues. The reduction of cell viability in treated tissues was compared to negative control and expressed as a %. The % reduction in viability is used to predict the corrosion potential. |
| Test duration: | Pre-incubation: 60 ± 5 minutes.  Exposure of test item: 3 minutes and 1 hour |
| Incubation conditions: | 37°C, 5 % CO2. |
| Validity of the controls: | positive control (KOH 8 N) mean viability should be ≤ 15 % of the negative control tissues after 1 hour.  The mean OD value of the three negative control tissues (DPBS) should be ≥ 0.8 and ≤ 2.8.  In the range between 20 % and 100 % viability the coefficient of variation (CV) should not exceed 0.3. |
| Results: | One valid experiment was performed. The mean viability of tissues exposed to the test item was 92.7 % after 3 minutes and 60.4 % after 1 hour compared with the mean value of the negative control. |

Table A 3: Skin irritation of IN233C1560/ AVTAR : 1 hour Treated tissues result

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Code No.** | **Tissue** | **Raw data OD** | | **Blanc corrected data** | | **OD Mean of aliquots** | **Corrected mead OD** | **% of Viability** |
| N° | Aliq. 1 | Aliq. 2 | Aliq. 1 | Aliq. 2 |
| 2102121 -00114 | 1 | 2.077 | 2.187 | 2.041 | 2.151 | 2.096 | 1.144 | 58.7 |
| 2 | 2.248 | 2.131 | 2.212 | 2.095 | 2.153 | 1.202 | 61.7 |
| 3 | 2.218 | 2.120 | 2.182 | 2.084 | 2.133 | 1.181 | 60.6 |
| Mean Value: | | | | | | | **1.176** | **60.4** |

Test item showed a slight reduced potential of cell viability in comparison to the negative control only after 1 hour application time. The mean viability of test item three replicates results was 92.7 % of the mean negative control value at 3 minutes application time and 60.4 % at 1 hour application time.

Positive and negative controls showed the expected cell viability values within acceptable limits. The experiment was considered to be valid and qualified.

*In this in vitro skin corrosion test with the EpiDermTM model on test item “Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/* AVTAR*”, results indicated that the test item isn’t Corrosive (Non-corrosive).*

Conclusion

Under the experimental conditions, IN233C1560/ AVTAR is not a skin Corrosive. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

|  |  |
| --- | --- |
| Comments of zRMS: | The skin corrosion of the product IN233C1560/ AVTAR was evaluated with a method OECD TG 431 “In Vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method with the EpiDermTM Model” in GLP conditions. The study is acceptable. The mean viability of tissues exposed to the product IN233C1560/ AVTAR was 92.7 % after 3 minutes and 60.4 % after 1 hour compared with the mean value of the negative control, thus it was above ≥ 50% after 3 min exposure and ≥ 15% after 60 min exposure. The results of this second study indicate that the product does not meet criteria for classification to Category 1 as skin corrosive, therefore based also on results of the first study done with OECD TG 439 it should be classified as Skin Irrit. 2; H315 |

* 1. Eye irritation (KCP 7.1.5)

The Bovine Corneal Opacity and Permeability (BCOP) test method is designed to correctly identify chemicals (both substances and mixtures) inducing serious eye damage as well as those not requiring classification for eye irritation or serious eye damage as defined by the UN GHS.

Test chemicals inducing serious eye damage are classified as UN GHS Category 1.

Chemicals not classified for eye irritation or serious eye damage are defined as those that do not meet the requirements for classification and they are referred to as UN GHS No Category.

The BCOP test method is an organotypic model that provides short-term maintenance of normal physiological and biochemical function of the bovine cornea *in vitro*.

In this test method, damage by the test item is assessed by quantitative measurements of changes in corneal opacity and permeability. Both measurements are used to calculate an IVIS (*in vitro* irritancy score), which is used to classify the test item in the UN Globally Harmonised System.

|  |  |
| --- | --- |
| Comments of zRMS: | Based on the content of eye corrosive/irritant ingredients in the product IN233C1560/AVTAR and on the results of two acceptable in vitro studies the formulation IN233C1560 / AVTAR should be classified as Eye Irrit. 2; H319: Causes serious eye irritation (see also part C) |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.5/01 |
| Report | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/ AVTAR:  *In vitro* Ocular Irritation Test with the EpiOcularTM Model, Cattaneo A., 2021, Draft Report No.- 0247/2021 |
| Guideline(s) | Yes  OECD Guideline No. 492 |
| Deviations | Yes  *Deviation No. 1:* Asterisk in “production date” was eliminated  *Reason of change:* The reference to the POS G20 has been removed only for “production date” because the production date was expressed as day/month/year in the TSDS  *Impact on the study:* None. |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | IN233C1560/ AVTAR |
| **Species** | Human cornea-like epithelium model (RhCE) |
| **No. of Human Cornea-like epithelieum** | 34924 - Killed tissues  30685 - Living tissues |
| **Initial test using one animal** | No |
| **Pre-treatment exposure with DPBS** | 20µl, 30 min |
| **Exposure** | 50µl (aliquot undiluated) 30 min (37°C, 5 % CO2,95 % RH.) |
| **Negative control** | 50 µl |
| **Positive control** | 50µl |
| **Irrigation (time point)** | e.g. Yes/No |
| **Vehicle/Dilution** | e.g. None |
| **Post incubation exposure observation period** | 120min |
| **Remarks** | None |

NUMBER OF REPLICATE : In this assay 3 replicates per test item, negative control and positive control were used.

1. Preparation of cornea

2. Test substance application

2.1Test substance exposure

2.2 Rising, post soak and final opacity measurement

3. Permeability Measurement

4. Calculation of opacity value

5. Calculation of permeabilty value

6. Calculation of IVIS (In Vitro Irritancy Score)

Results and discussions

Table A 4: Eye irritation of IN233C1560/ AVTAR: summary results

|  |  |
| --- | --- |
| Evaluations: | Corneal opacity is measured quantitatively as the amount of light transmission through the cornea. Permeability is measured quantitatively as the amount of sodium fluorescein dye that passes across the full thickness of the cornea, as detected in the medium in the posterior chamber. Both measurements are used to calculate an IVIS, which is used to classify the test item in the UN GHS System. |
| Test duration: | Exposure of test item: 10 minutes.  Post incubation: 120 minutes. |
| Incubation conditions: | 32 ± 1°C |
| Validity of the controls: | Positive controls (Ethanol) IVIS value falls within 2 standard deviations of the current historical mean (reported in the report).  The negative controls (0.9 % NaCl solution) opacity and permeability values are less than the upper limits of the background values (reported in the report). |
| Results: | One valid experiment was performed.  Under the conditions of this study, the test item showed a slight effect on the cornea of the bovine eye. The calculated mean IVIS (*in vitro* irritancy score) is 12.9. |

Table A 5: Eye irritation of IN233C1560/ AVTAR: Values of OD and viability for the test item and reference items

|  |  |  |  |
| --- | --- | --- | --- |
| **Substance** | **Optical Density** (OD) | | **Viability** (%) |
| **Negative Control** | 1 | 2.080 | 101.1 |
| 2 | 1.918 | 93.2 |
| 3 | 2.176 | 105.8 |
| Mean: | **2.058** | **100.0** |
| Standard deviation (%): | | **6.3** |
| **Positive Control** | 1 | 0.878 | 42.7 |
| 2 | 0.884 | 43.0 |
| 3 | 0.924 | 44.9 |
| Mean: | **0.895** | **43.5** |
| Standard deviation (%): | | **1.2** |
| **2102121-00113** | 1 | 0.675 | 32.8 |
| 2 | 1.027 | 49.9 |
| 3 | 0.948 | 46.1 |
| Mean: | **0.884** | **42.9** |
| Standard deviation (%): | | **9.0** |

Test item showed a reduced cell viability in comparison to the negative control.

The mean viability of test item’s three replicates was 42.9 % of the mean value of negative control. Positive and negative controls showed the expected cell viability values within acceptable limits. The experiment was considered to be valid.

In this *in vitro* ocular irritation test with the EpiOcularTM model on test item “Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/ AVTAR” results indicated that the test item is at least irritant to eye [Category 2 according to EU CLP and UN GHS].

Conclusion

Under the experimental conditions, IN233C1560/ AVTAR is an eye irritant. Thus, a classification is required according to Regulation (EC) No. 1272/2008.

|  |  |
| --- | --- |
| Comments of zRMS: | The study *“Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: In vitro Ocular Irritation Test with the EpiOcularTM Model”* ( KCP 7.1.5/01) was performed in GLP conditions and according to OECD Test Guideline No. 492 “Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage” adopted in 2019. Positive and negative controls showed the expected cell viability values within acceptable limits, therefore the study is considered to be acceptable. In this study a formulation IN233C1560 has considerably reduced cell viability in comparison to the negative control. The mean viability of treated cells was 42.9 % of the mean value of negative control, thus below a cut-off values of 60% for non-irritant substances, therefore the product should be considered as either eye irritant (Cat. 2) or eye corrosive Cat. 1), therefore further testing is required to decide on its final classification. |

* + 1. Study 2

The Bovine Corneal Opacity and Permeability (BCOP) test method is designed to correctly identify chemicals (both substances and mixtures) inducing serious eye damage as well as those not requiring classification for eye irritation or serious eye damage as defined by the UN GHS.

Test chemicals inducing serious eye damage are classified as UN GHS Category 1.

Chemicals not classified for eye irritation or serious eye damage are defined as those that do not meet the requirements for classification and they are referred to as UN GHS No Category.

The BCOP test method is an organotypic model that provides short-term maintenance of normal physiological and biochemical function of the bovine cornea *in vitro*.

In this test method, damage by the test item is assessed by quantitative measurements of changes in corneal opacity and permeability. Both measurements are used to calculate an IVIS (*in vitro* irritancy score), which is used to classify the test item in the UN Globally Harmonised System.

|  |  |
| --- | --- |
| Reference | KCP 7.1.5/02 |
| Report | Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560/ AVTAR: *In vitro* EyeIrritation and Corrosion with the BCOP Test, Cattaneo A., 2021, Draft Report No.- 0248/2021 |
| Guideline(s) | Yes  OECD Guideline No. 437 (2020) |
| Deviations | None |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | IND\_F032\_0321\_1 |
| **Species** | Human cornea-like epithelium model (RhCE) |
| **No. of Bovine Cornea** | Duratec Analysentechnik GmbH (N°10,28,20,3,25,8,7,23,1) |
| **Initial test using one animal** | No |
| **Pre-treatment exposure with DPBS** | 20µl, 30 min |
| **Exposure** | 750µl, 10 min (32°C± 1°C) |
| **Negative control** | 750 µl (0.9% NaCl) |
| **Positive control** | 750 µl Ethanol |
| **Vehicle/Dilution** | None |
| **Post incubation exposure observation period** | 120min |
| **Remarks** | None |

NUMBER OF REPLICATE : In this assay 3 replicates per test item, negative control and positive control were used.

1. Test substance application

2. Test substance exposure

3. Rinsing, post soak and final opacity measurement

4. Permeability measurement

5. Calculation of opacity value

6. Calculation of permeability value

7. Calculation of IVIS (*In Vitro* Irritancy Score)

Results and discussions

Table A 6: Eye Irritation and Corrosion of IN233C1560/ AVTAR : summary results

|  |  |
| --- | --- |
| Evaluations: | Corneal opacity is measured quantitatively as the amount of light transmission through the cornea. Permeability is measured quantitatively as the amount of sodium fluorescein dye that passes across the full thickness of the cornea, as detected in the medium in the posterior chamber. Both measurements are used to calculate an IVIS, which is used to classify the test item in the UN GHS System. |
| Test duration: | Exposure of test item: 10 minutes.  Post incubation: 120 minutes. |
| Incubation conditions: | 32 ± 1°C |
| Validity of the controls: | Positive controls (Ethanol) IVIS value falls within 2 standard deviations of the current historical mean (reported in the report).  The negative controls (0.9 % NaCl solution) opacity and permeability values are less than the upper limits of the background values (reported in the report). |
| Results: | One valid experiment was performed.  Under the conditions of this study, the test item showed a slight effect on the cornea of the bovine eye. The calculated mean IVIS (*in vitro* irritancy score) is 12.9. |

Table A 7: Eye Irritation and Corrosion of IN233C1560/ AVTAR : In vitro Irritancy Score (IVIS)

|  |  |  |  |
| --- | --- | --- | --- |
| Sample | Cornea Holder # | IVIS | Mean IVIS |
| Negative control  (0.9 % NaCl) | 10 | -0.4 | -0.4 |
| 28 | -0.4 |
| 20 | -0.4 |
| Positive control  (Ethanol) | 3 | 45.9 | 47.9 |
| 25 | 46.0 |
| 8 | 52.0 |
| **Test item**  **(2102121-00112)** | 7 | 11.1 | **12.9** |
| 23 | 15.1 |
| 18 | 12.6 |

INTERPRETATION OF TEST RESULTS :According to OECD Guideline no. 437, a substance with an IVIS > 55 induces serious eye damage and should be classified as UN GHS Category 1 while a substance with an IVIS ≤ 3 requires no classification for eye irritation or serious eye damage (No Category).

Substances with IVIS > 3 and ≤ 55 cannot be assessed.

Under the conditions of this test, the test item “Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C156/ AVTAR 0” showed an effect on the cornea of the bovine eye. The calculated IVIS (in vitro irritancy score) is 12.9.

The negative control (NaCl 0.9 %) and the positive control (Ethanol) have met the validity criteria.

Conclusion

Under the experimental conditions, IN233C1560/ AVTAR showed an effect on the cornea. But according to OECD Guideline no. 437 (2020), a substance with an IVIS > 3 and ≤ 55 induce effects on the cornea, that cannot be classified in a UN GHS Category for eye damage.

Thus, a classification is not required according to Regulation (EC) No. 1272/2008.

|  |  |
| --- | --- |
| Comments of zRMS: | The study “Difenoconazole 130 g/L + Prothioconazole 250 g/L EC – IN233C1560: In vitro Eye Irritation and Corrosion with the Bovine Corneal Opacity and Permeability (BCOP) Test” (KCP 7.1.5/02) was performed in GLP conditions and according to OECD Guidelines for the Testing of Chemicals No. 437, “Bovine Corneal Opacity and Permeability Test Method For Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage adopted 26 June 2020.“ The negative control (NaCl 0.9 %) and the positive control (Ethanol) have met the validity criteria. The study is considered as acceptable. In this study a formulation IN233C1560 has caused effects on the cornea of the bovine eye. The calculated IVIS (in vitro irritancy score) is 12.9. Since an in vitro irritancy score (IVIS) was above 3 formulation IN233C1560 does meet criteria for no classification for eye irritation or serious eye damage (No Category). On the other hand a formulation IN233C1560 does not meet criteria for serious eye damage because IVIS was well below 55. Since in vitro irritancy score of 12.9 is between 3 and 55 no stand-alone prediction can be made on eye irritancy/corrosion test, however with the results of the first study showing that the mean viability of treated cells was 42.9 % of the mean value of negative control indicate that a formulation IN233C1560 is an eye irritant and should be classified as Eye Irrit. 2, H319: Causes serious eye irritation. |

* 1. Skin sensitisation (KCP 7.1.6)

|  |  |
| --- | --- |
| Comments of zRMS: | The proposal of the applicant to not classify AVTAR (IN233C1560) for skin sensitisation is supported because none of the product ingredients is classify for skin sensitisation. |

A skin sensitization study for AVTAR is not provided. Instead, the skin sensitization classification of the product was determined using the calculation method as described in Regulation (EC) No. 1272/2008.

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

No supplementary study was carried out.

* 1. Data on co-formulants (KCP 7.4)
     1. Material safety data sheet for each co-formulant

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

* + 1. Available toxicological data for each co-formulant

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

* 1. Studies on dermal absorption (KCP 7.3)
     1. Study 1 – Difenoconazole in IN233C1560

Comparative dermal absorption, in vitro using rat and human skin

|  |  |
| --- | --- |
| Comments of zRMS: | The study performed according to internationally recognized OECD guidelines and in GLP conditions is acceptable  The number of replicates for the concentrate was 8 and for dilution 8.  According to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the dermal absorption is equal:   * when less than 75% of the absorption occurs within half the duration of the study then dermal absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2) * mean value + ks, where s is the sample standard deviation:   Mean absorption of the concentrate: 2.11 + 0.84 x 1.17= 2.11 + 0.983 = 3.10 %  Mean absorption of the 1:560 spray dilution : 16.79+ 0.84 x 6.32 = 16.79 + 5.31 = 22.0%  Thus, the conservative dermal penetration estimates to be used for risk assessment is 3.10 % for the concentrate (130 g a.s. /L) and 22.0% for the spray dilution (0.23 g a.s. /L ) based on the EFSA guidance 2017 criteria |

|  |  |
| --- | --- |
| Reference | KCP 7.3/01 |
| Report | *In vitro* dermal absorption of difenoconazole from difenoconazole 130 g/l + prothioconazole 250 g/L EC - IN233C1560 using human split-thickness skin in a flow through diffusion system, 2022, Report No.: 617-1-06-29169 |
| Guideline(s) | Yes  OECD 428 |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |  |
| --- | --- | --- |
| **Test material** | Difenoconazole | |
|  | Test preparation | Radioformulation |
| Specific activity | 56.6 mCi/mmol |
| Radiochemical purity | 100% |
| Product | Name (Lot/Batch No.) | Difenoconazole 130 G/L + Prothioconazole 250 g/L EC - IN233C1560 (IND\_F032\_0321\_1) |
| Company code | XXXX |
| Concentration a.s. | 130 [g/L] |
| Formulation type | EC |
| Blank product | Name (Lot/Batch No.) | Placebo Difenoconazole 130 g/L + Prothioconazole 250 g/L EC - IN233C1560 (IND\_F032\_0321\_1) |
| Concentration a.s. | 0 [g/L] |

|  |  |  |
| --- | --- | --- |
| **Test system** |  |  |
| Diffusion cell | Cell type | Static |
| (if dynamic) Flow rate | Not applicable |
| Exposed skin area | 0.64 cm² |
| Cover | Occlusive |
| Membrane | Skin type | Dermatomed |
| Skin thickness range | 300 - 400 µm |
| Location | Abdomen |
| Source | *Ex vivo* |
| Integrity test | Yes |
| Receptor | Receptor medium | Dulbecco's phosphate buffered saline (DPBS) with pH 7.4, supplemented with 6% PEG, 0.01% sodium azide and antibiotics, i.e. penicillin (50 IU/mL) and streptomycin (50 µg/mL) |
| Solubility in receptor medium | Yes |
| Sample Time | Exposure time | 6 h ± 10 minutes |
| Observation time | 24h |
| Sampling | Sample intervals (h) | 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 |
| Washing |  | Post exposure and post observation |
| Final Procedure | Tape stripping | Yes |
| TS1-2 analysed separately | Yes |
| Remarks: none | | |

|  |  |  |
| --- | --- | --- |
| **Tested doses** | Concentrate | Spray dilution 1 |
| Target concentration [mg/ml] | 130 | 0.23 |
| Area dose [µg/cm²] | 1300 | 2.3 |
| Total dose [µg/cell] | 832 | 1.5 |
| Specific activity [kBq/ml] | 56.6 mCi/mmol | 56.6 mCi/mmol |
| No. of donors | 4 | 4 |
| No of cells used/valid cells | 8/8 | 8/8 |

Results and discussions

Table A 8: In-vitro dermal penetration of difenoconazole formulated as IN233C1560 through human skin - Recovery data

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Test Preparation I**  (Concentrate) | | **Test Preparation II**  **(**Field spray dilution-1) | |
| Test Formulation Concentration | 130 g/L | | 0.23 g /L | |
| Applied Dose (µg/cm2) | 1300 µg/cm2 | | 2.3 µg/cm2 | |
| Number of replicates | 8 from 4 donors | | 8 from 4 donors | |
| Cumulative Absorption into the Receptor Fluid | % of dose | µg/cm2 | % of dose | µg/cm2 |
| after 12 h | 0.07 | 0.8483 | 4.44 | 0.0999 |
| after 24 h | 0.10 | 1.2997 | 6.41 | 0.1443 |
| Mean Maximal Flux (µg/cm2/h) | 0.069 | | 0.002 | |
| Lag Time (h) | -1.10 | | 0.18 | |
|  | **Recovery of [14C] Difenoconazole (% of dose)** | | | |
| Mean | SD | Mean | SD |
| Receptor Fluid (0-24h) | 0.10 | 0.06 | 6.41 | 3.02 |
| Receptor Compartment Wash | 0.02 | 0.01 | 0.14 | 0.07 |
| Dermis | 0.20 | 0.17 | 2.26 | 1.38 |
| Epidermis (without *stratum corneum*) | 0.77 | 0.52 | 3.00 | 1.11 |
| Tape Strips (1-2) | 0.55 | 0.55 | 2.16 | 2.22 |
| Tape Strips (3 to 15) | 1.03 | 0.68 | 4.99 | 2.19 |
| *Stratum corneum* | 1.57 | 1.15 | 7.14 | 3.27 |
| Skin Wash at 6h | 90.63 | 6.18 | 73.95 | 8.88 |
| Skin Wash at 24h | 6.19 | 3.60 | 6.61 | 1.82 |
| Donor Compartment Wash | 0.80 | 0.77 | 0.62 | 0.36 |
| **Total Recovery** | 100.27 | 2.04 | 100.11 | 2.84 |
| **1Absorbed dose I** | 0.32 | 0.17 | 8.81 | 4.23 |
| **2Absorbed dose II** | 1.08 | 0.61 | 11.80 | 4.56 |
| **3Absorbed dose III** | 2.11 | 1.17 | 16.79 | 6.32 |
| **4Unabsorbed dose** | 98.16 | 2.32 | 83.33 | 6.84 |
| **Dermal Absorption Corrected Values as per EFSA 2017** | | | | |
| LLC of t\_0.5 absorption | 53.66 | 11.45 | 57.38 | 9.63 |
| Absorption complete? | No | | No | |
| Measured absorption, if LLC of t\_0.5<=75% | 2.11 | 1.17 | 16.79 | 6.32 |
| Measured absorption, if LLC of t\_0.5>75% | N/A | N/A | N/A | N/A |
| Measured absorption corrected | 2.11 | 1.17 | 16.79 | 6.32 |
| Relevant absorption estimate | 3.089 | | 22.094 | |
| Final estimate (rounded) | 3.1 | | 22 | |

**1Absorbed dose I** was calculated from the amounts recovered in the receptor fluid, the receptor compartment wash, and the vascular dermis.

**2Absorbed dose II** was calculated from the absorbed dose I, plus the non-vascular epidermis (without *stratum corneum*). The absorbed dose II can be considered conservative.

**3Absorbed dose III** was calculated from the absorbed dose II plus the dead *stratum corneum* (tape strips 3 to last). The absorbed dose III can be considered highly conservative.

**4Unabsorbed dose** was calculated from the amounts recovered from skin washings at 6 h and 24 h, donor compartment wash and the first two tape strips

LLC = Lower limit of confidence; Mean T0.5 value corrected for standard deviation (lower 95% confidence value of mean)

T0.5 = Amount permeated into the receptor fluid at 12 h of amount permeated at 24 h.

Conclusion/endpoint:

In conclusion, the absorbed dose I for Test Preparation I and II was 0.32% and 8.81%, respectively. The absorbed dose II and III, which were considered conservative and included non-vascular epidermis and dead stratum corneum (excluding tape strips 1 and 2), was 1.08% and 2.11%, respectively, for Test Preparation I; 11.8% and 16.79%, respectively for Test Preparation II. The corrected dermal absorption value based on EFSA, 2017 was 3.1% for Test Preparation I and 22% for Test Preparation II.

* + 1. Study 2 – Prothioconazole in IN233C1560

Comparative dermal absorption, in vitro using rat and human skin

|  |  |
| --- | --- |
| Comments of zRMS: | The study performed according to internationally recognized OECD guidelines and in GLP conditions is acceptable  According to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the dermal absorption is equal:   * when less than 75% of the absorption occurs within half the duration of the study then dermal absorption = receptor fluid + receptor chamber washes + skin sample (excluding tape strips 1 and 2) * mean value + ks, where s is the sample standard deviation: * number of replicates for the concentrate was 8 and for dilution 8.   Mean absorption of prothioconazole from the concentrate: 0.237+0.84x0.075= 0.237 + 0.063 = 0.3%  Mean absorption of prothioconazole from the 1:560 spray dilution : 10.36+ 0.84 x 5.87= 10.36 + 4.93 = 15.290% rounded to 15%  Thus, the conservative dermal penetration estimates to be used for risk assessment is 0.3 % for the concentrate (250 g a.s. /L) and 15 % for the spray dilution (0.44 g /L ) |

|  |  |
| --- | --- |
| Reference | KCP 7.3/01 |
| Report | *In vitro* dermal absorption of prothioconazole from difenoconazole 130 g/l + prothioconazole 250 g/L EC - IN233C1560 using human split-thickness skin in a flow through diffusion system, 2022, Report No.: 617-1-06-29234 |
| Guideline(s) | Yes  OECD 428 |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Table A 9: Summary of Dermal absorption of Prothioconazole from Difenoconazole 130 g/L + Prothioconazole 250 g/L EC - IN233C1560 through Human Split-thickness Skin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Test Preparation I**  (Concentrate) | | **Test Preparation II**  **(**Field spray dilution-1) | |
| Test Formulation Concentration | 250 g/L | | 0.44 g /L | |
| Applied Dose (µg/cm2) | 2500 µg/cm2 | | 4.4 µg/cm2 | |
| Number of replicates | 8 from 4 donors | | 8 from 4 donors | |
| Cumulative Absorption into the Receptor Fluid | % of dose | µg/cm2 | % of dose | µg/cm2 |
| after 12 h | 0.057 | 1.3883 | 2.815 | 0.1245 |
| after 24 h | 0.091 | 2.2174 | 4.146 | 0.1833 |
| Mean Maximal Flux (µg/cm2/h) | 0.101 | | 0.004 | |
| Lag Time (h) | -1.22 | | 0.99 | |
|  | **Recovery of [14C] Prothioconazole (% of dose)** | | | |
| Mean | SD | Mean | SD |
| Receptor Fluid (0-24h) | 0.091 | 0.052 | 4.146 | 2.201 |
| Receptor Compartment Wash | 0.016 | 0.013 | 0.068 | 0.068 |
| Dermis | 0.027 | 0.009 | 1.800 | 2.131 |
| Epidermis  (Without *stratum corneum*) | 0.056 | 0.040 | 2.395 | 1.486 |
| Tape Strips (1-2) | 0.016 | 0.017 | 0.606 | 0.362 |
| Tape Strips (3 to 15) | 0.046 | 0.029 | 1.950 | 1.055 |
| *Stratum corneum* | 0.062 | 0.045 | 2.556 | 1.328 |
| Skin Wash at 6h | 99.809 | 1.123 | 86.958 | 6.804 |
| Skin Wash at 24h | 0.196 | 0.302 | 1.937 | 0.655 |
| Donor Compartment Wash | 0.070 | 0.084 | 0.189 | 0.142 |
| **Total Recovery** | 100.328 | 0.985 | 100.048 | 1.578 |
| **1Absorbed dose I** | 0.135 | 0.060 | 6.014 | 4.149 |
| **2Absorbed dose II** | 0.191 | 0.061 | 8.409 | 5.283 |
| **3Absorbed dose III** | 0.237 | 0.075 | 10.359 | 5.865 |
| **4Unabsorbed dose** | 100.092 | 0.997 | 89.689 | 6.016 |
| **Dermal Absorption Corrected Values as per EFSA 2017** | | | | |
| LLC of t\_0.5 absorption | 58.71 | 2.62 | 61.04 | 6.89 |
| Absorption complete? | No | | No | |
| Measured absorption, if LLC of t\_0.5<=75% | 0.24 | 0.08 | 10.36 | 5.87 |
| Measured absorption, if LLC of t\_0.5>75% | N/A | N/A | N/A | N/A |
| Measured absorption corrected | 0.24 | 0.08 | 10.36 | 5.87 |
| Relevant absorption estimate | 0.285 | | 14.113 | |
| Final estimate (rounded) | 0.28 | | 14 | |

**1Absorbed dose I** was calculated from the amounts recovered in the receptor fluid, the receptor compartment wash, and the vascular dermis.

**2Absorbed dose II** was calculated from the absorbed dose I, plus the non-vascular epidermis (without *stratum corneum*). The absorbed dose II can be considered conservative.

**3Absorbed dose III** was calculated from the absorbed dose II plus the dead *stratum corneum* (tape strips 3 to last). The absorbed dose III can be considered highly conservative.

**4Unabsorbed dose** was calculated from the amounts recovered from skin washings at 8h and 24h, donor compartment wash and the first two tape strips

LLC = Lower limit of confidence; Mean T0.5 value corrected for standard deviation (lower 95% confidence value of mean)

T0.5 = Amount permeated into the receptor fluid at 12 h of amount permeated at 24 h.

Table A 10: Summary of Absorbed dose from Test preparation I and II

| **Species** | **Parameters** | **Test Preparation I (Concentrate)** | **Test Preparation II (Field Spray**  **Dilution-1)** |
| --- | --- | --- | --- |
| **Mean ± SD** | **Mean ± SD** |
| **Human Skin** | Absorbed dose I (%) | 0.135 ± 0.06 | 6.01 ± 4.15 |
| Absorbed dose II (%) | 0.191 ± 0.061 | 8.41 ± 5.28 |
| Absorbed dose III (%) | 0.237 ± 0.075 | 10.36 ± 5.87 |
| Dermal absorption corrected values as per EFSA 2017 | 0.28 | 14 |
| Maximal flux [µg/cm2/h] | 0.101 ± 0.055 | 0.004 ± 0.005 |

* + 1. Study 3 – Prothioconazole-desthio in IN233C1560

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

|  |  |
| --- | --- |
| Comments of zRMS: | The study performed according to internationally recognized OECD guidelines and in GLP conditions is acceptable  According to EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the dermal absorption is equal:   * When over 75% of the permeation occurred within half of the duration of the total sampling period a dermal absorption equals = receptor fluid + receptor chamber washes + skin sample (excluding all tape strips) * mean value + ks, where s is the sample standard deviation: * number of replicates for the concentrate was 8 and for dilution 8.   Mean absorption of Prothioconazole-desthio from the field dilution I (1.59 g/L):  9.59+0.84 x 2.87= 9.59 + 2.41 = 12 %  Mean absorption of Prothioconazole-desthio from the field dilution II (0.4 g /L):  11.54+ 0.84 x 1.84= 11.54 + 1.5456 = 13.08% rounded to 13%  Thus, the conservative dermal penetration estimates to be used for risk assessment is 12 % for the field dilution I (1.59 g/L) and 13% for the spray dilution (0.44 g /L) |

|  |  |
| --- | --- |
| Reference | KCP 7.3/01 |
| Report | *In vitro* dermal absorption of prothioconazole-desthio from difenoconazole 130 g/l + prothioconazole 250 g/L EC - IN233C1560 using human split-thickness skin in a flow through diffusion system, 2022, Report No.: 617-1-06-29977 |
| Guideline(s) | Yes  OECD 428 |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Table A 11: Summary of Dermal absorption of Prothioconazole-desthio from Difenoconazole 130 g/L + Prothioconazole 250 g/L EC - IN233C1560 through Human Split-thickness Skin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Test Preparation I**  (Field spray dilution-1) | | **Test Preparation II**  **(**Field spray dilution-2) | |
| Test Formulation Concentration | 1.59 g/L | | 0.4 g /L | |
| Applied Dose (µg/cm2) | 15.9 µg/cm2 | | 4 µg/cm2 | |
| Number of replicates | 8 from 4 donors | | 8 from 4 donors | |
| Cumulative Absorption into the Receptor Fluid | % of dose | µg/cm2 | % of dose | µg/cm2 |
| after 12 h | 7.25 | 1.1449 | 8.02 | 0.3440 |
| after 24 h | 8.63 | 1.3633 | 9.56 | 0.4098 |
| Mean Maximal Flux (µg/cm2/h) | 0.138 | | 0.036 | |
| Lag Time (h) | 1.09 | | 1.02 | |
|  | **Recovery of [14C] Prothioconazole-desthio (% of dose)** | | | |
| Mean | SD | Mean | SD |
| Receptor Fluid (0-24h) | 8.63 | 2.74 | 9.56 | 2.01 |
| Receptor Compartment Wash | 0.07 | 0.04 | 0.06 | 0.03 |
| Dermis | 0.57 | 0.21 | 1.62 | 0.53 |
| Epidermis  (Without *stratum corneum*) | 0.32 | 0.23 | 0.31 | 0.40 |
| Tape Strips (1-2) | 0.22 | 0.17 | 0.10 | 0.07 |
| Tape Strips (3 to 15) | 0.42 | 0.33 | 0.31 | 0.23 |
| *Stratum corneum* | 0.64 | 0.49 | 0.41 | 0.26 |
| Skin Wash at 6h | 86.79 | 5.57 | 85.78 | 3.77 |
| Skin Wash at 24h | 2.22 | 1.23 | 1.77 | 1.00 |
| Donor Compartment Wash | 0.14 | 0.14 | 0.12 | 0.22 |
| **Total Recovery** | 99.37 | 2.59 | 99.63 | 2.04 |
| **1Absorbed dose I** | 9.27 | 2.80 | 11.24 | 1.88 |
| **2Absorbed dose II** | 9.59 | 2.87 | 11.54 | 1.84 |
| **3Absorbed dose III** | 10.00 | 2.99 | 11.86 | 1.94 |
| **4Unabsorbed dose** | 89.37 | 4.64 | 87.77 | 3.09 |
| **Dermal Absorption Corrected Values as per EFSA 2017** | | | | |
| LLC of t\_0.5 absorption | 78.69 | 5.06 | 80.17 | 3.75 |
| Absorption complete? | Yes | | Yes | |
| Measured absorption, if LLC of t\_0.5<=75% | N/A | N/A | N/A | N/A |
| Measured absorption, if LLC of t\_0.5>75% | 9.59 | 2.87 | 11.54 | 1.84 |
| Measured absorption corrected | 9.59 | 2.87 | 11.54 | 1.84 |
| Relevant absorption estimate | 11.422 | | 12.723 | |
| Final estimate (rounded) | 11 | | 13 | |

**1Absorbed dose I** was calculated from the amounts recovered in the receptor fluid, the receptor compartment wash, and the vascular dermis.

**2Absorbed dose II** was calculated from the absorbed dose I, plus the non-vascular epidermis (without *stratum corneum*). The absorbed dose II can be considered conservative.

**3Absorbed dose III** was calculated from the absorbed dose II plus the dead *stratum corneum* (tape strips 3 to last). The absorbed dose III can be considered highly conservative.

**4Unabsorbed dose** was calculated from the amounts recovered from skin washings at 8h and 24h, donor compartment wash and the first two tape strips

LLC = Lower limit of confidence; Mean T0.5 value corrected for standard deviation (lower 95% confidence value of mean)

T0.5 = Amount permeated into the receptor fluid at 12 h of amount permeated at 24 h.

Table A 12: Summary of Absorbed dose from Test preparation I and II

| **Species** | **Parameters** | **Test Preparation I (Field Spray**  **Dilution-1)** | **Test Preparation II (Field Spray**  **Dilution-2)** |
| --- | --- | --- | --- |
| **Mean ± SD** | **Mean ± SD** |
| **Human Skin** | Absorbed dose I (%) | 9.27 ± 2.8 | 11.24 ± 1.88 |
| Absorbed dose II (%) | 9.59 ± 2.87 | 11.54 ± 1.84 |
| Absorbed dose III (%) | 10 ± 2.99 | 11.86 ± 1.94 |
| Dermal absorption corrected values as per EFSA 2017 | 11 | 13 |
| Maximal flux [µg/cm2/h] | 0.138 ± 0.085 | 0.036 ± 0.017 |

* 1. Other/Special Studies

No supplementary study was carried out.

1. Exposure calculations
   1. Operator exposure calculations (KCP 7.2.1.1)
      1. Calculations for Difenoconazole - Cereals

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



Table A 14: Estimation of acute operator exposure towards Difenoconazole according to EFSA guidance



Table A 15: Estimation of longer-term operator exposure towards Difenoconazole according to EFSA guidance



* + 1. Calculations for Difenoconazole - Oilseeds

Table A 16: Input parameters considered for the estimation of operator exposure



Table A 17: Estimation of acute operator exposure towards Difenoconazole according to EFSA guidance



Table A 18: Estimation of longer-term operator exposure towards Difenoconazole according to EFSA guidance



* + 1. Calculations for Prothioconazole - Cereals

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



Table A 20: Estimation of acute operator exposure towards Prothioconazole according to EFSA guidance



Table A 21: Estimation of longer-term operator exposure towards Prothioconazole according to EFSA guidance



Table A21 A Estimation of longer-term operator exposure towards Prothioconazole according to EFSA guidance assuming dermal absorption of 0.3% for concentrate and 15% for dilution



* + 1. Calculations for Prothioconazole - Oilseeds

Table A 22: Input parameters considered for the estimation of operator exposure



Table A 23: Estimation of acute operator exposure towards active Prothioconazole to EFSA guidance



Table A 24: Estimation of longer-term operator exposure towards Prothioconazole according to EFSA guidance



Table A 25A: Estimation of longer-term operator exposure towards Prothioconazole according to

EFSA guidance assuming dermal absorption of concentrate of 0.3% and dilution 15%



* + 1. Calculations for Prothioconazole-desthio - Cereals

Table A 26: Input parameters considered for the estimation of operator exposure



Table A 27: Estimation of acute operator exposure towards Prothioconazole-desthio according to EFSA guidance



Table A 28: Estimation of longer-term operator exposure towards Prothioconazole-desthio according to EFSA guidance



Table A 29A: Estimation of longer-term operator exposure towards Prothioconazole-desthio according to EFSA guidance assuming dermal absorption 13%



* + 1. Calculations for Prothioconazole-desthio - Oilseeds

Table A 30: Input parameters considered for the estimation of operator exposure



Table A 31: Estimation of acute operator exposure towards active Prothioconazole-desthio to EFSA guidance



Table A 32: Estimation of longer-term operator exposure towards Prothioconazole-desthio according to EFSA guidance



* 1. Worker exposure calculations (KCP 7.2.3.1)
     1. Calculations for Difenoconazole - Cereals

Table A 33: Input parameters considered for the estimation of worker exposure



Table A 34: Estimation of worker exposure towards Difenoconazole according to EFSA guidance



* + 1. Calculations for Difenoconazole - Oilseeds

Table A 35: Input parameters considered for the estimation of worker exposure



Table A 36: Estimation of worker exposure towards Difenoconazole according to EFSA guidance



* + 1. Calculations for Prothioconazole - Cereals

Table A 37: Input parameters considered for the estimation of worker exposure



Table A 38: Estimation of worker exposure towards Prothioconazole according to EFSA guidance



Table A37A Estimation of worker exposure towards Prothioconazole according to EFSA guidance assuming dermal absorption of 0.3% for concentrate and 15% for dilution



* + 1. Calculations for Prothioconazole - Oilseeds

Table A 39: Input parameters considered for the estimation of worker exposure



Table A 40: Estimation of worker exposure towards Prothioconazole according to EFSA guidance



Table A 41A: Estimation of worker exposure towards Prothioconazole according to EFSA guidance assuming dermal absorption of concentrate 0.3% and dilution 15%



* + 1. Calculations for Prothioconazole-desthio - Cereals

Table A 42: Input parameters considered for the estimation of worker exposure



Table A 43: Estimation of worker exposure towards Prothioconazole-desthio according to EFSA guidance



* + 1. Calculations for Prothioconazole-desthio - Oilseeds

Table A 44: Input parameters considered for the estimation of worker exposure



Table A 45: Estimation of worker exposure towards Prothioconazole-desthio according to EFSA guidance



* 1. Resident and bystander exposure calculations (KCP 7.2.2.1)
     1. Calculations for Difenoconazole - Cereals

Table A 46: Input parameters considered for the estimation of resident exposure



Table A 47: Estimation of resident exposure towards Difenoconazole according to EFSA guidance



Table A 48: Input parameters considered for the estimation of acute bystander exposure



Table A 49: Estimation of bystander exposure towards active substance according to EFSA guidance



* + 1. Calculations for Difenoconazole - Oilseeds

Table A 50: Input parameters considered for the estimation of resident exposure



Table A 51: Estimation of resident exposure towards Difenoconazole according to EFSA guidance



Table A 52: Input parameters considered for the estimation of bystander exposure



Table A 53: Estimation of bystander exposure towards Difenoconazole according to EFSA guidance



* + 1. Calculations for Prothioconazole - Cereals

Table A 54: Input parameters considered for the estimation resident exposure



Table A 55: Estimation of resident exposure towards Prothioconazole according to EFSA guidance



Table A 56A: Estimation of resident exposure towards Prothioconazole according to EFSA guidance assuming dermal absorption of concentrate 0.3% and dilution 15%



Table A 57: Input parameters considered for the estimation of bystander exposure



Table A 58: Estimation of bystander exposure towards Prothioconazole according to EFSA guidance



* + 1. Calculations for Prothioconazole - Oilseeds

Table A 59: Input parameters considered for the estimation resident exposure



Table A 60: Estimation of resident exposure towards Prothioconazole according to EFSA guidance



Table A 61A: Estimation of resident exposure towards Prothioconazole according to EFSA guidance assuming dermal absorption from the concentrate 0.3% and dilution 15%



Table A 62: Input parameters considered for the estimation of bystander exposure



Table A 63: Estimation of bystander exposure towards Prothioconazole according to EFSA guidance



* + 1. Calculations for Prothioconazole-desthio - Cereals

Table A 64: Input parameters considered for the estimation resident exposure



Table A 65: Estimation of resident exposure towards Prothioconazole-desthio according to EFSA guidance



Table A 66: Input parameters considered for the estimation of bystander exposure



Table A 67: Estimation of bystander exposure towards Prothioconazole-desthio according to EFSA guidance



* + 1. Calculations for Prothioconazole-desthio - Oilseeds

Table A 68: Input parameters considered for the estimation resident exposure



Table A 69: Estimation of resident exposure towards Prothioconazole-desthio according to EFSA guidance



Table A 70: Input parameters considered for the estimation of bystander exposure



Table A 71: Estimation of bystander exposure towards Prothioconazole-desthio according to EFSA guidance



* 1. Combined exposure calculations for difenoconazole and prothioconazole or prothioconazole-desthio

For every scenario, the worst-case estimated exposure between the prothioconazole and the prothioconazole-desthio was considered in combination with the estimated exposure of difenoconazole to have the most conservative approach. In order to estimate the combined exposure for difenoconazole, prothioconazole and prothioconazole-desthio for operator, worker and resident, the following calculations were used:

Acute exposure

or

Where:

* Expdif is the exposure for difenoconazole (mg/kg bw/d);
* AAOELdif is equal to 0.16 mg/kg bw/d;
* Exppro is the exposure for prothioconazole (mg/kg bw/d);
* AAOELpro is equal to 0.01 mg/kg bw/d;
* Expdesthio is the exposure for prothioconazole-desthio (mg/kg bw/d);
* AAOELdesthio is equal to 0.01 mg/kg bw/d.

Long-term exposure

or

Where:

* Expdif is the exposure for difenoconazole (mg/kg bw/d);
* AOELdif is equal to 0.16 mg/kg bw/d;
* Exppro is the exposure for prothioconazole (mg/kg bw/d);
* AOELpro is equal to 0.2 mg/kg bw/d;
* Expdesthio is the exposure for prothioconazole-desthio (mg/kg bw/d);
* AOELdesthio is equal to 0.01 mg/kg bw/d.

1. RMS Revised exposure calculations
   1. Operator exposure calculations (KCP 7.2.1.1)
      1. Calculations for Difenoconazole – Cereals



* + 1. Calculations for Difenoconazole – Cereals



* + 1. Calculations for Difenoconazole – Oilseed rape



* + 1. Calculations for Difenoconazole – Oilseed rape



* + 1. Calculations for Prothioconazole – cereals



* + 1. Calculations for Prothioconazole – cereals



* + 1. Calculations for Prothioconazole – oilseed rape



* + 1. Calculations for Prothioconazole – oilseed rape



* + 1. Calculations for Prothioconazole-desthio – cereals



* + 1. Calculation for Prothioconazole-desthio cereals



* + 1. Calculations for prothioconazole-desthio oilseed rape



* + 1. Calculations for prothioconazole desthio oilseed rape



* 1. Worker exposure calculations (KCP 7.2.3.1)
     1. Calculations for Difenoconazole - Cereals



* + 1. Calculations for Difenconazole- oilseed rape



* + 1. Calculations for Prothioconazole – cereals



* + 1. Calculations for Prothioconazole – oilseed rape



* + 1. Calculations for Prothioconazole Desthio – Cereals



* + 1. Calculations for Prothioconazole Desthio- Oilseed rape



* 1. Resident and bystander exposure calculations (KCP 7.2.2.1)
     1. Calculations for Difenoconazole – Cereals



* + 1. Calculations for Difenoconazole \_Oilseed rape



* + 1. Calculations for Prothioconazole – Cereals



* + 1. Calculations for Prothioconazole – Oilseed rape



* + 1. Calculations for Prothioconazole\_desthio- cereals



* + 1. Calculations for Prothioconazole desthio -oilseed rape



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

No study provided.