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| REGISTRATION REPORT  **Part B**  Section 6  Mammalian Toxicology  Detailed summary of the risk assessment |
| Product code: A17960B  Product name(s): FORTENZA  Chemical active substance:  Cyantraniliprole, 600g/L |
| Interzonal  Zonal Rapporteur Member State: Poland |
| CORE ASSESSMENT  (New authorization) |
| Applicant: Syngenta  Submission date: 30/10/2020  MS Finalisation date: August 2021 (initial Core Assessment)  December 2021 (final Core Assessment) |

Version history

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| --- | --- |
| When | What |
| October 2020 | Initial dRR – Syngenta |
| August 2021 | Initial izRMS assessment  The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~. |
| December 2021 | Final report (Core Assessment updated following the commenting period)  Additional information/assessments included by the zRMS in the report in response to comments recieved from the cMS and the Applicant are highlighted in yellow. Information no longer relevant ~~is struck through and shaded~~. |
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| **General comments of ZRMS:**  This dossier has been prepared to support the zonal registration of the product A17960B / Fortenza. Product contains cyantraniliprole to be used as insecticide FS (Flowable concentrate for seed treatment). Mentioned above document summarizes the data related to the toxicological studies and exposure data for the plant protection product A17960B / Fortenza.  Acute toxicity studies for A17960B were not evaluated as part of the EU review of the active ingredient. A17960B containing 600.0 g/L cyantraniliprole has a low toxicity in respect to acute oral, inhalation and dermal toxicity. The product is neither irritant to the skin or eye of rabbits, nor a skin sensitizer (guinea pig; Buehler x9 applications). Taking into account all submitted data, A17960B does not meet the criteria for classification and labeling for acute toxicity according to the CLP Regulation 1172/2008.  There are no proposals for cyantraniliprole classification have been done by the EFSA and ECHA.  Additional studies has been submitted by the APPL regarding insufficient toxicological data for ground water metabolite IN-M2G98 (recognized during the peer review carried out by the RMS UK; see EFSA Journal 2014;12(9):3814) to conclude on reference values (data gap): Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats and Acute Oral Toxicity Study in Rats.  For detail information considering evaluation of the studies relied upon (toxicity properties) refer our comments in Appendix 2 to this dRR. Exposure assessment to the active substances A17960B based on the Seed-TROPEX Model assuming personal protective equipment is worn during seed treatment is exceeds 100% of the AOEL. Higher tier refinements (monitoring studies; Xxxxxxx, 2009 and 2015) have been applied to demonstrate acceptable risk assessments for seed treatment. Based on the inputs from this refinements study, exposure to the cyantraniliprole present in A17960B is predict to be acceptable during seed treatment (see Critical use Table 6.1-4) with the use of the following PPE: Standard long workwear, gloves when handling product and contaminated surfaces and in addition an impermeable coverall (Tyvek) during cleaning. |

# Mammalian Toxicology (KCP 7)

## Summary

Table 6.1‑1: Information on A17960B/Fortenza \*

|  |  |
| --- | --- |
| Product name and code | A17960B/Fortenza |
| Formulation type | FS (Flowable concentrate for seed treatment) |
| Active substance(s) (incl. content) | Cyantraniliprole; 600g/L |
| Function | Insecticide |
| Product already evaluated as the ‘representative formulation’ during the approval of the active substance(s) | No |
| Product previously evaluated in another MS according to Uniform Principles | No |

\* Information on the detailed composition of A17960B/Fortenza 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 A17960B/Fortenza according to Regulation (EC) No 1272/2008

|  |  |
| --- | --- |
| Hazard class(es), categories | n/a |
| Hazard pictograms or Code(s) for hazard pictogram(s) | n/a |
| Signal word | n/a |
| Hazard statement(s) | n/a |
| Precautionary statement(s) | n/a |
| Additional labelling phrases | EUH208 Contains 1,2-benzisothiazol-3-one.  May produce an allergic reaction. |

Table 6.1‑3: Summary of risk assessment for operators, workers, residents and bystanders for A17960B/Fortenza

|  | Result | PPE / Risk mitigation measures |
| --- | --- | --- |
| Operators | Acceptable | Coveralls, gloves during mixing/loading, calibration and cleaning. Coveralls during bagging. |
| Workers | Not applicable | Gloves while loading hopper |
| Residents | Not applicable |  |
| Bystanders | Not applicable |  |

No unacceptable risk for operators and workers was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in **Błąd! Nie można odnaleźć źródła odwołania.** are applied.

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Use-No.\* | Crops and situation (e.g. growth stage of crop) | F, Fn, Fpn G, Gn, Gpn or I \*\* | Application | | Application rate | | PHI (d) | Remarks:   (e.g. safener/synergist (L/ha))  critical gap for operator, worker, resident or bystander exposure based on [Exposure model] | Acceptability of exposure assessment | | | |
| Method / Kind  (incl. application technique \*\*\* | Max. number (min. interval between applications)  a) per use  b) per crop/ season | Max. application rate  kg as/tonne seed   a) Cyantraniliprole | Dilution factor | Operator | Worker | Residents | Bystander |
| 1 – 3 | Maize [ZEAMX] | I | Commercial Seed treatment | a) 1  b) 1 | a) 2.25 | Not applicable: concentrate is used as worst case | n/a | Operator; Worker [SeedTROPEX/study] |  |  | n/a | n/a |

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

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

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

Explanation for column 10 “Acceptability of exposure assessment”

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

Data gaps

Noticed data gaps are:

* None

## Toxicological Information on Active Substance(s)

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

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

|  | Cyantraniliprole |
| --- | --- |
| Common Name | Cyantraniliprole |
| CAS-No. | 736994-63-1 |
| Classification and proposed labelling | |
| With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended) | Hazard classes (s), categories: n/a  Code(s) for hazard pictogram(s): n/a  Signal word: n/a  Hazard statement(s): n/a  Precautionary statement(s): n/a |
| Additional C&L proposal | None |
| Agreed EU endpoints | |
| AOEL systemic | 0.007 mg/kg bw/d (corrected for 70% oral absorption) |
| Reference | EFSA Journal 2014;12(9):3814 |
| Conditions to take into account/critical areas of concern with regard to toxicology | |
| Review Report/EFSA Conclusion for active substance | None |

## Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for A17960B/Fortenza 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 A17960B/Fortenza

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of test, species, model system (Guideline) | Result | ATE & Additivity Calculation Result | Acceptability | Classification 1 (acc. to the criteria in Reg. 1272/2008) | Reference |
| LD50 oral, rat  (OECD 425) | LD50 = >5000 mg/kg bw | >2000 mg/kg  Not classified | Yes | None | Xxxxxxx, 2011  Syngenta File No A17960B\_10010 |
| LD50 dermal, rat  (OECD 402) | LD50 >5000 mg/kg bw | >2000 mg/kg  Not classified | Yes | None | Xxxxxxx,.2011  Syngenta File No A17960B\_10016 |
| LC50 inhalation, rat  (OECD 403) | LC50 >5.16 mg/l | >5 mg/L  Not classified | Yes | None | Xxxxxxx, 2011  Syngenta File No A17960B\_10033 |
| Skin irritation, rabbit  (OECD 404) | Non-irritant | n/a  Not classified | Yes | None | Xxxxxxx, 2011  Syngenta File No A17960B\_10011 |
| Eye irritation, rabbit (OECD 405) | Non-irritant | n/a  Not classified | Yes | None | Xxxxxxx, 2011  Syngenta File No A17960B\_10032 |
| Skin sensitisation, guinea pig  (OECD 406, Buehler (x9 applications) | Non-sensitising | n/a  Not classified | Yes | None | Xxxxxxx, 2011  Syngenta File No A17960B\_10002 |
| Supplementary studies for combinations of  plant protection products | No data – not required | - | - | - | - |

1 Proposed acute toxicity classifications are based on A17960B study results.

Table 6.3‑2: Additional toxicological information relevant for classification/labelling of A17960B/ Fortenza

|  | 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) | Cyantraniliprole (736994-63-1 >= 30 - < 50% (w/w)) | Hazard statement(s)  n/a | Reg. 1272/2008 / MSDS\*\* | Hazard statement(s)  n/a |
| Toxicological properties of non-active substance(s) (relevant for classification of product) | 1,2-benzisothiazol-3(2H)-one (CAS no. 2634-33-5, >= 0.025 - < 0.05% (w/w)) | Hazard statement(s)  Acute Tox. 4; H302  Skin Irrit. 2; H315  Eye Dam. 1; H318  Skin Sens. 1; H317 |
| Bronopol (INN)  (CAS no 52-51-7, >= 0.025 - < 0.1% (w/w)) | Hazard statement(s)  Acute Tox. 4; H302  Acute Tox. 4; H312  Skin Irrit. 2; H315  Eye Dam. 1; H318  STOT se 3: H335 |
| Further toxicological information | No data – not required |  |  |  |

\*Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS (Syngenta NoVV-874872)

\*\*Material safety data sheet by the applicant

## Toxicological Evaluation of Groundwater Metabolites

The following data on metabolites with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites is reported in Part B.10; the submitted toxicological studies are summarised in this document.

### Cyantraniliprole

**IN-M2G98**

An overview of the results of the accepted toxicological studies for groundwater metabolite IN-M2G98 is given in the following table. Full summaries of studies on the metabolite that have not previously been considered within an EU peer review process are described in detail in Appendix 2 (A 2.11 Other/Special Studies).

Table 6.4‑1: Summary of the results of toxicity studies for IN-M2G98

| Type of test, species (Guideline) | Result | Acceptability | Reference |
| --- | --- | --- | --- |
| Acute oral study in rats (Up-and-Down procedure)  (OECD 425) | Oral LD50 in females 175 mg/kg bw | Yes,  for detail information reflecting evaluation of the study relied upon (toxicity properties) refer our comments in Appendix 2 to this dRR. | Xxxxxxx., 2016  DuPont-45346  Syngenta file No. SYN548397\_10003 |
| Repeated dose oral toxicity 28-day feeding study in rats  (OECD 407) | The NOAEL for males and females was not established due to the observation of adverse effects in males and females at the lowest dietary concentration evaluated, 150 ppm (12 mg/kg bw/day for both sexes). | Yes,  for detail information reflecting evaluation of the study relied upon (toxicity properties) refer our comments in Appendix 2 to this dRR. | Xxxxxxx., 2016  DuPont-45277  Syngenta file No. SYN548397\_10004 |
| Bacterial Reverse Mutation Test  (OECD 471) | Negative for mutagenic activity in non-activated and S9-activated test systems. | Yes | Wagner V O., 2013  DuPont-37572  EFSA Journal 2014;12(9):3814 |
| |  | | --- | | *In vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes  (OECD 473) | | Negative for the induction of structural and numerical chromosome aberrations in cultured human peripheral blood lymphocytes with and without an exogenous metabolic activation system | Yes | Glover K P., 2013  DuPont-37573  EFSA Journal 2014;12(9):3814 |
| *In vitro* mammalian cell gene mutation test (CHO/HGPRT assay)  (OECD 476) | Negative in the non-activated and S9-activated test systems | Yes | Clarke, J J., 2013  DuPont-37574  EFSA Journal 2014;12(9):3814 |

## Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substance cyantraniliprole in A17960B/Fortenza are presented in the following table.

Table 6.5‑1: Dermal absorption rates for active substance in A17960B/Fortenza

|  | Cyantraniliprole | |
| --- | --- | --- |
|  | Value | Reference |
| Concentrate | 0.3% | Xxxxxxx., 2014,  Syngenta File No A17960B\_10054 |

### Justification for proposed values - Cyantraniliprole

Proposed dermal absorption rates for Cyantraniliprole are based on a dermal absorption study conducted with the current product/formulation. The study results are summarized in the following table. Full summary of the study on the dermal absorption of Cyantraniliprole/A17960B are described in detail in Appendix 2.

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

| Test | Concentrate | Spray dilution  (dilution factor) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| In vitro (human) | 0.3% | n/a | A17960B/Fortenza | Yes,  dermal absorption values have been derived in accordance with the EFSA GD on Dermal Absorption (EFSA Journal 2012;10(4):2665). ZRMS PL agrees that proposed dermal absorption value can be used for risk assessment. | Yes  (see Appendix A 2.10) | Justification accepted. | Xxxxxxx, 2014  Syngenta File No A17960B\_10054 |

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

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

|  |  |
| --- | --- |
| Product name and code | A17960B/Fortenza |
| Formulation type | FS (Flowable concentrate for seed treatment) |
| Category | Insecticide |
| Active substance(s) (incl. content) | Cyantraniliprole, 600g/L |
| AOEL systemic | 0.007 mg/kg bw/d |
| Inhalation absorption | 100% |
| Oral absorption | 70% |
| Dermal absorption | Concentrate: 0.3%  (Based on product (formulation))  Concentrate is used as worst case |

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

The critical GAP used for the exposure assessment of the plant protection product is shown in No unacceptable risk for operators and workers was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in **Błąd! Nie można odnaleźć źródła odwołania.** are applied.

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

Table 6.1‑4. A list of all intended uses within the zone/ EU is given in Part B, Section 0.

Justification

There is only one proposed application rate for the treatment of maize with A17960B. This application rate has been used for all exposure estimates.

### Operator exposure (KCP 7.2.1)

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| **Reviewers comment:**  Exposure assessment to the active substances A17960B based on the Seed-TROPEX Model assuming personal protective equipment is worn during seed treatment is exceeds 100% of the AOEL. Higher tier refinements (monitoring study 01 Wilson 2015, Syngenta Study No VV-414714 and monitoring study 02; Wilson 2009, Syngenta File No ASF827\_10000) have been applied to demonstrate acceptable risk assessments for seed treatment. Based on the inputs from this refinements study, exposure to the cyantraniliprole present in A17960B is predict to be acceptable during seed treatment (see Critical use Table 6.1-4) with the use of the following PPE: Standard long workwear, gloves when handling product and contaminated surfaces and in addition an impermeable coverall (Tyvek) during cleaning  Note:  Considering the fact that the exposure information underlying the SeedTROPEX model is from the early 1990s, ZRMS PL accepted for the purpose of current assessment, monitoring studies Xxxxxxx, 2009 and 2015 as higher tier refinements, sponsored by the Seed-TROPEX Group which defines more precisely the Seed-TROPEX data base with a modern low dust seed treatment formulation and modern fast-coupling systems mobile treaters and static plants. |

#### Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substance during application of A17960B according to the critical use(s) is presented in **Błąd! Nieprawidłowy odsyłacz do zakładki: wskazuje na nią samą.**. The outcome of the estimation is presented in **Błąd! Nie można odnaleźć źródła odwołania.**. Detailed calculations are in Appendix 3.

At this time, no acute AOEL has been set for cyantraniliprole. Consequently, no acute risk assessment has been provided for this active substance.

Table 6.6-2: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Maize seed (max 3.75 L product/tonne seeds) |
| Model(s) | SeedTROPEX  [Chester, G., Wiseman, M., Pontal, P-G., Worker Exposure During Seed Treatment and Sowing of Treated Seed in the UK and France: An Overview. Zeneca Agrochemicals, Fernhurst, Haslemere. Report No. TMF 4896.] |

Operator exposure is estimated using the “Seed-TReatment OPerator EXposure” data (Seed-TROPEX). Seed-TROPEX is an exposure data base submitted to UK-PSD in 1996 for national registrations by an Industry Task Force and contains results from studies performed in the UK and France.

The Seed-TROPEX data base submitted in 1996 consists of two parts: Exposure values for operators involved in seed treatment activities and exposure values for workers loading and sowing treated seed.

Seed treatment

Data from two Seed-TROPEX studies carried out in 1993 have been used, one study in the UK monitored operators’ exposure to ‘Baytan’ containing triadimenol, applied at 370 g/tonne seed[[1]](#footnote-2) and one study in France monitored the exposure of operators to 'Germinate Double' containing anthraquinone[[2]](#footnote-3), applied at 500 g/tonne seed. In the studies, operator exposure was assessed separately for the activities of equipment calibration, slurry preparation (“mixing and loading”), bagging of treated seed and cleaning of the equipment.

Data from both these studies have been combined to form a generic database that can be used to calculate potential exposure to other seed treatment products. The overview[[3]](#footnote-4) summarises the UK and French data and provides guidance on how to calculate exposure to a seed treatment product using the generic data in the form of a worked example.

For all tasks, except for bagging, it is assumed that operator exposure is a result of contact with the (neat or diluted) seed dressing liquid. Therefore, the generic exposure figures are expressed in mL/operation so that the respective concentration of active substance present in the neat formulation or in the diluted seed dressing liquid is taken into account. For bagging, a constant generic exposure figure – expressed as mg/hr – is used, meaning that the amount of product applied to the seeds is not taken into account.

Since the delivery, some of the generic exposure values have been revised and the values currently being used are presented in **Błąd! Nie można odnaleźć źródła odwołania.**a.

Table 6.6-3a: Generic Seed-TROPEX (UK Data) exposure values for seed treatment activities (geometric mean values)

|  |  |  |  |
| --- | --- | --- | --- |
| Task | Data normalisation | Estimated Actual Dermal Exposure | Inhalation  Exposurea |
| Calibration | [mL/operation] | 0.014 | 0.001 |
| Mixing / Loading (pre-mix) | [mL/operation] | 0.001 | 0.0001 |
| Mixing / Loading (fast-coupling)b | [mL/operation] | 0.005 | 0.0001 |
| Bagging (25 kg bags) | [mg/hour] | 0.698 | 0.0054 |
| Cleaning | [mL/operation] | 0.083 | 0.016 |

a) Based on an average ventilation rate of 29 L/min

b) Baytan in 10 L bags-in-boxes was used in the original Seed-TROPEX studies performed in the UK. These bags were directly linked to the treater. This system did not have a high level of operator protection built in, and potential dermal exposure in mL/operator was the same for both loading systems, pre-mix and fast-couple. The 10 L bags-in-boxes have now been replaced by more sophisticated packaging designs. The Seed-TROPEX data are therefore of limited relevance for the use of more modern fast-coupling systems.

Table 6.6-4a: Estimated operator exposure during seed treatment

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Cyantraniliprole** | |
| Model data | Level of PPE | Total absorbed dose  (mg/kg/day) | % of systemic AOEL  (0.007 mg/kg bw/d) |
| Industrial Seed Treatment | | Application rate: 2250 g ai/tonne | |
| **SeedTROPEX** (Geometric mean)  Body weight: 60 kg  Container: 20 L  Throughput : 60 tonnes maize seed treated/day | | | |
| Calibration | Gloves and respiratory protection | 0.00181 | 26 |
| Mixing/loading –fast-coupling | Gloves and respiratory protection | 0.00312 | 45 |
| Bagging (25 kg bags) | Standard Work Clothing | 0.00100 | 14 |
| Cleaning | Gloves and respiratory protection | 0.01850 | 264 |
| **Multi Activity Taska** | Gloves while handling product and cleaning equipment and respiratory protection during all tasks except bagging | 0.0244 | 349 |
| Body weight: 70 kg  Container: 20 L | | | |
| Calibration | Gloves | 0.00155 | 22 |
| Mixing/loading –fast-coupling | Gloves and respiratory protection | 0.00268 | 38 |
| Bagging (25 kg bags) | Standard Work Clothing | 0.00086 | 12 |
| Cleaning | Gloves and respiratory protection | 0.01586 | 227 |
| **Multi Activity Taska** | Gloves while handling product and cleaning equipment and respiratory protection during all tasks except bagging | 0.0209 | 299 |

Seed-TROPEX Model: Operator wearing long sleeved jacket and long trousers (standard work clothing).

a) Sum of absorbed doses and AOELs for a single operator performing calibration, fast couple mixing/loading, bagging and cleaning.

Mobile treaters

The Seed-TROPEX model does not contain data for the assessment of exposure of operators treating seeds on mobile equipment.

For the following reasons exposure to operators treating seed on mobile equipment is considered to be in the same range or less than the exposure to operators working in static plants:

1. Treatment on mobile equipment is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
2. Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) on mobile equipment compared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
3. Exposure time is likely to be shorter than in static plants because part of the working day is used for movement of the treatment equipment to the farms or between farms.

On-farm treatment

The Seed-TROPEX model does not contain data for the assessment of exposure of operators treating seeds using on-farm treatment equipment.

For the following reasons exposure to operators treating seed on-farm is considered to be in the same range or less than the exposure to operators working in static plants:

1. Treatment on-farm is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
2. Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) with on-farm equipment compared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
3. Exposure time is likely to be shorter than in static plants because the operator will only treat sufficient seed for planting on the farm.

#### Measurement of operator exposure

Since the operator exposure estimations carried out exceed the acceptable operator exposure level (AOEL) using the Tier 1 SeedTropex model, two higher tier refinements are presented below, based on measured exposure data from two operator studies. Given the age of the studies in the SeedTROPEX model, these modern studies better reflect the equipment and work practices now found in seed treatment plants and are therefore expected to provide more realistic exposure measurements for the individual tasks.

* + - * 1. **Study one**

A higher tier assessment has been performed, based on an exposure study (Wilson 2015, Syngenta Study No VV-414714) which is representative of modern maize treatment practice. This study monitored the exposures for 42 operators divided into four categories depending on the task carried out (slurry preparation, calibration, bagging or cleaning the treatment chamber). An OECD summary of this study (Wilson, 2015, Syngenta Study NoVV-414714) is presented in Appendix 4. The following risk assessment is based on the results from the study.

During industrial seed treatment, much of the process is automated and exposure is limited, as evidenced by the study. During mixing/loading and calibration, the likelihood is that liquid formulation type and composition will have limited influence on the level of surface contamination experienced by operators. For bagging and cleaning, exposure will be primarily to dried residues and the influence of formulation type on exposure from these activities is expected to be negligible. It is also noted that the EFSA guidance on non-dietary exposure assessment does not distinguish between formulation types for liquids during mixing and loading as the data did not support a robust differentiation between water and solvent based types (Großkopf *et al*., 2013, Joint development of a new Agricultural Operator Exposure Model, p 30). The expert group working on the AOEM also completely rejected the idea that formulation type may have an impact on exposure during application (Großkopf *et al*., 2013, p. 21). Whilst there is no immediate reason why the same observations should not apply to seed treatment formulations, conceptually, it might be suggested that the penetration of tefluthrin through clothing could be enhanced by the presence of 15% organic solvent, which is not present in an FS formulation. Großkopf *et al*., 2013 concluded ‘according to the data, wearing work clothes reduces the body exposure by 85 to 98% depending on the scenario considered’. The protective coveralls worn in the tefluthrin study gave an average 95% protection, which is in very good agreement with the conclusions made for the AOEM (i.e. this finding does not imply that the CS formulation or tefluthrin behaved atypically).

Consequently, actual dermal exposures for A17960Bare expected to be no worse than for those measured A13219F. As the maize study (Wilson, 2015) involved robust measurement of exposure during industrial treatment of maize seed with a high degree of replication, this study is expected to provide a more realistic and representative risk assessment for the use of A17960B than the generic (SeedTropex) first tier model, which is based on cereal seed treatment practices, is not underpinned by a large dataset and normalizes exposures in a way which does not fully account for seed loading. In conclusion, the specificity and relevance of the study by Wilson, 2015 for the risk assessment for A17960B far outweigh any possible difference in exposure which may occur through differences in formulation type.

The appropriate percentile values for each activity are chosen based on the selection criteria agreed in the EFSA guidance on Guidance on Pesticides Exposure Assessment of Operators, Workers, Residents and Bystanders. For comparison with a medium/long term repeat dose endpoint (i.e. the AOEL), the 75th percentile is considered to be suitably protective.

Using the respective dermal and inhalation absorption values reported in **Błąd! Nie można odnaleźć źródła odwołania.**, the actual dermal and potential inhalation exposure to cyantraniliprole for operators applying A17960B can be calculated as shown below. Measured exposures for each individual task are reported, as well as for a single operator assumed to carry out all 4 tasks in a single day. The application rate of tefluthrin used in the study was 513 g a.s./tonne seed to 943 g a.s./tonne seed. Since this application rate is lower than the application rates of cyantraniliprole in A17960B, the exposure data have been normalised for differences in application rate. The amount of teflluthrin handled by each operator during calibration and cleaning is not stated in the study report. Therefore, exposure values have only been normalized for mixing/loading and bagging. Since there is a comfortable margin of safety for calibration and cleaning tasks, the operator exposure during these tasks is expected to be within acceptable level even if higher amount of active substance is handled. For mixing, quantities of product handled is only reported where slurry tank mixing occurred, there is no data for dry coupling. Therefore normalized values only take into consideration tank mixing (7 operators), which is a conservative approach since it is expected to be worst case in modern systems. The risk assessment performed using these data is this manner is therefore expected to be precautionary. Results are summarized in **Błąd! Nie można odnaleźć źródła odwołania.**5a.

Table 6.6‑5a: Measured 75th percentile exposures for operator applying A17960B– PPE includes gloves worn during bagging

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **OPERATOR EXPOSURE 75th percentile§** | | | | | | |
|  | **Measured Exposure** | | **Systemic Exposure** | | | |
| **Task** | **Actual Dermal Exposure** | **Inhalation Exposure 1)** | **Estimated Actual Dermal Exposure2)** | **Inhalation Exposure 3)** | **Total** | **% AOEL** |
| **Cyantraniliprole** | [mg/kg bw/day]4) | | [mg/kg bw/day]4) | | |  |
| Calibration 6) | 0.001008 | 0.0000130 | 0.00000302 | 0.0000130 | 0.0000161 | **0.2** |
| Mixing/Loading | 0.097204 | 0.0004967 | 0.00029161 | 0.0004967 | 0.0007883 | **11.3** |
| Bagging | 0.006883 | 0.0005282 | 0.00002065 | 0.0005282 | 0.0005489 | **7.8** |
| Cleaning 6) | 0.001176 | 0.0000301 | 0.00000353 | 0.0000301 | 0.0000336 | **0.5** |
| **Multiple Activity Task 5)** | | | | | 0.0013869 | **19.8** |

§ The agreed selection rule in the EFSA Guidance on Pesticides Exposure Assessment of Operators, Workers, Residents and Bystanders considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen. (EFSA Journal 2014;12(10):3874)

1) Based on an average ventilation rate of 20.83333 L/min (1.25 m3/h, EFSA Journal 2014;12(10):3874, p. 15).

2) Estimated actual dermal exposure multiplied by percentage of dermal absorption.

3) Inhalation exposure multiplied by percentage of inhalation absorption.

4) Based on a standard bodyweight of 60 kg

5) Sum of exposure for a single operator performing calibration, mixing/loading, bagging and cleaning.

6) The amount of active substance handled by each operator during calibration and cleaning is not stated in the study report. Therefore, exposure values cannot be normalized to the application rate for these two tasks

It is evident that measured exposures for operators working under real conditions are within the AOEL of cyantraniliprole. In order to represent the level of personal protection achieved in the study, the following PPE can be recommended:

* Suitable protective coverall (Tyvek type), woven coverall (normal work clothing) and impermeble (nitrile) gloves during slurry preparation, calibration and cleaning,
* Woven coverall (normal work clothing) and impermeable (nitrile) gloves during bagging of treated seed.

The studies which underpin SeedTROPEX result in a model which does not indicate a requirement for gloves during the bagging of treated seed. It is similarly possible to determine exposures for the bagging operation from this specific study by adding the residues determined on the nitrile gloves to the hand wash residues to give a measure of potential (total) hand exposure which is included in the actual dermal exposure (ADE). This results in the following amended exposure values for the 12 operators involved in bagging:

**Table 6.6‑2b: Measured exposures to tefluthrin for bagging (no gloves scenario)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| **Outer dosimeter (µg)** | 129.0 | 98.86 | 78.62 | 559.4 | 67.93 | 98.2 | 131.9 | 53.13 | 82.05 | 349.1 | 68.52 | 50.98 |
| **Inner dosimeter (µg)** | 14.495 | 3.790 | 6.114 | 23.68 | 3.451 | 7.512a | 11.254a | 4.192 | 10.67 | 3.564 | 7.127 | 4.226 |
| **Head (µg)** | 0.500 | 3.380 | 0.500 | 2.350 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 |
| **Potential handb (µg)** | 113.66 | 102.23 | 28.26 | 61.25 | 5.000 | 20.03 | 62.84 | 87.16 | 22.06 | 11268.2 | 15.00 | 52.67 |
| **Air filter (µg)** | 0.180 | 0.0375 | 0.105 | 0.435 | 0.106 | 0.103 | 0.201 | 0.0375 | 0.111 | 0.237 | 0.0375 | 0.080 | Log normal? | Empirical 75th percentile | Parametric 75th percentile |
| **PDE (µg/kg bw/d)** | 4.294 | 3.471 | 1.892 | 18.03 | 1.281 | 2.105 | 3.441 | 2.416 | 1.921 | 193.690 | 1.519 | 1.806 | no | 3.882 | 10.828 |
| **ADEc (µg/kg bw/d)** | 2.144 | 1.823 | 0.581 | 8.704 | 0.149 | 0.467 | 1.243 | 1.531 | 0.554 | 187.871 | 0.377 | 0.957 | no | 1.984 | 5.581 |
| **PIEd (µg/kg bw/d)** | 0.0417 | 0.00868 | 0.0243 | 0.1007 | 0.0245 | 0.02384 | 0.0465 | 0.00868 | 0.02569 | 0.0549 | 0.00868 | 0.01852 | yes | 0.0441 | 0.0431 |

a - includes sweatshirt (Outer 1)

b - hand wash plus nitrile gloves

c - includes potential hand exposure

d - corrected for breathing rate of 20.83333 L/min

Taking the same dermal and inhalation absorption values as in the previous assessment, actual dermal and potential inhalation exposures to Cyantraniliprole for operators applying A17960B without gloves during the bagging phase can be calculated as follows.

Table 6.6‑3b: Measured 75th percentile exposures for operator applying A17960B- Gloves are not worn during bagging

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **OPERATOR EXPOSURE 75th percentile§** | | | | | | |
|  | **Measured Exposure** | | **Systemic Exposure** | | | |
| **Task** | **Actual Dermal Exposure** | **Inhalation Exposure 1)** | **Estimated Actual Dermal Exposure2)** | **Inhalation Exposure 3)** | **Total** | **% AOEL** |
| **Cyantraniliprole** | [mg/kg bw/day]4) | | [mg/kg bw/day]4) | | |  |
| Calibration 6) | 0.001008 | 0.0000130 | 0.00000302 | 0.0000130 | 0.0000161 | **0.2** |
| Mixing/Loading | 0.097204 | 0.0004967 | 0.00029161 | 0.0004967 | 0.0007883 | **11.3** |
| Bagging | 0.069838 | 0.0005282 | 0.00020951 | 0.0005282 | 0.0007377 | **10.5** |
| Cleaning 6) | 0.001176 | 0.0000301 | 0.00000353 | 0.0000301 | 0.0000336 | **0.5** |
| **Multiple Activity Task 5)** | | | | | 0.0015757 | **22.5** |

§ The agreed selection rule in the EFSA Guidance on Pesticides Exposure Assessment of Operators, Workers, Residents and Bystanders considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen. (EFSA Journal 2014;12(10):3874)

1) Based on an average ventilation rate of 20.83333 L/min (1.25 m3/h, EFSA Journal 2014;12(10):3874, p. 15).

2) Estimated actual dermal exposure multiplied by percentage of dermal absorption.

3) Inhalation exposure multiplied by percentage of inhalation absorption.

4) Based on a standard bodyweight of 60 kg

5) Sum of exposure for a single operator performing calibration, mixing/loading, bagging and cleaning.

6) The amount of active substance handled by each operator during calibration and cleaning is not stated in the study report. Therefore, exposure values cannot be normalized to the application rate for these two tasks

Clearly, making the assumption that the operator may not wear gloves during the bagging process (indeed operator 5 chose not to wear protective nitrile gloves and experienced the lowest measured hand exposure), the estimated systemic exposures are still well within the respective AOELs for cyantraniliprole. Taking this into account, it is possible to identify the following protective measures to ensure that exposure does not exceed the acceptable operator exposure level.

1. Suitable protective coverall (Tyvek type), woven coverall (normal work clothing) and impermeable (nitrile) gloves during slurry preparation, calibration and cleaning.
2. Woven coverall (normal work clothing) during bagging of treated seed.

**Conclusions**

Using the measured exposures values from the tefluthrin study (Wilson 2015), the estimated systemic doses of cyantraniliprole are well within acceptable levels for an operator carrying out slurry preparation, calibration, bagging of treated seeds, or equipment cleaning. This is also true for the operator assumed to carry out multiple tasks on each working day, which is expected to be a precautionary assumption.

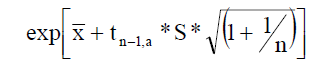
* + - * 1. **Study two**

The second higher tier assessment is based on a study which measures operator exposure to prochloraz and fluquinconazole during seed treatment tasks (Wilson 2009, Syngenta File No ASF827\_10000). The OECD summary of this study is presented in Appendix 4.

Whilst nine subjects were monitored during mixing and loading, the four using the dry-couple (closed-transfer) procedure for transferring the product from the product container to the seed treater had significantly lower levels of exposure than the five who used a pre-mix procedure. Therefore, these data cannot be combined into a single dataset. In addition, inhalation exposure was not measured for all operators during mixing/loading/calibration.

Therefore, in order to obtain estimates for operator exposure for all of the tasks during seed treatment, predicted exposures from the SeedTROPEX model were used for mixing/loading, calibration and bagging tasks. These were combined with the cleaning exposures from the prochloraz and fluquinconazole study to give a combined exposure for the four activities.

The EFSA opinion[[4]](#footnote-5) recommends for longer term exposure assessment, the realistic upper estimate of daily exposure should be taken as the higher of a) the 75th percentile calculated from the empirical dataset or b) a statistical estimate of the 75th percentile for a theoretical population of measurements from which the empirical dataset was derived. The EFSA opinion concludes “it is expected that using the 75th percentile provides a realistic upper estimate (for longer term exposure) that will very rarely, if ever, be exceeded”. Following this approach empirical and parametric 75th percentile values have been calculated from the prochloraz exposure study for total systemic exposure. This is done with the assumption that the population has a log-normal distribution using the following formula:



where ‘’ is the mean of the natural logarithms of the sample measurements, ‘S’ is the standard deviation of the logarithms of the sample measurements, ‘tn-1’ is a t statistic with ‘n 1’ degrees of freedom (n being the number of measurements in the sample), and ‘a’ is the relevant centile. Statistical analysis shows the data within the study are log normally distributed.

The predicted total systemic exposure values during the cleaning task are given in Table 6.6‑4b. Only exposures from the fluquinconazole study were used, as the application rate used was closer to that of cyantraniliprole (751.5 kg/tonne for fluquinconazole vs 140.4 kg/tonne for prochloraz). The empirical and parametric 75th percentile values for 60 kg and 70 kg body weights are shown in Table 6.6-6, the larger of the two will be used in the risk assessment.

Table 6.6‑4b: Measured values used to calculate operator exposure during seed treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Estimated Total Systemic Exposurea (mg/kg bw/day) | | | |
| Active substance | TASK | PPE (gloves) | 60 kg body weight | | 70 kg body weight | |
| Empiricalb | Parametricb | Empiricalb | Parametricb |
| Cyantraniliprole | Cleaning | Yes | 0.00020 | **0.00030** | 0.00017 | **0.00026** |

(a) Inhalation exposure values from prochloraz study have been adjusted to 21 L/min.

(b) Fluquinconazole study values (75th percentile).

The predicted exposures for all tasks, based on a 60 kg and 70 kg body weight are given in **Błąd! Nie można odnaleźć źródła odwołania.**6.

Table 6.6‑5: Estimated operator exposure during seed treatment using higher tier study data

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Cyantraniliprole** | |
| Model data | Level of PPE | Total absorbed dose  (mg/kg/day) | % of systemic AOEL  (0.007 mg/kg bw/d) |
| Industrial Seed Treatment | | Application rate: 2250 g ai/tonne | |
| **SeedTROPEX** (Geometric mean) Calibration, Mixing/loading and Bagging  **Fluquinconazole study** (parametric 75th percentile) Cleaning  Body weight: 60 kg  Container: 20 L  Throughput : 60 tonnes maize seed treated/day | | | |
| Calibration | Gloves and respiratory protection | 0.00181 | 26 |
| Mixing/loading –fast-coupling | Gloves and respiratory protection | 0.00312 | 45 |
| Bagging (25 kg bags) | Standard Work Clothing | 0.00100 | 14 |
| Cleaning | Gloves | 0.00030 | 4.3 |
| **Multi Activity Taska** | Gloves while handling product and cleaning equipment and respiratory protection during calibration and mixing/loading | 0.00608 | 89.3 |
| Body weight: 70 kg  Container: 20 L | | | |
| Calibration | Gloves | 0.00155 | 22 |
| Mixing/loading –fast-coupling | Gloves and respiratory protection | 0.00268 | 38 |
| Bagging (25 kg bags) | Standard Work Clothing | 0.00086 | 12 |
| Cleaning | Gloves | 0.00026 | 3.7 |
| **Multi Activity Taska** | Gloves while handling product and cleaning equipment and respiratory protection during calibration and mixing/loading | 0.00522 | 75.7 |

Conclusion

During the treatment of maize, operator exposure to cyantraniliprole is estimated to be below the AOEL using the SeedTROPEX model to predict exposure from the mixing/loading, calibration and bagging tasks and data from the fluquinconazole study to estimate exposure from cleaning. This estimate of exposure assumes gloves are worn for the calibration, mixing/loading and cleaning tasks and respiratory protection during calibration and mixing/loading.

### Worker exposure (KCP 7.2.3)

#### Estimation of worker exposure

A summary of the exposure models used for estimation of worker exposure to the active substances during loading and sowing of maize seed treated with A17960B according to the critical use(s) is presented in Table 6.6-7. The outcome of the estimation is presented in Table 6.6-. Detailed calculations are in Appendix 3.

At this time, no acute AOEL has been set for cyantraniliprole. Consequently, no acute risk assessment has been provided for these active substances.

Table 6.6-7: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Maize seed (max 3.75 L product/tonne seeds) |
| Model(s) | SeedTROPEX  [Chester, G., Wiseman, M., Pontal, P-G., Worker Exposure During Seed Treatment and Sowing of Treated Seed in the UK and France: An Overview. Zeneca Agrochemicals, Fernhurst, Haslemere. Report No. TMF 4896.] |

Worker exposure is estimated using the “Seed-TReatment OPerator EXposure” data (Seed-TROPEX). Seed-TROPEX is an exposure data base submitted to UK-PSD in 1996 for national registrations by an Industry Task Force and contains results from studies performed in the UK and France.

The Seed-TROPEX data base submitted in 1996 consists of two parts: Exposure values for operators involved in seed treatment activities and exposure values for workers loading and sowing treated seed.

Loading and sowing of treated seeds

In order to estimate the likely exposure to workers involved in the loading and sowing of treated seed data combined from two worker exposure studies carried out in 1993 the UK and France have been used as a source of generic exposure data (Seed-TROPEX Studies).

The UK study monitored the sowing of wheat seed treated with ‘Baytan’ and measured exposure to the triadimenol component of the formulation[[5]](#footnote-6). The French study measured exposure to anthraquinone during a day of sowing of wheat seed treated with ‘Germinate Double’[[6]](#footnote-7).

The generic Seed-TROPEX exposure figures to estimate dermal and inhalation exposure of the operator cover exposure during both activities, loading and sowing of treated seed. These exposure figures are normalised to mg/hour and accordingly do not take into account the amount of product applied to the seed. The generic Seed-TROPEX exposure values for loading and sowing treated seeds are given in

Table 6.6-8 below.

Table 6.6-8: Generic Seed-TROPEX exposure values for loading and sowing treated seeds (geometric mean values)

|  |  |  |  |
| --- | --- | --- | --- |
| Task | Unit of exposure | Estimated Actual Dermal Exposure | Inhalation Exposurea |
| Loading and sowing seeds | [mg/person/hour] | 0.733 | 0.02 |

a) Based on an average ventilation rate of 29 L/min.

Exposure by inhalation of workers loading and sowing of treated seed is based on an average ventilation rate of 29 L/min, which is in accordance with the value applied in the 1993 Seed-TROPEX studies for this activity. Although loading of the hopper may be physically demanding where manual handling of seed bags is involved, this activity is usually of short duration compared to the actual sowing of the seed. During the latter the operator is driving the tractor, possibly leaving it occasionally to verify the drilling depth or to check and equalise remaining amount of seeds in the hopper. An average ventilation rate of 29 L/min for the combined loading and sowing task is therefore considered conservative.

Table 6.6-9: Estimated worker exposure

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Cyantraniliprole | |
| Model data | Level of PPE | Total absorbed dose  (mg/kg/day) | % of systemic AOEL  (0.007 mg/kg bw/d) |
| Loading and Sowing Treated Seed | | | |
| SeedTROPEX 60 kg | Gloves while loading hopper | 0.0036999 | 53 |

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

Not applicable for seed treatment products.

#### 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 consideration of the above mentioned personal protective equipment (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)

In industrial seed treatment facilities the incidental presence of bystanders can be excluded by technical management measures. If occurring, exposure of bystanders would be of short duration and normally lower than that of seed treatment operators who are occupationally exposed all day long. The same applies for seed loading and sowing activities. Therefore, it is reasonable to assume that there will be no undue risk to persons being incidentally exposed to seed treatment or seed sowing operations.

#### Estimation of resident and bystander exposure

Not applicable for seed treatment products.

#### Measurement of resident and/or bystander exposure

Not applicable for seed treatment products.

### Combined exposure

The product is a solo product containing only one active substance. As such there is no requirement for an estimate of combined exposure.

1. Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Data point | Author(s) | Year | Title Company Report No.  Source (where different from company) GLP or GEP status Published or not | Vertebrate study  Y/N | Owner |
| KCP 7.1.1 | **xxxxxxxxxx** | 13/04/2011 | Cyantraniliprole FS (A17960B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure) Report No. 11/015-001P Document No. VV-505820 , A17960B\_50000 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.1.2 | **xxxxxxxxxx** | 05/05/2011 | Cyantraniliprole FS (A17960B) - Acute Dermal Toxicity Study in Rats Report No. 11/015-002P Document No. VV-505821 , A17960B\_50001 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.1.3 | **xxxxxxxxxx**  . | 19/05/2011 | Amended - Cyantraniliprole FS (A17960B) - Acute Inhalation Toxicity Study (Nose-Only) in the Rat Report No. 11/015-004P Document No. VV-505822 , A17960B\_50002 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.1.4 | **xxxxxxxxxx** | 26/04/2011 | Cyantraniliprole FS (A17960B) - Primary Skin Irritation Study in Rabbits Report No. 11/015-006N Document No. VV-505823 , A17960B\_50003 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.1.5 | **xxxxxxxxxx** | 13/05/2011 | Cyantraniliprole FS (A17960B) - Acute Eye Irritation Study in Rabbits Report No. 11/015-005N Document No. VV-505824 , A17960B\_50004 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.1.6 | **xxxxxxxxxx** | 07/04/2011 | Cyantraniliprole FS (A17960B) - Skin Sensitization in Guinea Pigs by the Buehler Method (9 Induction) Report No. 11/015-104T Document No. VV-505825 , A17960B\_50005 Test Facility LAB Research Ltd. GLP Unpublished | Y | SYN |
| KCP 7.2.1.2 | **xxxxxxxxxx** | 23/02/2009 | Fluquinconazole and Prochloraz: Determination of Operator Exposure During Cereal Seed Treatment with “Jockey” Fungicide in Germany, United Kingdom and France. Report No. ACI07-006 Document No. VV-393832 , ASF827\_10000 Test Facility Agrochemex International Ltd. GLP Unpublished | N | SYN |
| KCP 7.2.1.2 | **xxxxxxxxxx** | 30/11/2015 | Tefluthrin - Determination of Operator Exposure during Typical Activities Associated with Treatment and Bagging of Maize Seeds using Force® 20CS (200 g/L w/v Tefluthrin as a Capsule Suspension) in Seed Treatment Facilities in Europe Report No. ACI14-008 Document No. VV-414714 , ICI993\_10177 Test Facility Agrochemex International Ltd. GLP Unpublished | N | SYN |
| KCP 7.3 | **xxxxxxxxxx**  . | 05/03/2014 | Cyantraniliprole FS (A17960B) - In Vitro Absorption through Dermatomed Human Skin Using [14C]-Cyantraniliprole Report No. JV2268-REG Document No. VV-406654 , A17960B\_10054 Test Facility Dermal Technology Laboratory Ltd. GLP Unpublished | N | SYN |
| KCA1 5.8.1 | **xxxxxxxxxx** | 26/02/2016 | IN-M2G98: Acute Oral Toxicity Study in Rats - Up-and-Down Procedure Report No. DuPont-45346 Document No. VV-463094 , SYN548397\_10003 Test Facility E.I. Du Pont de Nemours GLP Unpublished | Y | DuPont # |
| KCA1 5.8.1 | **xxxxxxxxxx** | 15/09/2016 | IN-M2G98: Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats Report No. DuPont-45277 Document No. VV-470125 , SYN548397\_10004 Test Facility E.I. Du Pont de Nemours GLP Unpublished | Y | DuPont # |

# Syngenta co-own study with FMC (In Nov 2017 DuPont divested cyantraniliprole to FMC)

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

| Data point | Author(s) | Year | Title Company Report No.  Source (where different from company) GLP or GEP status Published or not | Vertebrate study  Y/N | Owner |
| --- | --- | --- | --- | --- | --- |
| KCP 7 | **xxxxxxxxxx** | 2013 | IN-M2G98: Bacterial reverse mutation test  BioReliance DuPont-37572  GLP: Yes  Published: No  Syngenta Study No VV-411296 | Y | DuPont |
| KCP 7 | **xxxxxxxxxx** | 2013 | IN-M2G98: In vitro mammalian chromosome aberration test in human peripheral blood lymphocytes DuPont Haskell Global Centers for Health & Environmental Sciences,  Alliance Pharma, Inc.  DuPont-37573  GLP: Yes  Published: No  Syngenta Study No VV-411334 | Y | DuPont |
| KCP 7 | **xxxxxxxxxx** | 2013 | IN-M2G98: In vitro mammalian cell gene mutation test (CHO/HGPRT assay)  BioReliance, Alliance Pharma, Inc.  DuPont-37574  GLP: Yes  Published: No  Syngenta Study No VV-411297 | Y | DuPont |

List of data submitted by the applicant and not relied on

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

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

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

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

Acute Toxicity Estimate (ATE) calculations have been conducted and are provided in the Part C Docu-ment (VV-857442). Syngenta has also conducted acute toxicity studies on the formulation. Syngenta testing strategy at the time these studies were conducted took into account data requirements of all regulatory agencies globally where authorization may be intended together with methods compliant with the 3R concept for refinement, reduction and replacement of animal testing where applicable and acceptable.

Where classification proposals have varied between the ATE calculation approach and the animal data generated it is Syngenta’s approach to base the product classification on the animal data, in accordance with CLP guidance.

|  |  |
| --- | --- |
| Comments of zRMS: | Since the animal data already exist, ZRMS Poland has accepted the data and evaluation has been based on these one. The information gained on animal studies are more than just a classification. By accepting the already existing animal studies, the identification of effects following a single exposure to the plant protection product can be established. The data is sufficient to indicate the time course and characteristics of the effect with full details of behavioral changes and possible gross pathological findings at post-mortem.  ZRMS is aware of some EU-countries are known for no longer accepting *in vivo* studies. On the other hand ZRMS believes that other EU-countries might be willing to see the reports that are available (if the classification based on them is different from the one obtained by calculation).  Information provided by the applicant is sufficient. ZRMS PL decided to conduct hazard assessment and classifications based on A17960B *in vivo* study results summarized below. |

* 1. Acute oral toxicity (KCP 7.1.1)

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 425. These study meets the current data requirements Regulation (EU) No 284/2013. Identified deviation: none. Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

|  |  |
| --- | --- |
| Reference | KCP 7.1.1 |
| Report | Cyantraniliprole FS (A17960B) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure).  Xxxxxxx, 2011  11/015-001P  A17960B\_10010 |
| Guideline(s) | Yes. Acute Oral Toxicity (rat): OECD Test Guideline 425 (2008): EPA OPPTS 870.1100 (2002). |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | A17960B/Fortenza (SMU1AP002) |
| Species | Rat, RjHan:WI |
| No. of animals (group size) | 3 rats (female) |
| Dose(s) | 5000 mg/kg bw |
| Exposure | Once by gavage |
| Vehicle/Dilution | None |
| Post exposure observation period | 14 days |
| Remarks | None |

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of A17960B/Fortenza

| **Dose (mg/kg bw)** | Toxicological results \* | Duration of signs | Time of death | LD50 (mg/kg bw) (14 days) |
| --- | --- | --- | --- | --- |
| Female rats | | | | |
| 5000 | 0/1/3 | Day 1 | Day 14 | > 5000 |

\* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 2: Summary of findings of acute oral toxicity study in rats of A17960B/Fortenza

|  |  |
| --- | --- |
| Mortality | No mortality occurred. |
| Clinical signs | Decreased activity was observed in 1 animal, treated at a dose level of 5000 mg/kg bw, on the day of dosing. The animal fully recovered and was symptom free from Day 1 until the end of the observation period. |
| Body weight | Body weight gain was considered to be normal. |
| Macroscopic examination | The necropsies performed at the end of the study revealed no apparent findings. |

Conclusion

Under the experimental conditions, the oral LD50 of A17960B/Fortenza is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

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

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 402. These data meets the current data requirements Regulation (EU) No 284/2013. There is no deviations from the study protocol. Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.2 |
| Report | Cyantraniliprole FS (A17960B) - Acute Dermal Toxicity Study in the Rat. |
|  | Xxxxxxx, 2011  11/015-002P  A17960B\_10016 |
| Guideline(s) | Acute Dermal Toxicity (rat) OECD 402 (1987): OPPTS 870.1200 (1998); EC 440/2008 (2008) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | A17960B/Fortenza (SMU1AP002) |
| Species | Rat, RjHan:(WI) Wistar |
| No. of animals (group size) | 10 rats (5 male & 5 female) |
| Dose(s) | 5000 mg/kg bw |
| Exposure | 24 hours (dermal, semi-occlusive) |
| Vehicle/Dilution | None |
| Post exposure observation period | 14 days |
| Remarks | None |

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of A17960B/Fortenza

| Dose (mg/kg bw) | Toxicological results \* | Duration of signs | Time of death | LD50 (mg/kg bw) (14 days) |
| --- | --- | --- | --- | --- |
| Male rats | | | | |
| 5000 | 0/0/5 | - | Day 14 | > 5000 |
| Female rats | | | | |
| 5000 | 0/0/5 | - | Day 14 | > 5000 |

\* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 4: Summary of findings of acute dermal toxicity study in rats of A17960B/Fortenza

|  |  |
| --- | --- |
| Mortality | No mortality occurred. |
| Clinical signs | No clinical signs of toxicity were observed. |
| Body weight | Body weight gain was considered to be normal. |
| Macroscopic examination | The necropsies performed at the end of the study revealed no apparent findings. |

Conclusion

Under the experimental conditions, the dermal LD50 of A17960B/Fortenza is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Acute inhalation toxicity (KCP 7.1.3)

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 403. These data meets the current data requirements Regulation (EU) No 284/2013. There is no deviations from the study protocol. Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.3 |
| Report | Cyantraniliprole FS (A17960B) - Acute Inhalation Toxicity Study (Nose-Only) in the Rat.  Xxxxxxx, 2011  11/015-004P  A17960B\_10033 |
| Guideline(s) | Yes. Acute Inhalation Toxicity Study (Nose-Only) in the Rat: OECD Test Guideline 403 (2009); EPA OPPTS 870.1300 (1998); EC 440/2008, Annex Part B, B.2 (2008). |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | A17960B/Fortenza (SMU1AP002) |
| Species | Rat, Wistar RjHan:(WI) |
| No. of animals (group size) | 10 rats (5 male & 5 female) |
| Concentration(s) | 5 mg/L air |
| Exposure | 4 hours (nose only) |
| Vehicle/Dilution | Due to the physical properties of the test item as supplied, suitable atmospheres could not be produced. A range of formulations and homogenisation techniques were therefore attempted in order to improve the physical characteristics of the test item and all data associated is retained in the raw data but not reported. Animals were exposed to a test atmosphere produced from a formulation with distilled water (TEVA Zrt., H-2100 Gödöllő, Táncsics Mihály u. 82, Hungary; Batch: 8490910; Expiry: September 2013). As the formulation (Cyantraniliprole FS (A17960B): distilled water, 70:30%, w/w) was prepared shortly before use, determination of the concentration, homogeneity and stability of the formulation were not required and were not performed. |
| Post exposure observation period | 14 days |
| Remarks | None |

Results and discussions

Table A 5: Concentration(s) and exposure conditions

|  |  |  |  |
| --- | --- | --- | --- |
| Target conc. (mg/L air) | Actual conc.  (mg/L air) | MMAD \* (µm) | GSD \*\* (µm) |
| 5.0 | 5.16 + 0.73 mg/L | 4.38 | 2.16 |

\* MMAD = Mass Median Aerodynamic Diameter

\*\* GSD = Geometric Standard Deviation

Table A 6: Results of acute inhalation toxicity study in rats of A17960B/Fortenza

| Concentration (mg/L air) | Toxicological results \* | Duration of signs | Time of death | LC50 (mg/L air) (14 days) |
| --- | --- | --- | --- | --- |
| Male rats | | | | |
| 5.16 | 0/5/5 | 1 day | Day 14 | >5.16 |
| Female rats | | | | |
| 5.16 | 0/5/5 | 1 day | Day 14 | >5.16 |

\* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 7: Summary of findings of acute inhalation toxicity study in rats of A17960B/Fortenza

|  |  |
| --- | --- |
| Mortality | No mortality occurred. |
| Clinical signs | Wet fur and fur staining were commonly recorded on the day of exposure. These observations were considered to be related to the restraint and exposure procedures and, in isolation, were considered not to be toxicologically significant.  In the three sighting exposures, the following significant clinical signs were recorded on the day of exposure: laboured respiration, respiratory rate increase and scab. Clinical signs ceased from Day 1 in all sighting groups.  In the main study at a target aerosol concentration of 5 mg/L, significant clinical signs were recorded on day of and the day following exposure. These were: laboured respiration and increased respiratory rate. All animals recovered and no significant clinical signs were noted from Day 2 of the observation period. |
| Body weight | In the three sighting groups, normal bodyweight gain was noted for all animals from Day 1 to the end of the observation period, with the exception of four females where slight bodyweight loss (5204 ♀ - Group 0.1; 5201♀, 5205 ♀ - Group 0.2, 5513 ♀ - Group 0.3) was recorded during the first week of the observation period.  Normal bodyweight gain was recorded in the main group during the whole observation period. |
| Macroscopic examination | At necropsy, there were no test item related macroscopic findings after a single four hour nose-only exposure to Cyantraniliprole FS (A17960B) to Wistar RjHan: (WI) strain rats at 1.17, 2.85 and 5.03 mg/L in the sighting exposure phase and at 5.16 mg/L in the main study. |

Conclusion

Under the experimental conditions, the inhalation LC50 of A17960B/Fortenza is higher than 5.16 mg/L air in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Skin irritation (KCP 7.1.4)

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 404. These data meets the current data requirements Regulation (EU) No 284/2013. Deviations from the study protocol has been identified. This deviation has no impact on the outcome of the study. Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

* + 1. Study 1 *(in-vivo)*

|  |  |
| --- | --- |
| Reference | KCP 7.1.4 |
| Report | Cyantraniliprole FS (A17960B) - Acute Skin Irritation Study in the Rabbits.  Xxxxxxx, 2011a  11/015-006N  A17960B\_10011 |
| Guideline(s) | Acute Skin Irritation (rabbit) OECD 404 (2002): OPPTS 870.2500 (1998); EC No 440/2008, B.4 (2008). |
| Deviations | On occasion during the study the humidity (30-70%) was recorded out of the target range. The actual range was at the humidity 24-44 %.  The animals arrived on 02 March 2011 instead of 16 February 2011 as it was indicated in the Study Plan. |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | A17960B/Fortenza (SMU1AP002) |
| **Species** | Rabbit, New Zealand White |
| **No. of animals (group size)** | 3 (males) |
| **Initial test using one animal** | Yes |
| **Exposure** | 0.5 mL (4 hours, semi-occlusive) |
| **Vehicle/Dilution** | None |
| **Post exposure observation period** | 3 days |
| **Remarks** | None |

Results and discussions

Table A 8: Skin irritation of A17960B/Fortenza

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Animal No. |  | Scores after treatment \* | | | | Mean scores (24-72 h) | Reversible (day) |
| 1 h | 24 h | 48 h | 72 h |
| 00793 | Erythema  Oedema | 0  0 | 0  0 | 0  0 | 0  0 | 0  0 | -  - |
| 00789 | Erythema  Oedema | 0  0 | 0  0 | 0  0 | 0  0 | 0  0 | -  - |
| 00790 | Erythema  Oedema | 0  0 | 0  0 | 0  0 | 0  0 | 0  0 | -  - |

\* scores in the range of 0 to 4

|  |  |
| --- | --- |
| Clinical signs: | No clinical signs of toxicity were observed. |

Conclusion

Under the experimental conditions, A17960B/Fortenza is not a skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Eye irritation (KCP 7.1.5)

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 405. These data meets the current data requirements Regulation (EU) No 284/2013. There is no deviations from the study protocol. Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

* + 1. Study 1 *(in-vivo)*

|  |  |
| --- | --- |
| Reference | KCP 7.1.5 |
| Report | Cyantraniliprole FS (A17960B) – Acute Eye Irritation Study in Rabbits.  Xxxxxxx, 2011  Aa/015-005N  A17960B\_10032 |
| Guideline(s) | Acute Eye Irritation (rabbit) OECD Test Guideline 405 (2004): EPA OPPTS 870.2400 (1998): EC No 440/2008, B.5 (2008) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | A17960B/Fortenza (SMU1AP002 |
| Species | Rabbit, New Zealand White |
| No. of animals (group size) | 3 (male) |
| Initial test using one animal | Yes |
| Exposure | 0.1 mL (single instillation in conjunctival sac) |
| Irrigation (time point) | Yes |
| Vehicle/Dilution | None |
| Post exposure observation period | 14 days |
| Remarks | None |

Results and discussions

Table A 9: Eye irritation of A17960B/Fortenza

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Animal No. |  | Scores after treatment \* | | | | Mean scores (24-72 h) | Reversible (day) |
| 1 h | 24 h | 48 h | 72 h |
| 00014 | Corneal opacity  Iritis  Redness conjunctivae  Chemosis conjunctivae | 0  0  2  1 | 0  0  2  1 | 0  0  1  0 | 0  0  1  0 | 0  0  1.33  0.33 | -  -  Week 2  2 |
| 00022 | Corneal opacity  Iritis  Redness conjunctivae  Chemosis conjunctivae | 0  0  2  1 | 0  0  1  0 | 0  0  1  0 | 0  0  1  0 | 0  0  1  0 | -  -  Week 2  Day 1 |
| 00023 | Corneal opacity  Iritis  Redness conjunctivae  Chemosis conjunctivae | 0  0  2  1 | 0  0  2  0 | 0  0  1  0 | 0  0  1  0 | 0  0  1.33  0 | -  -  Week 2  Day 1 |

\* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

|  |  |
| --- | --- |
| Clinical signs: | Conjunctival redness, chemosis and conjunctival discharge were observed in all rabbits, 1 hour after application. Conjunctival redness and discharge persisted in all animals at the 24, 48 and 72 hours observation. At the 24 hour observation, one rabbit was recorded with conjunctival chemosis, which fully reverse before the 48 hours observation. One week after treatment, all rabbits showed slight redness and two animals displayed conjunctival discharge. No other signs were observed and all animals were symptom free 2 weeks after treatment.  Fluorescein staining was positive in one animal at 24 hours after the treatment but no more positive response was found during the observation period.  Three days after treatment, increased salivation and erosion of the oral-nasal area were observed in all animals. Additionally, wet fur, redness, oedema and inflammation of the ventral area of the neck were recorded in 1/3 rabbit. |

Conclusion

Under the experimental conditions, A17960B/Fortenza is not an eye irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Skin sensitisation (KCP 7.1.6)

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 406.  Results of this is modified Buehler test (9 applications) are confirmed by the calculation method using the generic and specific concentration limits of components of a mixture classified as a skin sensitizer that trigger classification of the mixture. The generic concentration limits can be found in Annex I: table 3.4.5 of the CLP Guidance to Regulation (EC) No 1272/2008, whilst the specific concentration limits are as per the Harmonised classification - Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).  The relevant material in this formulation that has been classified as skin sensitizers is:  •1,2-benzisothiazol-3-one, which is present at 20% in PROXEL GXL and at 0.037% in the formulation.  The concentration of 1,2-benzisothiazol-3-one in the A17960B formulation is below its concentration triggering classification threshold of ≥ 0.05%. Therefore the A17960B formulation is considered not to be a skin sensitizer.  Study is acceptable.  Classification is not required according to CLP Regulation (EC) No 1272/2008. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.6 |
| Report | Cyantraniliprole FS (A17960B) - Skin Sensitization in Guinea Pigs by the Buehler Method (9 induction).  Xxxxxxx, 2011  11/015-104T  A17960B\_10002 |
| Guideline(s) | Dermal Sensitisation (guinea pig) OECD 406 (1992); OPPTS 870.2600 (2003); Directive 440/2008/EC B.6 (2008) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

Materials and methods

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | A17960B/Fortenza (SMU1AP002) |
| Species | Guinea pig, LAL/HA/BR strain |
| No. of animals (group size) | Test substance group: 20 female guinea pigs  Vehicle control goup: 10 female guinea pigs |
| Range finding | Yes |
| Exposure (concentration(s), no. of applications) | Topical inductione undiluted (9 x)  Challenge undiluted test item and 50 (w/v)% in distilled water |
| Vehicle | Distilled water |
| Pretreatment prior to topical application | Approximately 24 hrs prior to the test, the hair was removed from the right and left flank of the animals (approximately 5 x 5 cm). |
| Reliability check | The sensitivity and reliability of the experimental technique employed was assessed by use of 2-Mercaptobenzothiazole. |
| Remarks | None |

Results and discussions

Table A 10: Results of skin sensitisation study of A17960B/Fortenza

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Test flank** | | | |
|  | **Challenge at 100 % (undiluted)** | | **Challenge at 50 (w/w) %** | |
| **Scored after:** | **24 hours** | **48 hours** | **24 hours** | **48 hours** |
| Main test – test group | 0/20 | 0/20 | 0/20 | 0/20 |
| Main test – negative (vehicle) control | 0/10 | 0/10 | 0/10 | 0/10 |
|  | **24 hours** | | **48 hours** | |
| Positive control – test group | 4/20 | | 4/20 | |
| Positive control – vehicle control | 0/10 | | 0/10 | |

|  |  |
| --- | --- |
| Clinical signs: | No clinical signs of toxicity were observed. |

Conclusion

Under the experimental conditions, A17960B/Fortenza is not a skin sensitiser. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

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

None.

* 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 – Cyantraniliprole in A17960B/Fortenza

Comparative dermal absorption, in vitro using rat and human skin

|  |  |
| --- | --- |
| Comments of zRMS: | This study follows the data requirements for the active substance laid down in Regulation (EC) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EC) No. 284/2013.  The study was performed according to the OECD Test Guideline 428. These data meets the current data requirements Regulation (EU) No 284/2013. There is no deviations from the study protocol. Study is acceptable. |

|  |  |
| --- | --- |
| Reference | KCP 7.3 |
| Report | Cyantraniliprole FS (A17960B) - *In Vitro* Absorption through Dermatomed Human Skin Using [14C]-Cyantraniliprole**.**  Xxxxxxx, 2014.  JV2268-REG  A17960B\_10054 |
| Guideline(s) | OECD 428 |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |

Materials and methods

|  |  |  |
| --- | --- | --- |
| **Test material** | Name (Lot/Batch No.) | [14C]-Cyantraniliprole (1726168) |
|  | Test preparation | radioformulation |
| Specific activity | 1.63 MBq/mg (43.99μCi/mg) |
| Radiochemical purity | 99.2% |
| Product | Name (Lot/Batch No.) | Cyantraniliprole (9182-3B) |
| Company code | A17960B |
| Concentration a.s. | 600g/L |
| Formulation type | FS |
| Blank product | Name (Lot/Batch No.) | Blank of A17960B |
| Concentration a.s. | N/A |

|  |  |  |
| --- | --- | --- |
| **Test system** |  |  |
| Diffusion cell | Cell type | static |
| (if dynamic) Flow rate | N/A |
| Exposed skin area | 2.54 cm² |
| Cover | open |
| Membrane | Skin type | dermatomed |
| Skin thickness range | 400 µm |
| Skin donors age | 76-82 |
| Skin donors sex | Female |
| Location | abdomen / back / unknown |
| Source | post mortem |
| Integrity test | Yes |
| Receptor | Receptor medium | 50% ethanol in water |
| Solubility in receptor medium | Yes |
| Sample Time | Exposure time | 6h |
| Observation time | 24h |
| Sampling | Sample intervals | 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 |
| Washing |  | post exposure |
| Final Procedure | Tape stripping | Yes |
| TS1-2 analysed separately | Yes |
| Remarks: | | |

|  |  |
| --- | --- |
| **Tested doses** | Concentrate |
| Target concentration [mg/ml] | 600 |
| Area dose [µL/cm²] | 10 |
| Total dose [µL/cell] | 25.4 |
| Specific activity [MBq/g] | 6.440 |
| No. of donors | 4 |
| No of cells used/valid cells\* | 8/8 |

\* Justification for excluded cells, if applicable

Results and discussions

Table A 11: In-vitro dermal penetration of Cyantraniliprole formulated as A17960B through

human skin - Recovery data

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose group** | | High dose | |
| (Formulation  concentrate) | |
| Target concentration | [mg/mL] | 600 | |
| Target dose | [µL/cm²] | 10 | |
| Mean actual applied dose | [µg/cm²] | 4779 | |
|  | | Recovery [%] | |
|  | | Mean | S.D. |
| **Dislodgeable dose** | |  | |
| e.g. Skin washing after 6 h | | 99.9 | 1.12 |
| e.g. Skin washing after 24 h | | 0.948 | 0.352 |
| Donor chamber wash | | 0.087 | 0.088 |
| **Dose associated to skin** | |  | |
| Tape strips: 1st sample, strips 1 + 2 | | 0.007 | 0.007 |
| Tape strips: 2nd sample; strips 3 – 20 | | 0.008 | 0.007 |
| Remaining Skin | | 0.152 | 0.117 |
| **Absorbed dose** | |  | |
| Receptor fluid | | 0.002 | 0.001 |
| **Total recovery1** | | 101.00 | 1.22 |
| Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at t0.5] | | No  48.7% | |
| If no:  Absorption estimates  =(absorbed dose + exposed skin + tape strips sample 2)2 | | 0.16 | 0.12 |
| If yes:  Absorption estimates  =(absorbed dose + exposed skin) | | N/A | N/A |
| Absorption estimate normalised3 | | N/A | |
| Relevant absorption estimate4 | | 0.28 | |
| **Absorption estimates used for risk assessment5** | | **0.3** | |

1 Values may not calculate exactly due to rounding of figures

2 In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study (see Table 7.6.2‑1) Finally, the skin preparation is also considered potentially absorbable.

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

4. In accordance with the EFSA Guidance on Dermal Absorption, one standard deviation was added to the mean% dermal penetration in cases where the standard deviation was ≥ 25% of the mean value.

5 Relevant absorption estimate was rounded to the required number of significant figures.

N/A: not applicable

**Remarks**

N/A.

Conclusion/endpoint:

The dermal penetration of Cyantraniliprole formulated as A17960B through human dermatomed skin was determined in vitro. The amount of applied dose penetrating within 24 hours was determined to be 0.16 ± 0.12 (mean ± standard deviation) for the formulation concentrate. The dermal penetration estimates to be used for risk assessment were set at 0.3% for the formulation concentrate based on the EFSA guidance criteria.

* 1. Other/Special Studies
     1. Study 1 – 2007 Seed-TROPEX study performed in Germany, UK and France

|  |  |
| --- | --- |
| Comments of zRMS: | The test provides empirical results (monitoring studies) sufficient to estimate the exposure to cyantraniliprole (A17960B/Fortenza) during seed-treatment, enabling the higher tier refinement of the calculation, taking into account devices both stationary (industrial) and mobile treaters.  Generic Seed-TROPEX exposure figures assumes conservative technical parameters from 1997, so according to ZRMS opinion it was justified to provide updated measurements. Study accepted. |

|  |  |
| --- | --- |
| Reference | KCP 7.2.1.2 |
| Report | Fluquincoazole and Prochloraz: Determination of Operator Exposure During Cereal Seed Treatment With “Jockey” Fungicide in Germany, United Kingdom and France  Xxxxxxx J, 2009.  ACI07-006  ASF827\_10000 |
| Guideline(s) | OCDE/GD(97)148 Series on Testing and Assessment No. 9, Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Organisation for Economic Cooperation and Development, Paris. |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |

**Executive Summary**

In 2007, a Good Laboratory Practice (GLP) operator exposure study was conducted with thirty-nine operators in Germany, United Kingdom and France. The study was performed to monitor potential dermal and inhalation exposure to fluquinconazole and prochloraz during a typical days' activities associated with mixing/loading, bagging of treated seed and cleaning of seed treatment equipment. Twenty two operators were monitored for exposure during procedures associated with bagging only. Eight operators were monitored for exposure during procedures associated with the cleaning of the treatment chamber. Nine operators were monitored for the exposure during procedures associated with mixing/loading and when performed calibration.

**Bagging**

The bagging activities were performed as closely as possible to normal practices whilst using commercial equipment in commercial seed treatment facilities.

The type of seed bagged were small grain cereals (wheat). The seed treatment was performed at 0.681 to 0.752 g/kg seed (fluquinconazole) and 0.128 to 0.140 g/kg seed (prochloraz) using ‘Jockey Plus AB’ containing 167 g/L fluquinconazole (nominal) and 31.2 g/L prochloraz (nominal). In some cases, the test item was diluted with water prior to treatment (either in the slurry tank, or directly at the treatment chamber). The duration of each bagging activity was 2.30 to 7.72 hours (average: 5.30 hours excluding any routine breaks) and the quantity of seed actually bagged was 25.05 to 86.00 tonnes (average: 56.4 tonnes) for each bagging line. One to three operators worked on the same bagging line. The total amount of fluquinconazole handled for each bagging line was 17.07 to 64.63 kg (average: 42.23 kg). The total amount of prochloraz handled for each bagging line was 3.189 to 12.08 kg (average: 7.907 kg).

**Cleaning**

The cleaning activity was performed as closely as possible to normal practices using commercial equipment in commercial seed treatment facilities. Cleaning was monitored at four locations in Germany, three locations in UK and one location in France.

Cleaning involved cleaning of the treatment chamber. Cleaning was conducted on either continuous flow or batch treatment chambers. The duration of each cleaning activity was between 0.12 to 0.55 hours (average: 17 min). The cleaning of the treatment chamber was performed by one operator (working alone).

**Mixing/loading/calibration**

Mixing/loading/calibration was monitored in four locations in Germany and one in France. The procedure involved either suction transfer from 200L drums, two locations in Germany, or a transfer into a mixing tank in two locations in Germany and the single location in France. Manual calibration was performed in two locations in Germany. Automatic calibration occurred in two locations in Germany and the location in France.

In the United Kingdom, mixing/loading was monitored in four locations. The procedure always involved dry-coupling and calibration was automatic.

**Materials**

|  |  |
| --- | --- |
| **Test Material:** | ‘Jockey’ (called Jockey Plus AB in France) |
| **Description:** | A flowable suspension for seed treatment |
| **Lot/Batch Number:** | 1159541, 1556013, 1239029, 1970163, 1816396, 1460359, 1859936, 1387219, 1816396, 1443159, 1816393, 1816396 |
| **Purity:** | Nominal 167 g/L fluquinonazole and 31.2 g/L prochloraz |
| **Stability of test compound:** | Stable for the duration of the study |

**Study Design and Methods**

**Field Phase dates:** 23 August 2007 to 14 September 2007

**Experimental dates:** 23 August 2007 to 19 December 2007

**Study Description:**

39 operators were monitored between 23 August 2007 and 14 September 2007.

The purpose of this study was to generate operator exposure data during the mixing/loading/calibration, bagging of treated seed and cleaning of seed treatment equipment at static sites in Germany (6 sites), United Kingdom (4 sites) and France (1 site) following treatment with a fungicide nominally containing 167 g/L fluquinconazole and 31.2 g/L prochloraz (34 g/L as copper chloride complex) using batch or continuous flow seed treatment equipment. The recommended use rate of the product is 4.5 L per tonne of seed, equivalent to 751.5 g fluquinconazole and 140.4 g prochloraz per tonne of seed.

The three main phases of seed treatment were followed in this study, namely the mixing/ loading/ calibration, bagging of treated seed and cleaning of seed treatment equipment.

Dermal exposure was measured by operators wearing standardised whole-body outer and inner dosimeters. For the bagging activities, each operator wore dosimeters consisting of a long sleeved jacket and long trousers (100% cotton), long sleeved vest and long-johns (100% cotton). The nitrile gloves were made available for the operators (worn at the discretion of the operator when touching contaminated surfaces). For the cleaning activities, each operator wore the same dosimeters as the bagging activities in addition to an impermeable coverall (‘Tyvek’) and impermeable gloves (nitrile), which were worn throughout the cleaning activities.

Head exposure was measured by face/neck wipes.

Actual hand exposure was measured by the handwash procedure. Protective gloves, worn in accordance with label recommendations, were analysed for the determination of potential hand exposure.

Inhalation exposure was measured by means of personal air sampling pumps connected to an IOM sampling cassette with glass fibre filter located in the operator’s breathing zone.

All samples collected were analysed for residues of fluquinconazole and prochloraz.

Inner and outer dosimeters, Tyvek, face/neck wipes and nitrile gloves were cut into small pieces and placed into glass vessels and extracted with methanol. Air sampling filters were extracted with acetone. All extracts were diluted for the determination of fluquinconazole and prochloraz by HPLC-MS/MS.

Hand wash solutions were directly analysed by HPLC-MS/MS.

**Results**

Since all mean field fortification recoveries for fluquinconazole were greater than 98% operator exposure results have not been corrected. Where a residue below the limit of quantification (LOQ) has been found a value of 0.5 x LOQ has been reported and used in summary calculations.

The following table gives a summary of the residues of test item on each dosimeter for each operator.

Actual dermal exposure is calculated by summing residues from inner dosimeters, hand wash and face/neck wipe specimens. Potential inhalation exposure is the residues measured in the breathing zone based upon a ventilation rate of 14 L/min for tasks.

All field fortified recovery samples for fluquinconazole, gave recoveries greater than 98%.

**Table 1a: Determined Residues of fluquinconazole during bagging (all values in µg/sample)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| Body Weight (kg) | 75.00 | 83.70 | 84.00 | 88.70 | 109.00 | 97.30 | 76.20 | 100.00 | 105.20 | 105.10 | 100.70 |
| Exposure time (min) | 284.0 | 426.0 | 403.0 | 408.0 | 398.0 | 458.0 | 265.0 | 460.0 | 402.0 | 285.0 | 285.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| arms | 66.45 | 42.75 | 196.5 | 113.000 | 831.00 | 211.50 | 333.00 | 75.60 | 41.3 | 289.50 | 18.00 |
| legs | 76.4 | 36.5 | 282.4 | 77.600 | 397.60 | 211.6 | 105.60 | 105.60 | 57.2 | 327.60 | 14.0 |
| torso | 98.36 | 101.9 | 529 | 152.000 | 636.00 | 231.20 | 518.4 | 270.0 | 86.32 | 810.0 | 71.44 |
| TOTAL | 241.2 | 181 | 1008 | 342.60 | 1864.60 | 654.3 | 957 | 451 | 185 | 1427.1 | 103.5 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| arms | 9.520 | 5.334 | 7.140 | 2.198 | 30.59 | 48.58 | 25.90 | 12.11 | 10.99 | 47.67 | 1.218 |
| legs | 5.920 | 5.624 | 8.560 | 3.944 | 14.56 | 23.84 | 7.384 | 6.352 | 5.296 | 8.080 | 0.7952 |
| torso | 11.430 | 8.480 | 8.888 | 7.244 | 55.54 | 30.340 | 22.500 | 23.300 | 17.880 | 24.12 | 1.2050 |
| TOTAL | 26.87 | 19.44 | 24.59 | 13.39 | 100.69 | 102.8 | 55.78 | 41.76 | 34.17 | 79.87 | 3.218 |
| **Handwash** | | | | | | | | | | | |
| Measured | 35.060 | 68.100 | 317.600 | 87.500 | 575.000 | 244.000 | 191.600 | 111.600 | 180.700 | 873.000 | 61.970 |
| TOTAL | 35.060 | 68.100 | 317.600 | 87.500 | 575.000 | 244.000 | 191.600 | 111.600 | 180.700 | 873.000 | 61.970 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 2.493 | 1.34 | 16.69 | 0.983 | 9.988 | 4.109 | 30.380 | 9.512 | 2.501 | 3.294 | 0.250 |
| TOTAL | 2.493 | 1.34 | 16.69 | 0.983 | 9.988 | 4.109 | 30.380 | 9.512 | 2.501 | 3.294 | 0.250 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | 37.12 | NA | NA | 16040 | 2024 | 140.8 | NA | 213.2 | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 1.8 | 1.208 | 2.000 | 0.864 | 1.3 | 0.397 | 6.48 | 1.752 | 1.44 | 1.728 | 0.076 |
| TOTAL | 1.8 | 1.208 | 2.000 | 0.864 | 1.3 | 0.397 | 6.48 | 1.752 | 1.44 | 1.728 | 0.076 |

Values in italics are <LOQ. Half the LOQ is taken for the calculations

**Table 1b: Determined Residues of fluquinconazole during bagging (all values in µg/sample)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| Body Weight (kg) | 90.00 | 118.00 | 63.20 | 80.50 | 63.00 | 81.00 | 65.60 | 90.10 | 81.30 | 71.00 | 97.70 |
| Exposure time (min) | 288.0 | 463.0 | 177.0 | 177.0 | 270.0 | 226.0 | 138.0 | 265.0 | 267.0 | 274.0 | 383.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| arms | 283.50 | 307.50 | 1.191 | 11.910 | 42.9 | 33.600 | 0.669 | 61.350 | 73.050 | 45.450 | 36.000 |
| legs | 109.60 | 234.4 | 2.356 | 8.280 | 31.480 | 44.800 | 3.600 | 32.400 | 69.200 | 40.400 | 40.800 |
| torso | 466.40 | 888.00 | 6.572 | 9.876 | 52.960 | 48.040 | 2.444 | 621.600 | 55.720 | 106.100 | 84.400 |
| TOTAL | 859.5 | 1429.9 | 10.119 | 30.066 | 127.340 | 126.440 | 6.713 | 715.350 | 197.970 | 191.950 | 161.200 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| arms | 64.89 | 105.7 | 0.4580 | 0.3920 | 5.859 | 1.967 | 0.4330 | 5.040 | 1.260 | 4.088 | 3.136 |
| legs | 7.336 | 86.40 | 0.2080 | 0.3730 | 1.528 | 1.280 | 1.382 | 1.400 | 0.544 | 0.8080 | 2.712 |
| torso | 19.250 | 47.080 | 0.6860 | 0.5930 | 4.4710 | 3.3690 | 1.4070 | 88.06 | 2.2360 | 10.6100 | 10.380 |
| TOTAL | 91.48 | 239.2 | 1.352 | 1.358 | 11.86 | 6.616 | 3.222 | 94.50 | 4.040 | 15.51 | 16.23 |
| **Handwash** | | | | | | | | | | | |
| Measured | 1868.000 | 1779.000 | 19.530 | 4.534 | 14.140 | 67.530 | 2.370 | 1222.000 | 110.000 | 17.120 | 56.400 |
| TOTAL | 1868.000 | 1779.000 | 19.530 | 4.534 | 14.140 | 67.530 | 2.370 | 1222.000 | 110.000 | 17.120 | 56.400 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 15.200 | 63.92 | *0.5* | *0.5* | 0.675 | 0.500 | 0.250 | 7.187 | 1.362 | 15.080 | 1.044 |
| TOTAL | 15.200 | 63.92 | *0.5* | *0.5* | 0.675 | 0.500 | 0.250 | 7.187 | 1.362 | 15.080 | 1.044 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | NA | NA | NA | NA | 23.44 | NA | NA | NA | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 1.36 | 27.52 | 0.056 | 0.038 | 0.584 | 0.33 | 0.035 | 0.126 | 0.154 | 2.008 | 0.363 |
| TOTAL | 1.36 | 27.52 | 0.056 | 0.038 | 0.584 | 0.33 | 0.035 | 0.126 | 0.154 | 2.008 | 0.363 |

Values in italics are <LOQ. Half the LOQ is taken for the calculations

**Table 2a: Summary of Field Results – fluquinconazole bagging**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| **Actual Dermal Exposure (µg/hr)** | 13.610 | 12.518 | 53.431 | 14.981 | 103.369 | 45.965 | 62.890 | 21.244 | 32.443 | 201.298 | 13.776 |
| **Potential Inhalation Exposure (µg/hr)** | 2.662 | 1.191 | 2.084 | 0.912 | 1.407 | 0.364 | 10.270 | 1.600 | 1.504 | 2.547 | 0.112 |
| **Active Substance handled (kg/day)** | 26.300 | 21.11 | 57.41 | 21.11 | 62.370 | 48.850 | 26.30 | 57.410 | 21.11 | 64.630 | 64.630 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

**Table 2b: Summary of Field Results – fluquinconazole bagging**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| **Actual Dermal Exposure (µg/hr)** | 411.391 | 269.819 | 7.248 | 2.167 | 5.927 | 19.818 | 2.540 | 299.703 | 25.933 | 10.447 | 11.541 |
| **Potential Inhalation Exposure (µg/hr)** | 1.983 | 24.964 | 0.133 | 0.090 | 0.908 | 0.613 | 0.107 | 0.200 | 0.242 | 3.078 | 0.398 |
| **Active Substance handled (kg/day)** | 64.63 | 57.410 | 36.820 | 36.82 | 23.670 | 37.580 | 17.070 | 49.86 | 49.860 | 23.670 | 62.370 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

**Table 3: Determined Residues of fluquinconazole during cleaning (all values in µg/sample)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 38 | 39 | 45 | 48 | 40 | 43 | 44 | 47 |
| Body Weight (kg) | 76.20 | 90.00 | 109.00 | 105.20 | 65.60 | 81.0 | 96.80 | 100.10 |
| Exposure time (min) | 33.00 | 20.00 | 9.00 | 15.00 | 26.00 | 16.00 | 7.0 | 13.00 |
| **Inner dosimeter (representing the skin)** | | | | | | | | |
| arms | 10.57 | 8.400 | 6.118 | 1.127 | 0.5215 | 0.7504 | 1.554 | 21.91 |
| legs | 1.968 | 9.760 | 92.00 | 0.576 | 1.896 | 0.4312 | 0.4448 | 11.04 |
| torso | 7.0980 | 10.240 | 35.840 | 1.9050 | 1.6130 | 1.2770 | 1.49500 | 2.2830 |
| TOTAL | 19.64 | 28.40 | 134.0 | 3.608 | 4.031 | 2.459 | 3.494 | 35.23 |
| **Handwash** | | | | | | | | |
| Measured | 13.700 | 53.100 | 717.000 | 109.000 | 3.880 | 4.630 | 2.81 | 51.300 |
| TOTAL | 13.700 | 53.100 | 717.000 | 109.000 | 3.880 | 4.630 | 2.81 | 51.300 |
| **Face/neck wipes** | | | | | | | | |
| Measured | 37.93 | 75.98 | 43.040 | 1.125 | 0.571 | 1.008 | 3.816 | 8.746 |
| TOTAL | 37.93 | 75.98 | 43.040 | 1.125 | 0.571 | 1.008 | 3.816 | 8.746 |
| **Residues in air sampling tubes** | | | | | | | | |
| Measured | 0.912 | 1.252 | 4.8 | 0.042 | 0.804 | 1.06 | 0.432 | 0.079 |
| TOTAL | 0.912 | 1.252 | 4.8 | 0.042 | 0.804 | 1.06 | 0.432 | 0.079 |

Values in italics are <LOQ. Half the LOQ is taken for the calculations

**Table 4: Summary of Field Results – fluquinconazole cleaning**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **Actual Dermal Exposure (µg/operation)** | 71.266 | 157.480 | 893.998 | 113.733 | 8.482 | 8.097 | 10.120 | 95.279 |
| **Potential Inhalation Exposure (µg/operation)** | 6.38 | 8.76 | 33.60 | 0.29 | 5.63 | 7.420 | 3.02 | 0.553 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

**Determined Residues of fluquinconazole during mixing/loading/calibration (all values in µg/sample)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedure | Pre-mix | | | | | Dry-couple | | | |
| Operator Number | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| Body Weight (kg) | 84.0 | 76.2 | 65.6 | 105.2 | 89.1 | 100.1 | 96.8 | 81.0 | 70.1 |
| Exposure time (min) | 10 | 25 | 32 | 32 | 459 | 6 | 3 | 2 | 2 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | |
| arms | 1.002 | 0.99 | 0.51 | 144.20 | 112.2 | 0.150 | 0.150 | 3.420 | 1.308 |
| legs | 8.56 | 11.720 | 4.520 | 39.48 | 135.2 | 1.120 | n.d. | 2.072 | 0.200 |
| torso | 71.32 | 3.408 | 2.412 | 1782 | 246.8 | 0.836 | n.d. | 14.68 | n.d. |
| TOTAL | 80.88 | 16.12 | 7.45 | 1965.7 | 494.2 | 2.106 | 0.150 | 20.17 | 1.508 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | |
| arms | 0.537 | 0.262 | 0.266 | 1.792 | 8.470 | 0.482 | *0.035* | 0.507 | *0.035* |
| legs | 0.968 | 0.270 | 1.856 | 1.704 | 5.032 | 0.606 | *0.040* | 0.429 | *0.040* |
| torso | 2.575 | 0.157 | 1.061 | 4.610 | 21.06 | 0.899 | *0.090* | 1.128 | 0.146 |
| TOTAL | 4.080 | 0.689 | 3.183 | 8.106 | 34.56 | 1.987 | 0.165 | 2.064 | 0.221 |
| **Handwash** | | | | | | | | | |
| Measured | 25.200 | 0.995 | 1.300 | 15.300 | 103.4 | 3.860 | *0.250* | 2.390 | *0.250* |
| TOTAL | 25.200 | 0.995 | 1.300 | 15.300 | 103.4 | 3.860 | *0.250* | 2.390 | *0.250* |
| **Face/neck wipes** | | | | | | | | | |
| Measured | 1.705 | *0.250* | *0.250* | 0.900 | 6.218 | *0.250* | *0.250* | *0.250* | n.d. |
| TOTAL | 1.705 | *0.250* | *0.250* | 0.900 | 6.218 | *0.250* | *0.250* | *0.250* | n.d. |
| **Residues in air sampling tubes** | | | | | | | | | |
| Measured | *0.005* | *0.005* | *0.062* | 0.076 | 0.147 | n.d. | n.d. | n.d. | n.d. |
| TOTAL | *0.005* | *0.005* | *0.062* | 0.076 | 0.147 | n.d. | n.d. | n.d. | n.d. |

Values in italics are <LOQ. Half the LOQ is taken for the calculations

**Summary of Field Results – fluquinconazole mixing/loading/calibration**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| **Actual Dermal Exposure (µg/operation)** | 30.985 | 1.934 | 4.733 | 24.306 | 144.18 | 6.097 | 0.665 | 4.704 | 0.471 |
| **Potential Inhalation Exposure (µg/operation)** | 0.035 | 0.035 | 0.434 | 0.532 | 1.029 | n.d. | n.d. | n.d. | n.d. |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

**Conclusions**

The study is considered to provide suitable data for the estimation of operator exposure for the tasks of bagging and equipment cleaning during the treatment of seed.

* + 1. Study 2 – IN-M2G98: Acute Oral Toxicity

|  |  |
| --- | --- |
| Comments of zRMS: | Additional studies has been submitted by the APPL regarding insufficient toxicological data for ground water metabolite IN-M2G98 (recognized during the peer review carried out by the RMS UK; see EFSA Journal 2014;12(9):3814) to conclude on reference values (data gap): Rats and Acute Oral Toxicity Study in Rats.  The study was performed according to the OECD Test Guideline 425. These data meets the current data requirements Regulation (EU) No 284/2013. There is no deviations from the study protocol. Study is acceptable.  Classification is required according to CLP Regulation (EC) No 1272/2008. |

|  |  |
| --- | --- |
| Reference | KCA 5.8.1 |
| Report | IN-M2G98: Acute Oral Toxicity Study in Rats - Up-and-Down Procedure  Xxxxxxx, 2016  DuPont 45346  SYN548397\_10003 |
| Guideline(s) | USEPA OPPTS 890.1100 (2002); OECD 425 (2008) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |

**Executive summary:**

A single oral dose of IN-M2G98 suspended in 0.1% Tween 80 (v/v) in 0.5% Methylcellulose, was administered by oral gavage to six fasted female rats at a dose of 55, 175 or 550 mg/kg body weight. The animals were dosed one at a time at a minimum of 48‑hour intervals. Animals were observed for clinical signs of toxicity, body weight effects, and mortality for up to 14 days after dosing. All animals were examined to detect grossly observable evidence of organ or tissue damage. A software package (AOT425StatPgm) was used to determine the dose progression and to estimate the LD50.

|  |  |  |  |
| --- | --- | --- | --- |
| Oral LD50 | Females | = | 175 mg/kg bw |

At 175 mg/kg, mortality occurred in 1/3 animals on test Day 3 mortality occurred in 2/2animals dosed at 550 mg/kg on test Day 1 (Table 6 and Table 7). Clinical abnormalities observed preceding death included abnormal gait, circling movement, splayed hind limbs, ataxia, cold to touch, dehydration, red nasal discharge, hypoactivity, moribund status, low posture, ruffled fur, and tremors. The surviving females dosed at 175 mg/kg displayed abnormal gait, circling movement, splayed hind limbs, ataxia, hypoactivity, ptosis, hunched posture, low posture and ruffled fur. All clinical abnormalities abated by test Day 5. At 55 mg/kg, no clinical abnormalities were observed. There were no overall (test Day 1-15) bodyweight losses among the surviving animals. Gross findings were limited to wet ventral skin and a red stained nose identified at unscheduled sacrifice in one female rat administered 175 mg/kg. No other gross lesions were observed.

According to the criteria of the U.S. EPA and under the conditions of this study, IN-M2G98 is classified in Toxicity Category II. According to the guidance provided by the U.N. *Globally Harmonized System of Classification and Labelling of Chemicals* (2015), IN-M2G98 is classified in Category 3. In accordance with Regulation (EC) No. 1272/2008, IN-M2G98 is classified in Category 3.

**MATERIALS AND METHODS**

|  |  |  |  |
| --- | --- | --- | --- |
| A. | MATERIALS | |  |
| 1. | Test material: | IN-M2G98 technical metabolite |
|  | Lot/Batch #: | M2G98-004 |
|  | Purity: | 95.9%, by analysis |
|  | Description: | Off-white solid (powder) |
|  | CAS #: | None |
|  | Stability of test compound: | Not determined. However, the test substance appeared to be stable under the conditions of the study. No evidence of instability, such as a change in colour or physical state, was observed |
| 2. | Vehicle: | 0.1% Tween 80 (v/v) in 0.5% Methylcellulose |
| 3. | Test animals |  |
|  | Species: | Rat |
|  | Strain: | Crl:CD (SD) |
|  | Age at dosing: | Approximately 10 weeks old |
|  | Weight at dosing: | 205.9–236.5 g |
|  | Source: | Charles River Laboratories, Raleigh, North Carolina, USA |
|  | Acclimation period: | 6 days |
|  | Diet: | PMI® Nutrition International, LLC Certified Rodent LabDiet® (#5002), *ad libitum* except when fasted |
|  | Water: | Tap water, *ad libitum* |
|  | Housing: | Animals were housed individually in solid-bottom caging with bedding and appropriate species-specific enrichment. |
| 4. | Environmental conditions |  |
|  | Temperature: | 20–26°C |
|  | Humidity: | 30–70% |
|  | Air changes: | Not reported |
|  | Photoperiod: | Alternating 12-hour light and dark cycles |

B. STUDY DESIGN AND METHODS

1. In-life initiated/completed

27-October-2015 to 24-November-2015

2. Animal assignment and treatment

A single oral dose of IN-M2G98, suspended in 0.1% Tween 80 (v/v) in 0.5% Methylcellulose, was administered by oral gavage to three fasted female rats at a dose of 55, 175 or 550 mg/kg. The animals were dosed one at a time at a minimum of 48‑hour intervals. The animals were observed for clinical signs at the beginning of fasting, just before dosing (test Day 1), once during the first 30 minutes after dosing and 2 more times on the day of dosing, and once each day thereafter. Animals were weighed on test Days -1, 1, 8, and 15 or on the day of sacrifice. On test Day 15, the rats were euthanized and necropsied to detect grossly observable evidence of organ or tissue damage.

3. Statistics

A software package (AOT425StatPgm) was used to determine the dose progression and to estimate the LD50.

**RESULTS AND DISCUSSION**

A. MORTALITY

The dose progression and mortality are detailed in Table 6 and Table 7 below.

AOT425statpgm (Version: 1.0) Test Results and Recommendations Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program.

1. Data

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 6: Acute oral toxicity of IN-M2G98: Dose progression and mortality** | | | |
| **Test sequence** | **Dose (mg/kg bw)** | **Short-term resulta** | **Long-term  resulta** |
| 1 | 175 | Ob | O |
| 2 | 550 | Xc | X |
| 3 | 175 | X | X |
| 4 | 55 | O | O |
| 5 | 175 | O | O |
| 6 | 550 | X | X |
| a Short-term result = animal response within 48 hours of dosing. Long-term result = animal response at the end of the 14-day observation period.  b Survived  c Died | | | |

2. Summary of long-term results

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 7: Acute oral toxicity of IN-M2G98: Summary of long-term results** | | | |
| **Dose (mg/kg bw)** | **Oa** | **Xb** | **Total** |
| 55 | 1 | 0 | 1 |
| 175 | 2 | 1 | 3 |
| 550 | 0 | 2 | 2 |
| **All doses** | 3 | 3 | 6 |
| a Survived  b Died | | | |

Statistical estimate based on long-term outcomes: The LD50 was 75 mg/kg, with a 95% confidence interval of 42.89 to 1040 mg/kg.

B. CLINICAL OBSERVATIONS

Clinical abnormalities observed preceding death included abnormal gait, circling movement, splayed hind limbs, ataxia, cold to touch, dehydration, red nasal discharge, hypoactivity, moribund status, low posture, ruffled fur, and tremors. The following clinical signs were observed in the surviving females dosed at 175 mg/kg: abnormal gait, circling movement, splayed hind limbs, ataxia, hypoactivity, ptosis, hunched posture, low posture and ruffled fur. All clinical abnormalities abated by test Day 5. At 55 mg/kg, no clinical abnormalities were observed.

C. BODY WEIGHT

There were no overall (test Day 1-15) bodyweight losses among the surviving.

D. NECROPSY AND GROSS PATHOLOGY

Gross findings were limited to wet ventral skin and a red stained nose identified at unscheduled sacrifice in one female rat administered 175 mg/kg. No other gross lesions were observed.

**CONCLUSION**

Under the conditions of this study, the oral LD50 for IN-M2G98 was 175 mg/kg bw for female rats.

According to the criteria of the U.S. EPA and under the conditions of this study, IN-M2G98 is classified in Toxicity Category II. According to the guidance provided by the U.N. *Globally Harmonized System of Classification and Labelling of Chemicals* (2015), IN-M2G98 is classified in Category 3. In accordance with Regulation (EC) No. 1272/2008, IN-M2G98 is classified in Category 3.

* + 1. Study 3 – IN-M2G98: Repeated-dose Oral Toxicity

|  |  |
| --- | --- |
| Comments of zRMS: | Additional studies has been submitted by the APPL regarding insufficient toxicological data for ground water metabolite IN-M2G98 (recognized during the peer review carried out by the RMS UK; see EFSA Journal 2014;12(9):3814) to conclude on reference values (data gap): Repeated-Dose Oral Toxicity 28-Day Feeding Study in Rats  Taking in to account fact that NOAEL for males and females was not established due to the observation of adverse effects in males and females at the lowest dietary concentration evaluated, 150 ppm (12 mg/kg bw/day for both sexes) ZRMS PL proposed to set LOAEL at 150 ppm based on reduction of body weight gain and food consumption observed at low dose. |

|  |  |
| --- | --- |
| Reference | KCA 5.8.1 |
| Report | IN-M2G98: Repeated-dose oral toxicity 28-day feeding study in rats  Xxxxxxx, 2016  DuPont 45277  SYN548397\_10004 |
| Guideline(s) | USEPA OPPTS 890.3050 (2000); OECD 407 (2008); EC Method B.7 (2014) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |

**Executive summary:**

In a 28‑day feeding study, IN-M2G98 was administered to male and female Crl:CD(SD) rats (10 animals/sex/concentration) at concentrations of 0, 150, 350, 750, and 1500 ppm. The mean daily intakes for males were 0, 12, 22, 22, and 22 mg/kg bw/day. The mean daily intakes for females were 0, 12, 21, 22, and 18 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, ophthalmological assessments, haematology, clinical chemistry, coagulation, urinalysis, biochemistry/mechanistic parameters, gross pathology, organ weights, and histopathology.

The 750 and 1500 ppm groups were terminated after 7 days of exposure (test Day 8) for humane reasons, without further evaluation. Food consumption in the two terminated groups was generally lower in proportion to the concentration of the test substance, such that the overall mean daily intake values were similar across the 350, 750, and 1500 ppm groups, in both sexes.

All animals consuming 0, 150, and 350 ppm survived to scheduled sacrifice. Males and females consuming 150 and 350 ppm exhibited test substance-related reductions in body weight, body weight gain, food consumption, and food efficiency. The mean final body weights for the 150 and 350 ppm groups, respectively, were 6 and 20% lower in males and 6 and 17% lower in females, compared with the controls. The reductions in body weight and food parameters were considered adverse at 350 ppm, and were likely adverse at 150 ppm as well due to consistent reductions in body weight gain throughout the exposure period. Test substance-related clinical signs in these two treatment groups were limited to light tan coloured faeces during the first week of the study. No abnormalities were noted in any animal during the ophthalmology evaluation. There were no adverse effects on clinical pathology parameters or thyroid hormones in males or females consuming 150 or 350 ppm. Adverse test substance-related anatomic effects were limited to microscopic findings in the nose of males and females in the 150 and 350 ppm treatment groups. These changes were characterised by degeneration of olfactory epithelium and, less commonly, by focal erosion or ulceration of the olfactory epithelium (both findings graded minimal in severity). Non-adverse test substance-related findings in the liver of 350 ppm males and females, associated with induction of liver metabolising enzymes, included increased liver weight relative to body weight and, in males only, minimal centrilobular hepatocellular hypertrophy. A minimal increase in the normal background levels of autophagic vacuoles in the pancreas of males and females at 350 ppm was considered to represent a non-adverse secondary response to decrements in body weight observed at this dietary concentration. There were no other test substance‑related or adverse pathology findings in males or females. Non-adverse, test substance-related effects on enzyme activity included an increase in total hepatic microsomal cytochrome P450 enzyme content and increases in UDP‑glucuronyl transferase (UDP‑GT) activity in male and female rats in the 350 ppm group, which corresponded to the anatomic effects noted in the liver at this dietary concentration. An increase in UDP-GT activity in male rats in the 150 ppm dose group was also noted. In the absence of anatomic pathology evidence of hepatic cellular injury, the changes noted in biochemical parameters were considered test substance-related but not adverse and were consistent with an adaptive response of increased metabolism due to exposure to a xenobiotic.

The no‑observed‑adverse‑effect‑level (NOAEL) for males was not established due to the observation of adverse effects in males at the lowest dietary concentration evaluated, 150 ppm (12 mg/kg bw/day). The NOAEL for females was not established due to the observation of adverse effects in females at the lowest dietary concentration evaluated, 150 ppm (12 mg/kg bw/day).

**MATERIALS AND METHODS**

|  |  |  |  |
| --- | --- | --- | --- |
| A. | | MATERIALS |  |
| 1. | Test material: | IN-M2G98 technical metabolite |
|  | Lot/Batch #: | M2G98-004 |
|  | Purity: | 95.9%, by analysis |
|  | Description: | White solid |
|  | CAS #: | None |
|  | Stability of test compound: | Analyses confirmed that test material was stable in feed for up to 14 days at room temperature or refrigerated, was distributed uniformly in the feed, and was present in the feed at targeted concentrations. |
| 2. | Vehicle and/or control: | Untreated diet |
| 3. | Test animals |  |
|  | Species: | Rat |
|  | Strain: | Crl:CD(SD) |
|  | Age at initial dosing: | Approximately 49 days old |
|  | Weight at initial dosing: | 208.0–269.1 g for males; 147.8–186.6 g for females |
|  | Source: | Charles River Laboratories, Inc., Raleigh, North Carolina, USA |
|  | Acclimation period: | 7 days |
|  | Diet: | PMI® Nutrition International, LLC Certified Rodent LabDiet® (#5002), *ad libitum* except when fasted. During the test period, test substance was incorporated into the feed of all animals except controls. |
|  | Water: | Tap water, *ad libitum* |
|  | Housing: | Animals were housed in pairs in solid‑bottom caging with bedding mixed with enrichment. |
| 4. | Environmental conditions |  |
|  | Temperature: | 20–26°C |
|  | Humidity: | 30–70% |
|  | Air changes: | Not reported |
|  | Photoperiod: | Alternating 12-hour light and dark cycles |

B. STUDY DESIGN

1. In-life initiated/completed

07-December-2015 to 08-January-2016

2. Animal assignment and treatment

Five groups of 10 animals/sex/concentration were administered concentrations of IN-M2G98 in feed daily for at least 28 days. Males received 0, 150, 350, 750, and 1500 ppm and females received 0, 150, 350, 750, and 1500 ppm. The dietary route of administration was selected because it is a potential route of human exposure. The dose levels were based on partial mortality and adverse clinical signs observed at 175 mg/kg in a previous study in which IN-M2G98 was evaluated for acute oral toxicity in rats. Animals were assigned to dose groups by computerised, stratified randomisation so that the weight variation of selected animals did not exceed ±20% of the mean weight for each sex. A control group received untreated diet. Animal housing and husbandry were in accordance with the provisions of the *Guide for the Care and Use of Laboratory Animals* (NRC 2011).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 8: Study design: 28-Day feeding study in rats** | | | | | | | |
| **Males** | | | | **Females** | | | |
| **Group no.** | **No./ group** | **Conc. in diet (ppm)a** | **Mean daily intakes mg/kg bw** | **Group no.** | **No./ group** | **Conc. in diet (ppm)a** | **Mean daily intakes mg/kg bw** |
| 1 | 10 | 0 (control) | 0 (control) | 1 | 10 | 0 (control) | 0 (control) |
| 2 | 10 | 150 | 12 | 2 | 10 | 150 | 12 |
| 3 | 10 | 350 | 22 | 3 | 10 | 350 | 21 |
| 4b | 10 | 750 | 22 | 4b | 10 | 750 | 22 |
| 5b | 10 | 1500 | 22 | 5b | 10 | 1500 | 18 |
| a Weight/weight concentration of test substance (adjusted for sponsor-supplied 95.9% purity of active substance).  b Groups 4 and 5 were terminated on test Day 8 for humane reasons. | | | | | | | |

3. Diet preparation and analysis

The test substance was added to the rodent diet and thoroughly mixed. Control diets were mixed for the same period of time. The stability, homogeneity, and concentration of IN‑M2G98 in the dietary mixtures were checked by analysis using HPLC at initial diet preparation. The test substance was at target concentrations ±11.7%, homogeneous (RSDs ≤2.6%) throughout the feed, and was stable (150‑1500 ppm) for up to 14 days at room temperature or refrigerated. Based on this information, it can be concluded that the animals received the targeted dietary concentrations of test substance during the study.

4. Statistics

Significance was judged at p <0.05. Separate analyses were performed on the data collected for each sex.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 9: Statistics: 28-Day feeding study in rats** | | | |
| **Parameter** | **Preliminary test** | **Method of statistical analysis** | |
| **If preliminary test  is not significant** | **If preliminary test  is significant** |
| Body weight  Body weight gain  Food consumption  Food efficiency  Clinical pathologya  Organ weight  Hormone analysis  Cytochrome P450  β-Oxidation  UDP-GT activity | Levene’s test for homogeneity and Shapiro‑Wilk test for normality | One‑way analysis of variance followed by Dunnett’s test | Transforms of the data to achieve normality and variance homogeneity will be used. The order of transforms attempted will be log, square‑root, and rank‑order. If the log and square‑root transforms fail, the rank‑order will be used. |
| a When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.10, 0.05 is used for any calculations performed with those bilirubin data. When an individual observation is recorded as being greater than a certain value, calculations are performed on the recorded value. For example, if specific gravity is reported as >1.100, 1.100 is used for any calculations performed with those specific gravity data. | | | |

C. METHODS

1. Observations

Animals were observed at least twice daily for mortality and morbidity and for signs of abnormal behaviour and appearance. On days when they were weighed, each animal was individually handled, examined for abnormal behaviour and appearance, and subjected to detailed clinical observations. On days when the animals were not weighed, an additional cage-side observation was performed to detect acute clinical signs of systemic toxicity.

2. Body weights

All animals were weighed once per week. An additional body weight was collected on test Day 4 to assess short-term effects. All animals were weighed on the day of sacrifice.

3. Food consumption, food efficiency, and daily intake

During the test period, the amount of food consumed by each rat over the weighing interval was determined by weighing the feeder at the beginning and end of the interval and subtracting the final weight from the initial weight divided by the number of rats in the cage. Food efficiency and daily intake were calculated from food consumption and body weight data.

4. Ophthalmological examinations

All animals were examined by focal illumination and indirect ophthalmoscopy prior to study start. All surviving animals were examined again prior to scheduled sacrifice.

5. Clinical pathology (haematology, clinical chemistry, coagulation, and urinalysis)

Blood and urine samples were collected from all animals approximately 5 weeks after initiation of the study. At sacrifice, blood, bone marrow, and urine were collected. Haematology, clinical chemistry, coagulation, and urinalysis were performed on the samples.

6. Biochemistry/ mechanistic parameters

Blood was collected from all animals near the end of the treatment period by tail vein bleeding. Serum was prepared and stored frozen until analysed for T4, T3, and TSH concentrations. At sacrifice, a portion of the liver from each of these animals was homogenised and hepatic microsomes and peroxisome prepared using differential centrifugation. The pellets were resuspended and stored frozen until analysed for UDP‑GT, peroxisomal β‑oxidation, and total cytochrome P‑450 content. The protein content of the microsomes was determined before and after analysis by the bicinchronic acid (BCA) method and Biorad method, respectively.

7. Evaluation of plasma concentration of test substance and metabolites

Near the end of the treatment period, blood was collected from all animals. Plasma was prepared and frozen until analysed. Concentrations of IN-M2G98 were measured by ultra-high performance liquid chromatography (UHPLC) coupled with tandem mass spectrometry (LC/MS/MS) by multiple reaction monitoring (MRM) (reported in a supplemental report, DuPont-45277 Supplement 1).

8. Sacrifice and pathology

The 750 and 1500 ppm groups were terminated on test Day 8 for humane reasons. All animals in these groups were euthanised by carbon dioxide inhalation while under isoflurane anaesthesia, and discarded without further evaluation.

At termination, animals in the 0, 150, and 350 ppm groups were sacrificed by isoflurane anaesthesia and exsanguination. Gross examinations were performed on all main study animals in these groups. Organs that were weighed are listed in Table 10. Organ weight/final body weight and organ weight/brain weight ratios were calculated. Tissues collected from animals receiving 350 ppm and control (0 ppm) were processed to slides and evaluated microscopically (Table 10). Gross lesions and suspected target tissues (nose, pancreas, and liver [males only]), as determined by examination of the control and high dose animals, were processed to slides and examined microscopically for all animals.

|  |  |  |
| --- | --- | --- |
| **Table 10: 28-Day feeding study in rats: Organs/tissues collected for pathological examination** | | |
| **Organ** | **Organs weighed** | **Microscopic/histopathologic evaluation conducted** |
| Brain | X | X |
| Spleen | X | X |
| Heart | X | X |
| Liver | X | X |
| Kidneys | X | X |
| Oesophagus |  | X |
| Adrenal glands | X | X |
| Duodenum |  | X |
| Jejunum |  | X |
| Ileum |  | X |
| Cecum |  | X |
| Colon |  | X |
| Rectum |  | X |
| Salivary glands |  | X |
| Pancreas |  | X |
| Skin |  | X |
| Trachea |  | X |
| Nose |  | X |
| Larynx/pharynx |  | X |
| Thymus | X | X |
| Mesenteric lymph node |  | X |
| Mandibular lymph node |  | X |
| Bone marrow |  | X |
| Peyer’s patches |  | X |
| Thyroid gland |  | X |
| Parathyroid glands |  | X |
| Eyes |  | X |
| Testes | X | X |
| Epididymides | X | X |
| Prostate | X | X |
| Seminal vesicles with coagulating glands (including fluids) | X | X |
| Ovaries (including oviducts) | X | X |
| Uterus (including cervix) | X | X |
| Mammary glands (females) |  | X |
| Vagina |  | X |
| Stomach |  | X |
| Pituitary |  | X |
| Lungs |  | X |
| Spinal cord |  | X |
| Sciatic nerve |  | X |
| Skeletal muscle |  | X |
| Femur/knee joint |  | X |
| Sternum |  | X |
| Aorta |  | X |
| Urinary bladder |  | X |
| Gross observations |  | X |

**RESULTS AND DISCUSSION**

A. OBSERVATIONS

1. Clinical signs of toxicity

Males and females in all test substance groups were observed with light tan coloured faeces during the first week of the study, which may indicate the consumption and excretion of bedding or enrichment material, and corresponded to the lower food consumption values during the same interval. No other test substance‑related clinical signs of toxicity were observed in the 150 and 350 ppm groups in either males or females.

Animals in the 750 and 1500 ppm groups exhibited dehydration, hunched posture, hypoactivity, high posture, ruffled fur, orbital tightening, and/or nose bulging (the final two were considered indications of pain/distress), which necessitated the early termination of these two groups.

2. Mortality

All animals in both sexes consuming 750 and 1500 ppm were terminated on test Day 8 for humane reasons. All remaining animals survived to scheduled sacrifice.

B. BODY WEIGHT AND BODY WEIGHT GAIN

Test substance-related reductions in body weight and body weight gain were observed in both sexes at all dietary concentrations. The severity of body weight loss, in addition to clinical signs, necessitated the termination of all males and females in the 750 and 1500 ppm groups on test Day 8. The mean body weights at termination for the 750 and 1500 ppm groups, respectively, were 34 and 43% lower in males and 25 and 35% lower in females, compared with the control group means on test Day 8.

Animals in the 150 and 350 ppm groups continued to exhibit lower body weight and body weight gain compared with controls for the remainder of the study. Overall (test Day 1–29) body weight gain was statistically significantly lower than controls in both sexes consuming 150 or 350 ppm. The mean final (test Day 29) body weights for the 150 and 350 ppm groups, respectively, were 6 and 20% lower in males and 6 and 17% lower in females, compared with the controls (statistically significant at 350 ppm for both sexes and at 150 ppm for males).

The body weight reductions were considered adverse at 350 ppm, due to the magnitude, and were likely adverse at 150 ppm as well, due to the fact that the reductions in body weight gain continued throughout the evaluation period.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 11: 28-Day feeding study in rats: Body weights (g)** | | | | | |
| **Day** | **0 ppm** | **150 ppm** | **350 ppm** | **750 ppm** | **1500 ppm** |
| **Males:** | | | | | |
| Day 1 | 241.8 | 238.6 | 245.1 | 240.9 | 236.8 |
| Day 4 | 265.4 | 248.7a | 240.1a | 214.5a | 203.4a |
| Day 8 | 301.6 | 287.5 | 262.4b | 198.7b | 170.6b |
| Day 15 | 351.0 | 335.0 | 291.1a | — | — |
| Day 22 | 394.0 | 374.8 | 323.6a | — | — |
| Day 29 | 425.4 | 399.1a | 340.4a | — | — |
| **Females:** | | | | | |
| Day 1 | 167.9 | 167.4 | 168.9 | 165.8 | 169.1 |
| Day 4 | 173.0 | 167.5 | 159.5a | 149.2a | 142.5a |
| Day 8 | 184.6 | 181.2 | 168.6a | 139.2a | 119.3a |
| Day 15 | 209.7 | 199.3 | 180.3a | — | — |
| Day 22 | 229.8 | 219.3 | 192.6a | — | — |
| Day 29 | 239.5 | 225.5 | 198.5a | — | — |
| a Significantly different from control by the Dunnett 2‑sided criteria, p <0.05.  b Significantly different from control by the Dunnett non-parametric 2‑sided criteria, p <0.05. | | | | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 12: 28-Day feeding study in rats: Body weight gain (g)** | | | | | |
| **Parameter** | **0 ppm** | **150 ppm** | **350 ppm** | **750 ppm** | **1500 ppm** |
| **Males:** | | | | | |
| Body weight gain, Day 1–4 (% difference) | 23.6  (control) | 10.1a  (-57.1) | -5.0a  (-121.0) | -26.4a  (-211.9) | -33.5a  (-242.0) |
| Body weight gain, Day 4–8 (% difference) | 36.2  (control) | 38.8  (7.1) | 22.3a  (-38.3) | -15.9a  (-143.8) | -32.8a  (-190.5) |
| Body weight gain, Day 1–8 (% difference) | 59.8  (control) | 48.9b  (-18.2) | 17.4b  (-70.9) | -42.2b  (-170.7) | -66.2b  (-210.8) |
| Body weight gain, Day 8–15 (% difference) | 49.5  (control) | 47.6  (-3.8) | 28.7b  (-42.0) | — | — |
| Body weight gain, Day 15–22 (% difference) | 43.0  (control) | 39.7  (-7.6) | 32.5b  (-24.5) | — | — |
| Body weight gain, Day 22–29 (% difference) | 31.4  (control) | 24.4a  (-22.3) | 16.9a  (-46.3) | — | — |
| Overall body weight gain Day 1–29 (% difference) | 183.6  (control) | 160.5b  (-12.6) | 95.4b  (-48.1) | — | — |
| **Females:** | | | | | |
| Body weight gain, Day 1–4 (% difference) | 5.1  (control) | 0.1  (-98.2) | -9.4a  (-284.0) | -16.6a  (-424.5) | -26.6a  (-620.0) |
| Body weight gain, Day 4–8 (% difference) | 11.7  (control) | 13.7  (17.6) | 9.0  (-22.8) | -10.0b  (-185.4) | -23.2b  (-298.8) |
| Body weight gain, Day 1–8 (% difference) | 16.8  (control) | 13.8  (-17.7) | -0.4b  (-102.3) | -26.6b  (-258.2) | -49.8b  (-396.6) |
| Body weight gain, Day 8–15 (% difference) | 25.1  (control) | 18.1b  (-27.8) | 11.7b  (-53.3) | — | — |
| Body weight gain, Day 15–22 (% difference) | 20.1  (control) | 20.0  (-0.6) | 12.4b  (-38.5) | — | — |
| Body weight gain, Day 22–29 (% difference) | 9.7  (control) | 6.2  (-36.3) | 5.9  (-39.6) | — | — |
| Overall body weight gain Day 1–29 (% difference) | 71.6  (control) | 58.0b  (-19.0) | 29.5b  (-58.8) | — | — |
| a Significantly different from control by the Dunnett non-parametric 2-sided criteria, p <0.05.  b Significantly different from control by the Dunnett 2‑sided criteria, p <0.05. | | | | | |

C. FOOD CONSUMPTION AND FOOD EFFICIENCY

Over the initial 8-day period of the study, food consumption was markedly reduced in the 750 and 1500 ppm males and females (73.9 and 87.7% for males, respectively, and 71.9 and 89.1% for females, respectively. Reductions in food consumption and food efficiency parameters in males and females at 750 and 1500 ppm corresponded to the losses in body weight described above, necessitating the early termination of these two groups.

Animals in the 150 and 350 ppm groups continued to exhibit lower food consumption compared with controls, for the remainder of the study. Overall (test Day 1–29) food consumption was statistically significantly lower than controls in both sexes consuming 150 or 350 ppm; means were 6 and 30% lower in males, and 14 and 40% lower in females, respectively, compared with control means. Due to the corresponding reductions in body weight gain, the reductions in food efficiency were less pronounced than for food consumption; the differences were statistically significant for most intervals including the overall study duration for both sexes at 350 ppm, but were not statistically significant in either sex at 150 ppm (except for one statistically significant difference in males during test Days 1‑4). Overall food efficiency means for the 150 and 350 ppm groups, respectively, were 7 and 26% lower in males and 5 and 30% lower in females, compared with the controls.

The reductions in food consumption and food efficiency were considered adverse at 350 ppm, and were likely adverse at 150 ppm as well, as noted in the evaluation of body weight.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 13: 28-Day feeding study in rats: Body weight gain, food consumption, and food efficiency** | | | | | |
| **Parameter** | **0 ppm** | **150 ppm** | **350 ppm** | **750 ppm** | **1500 ppm** |
| **Males:** | | | | | |
| Body weight gain (g), Day 1–29  (% difference) | 183.6  (control) | 160.5a  (-12.6) | 95.4a  (-48.1) | — | — |
| Food consumption (g/animal/day), Day 1–4 (% difference) | 23.3  (control) | 15.8b  (-32.3) | 10.9b  (-53.4) | 5.7b  (-75.8) | 3.1b  (-86.8) |
| Food consumption (g/animal/day), Day 4–8 (% difference) | 25.1  (control) | 24.7  (-1.8) | 17.4b  (-30.6) | 6.9b  (-72.6) | 3.0b  (-88.3) |
| Food consumption (g/animal/day), Day 1–8 (% difference) | 24.4  (control) | 20.9b  (-14.3) | 14.6b  (-40.0) | 6.4b  (-73.9) | 3.0b  (-87.7) |
| Food consumption (g/animal/day), Day 8–15 (% difference) | 26.2  (control) | 25.5  (-2.6) | 18.5a  (-29.6) | — | — |
| Food consumption (g/animal/day), Day 15–22 (% difference) | 26.0  (control) | 25.5  (-2.2) | 19.3b  (-25.8) | — | — |
| Food consumption (g/animal/day), Day 22–29 (% difference) | 26.7  (control) | 25.0b  (-6.2) | 19.6b  (-26.5) | — | — |
| Food consumption (g/animal/day), Day 1–29 (% difference) | 25.8  (control) | 24.2b  (-6.2) | 18.0b  (-30.3) | — | — |
| Food efficiency (body weight gain / food consumed), Day 1–4 (% difference) | 0.337  (control) | 0.212b  (-37.2) | -0.195b  (-157.7) | -1.556b  (-561.2) | -3.690b  (-1193.7) |
| Food efficiency (body weight gain / food consumed), Day 4–8 (% difference) | 0.361  (control) | 0.391  (8.4) | 0.319  (-11.5) | -0.589b  (-263.2) | -2.818b  (-880.7) |
| Food efficiency (body weight gain / food consumed), Day 1–8 (% difference) | 0.351  (control) | 0.333  (-5.2) | 0.166b  (-52.7) | -0.955b  (-372.0) | -3.197b  (-1010.5) |
| Food efficiency (body weight gain / food consumed), Day 8–15 (% difference) | 0.270  (control) | 0.266  (-1.3) | 0.223b  (-17.5) | — | — |
| Food efficiency (body weight gain / food consumed), Day 1–29 (% difference) | 0.254  (control) | 0.237  (-7.0) | 0.189a  (-25.8) | — | — |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 13: 28-Day feeding study in rats: Body weight gain, food consumption, and food efficiency (continued)** | | | | | |
| **Parameter** | **0 ppm** | **150 ppm** | **350 ppm** | **750 ppm** | **1500 ppm** |
| **Females:** | | | | | |
| Body weight gain (g), Day 1–29  (% difference) | 71.6  (control) | 58.0a  (-19.0) | 29.5a  (-58.8) | — | — |
| Food consumption (g/animal/day), Day 1–4 (% difference) | 15.0  (control) | 9.9b  (-34.2) | 7.9b  (-47.8) | 3.7b  (-75.7) | 1.5b  (-89.9) |
| Food consumption (g/animal/day), Day 4–8 (% difference) | 15.8  (control) | 15.5  (-1.7) | 10.4b  (-34.1) | 4.9b  (-69.1) | 1.8b  (-88.5) |
| Food consumption (g/animal/day), Day 1–8 (% difference) | 15.5  (control) | 13.1b  (-15.2) | 9.3b  (-39.8) | 4.4b  (-71.9) | 1.7b  (-89.1) |
| Food consumption (g/animal/day), Day 8–15 (% difference) | 17.4  (control) | 15.5b  (-10.9) | 10.8b  (-37.8) | — | — |
| Food consumption (g/animal/day), Day 15–22 (% difference) | 18.1  (control) | 15.9b  (-12.1) | 10.6b  (-41.2) | — | — |
| Food consumption (g/animal/day), Day 22–29 (% difference) | 19.3  (control) | 15.7b  (-18.7) | 11.1b  (-42.6) | — | — |
| Food consumption (g/animal/day), Day 1–29  (% difference) | 17.6  (control) | 15.1b  (-14.3) | 10.5b  (-40.4) | — | — |
| Food efficiency (body weight gain / food consumed), Day 1–4 (% difference) | 0.111  (control) | 0.005  (-95.9) | -0.516b  (-565.5) | -1.599b  (-1541.1) | -5.919b  (-5435.2) |
| Food efficiency (body weight gain / food consumed), Day 4–8 (% difference) | 0.184  (control) | 0.219  (18.7) | 0.209  (13.5) | -0.531b  (-388.1) | -3.828b  (-2178.6) |
| Food efficiency (body weight gain / food consumed), Day 1–8 (% difference) | 0.154  (control) | 0.151  (-1.8) | -0.008b  (-105.1) | -0.886b  (-674.5) | -4.571b  (-3065.2) |
| Food efficiency (body weight gain / food consumed), Day 1–29 (% difference) | 0.145  (control) | 0.137  (-5.1) | 0.101a  (-30.3) | — | — |
| a Significantly different from control by the Dunnett 2‑sided criteria, p <0.05.  b Significantly different from control by the Dunnett non-parametric 2-sided criteria, p <0.05. | | | | | |

D. OPHTHALMOLOGICAL EXAMINATIONS

No ophthalmological observations were observed for any dietary concentration in either males or females.

E. CLINICAL PATHOLOGY

1. Haematology

There were no test substance‑related changes in haematology parameters.

2. Clinical chemistry

Cholesterol was higher in males and females at 350 ppm. Triglycerides were also higher in females at 350 ppm. Changes in serum lipids are frequent findings in toxicology studies in rats and are generally believed to represent minor effects on lipid metabolism that do not adversely affect the health of the animals. Therefore, the increases in serum lipids in the 350 ppm groups were considered to be possibly test substance-related, but non-adverse.

There were no test substance‑related changes in any other clinical chemistry parameters.

3. Coagulation

There were no changes in coagulation parameters.

4. Urinalysis

There were no adverse, test substance‑related changes in urine parameters.

F. BIOCHEMISTRY/MECHANISTIC PARAMETERS

There were no changes in hepatic peroxisomal β-oxidation.

Under the conditions of this study, IN-M2G98 caused an increase in total hepatic microsomal cytochrome P450 enzyme content and increases in UDP-GT activity in male and female rats in the 350 ppm dose groups. An increase in UDP-GT activity in male rats in the 150 ppm dose group was also noted. The effects on hepatic enzymes were accompanied by increases in relative (to final body weight) liver weight and liver hypertrophy. In the absence of anatomic pathology evidence of hepatic cellular injury, the changes noted in biochemical parameters were considered test substance-related but not adverse and were consistent with an adaptive response of increased metabolism due to exposure to xenobiotics.

In male rats, there were no statistically significant differences in serum T3, T4, or TSH concentrations at any dose level compared to the control group. There was a statistically significant decrease in serum T3 and T4 in female rats in the 350 ppm dose group (0.6‑ and 0.8‑fold inhibition, respectively) compared to the control group, likely secondary to the observed induction of liver metabolising enzymes. In the absence of a concurrent increase in serum TSH or microscopic alterations of the thyroid gland, this effect is considered non‑adverse. Under the conditions of this study, IN‑M2G98 did not induce changes in thyroid parameters that would be consistent with the potential to modulate thyroid hormone homeostasis, when tested at dietary concentrations up to 350 ppm.

G. PLASMA CONCENTRATION OF IN-M2G98 AND METABOLITES

The plasma concentrations of IN‑M2G98 were approximately linear with respect to dose in both male and female rats over the range of doses tested. There did not appear to be a sex difference in plasma concentration of IN‑M2G98.

H. SACRIFICE AND PATHOLOGY

1. Organ weight

Test substance-related organ weight changes were present in the liver of males and females in the 350 ppm group. In addition, decrements in terminal body weight in the 350 ppm male and female groups were associated with secondary weight changes in a number of other organs. There were no test substance-related organ weight changes in the 150 ppm male and female groups. Liver weight relative to body weight was increased 17% and 8% above control in the 350 ppm males and females, respectively. In males, the liver weight increases were associated with minimal hepatocellular hypertrophy microscopically. These liver weight increases were not associated with changes in liver clinical chemistry parameters or liver histopathology indicative of liver injury. Therefore, these increases in liver weight relative to body weight were considered to be test substance‑related but non‑adverse and due to induction of liver metabolising enzymes. Absolute and relative‑to‑brain weights of the liver in these groups (statistically significant in females) were decreased, reflecting the countervailing secondary effects of the decrements in body weight, as the liver weight is generally body weight dependent.

No test substance‑related changes in other mean organ weights or organ weights relative to final body weight were apparent at any dietary concentration.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 14: 28-Day feeding study in rats: Organ weights** | | | |
| **Parameter** | **0 ppm** | **150 ppm** | **350 ppm** |
| **Males:** | | | |
| Absolute liver weight (g)  (% difference) | 11.672  (control) | 11.047  (-5.4) | 10.679  (-8.5) |
| Relativea liver weight  (% difference) | 2.923  (control) | 2.968  (1.5) | 3.427b  (17.3) |
| Liver to brain weight  (% difference) | 561.355  (control) | 546.002  (-2.7) | 545.812  (-2.8) |
| **Females:** | | | |
| Absolute liver weight (g)  (% difference) | 6.939  (control) | 6.755  (-2.7) | 6.146b  (-11.4) |
| Relativea liver weight  (% difference) | 3.195  (control) | 3.262  (2.1) | 3.465b  (8.4) |
| Liver to brain weight  (% difference) | 384.858  (control) | 379.377  (-1.4) | 344.246b  (-10.6) |
| a Relative weight is defined as the organ to body weight ratio.  b Significantly different from control by the Dunnett 2‑sided criteria, p <0.05. | | | |

2. Gross pathology and histopathology

No test substance‑related gross lesions were observed at necropsy.

Adverse test substance-related effects were limited to microscopic findings in the nose of males and females in both treated groups (150 and 350 ppm). These changes were characterised by degeneration of olfactory epithelium and, less commonly, by focal erosion or ulceration of the olfactory epithelium. Non‑adverse test substance-related findings in the liver of 350 ppm males and females, associated with induction of liver metabolising enzymes, included increased liver weight relative to body weight and, in males only, minimal centrilobular hepatocellular hypertrophy. A minimal increase in the normal background levels of autophagic vacuoles in the pancreas of males and females at 350 ppm was considered to represent a non-adverse secondary response to decrements in body weight observed at this dietary concentration. All other histopathological observations in this study were consistent with normal background lesions of rats of this age and strain.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 15 : 28-Day feeding study in rats: Incidences of microscopic effects** | | | |
| **IN-M2G98 (ppm):** | **0** | **150** | **350** |
| **Number of rats/group:** | **20** | **20** | **20** |
| **Males:** | | | |
| Nose |  |  |  |
| Degeneration, olfactory epithelium, minimal | 1a | 7 | 10 |
| Erosion/ulceration, olfactory epithelium, focal, minimal | 0 | 1 | 2 |
| **Females:** | | | |
| Nose |  |  |  |
| Degeneration, olfactory epithelium, minimal | 0 | 9 | 10 |
| Erosion/ulceration, olfactory epithelium, focal, minimal | 0 | 5 | 2 |
| a Number of organs with microscopic change. | | | |

**CONCLUSION**

The NOAEL for males and females was not established due to the observation of adverse effects in males and females at the lowest dietary concentration evaluated, 150 ppm (12 mg/kg bw/day for both sexes).

1. Exposure calculations
   1. Operator exposure calculations (KCP 7.2.1.1)

Table A 12: Input parameters considered for the estimation of operator exposure

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Formulation type: | FS | | Application technique: | Industrial scale seed treatment | |
| Application rate (AR): | 2.25 | kg a.s./tonne seed |
| Seed treated per day: | 60 | tonnes/d | Amount of a.s. applied: | 135 | kg a.s./d |
| Bag size | 25 | kg | Amount of product used: | 225 | litres/d |
| Dermal absorption (DA): | 0.3 | % | Dilution factor: | 1: undiluted product taken as the worst case scenario | |
| Cleaning tasks performed: | 1 | per day |
| Inhalation absorption (IA): | 100 | % | Mixing/loading tasks performed: | 11 | per day (20L container) |
| Body weight (BW): | 60 | kg/person | Calibration tasks performed | 1 | per day |
| AOEL | 0.007 | mg/kg bw/d | Duration of bagging | 8 | Hours |

Table A 13: Estimation of operator exposure towards cyantraniliprole according to Seed TROPEX Model- 60 kg bodyweight



**Table A 14: Estimation of operator exposure towards cyantraniliprole according to Seed TROPEX Model- 70 kg bodyweight**

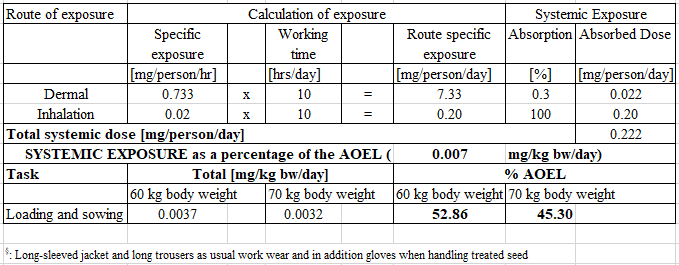
**Worker exposure calculations (KCP 7.2.3.1)**

* + 1. **Calculations for Cyantraniliprole**

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Formulation type:** | FS | | **Application technique:** | Loading and sowing of treated seed | |
| **Application rate (AR):** | 2.25 | kg a.s./tonne seed |
| **Seed treated per day** | 60 | tonnes/d | **Amount of a.s. applied:** | 135 | kg a.s./d |
| **Bag size** | 25 | kg | **Amount of product used:** | 225 | litres/d |
| **Dermal absorption (DA):** | 0.3 | % |
| **Inhalation absorption (IA):** | 100 | % | **Duration of loading/sowing** | 10 | hours |
| **Body weight (BW):** | 60 | kg/person |
| **AOEL** | 0.007 | mg/kg bw/d |

Table A 1715: Estimation of worker exposure towards cyantraniliprole using the Seed-TROPEX model – seed loading and sowing



1. Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1)
   1. OECD Summary Tefluthrin (Xxxxxxx, 2015)

|  |  |
| --- | --- |
| Reference: | 7.2.1.1 |
| Report | Tefluthrin - Determination of Operator Exposure during Typical Activities Associated with Treatment and Bagging of Maize Seeds using Force® 20 CS (200 g/L w/v Tefluthrin as a Capsule Suspension) in Seed Treatment Facilities in Europe.  Xxxxxxx, 2015  ACI14-008  VV-414714 |
| Guidelines: | OECD Series on Testing and Assessment No. 9 “Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application”, Paris 1997. [OCDE/GD(97)148](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ocde/gd(97)148&doclanguage=en). |
| Deviations: | None |
| GLP: | Yes |

**Executive Summary**

In 2014/2015, a GLP compliant operator exposure study was conducted with 42 operators. The study was performed to monitor potential dermal and inhalation exposure to tefluthrin during a typical day’s activities associated with the treatment and bagging of maize seed using Force 20 CS. Operators were separated into four categories; slurry preparation, calibration, bagging and cleaning the treatment chamber.

**Preparation of the test item slurry**

11 operators prepared the test item slurry at 9 different seed treatment sites (11 separate shifts). In all cases the preparation of the test item slurry was performed by a single operator working according to his normal practices.

At 3 sites (monitoring operators 13, 17, 18 and 21) there was no slurry tank and the mixing was performed “in-line” with the test item being mixed automatically at the treatment chamber. The monitored activity involved connecting the delivery tubes to the test item container. All other activities were computerised.

At 3 sites (monitoring operators 19, 20, 22 and 23) there was a slurry tank between the test item container and the treatment chamber. The monitored activity involved connecting the delivery tubes to the test item container and also connecting the slurry tank to the delivery tubes, where necessary. In addition, operator 22 manually prepared slurry pre-mix prior to automated mixing. All other activities were computerised.

At 3 sites (monitoring operators 14, 15 and 16) the slurry tank was “stand-alone” and the monitored activity involved manually adding the test item to the slurry tank and then connecting the delivery tubes to the slurry tank, where necessary. All other activities were computerised.

The duration of the slurry preparation activities at each site was 0.150 to 1.667 hours (excluding any scheduled breaks). Each operator performed a single mixing to have sufficient slurry preparation for the corresponding bagging session, except operator 14 who performed two mixings.

**Calibration of the application equipment**

8 operators performed the calibration of the application equipment at 6 different seed treatment sites (8 separate shifts). In all cases the calibration was performed by a single operator working according to his normal practices. At 3 of the sites calibration was not performed manually, but was fully automated and not monitored.

At 1 site (operators 38 and 39) the monitored activity involved placing the output tubing directly into a graduated cylinder and collecting the delivered volume during a known period of time. The test item was then poured back into the slurry tank.

At 5 sites (operators 37, 40, 41, 42, 43 and 44) the monitored activity involved collecting a sample of the slurry and measuring the density, which was used for computer calculations of the application rate. The test item was then poured back into the slurry tank.

The duration of the calibration activities at each site was 0.117 to 1.417 hours (excluding any scheduled breaks) and the calibration was only performed once by each operator.

**Bagging of treated seed**

12 operators were involved in the bagging of treated seed at 9 different treatment sites. In all cases the bagging was performed by a single operator working according to his normal practices directly at the bagging point. The operator predominantly stands adjacent to the bagging line checking for problems (e.g. jamming of the stitching machine) and taking quality control samples of treated seeds. They are not involved in any cleaning activities.

The seed treatment was performed at 513 to 943 g tefluthrin/tonne seed, depending on the thousand grain weights and assuming 200 g/L tefluthrin. This equates to a nominal application rate of 0.2 mg tefluthrin/seed.

The duration of the bagging sessions at each site was 3.083 to 7.583 hours (excluding any scheduled breaks). The quantity of seed actually bagged was 5.969 to 84.694 tonnes. The total amount of tefluthrin used was 3.44 to 59.02 kg.

**Cleaning of the treatment chamber**

11 operators performed the cleaning of the treatment chamber at 8 different seed treatment sites. In all cases, cleaning was performed by a single operator working according to his normal practices. The monitored activity involved the cleaning of the treatment chamber only.

The duration of the cleaning activities at each site was 0.117 to 0.567 hours (excluding any scheduled breaks) and the number of cleaning activities was 1 to 3 for each operator.

**Materials**

|  |  |
| --- | --- |
| **Test Material:** | Force® 20 CS |
| **Description:** | A capsule suspension for seed treatment |
| **Lot/Batch Number:** | BSN3K0182 (operators 1,2,10,13,14,21,25,33,37,42)  BSN3G1280 (operators 3,15,26)  BSN4J0380 (operators 4,5,16,27,28,38,39)  BSN4J1681 (operators 6,7,17,18,29,30)  BSN4F2581 (operators 8,9,19,20,31,32,40,41)  BSN4J0882 (operators 11,12,22,23,34,35,43,44) |
| **Purity:** | Nominal 200 g/L |
| **Stability of test compound:** | Stable for the duration of the study |

**Study Design and Methods**

**Residue analysis period:** 20th May 2015 to 4th September 2015

**Experimental dates:** 27th November 2014 to 4th September, 2015

**Study Description:**

This study was carried out to determine the dermal and inhalation exposures to tefluthrin associated with the preparation of the slurry, calibration, cleaning and bagging of seed during the treatment of maize seed with Force 20CS, a 200 g/l capsule suspension. A total of 42 experienced operators were monitored, divided between the 4 key tasks. This allows exposures to be predicted for each task and for a single operator carrying out multiple tasks.

The conditions and practices monitored for each operator were intended to be representative of conditions at commercial maize seed treatment facilities throughout Europe and the test sites comprised 9 facilities in France, Italy and Hungary, 8 of which employed batch treaters and the other a continuous flow chamber.

Each operator wore personal protective clothing provided as appropriate, which was subsequently collected for analysis.

Dermal exposure was monitored on whole body dosimeter clothing. The inner dosimeter comprised a long sleeved vest and long-johns (100% cotton), this representing the skin.

For slurry preparation, calibration and cleaning, as a result of the low ambient temperatures, a long sleeved sweatshirt (outer dosimeter 1) was worn at the discretion of the operators (4 operators). A cotton/polyester coverall (outer dosimeter 2), Tyvek coverall (outer dosimeter 3) and impermeable gloves (nitrile) were worn to represent normal work clothing.

For the bagging activities, as above, a long sleeved sweatshirt (outer dosimeter 1) was worn at the discretion of the operators (2 operators). A cotton/polyester coverall (outer dosimeter 2) was worn to represent “normal” work clothing. Impermeable gloves (nitrile) were provided to each operator and worn at their discretion.

At the end of the individual activities the Tyvek coverall (if worn) the cotton/polyester coverall, sweatshirt (if worn) and long sleeved vest/long-johns were sectioned as appropriate. The gloves (if worn) were sampled as a pair.

In addition, hand wash and face/neck wipe samples were taken to monitor exposure of the hands and face when requested by the operators and also prior to removing the body dosimeters. For the hand wash, 2 x 500 mL of soap solution were used and 100 mL aliquots of the resulting solution placed into frozen storage. Face/neck wipes involved two swabs (10 cm x 10 cm), each wetted with 4 mL of the same soap solution. All the face/neck wipe samples performed during each monitored activity for each operator were combined into a single sample.

Inhalation exposure was monitored using a personal air sampling pump connected to an XAD-2 OVS sampling tube, chosen as suitable to measure residues of tefluthrin including any vapour. The air filter was taken at the end of each monitored activity.

All the dosimeter samples were wrapped in aluminium foil. The air filter was capped and placed into a polyethylene bag and the face/neck wipe samples and hand wash samples were placed into HDPE bottles. All samples were subsequently placed into labelled polyethylene bags prior to freezing. The samples were shipped to the analytical laboratory in a freezer trailer and arrived in good frozen condition.

Residues of tefluthrin on outer dosimeter 3 (Tyvek), outer dosimeter 2 (coverall), outer dosimeter 1 (sweatshirt), inner dosimeter, gloves, hand wash and face/neck wipes, were determined according to the analytical method GRM 002.01A.

Residues of tefluthrin on air sampling tubes were determined according to the analytical method RCC 855693.

Outer dosimeter 3 (Tyvek), outer dosimeter 2 (coverall), outer dosimeter 1 (sweatshirt), inner dosimeter, gloves and face wipes were extracted in methanol. Hand wash samples were extracted in acetonitrile and the air filters were extracted in toluene. For all matrices, quantification was by GC-MS analysis.

Field fortifications were carried out for all dosimeters on each day of exposure to assess the stability of the test item under field, storage and transit conditions in or on the sampling matrix. Each dosimeter type was fortified in triplicate at two fortification levels and duplicate controls. The whole body dosimeter specimens (including gloves) were exposed to field conditions for the full exposure monitoring period. Outer dosimeters 2 and 3 were left uncovered and the inner dosimeter and outer dosimeter 1 were covered with a single layer of outer dosimeter 2 material during exposure to ambient conditions. Face/neck wipe specimens and hand wash specimens were frozen immediately after fortification. Air filter specimens were exposed to field conditions for the duration of the monitoring period. Transit spikes were performed for each sampling matrix on the first day of monitored activity and frozen immediately to assess the stability during the storage and transit of the samples. Each dosimeter type was fortified in duplicate at two fortification levels.

Air temperature and humidity were recorded at regular intervals.

**Results**

The results of the field fortifications generally showed acceptable recoveries in the range of 70 to 120% and all overall means were within this range. However, where recoveries were <70%, results were corrected:

**Table A 16: Field recoveries requiring correction**

|  |  |  |  |
| --- | --- | --- | --- |
| **Dosimeter** | **Day** | **Recovery** | **Operators** |
| Hand wash | 3 | 43% | 3, 15, 26 |
|  | 4 | 34% | 4, 16, 27, 38 |
| Inner dosimeter | 1 | 51% | 1, 13 |
| Outer dosimeter 1 | 1 | 61% | None |
| Outer dosimeter 3 | 1 | 60% | 13 |
|  | 2 | 61% | 14, 25, 37 |
|  | 5 | 69% | 28, 39 |
|  | 9 | 57% | 22, 34, 43 |

Transit and procedural recoveries were all in the range 70% to 120% with the exception of one batch which gave a procedural recovery of 68% (considered acceptable).

The following tables present the results of the residue measurements for all dosimeters for each task and each operator. Throughout, values <LOQ (shown in italics) are assigned a value of ½ LOQ. Corrections for low recoveries (underlined) were made according to Table A 17:

**Table A 17: Determined residues of tefluthrin during slurry preparation**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
| Amount of tefluthrin handled (kg) a) | | | | | | | | | | | |
|  | / | 9.760 | 13.700 | 48.040 | / | / | 13.900 | 6.960 | / | 24.480 | 17.700 |
| Inner dosimeter (µg/sample) | | | | | | | | | | | |
| Lower arms | *0.98* | 26.45 | 7.04 | *0.50* | *0.50* | 1.50 | 13.13 | *0.50* | *0.50* | *0.50* | *0.50* |
| Upper arms | *0.98* | 3.88 | 2.01 | *0.50* | *0.50* | *0.50* | 4.17 | *0.50* | *0.50* | *0.50* | *0.50* |
| Lower legs | 16.00 | 43.25 | 5.58 | *0.50* | 4.67 | 1.16 | 2.69 | 1.12 | *0.50* | 2.19 | *0.50* |
| Upper legs | 4.37 | 17.42 | 6.59 | *0.50* | 5.25 | 1.90 | 1.27 | 2.70 | *0.50* | 2.57 | *0.50* |
| Torso | 5.05 | 43.70 | 11.73 | 1.04 | 7.03 | 5.07 | 4.51 | 4.50 | *0.50* | 3.91 | *0.50* |
| TOTAL | 27.38 | 134.71 | 32.95 | 3.04 | 17.96 | 10.13 | 25.78 | 9.32 | 2.50 | 9.67 | 2.50 |
| Outer 1 - sweatshirt (µg/sample) | | | | | | | | | | | |
| Lower arms |  |  |  |  | *0.50* | *0.5* |  |  |  |  |  |
| Upper arms |  |  |  |  | *0.50* | *0.5* |  |  |  |  |  |
| Torso |  |  |  |  | *0.50* | 1.19 |  |  |  |  |  |
| TOTAL |  |  |  |  | 1.5 | 2.19 |  |  |  |  |  |
| Outer 2 - coverall (µg/sample) | | | | | | | | | | | |
| Lower arms | *5.00* | 242.26 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper arms | *5.00* | 45.59 | 11.60 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Lower legs | *5.00* | 243.36 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper legs | *5.00* | 135.28 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Torso | *5.00* | 559.04 | 64.10 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| TOTAL | 25.00 | 1225.53 | 90.70 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| Outer 3 -Tyvek (µg/sample) | | | | | | | | | | | |
| Lower arms | 267.65 | 65464.37 | 9274.42 | *50.00* | *50.00* | 121.63 | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Upper arms | *83.33* | 7109.87 | 121.19 | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Lower legs | 183.59 | 50274.65 | 1331.73 | *50.00* | *50.00* | 1085.73 | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Upper legs | 613.22 | 7090.47 | 12428.44 | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Torso | 5208.28 | 15900.50 | 2151.77 | *50.00* | 192.79 | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Hood | *83.33* | *81.97* | 151.25 | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| TOTAL | 6439.41 | 145921.82 | 25458.81 | 300.00 | 442.79 | 1407.36 | 300.00 | 300.00 | 300.00 | 526.32 | 300.00 |
| Gloves (µg/sample) | | | | | | | | | | | |
| TOTAL | 3396.37 | 30214.83 | 135766.11 | 123.78 | 757177.17 | 310505.53 | 3583.11 | 757.74 | 1997.66 | 10.93 | 314.57 |
| Face/neck wipes (µg/sample) | | | | | | | | | | | |
| TOTAL | 2.49 | 5.97 | 1.56 | *0.50* | 1.20 | *0.50* | 1.69 | *0.50* | *0.50* | *0.50* | *0.50* |
| Hand wash (µg /sample) | | | | | | | | | | | |
| TOTAL | 19.46 | 666.83 | 4311.87 | *14.71* | *5.00* | *5.00* | 23.50 | *5.00* | *5.00* | *5.00* | *5.00* |
| Air sampling filter (µg /sample) | | | | | | | | | | | |
| TOTAL | 0.080 | 1.019 | 0.151 | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* |

1. Quantities of product handled are only reported where slurry tank mixing occurred, there is no data for dry coupling performed by operators 13, 17, 18 and 21. Therefore normalized values only take into consideration tank mixing (7 operators), which is a conservative approach since it is expected to be worst case in modern systems.

**Table A 18: Determined residues of tefluthrin during calibration**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 |
| Inner dosimeter (µg/sample) | | | | | | | | |
| Lower arms | *0.50* | *0.50* | 1.81 | 11.28 | *0.50* | *0.50* | *0.50* | *0.50* |
| Upper arms | *0.50* | *0.50* | *0.50* | 2.14 | *0.50* | *0.50* | *0.50* | *0.50* |
| Lower legs | 1.42 | 1.64 | 1.18 | 2.43 | *0.50* | *0.50* | *0.50* | *0.50* |
| Upper legs | *0.50* | 3.19 | 1.41 | 1.89 | *0.50* | *0.50* | *0.50* | *0.50* |
| Torso | *0.50* | 10.43 | 1.85 | 5.77 | 2.82 | *0.50* | *0.50* | *0.50* |
| TOTAL | 3.42 | 16.26 | 6.75 | 23.51 | 4.82 | 2.50 | 2.50 | 2.50 |
| Outer 2 - coverall (µg/sample) | | | | | | | | |
| Lower arms | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper arms | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Lower legs | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper legs | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Torso | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| TOTAL | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| Outer 3 -Tyvek (µg/sample) | | | | | | | | |
| Lower arms | 9476.69 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Upper arms | 755.59 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Lower legs | 627.56 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Upper legs | 688.82 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Torso | 2159.66 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Hood | 2415.25 | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| TOTAL | 16123.57 | 300.00 | 434.78 | 300.00 | 300.00 | 300.00 | 526.32 | 300.00 |
| Gloves (µg/sample) | | | | | | | | |
| TOTAL | 37845.07 | 704.21 | 1465.73 | 494.22 | 3574.27 | 13236.37 | 565.44 | *5.00* |
| Face/neck wipes (µg/sample) | | | | | | | | |
| TOTAL | 527.62 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* |
| Hand wash (µg /sample) | | | | | | | | |
| TOTAL | *5.00* | *14.71* | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Air sampling filter (µg /sample) | | | | | | | | |
| TOTAL | 0.106 | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* | *0.0375* |

**Table A 19: Determined residues of tefluthrin during bagging**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|  | Amount of tefluthrin handled (kg) | | | | | | | | | | | |
|  | 59.0200 | 8.92000 | 9.9800 | 14.9400 | 11.2800 | 14.96000 | 15.3400 | 12.42000 | 7.62000 | 8.3800 | 10.18000 | 3.44000 |
| Inner dosimeter (µg/sample) | | | | | | | | | | | | |
| Lower arms | *2.70* | *0.50* | 2.70 | 3.09 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | 2.27 | 1.19 |
| Upper arms | *0.98* | *0.50* | *0.50* | 1.68 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* |
| Lower legs | *0.98* | 1.10 | *0.50* | 4.02 | *0.50* | *0.50* | 1.05 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* |
| Upper legs | *0.98* | *0.50* | 0.50 | 7.01 | *0.50* | *0.50* | 1.25 | *0.50* | 7.23 | *0.50* | *0.50* | *0.50* |
| Torso | *8.86* | 1.19 | 1.92 | 7.88 | 1.45 | *0.50* | 1.60 | 2.19 | 1.95 | 1.56 | 3.36 | 1.54 |
| TOTAL (μg) | 14.50 | 3.79 | 6.11 | 23.68 | 3.45 | 2.50 | 4.89 | 4.19 | 10.67 | 3.56 | 7.13 | 4.23 |
| Outer 1 - sweatshirt (µg/sample) | | | | | | | | | | | | |
| Lower arms |  |  |  |  |  | 2.47 | 4.69 |  |  |  |  |  |
| Upper arms |  |  |  |  |  | *0.50* | 0.50 |  |  |  |  |  |
| Torso |  |  |  |  |  | 2.05 | 1.17 |  |  |  |  |  |
| TOTAL |  |  |  |  |  | 5.01 | 6.36 |  |  |  |  |  |
| Outer 2 - coverall (µg/sample) | | | | | | | | | | | | |
| Lower arms | 22.98 | 11.04 | 11.96 | 73.62 | 10.06 | 22.34 | 24.62 | *5.00* | 23.59 | 87.06 | 12.34 | *5.00* |
| Upper arms | *5.00* | *5.00* | *5.00* | 21.00 | *5.00* | 21.63 | 15.45 | *5.00* | *5.00* | 17.05 | *5.00* | *5.00* |
| Lower legs | 20.08 | 28.80 | 12.69 | 115.85 | 23.90 | 14.57 | 18.61 | *5.00* | *5.00* | 10.99 | *5.00* | *5.00* |
| Upper legs | 22.91 | 10.26 | *5.00* | 113.34 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | 87.78 | *5.00* | *5.00* |
| Torso | 58.01 | 43.76 | 43.98 | 235.56 | 23.97 | 34.69 | 68.18 | 33.13 | 43.46 | 146.25 | 41.18 | 30.98 |
| TOTAL | 128.99 | 98.86 | 78.62 | 559.36 | 67.93 | 98.24 | 131.86 | 53.13 | 82.05 | 349.13 | 68.52 | 50.98 |
| Gloves (µg/sample) | | | | | | | | | | | | |
| TOTAL | 88.178 | 92.23 | *5.00* | 434.97 | No gloves | 10.03 | 52.84 | 77.16 | 12.06 | 11258.20 | *5.00* | 37.67 |
| Face/neck wipes (µg/sample) | | | | | | | | | | | | |
| TOTAL | *0.50* | 3.38 | *0.50* | 2.35 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* |
| Hand wash (µg /sample) | | | | | | | | | | | | |
| TOTAL | 25.48 | *10.00* | 23.26 | 61.25 | *5.00* | *10.00* | *10.00* | *10.00* | *10.00* | *10.00* | *10.00* | *15.00* |
| Air sampling filter (µg /sample) | | | | | | | | | | | | |
| TOTAL | 0.180 | *0.0375* | 0.105 | 0.435 | 0.106 | 0.103 | 0.201 | *0.0375* | 0.111 | 0.237 | *0.0375* | 0.080 |

**Table A 20: Determined residues of tefluthrin during cleaning**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |
| Inner dosimeter (µg/sample) | | | | | | | | | | | |
| Lower arms | *0.50* | *0.50* | 2.12 | 3.23 | 2.74 | 1.84 | 9.16 | 2.61 | *0.50* | *0.50* | *0.50* |
| Upper arms | *0.50* | *0.50* | *0.50* | *0.50* | 1.67 | *0.50* | 2.99 | *0.50* | *0.50* | *0.50* | *0.50* |
| Lower legs | *0.50* | *0.50* | 4.71 | *0.50* | 5.32 | 1.30 | *0.50* | *0.50* | *0.50* | *0.50* | *0.50* |
| Upper legs | *0.50* | 1.03 | 8.26 | *0.50* | 9.44 | 1.66 | 1.02 | 2.81 | *0.50* | *0.50* | *0.50* |
| Torso | *0.50* | 3.29 | 13.88 | *1.62* | 29.62 | 1.83 | 5.79 | 8.48 | *0.50* | 1.88 | *0.50* |
| TOTAL | 2.50 | 5.82 | 29.47 | 6.35 | 48.79 | 7.12 | 19.46 | 14.90 | 2.50 | 3.88 | 2.50 |
| Outer 1 - sweatshirt (µg/sample) | | | | | | | | | | | |
| Lower arms |  |  |  |  | 2.422 | *0.5* |  |  |  |  |  |
| Upper arms |  |  |  |  | *0.5* | *0.5* |  |  |  |  |  |
| Torso |  |  |  |  | 3.817 | *0.5* |  |  |  |  |  |
| TOTAL |  |  |  |  | 6.739 | 1.5 |  |  |  |  |  |
| Outer 2 - coverall (µg/sample) | | | | | | | | | | | |
| Lower arms | *5.00* | *5.00* | *5.00* | 22.35 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper arms | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Lower legs | *5.00* | *5.00* | *5.00* | 13.86 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Upper legs | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| Torso | *5.00* | *5.00* | *5.00* | *5.00* | 16.25 | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* | *5.00* |
| TOTAL (μg) | 25.00 | 25.00 | 25.00 | 51.21 | 36.25 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| Outer 3 -Tyvek (µg/sample) | | | | | | | | | | | |
| Lower arms | 412.37 | *50.00* | 21469.60 | 56600.03 | 5220.05 | *50.00* | 235.33 | 267.71 | 1097.82 | 216.81 | *50.00* |
| Upper arms | 429.26 | *50.00* | 50304.65 | 20493.49 | *50.00* | *50.00* | 1619.65 | 239.97 | 142.75 | *87.72* | *50.00* |
| Lower legs | *81.97* | *50.00* | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Upper legs | 900.68 | *50.00* | *50.00* | *72.46* | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| Torso | 183.19 | *50.00* | 6734.88 | 3241.25 | 976.09 | *50.00* | 396.38 | *50.00* | 296.91 | *87.72* | *50.00* |
| Hood | *81.97* | *50.00* | 256.49 | 12075.41 | *50.00* | *50.00* | *50.00* | *50.00* | *50.00* | *87.72* | *50.00* |
| TOTAL (μg) | 2089.43 | 300.00 | 78865.62 | 92555.11 | 6396.14 | 300.00 | 2401.36 | 707.68 | 1687.48 | 655.40 | 300.00 |
| Gloves (µg/sample) | | | | | | | | | | | |
| TOTAL | 3311.44 | 684.34 | 84640.72 | 49306.83 | 1839.65 | 271.10 | 4969.91 | 987.95 | 3522.87 | 789.19 | 135.91 |
| Face/neck wipes (µg/sample) | | | | | | | | | | | |
| TOTAL | 1.04 | 11.19 | *0.50* | 2.84 | 1.72 | *0.50* | 6.83 | 1.15 | 2.96 | *0.50* | *0.50* |
| Hand wash (µg /sample) | | | | | | | | | | | |
| TOTAL | *5.00* | *23.26* | 89.46 | 64.40 | 10.25 | *5.00* | 50.83 | *5.00* | 27.62 | *15.00* | *5.00* |
| Air sampling filter (µg /sample) | | | | | | | | | | | |
| TOTAL | *0.0375* | 0.358 | *0.0375* | 0.138 | 0.271 | *0.0375* | *0.0375* | *0.0375* | *0.0375* | 0.104 | *0.0375* |

Definitions and formulae for the calculation of exposure:

**Potential Dermal Exposure (PDE)** is the sum of the residues detected on all outer dosimeters, inner dosimeter, gloves, hand wash and face/neck wipes.

**Actual Dermal Exposure (ADE)** is the sum of the residues detected on the inner dosimeter, sweatshirt, hand wash and face/neck wipes. Although the sweatshirt has been termed an outer dosimeter, it is included in the ADE for the risk assessment as the measured residues could otherwise have been deposited on the inner dosimeter. This is considered to be a precautionary measure as, in practice, operators may well wear additional layers of clothing at the time when maize seed is being treated.

**Potential Inhalation Exposure** is calculated as follows:

|  |
| --- |
| residues on filter [µg] x average ventilation rate [L/min] |
| average pump air flow rate [L/min] |

The nominal average flow rate of the pumps was 1.5 L/min. A ventilation rate of 20.83333 L/min (equivalent to 1.25 m3/hour) has been used which is thought to be protective for activities associated with seed treatment and in line with the EFSA guidance.

The following tables summarise the measured exposures for each activity and each operator assuming a standard bodyweight of 60 kg:

**Table A 21: Measured exposures to tefluthrin for slurry preparation**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** |
| **Protective coverall (µg)** | 6439 | 145922 | 25459 | 300.0 | 442.8 | 1407.4 | 300.0 | 300.0 | 300.0 | 526.3 | 300.0 |
| **Outer dosimeter (µg)** | 25.00 | 1225.5 | 90.70 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| **Inner dosimeter (µg)** | 27.38 | 134.7 | 32.95 | 3.037 | 19.46$ | 12.32a | 25.78 | 9.318 | 2.500 | 9.669 | 2.500 |
| **Head (µg)** | 2.486 | 5.974 | 1.561 | 0.500 | 1.198 | 0.500 | 1.694 | 0.500 | 0.500 | 0.500 | 0.500 |
| **Gloves (µg)** | 3396 | 30215 | 135766 | 123.8 | 757177 | 310506 | 3583 | 757.7 | 1998 | 10.92 | 314.6 |
| **Hand wash (µg)** | 19.46 | 666.8 | 4312 | 14.710 | 5.000 | 5.000 | 23.50 | 5.000 | 5.000 | 5.000 | 5.000 |
| **Air filter (µg)** | 0.080 | 1.019 | 0.151 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | Log normal? | Empirical 75th percentile | Parametric 75th percentile |
| **PDE (µg/kg bw/d)** | 165.17 | 2969 | 2761 | 7.784 | 12628 | 5199 | 65.98 | 18.29 | 38.84 | 9.624 | 10.793 | yes | 2865 | 1335 |
| **ADE (µg/kg bw/d)** | 0.822 | 13.459 | 72.440 | 0.304 | 0.428 | 0.297 | 0.849 | 0.247 | 0.133 | 0.253 | 0.133 | no | 0.836 | 3.106 |
| **PIEb (µg/kg bw/d)** | 0.01852 | 0.236 | 0.0350 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.0087 | 0.00868 | 0.00868 | no | 0.01360 | 0.0304 |
| **Amounf of tefluthrin handled (kg) c** | / | 9.760 | 13.700 | 48.040 | / | / | 13.900 | 6.960 | / | 24.480 | 17.700 | / | 6188 | 2581 |
| **PDE (µg/kg a.i/kg bw/d)** | / | 304.252 | 201.535 | 0.162 | / | / | 4.747 | 2.628 | / | 0.393 | 0.610 | / | 43.202 | 32.073 |
| **ADE (µg/kg a.i/kg bw/d)** | / | 1.379 | 5.288 | 0.006 | / | / | 0.061 | 0.035 | / | 0.010 | 0.008 | / | 0.11396 | 0.2208 |
| **PIE (µg/kg a.i/kg bw/d)** |  | 0.024 | 0.0026 | 0.00018 |  |  | 0.00062 | 0.00125 |  | 0.00035 | 0.00049 |  |  |  |

a - includes sweatshirt (Outer 1)

b – corrected for breathing rate of 20.83333 L/min

1. c- Quantities of product handled are only reported where slurry tank mixing occurred, there is no data for dry coupling performed by operators 13, 17, 18 and 21. Therefore normalized values only take into consideration tank mixing (7 operators), which is a conservative approach since it is expected to be worst case in modern systems.

**Table A 22: Measured exposures to tefluthrin for calibration**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator** | **37** | **38** | **39** | **40** | **41** | **42** | **43** | **44** |
| **Protective coverall (µg)** | 16124 | 300.0 | 433.8 | 300.0 | 300.0 | 300.0 | 526.3 | 300.0 |
| **Outer dosimeter (µg)** | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| **Inner dosimeter (µg)** | 3.423 | 16.255 | 6.751 | 23.506 | 4.818 | 2.500 | 2.500 | 2.500 |
| **Head (µg)** | 527.6 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 |
| **Gloves (µg)** | 37845 | 704.2 | 1466 | 494.2 | 3574 | 13236 | 565.4 | 5.000 |
| **Hand wash (µg)** | 5.000 | 14.710 | 5.000 | 5.000 | 5.000 | 5.000 | 5.000 | 5.000 |
| **Air filter (µg)** | 0.106 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | Log normal? | Empirical 75th percentile | Parametric 75th percentile |
| **PDE (µg/kg bw/d)** | 908.83 | 17.68 | 32.28 | 14.137 | 65.16 | 226.2 | 18.75 | 5.633 | yes | 105.41 | 149.4 |
| **ADE (µg/kg bw/d)** | 8.934 | 0.524 | 0.204 | 0.483 | 0.172 | 0.133 | 0.133 | 0.1333 | no | 0.494 | 1.008 |
| **PIEa (µg/kg bw/d)** | 0.02454 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | no | 0.00868 | 0.01304 |

a - corrected for breathing rate of 20.83333 L/min

**Table A 23: Measured exposures to tefluthrin for bagging**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| **Outer dosimeter (µg)** | 129.0 | 98.86 | 78.62 | 559.4 | 67.93 | 98.2 | 131.9 | 53.13 | 82.05 | 349.1 | 68.52 | 50.98 |
| **Inner dosimeter (µg)** | 14.495 | 3.790 | 6.114 | 23.68 | 3.451 | 7.512a | 11.254a | 4.192 | 10.67 | 3.564 | 7.127 | 4.226 |
| **Head (µg)** | 0.500 | 3.380 | 0.500 | 2.350 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 | 0.500 |
| **Gloves (µg)** | 88.18 | 92.23 | 5.000 | 435.0 |  | 10.03 | 52.84 | 77.16 | 12.06 | 11258 | 5.000 | 37.671 |
| **Hand wash (µg)** | 25.48 | 10.00 | 23.26 | 61.25 | 5.000 | 10.00 | 10.00 | 10.00 | 10.00 | 10.00 | 10.00 | 15.00 |
| **Air filter (µg)** | 0.180 | 0.0375 | 0.105 | 0.435 | 0.106 | 0.103 | 0.201 | 0.0375 | 0.111 | 0.237 | 0.0375 | 0.080 | Log normal? | Empirical 75th percentile | Parametric 75th percentile |
| **PDE (µg/kg bw/d)** | 4.294 | 3.471 | 1.892 | 18.03 | 1.281 | 2.105 | 3.441 | 2.416 | 1.921 | 193.690 | 1.519 | 1.806 | no | 3.882 | 10.828 |
| **ADE (µg/kg bw/d)** | 0.675 | 0.286 | 0.498 | 1.455 | 0.149 | 0.300 | 0.363 | 0.245 | 0.353 | 0.234 | 0.294 | 0.329 | no | 0.430 | 0.545 |
| **PIEb (µg/kg bw/d)** | 0.0417 | 0.00868 | 0.0243 | 0.1007 | 0.0245 | 0.02384 | 0.0465 | 0.00868 | 0.02569 | 0.0549 | 0.00868 | 0.01852 | yes | 0.0441 | 0.0431 |
| **Amounf of tefluthrin handled (kg)** | 59.0200 | 8.92000 | 9.9800 | 14.9400 | 11.2800 | 14.96000 | 15.3400 | 12.42000 | 7.62000 | 8.3800 | 10.18000 | 3.44000 |  | 25.3870 | 60.946 |
| **PDE (µg/kg a.i/kg bw/d)** | 0.0728 | 0.3891 | 0.1895 | 1.2066 | 0.1136 | 0.1407 | 0.2243 | 0.1945 | 0.2521 | 23.1133 | 0.1492 | 0.5251 |  | 16.9247 | 40.631 |
| **ADE (µg/kg a.i/kg bw/d)** | 0.0114 | 0.0321 | 0.0499 | 0.0974 | 0.0132 | 0.0201 | 0.0236 | 0.0197 | 0.0463 | 0.0280 | 0.0289 | 0.0956 |  | 1.8881 | 2.040 |
| **PIE (µg/kg a.i/kg bw/d)** | 0.0007 | 0.0010 | 0.0024 | 0.0067 | 0.0022 | 0.0016 | 0.0030 | 0.0007 | 0.0034 | 0.0065 | 0.0009 | 0.0054 |  | 0.1550 | 0.1565 |

a - includes sweatshirt (Outer 1)

b - corrected for breathing rate of 20.83333 L/min

**Table A 24: Measured exposures to tefluthrin for cleaning**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** | **33** | **34** | **35** |
| **Protective coverall (µg)** | 2089 | 300.0 | 78866 | 92555 | 6396 | 300.0 | 2401 | 707.7 | 1687 | 655.4 | 300.0 |
| **Outer dosimeter (µg)** | 25.00 | 25.00 | 25.00 | 51.21 | 42.99 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 | 25.00 |
| **Inner dosimeter (µg)** | 2.500 | 5.822 | 29.467 | 6.349 | 48.79a | 8.62a | 19.46 | 14.90 | 2.500 | 3.883 | 2.500 |
| **Head (µg)** | 1.044 | 11.19 | 0.500 | 2.836 | 1.720 | 0.500 | 6.825 | 1.152 | 2.961 | 0.500 | 0.500 |
| **Gloves (µg)** | 3311 | 684.3 | 84641 | 49307 | 1840 | 271.1 | 4970 | 988.0 | 3523 | 789.2 | 135.9 |
| **Hand wash (µg)** | 5.000 | 23.26 | 89.46 | 64.40 | 10.25 | 5.000 | 50.83 | 5.000 | 27.62 | 15.00 | 5.000 |
| **Air filter (µg)** | 0.0375 | 0.358 | 0.0375 | 0.138 | 0.271 | 0.0375 | 0.0375 | 0.0375 | 0.0375 | 0.104 | 0.0375 | Log normal? | Empirical 75th percentile | Parametric 75th percentile |
| **PDE (µg/kg bw/d)** | 90.57 | 17.49 | 2728 | 2366 | 138.99 | 10.170 | 124.56 | 29.03 | 87.81 | 24.82 | 7.815 | yes | 131.77 | 338.8 |
| **ADE (µg/kg bw/d)** | 0.142 | 0.671 | 1.991 | 1.226 | 1.125 | 0.235 | 1.285 | 0.351 | 0.551 | 0.323 | 0.1333 | yes | 1.176 | 1.011 |
| **PIEb (µg/kg bw/d)** | 0.00868 | 0.0829 | 0.00868 | 0.0319 | 0.0627 | 0.00868 | 0.00868 | 0.00868 | 0.00868 | 0.0241 | 0.00868 | no | 0.0280 | 0.0301 |

a - includes sweatshirt (Outer 1)

b - corrected for breathing rate of 20.83333 L/min

**Conclusion**

The study provides valid and relevant data for the refinement of the risk assessment for operators carrying out seed treatment including slurry preparation, calibration, bagging and cleaning.

(Wilson, AJ, 2015)

* 1. OECD Summary Fluquinconazole and Prochloraz (Wilson, 2009)

|  |  |
| --- | --- |
| Reference: | 7.2.1.2 |
| Report | Fluquinconazole and Prochloraz: Determination of Operator Exposure During Cereal Seed Treatment With “Jockey” Fungicide in Germany, United Kingdom and France.  Xxxxxxx, 2009  ACI07-006  VV-393832 |
| Guidelines: | OCDE/GD(97)148 Series on Testing and Assessment No. 9, Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Organisation for Economic Cooperation and Development, Paris. |
| Deviations: | None |
| GLP: | Yes |

**Executive Summary**

In 2007, a Good Laboratory Practice (GLP) operator exposure study was conducted with thirty-nine operators in Germany, United Kingdom and France. The study was performed to monitor potential dermal and inhalation exposure to fluquinconazole and prochloraz during a typical days' activities associated with mixing/loading, bagging of treated seed and cleaning of seed treatment equipment. Twenty two operators were monitored for exposure during procedures associated with bagging only. Eight operators were monitored for exposure during procedures associated with the cleaning of the treatment chamber. Nine operators were monitored for the exposure during procedures associated with mixing/loading and when performed calibration.

**Bagging**

The bagging activities were performed as closely as possible to normal practices whilst using commercial equipment in commercial seed treatment facilities.

The type of seed bagged were small grain cereals (wheat). The seed treatment was performed at 0.681 to 0.752 g/kg seed (fluquinconazole) and 0.128 to 0.140 g/kg seed (prochloraz) using ‘Jockey Plus AB’ containing 167 g/L fluquinconazole (nominal) and 31.2 g/L prochloraz (nominal). In some cases, the test item was diluted with water prior to treatment (either in the slurry tank, or directly at the treatment chamber). The duration of each bagging activity was 2.30 to 7.72 hours (average: 5.30 hours excluding any routine breaks) and the quantity of seed actually bagged was 25.05 to 86.00 tonnes (average: 54.1 tonnes) for each bagging line. One to three operators worked on the same bagging line. The total amount of fluquinconazole handled for each bagging line was 17.07 to 64.63 kg (average: 42.23 kg). The total amount of prochloraz handled for each bagging line was 3.189 to 12.08 kg (average: 7.907 kg).

**Cleaning**

The cleaning activity was performed as closely as possible to normal practices using commercial equipment in commercial seed treatment facilities. Cleaning was monitored at four locations in Germany, three locations in UK and one location in France.

Cleaning involved cleaning of the treatment chamber. Cleaning was conducted on either continuous flow or batch treatment chambers. The duration of each cleaning activity was between 0.12 to 0.55 hours (average: 17 min). The cleaning of the treatment chamber was performed by one operator (working alone).

**Mixing/loading/calibration**

Mixing/loading/calibration was monitored in four locations in Germany and one in France. The procedure involved either suction transfer from 200L drums, two locations in Germany, or a transfer into a mixing tank in two locations in Germany and the single location in France. Manual calibration was performed in two locations in Germany. Automatic calibration occurred in two locations in Germany and the location in France.

In the United Kingdom, mixing/loading was monitored in four locations. The procedure always involved dry-coupling and calibration was automatic.

**Materials**

|  |  |
| --- | --- |
| **Test Material:** | ‘Jockey’ (called Jockey Plus AB in France) |
| **Description:** | A flowable suspension for seed treatment |
| **Lot/Batch Number:** | 1159541, 1556013, 1239029, 1970163, 1816396, 1460359, 1859936, 1387219, 1816396, 1443159, 1816393, 1816396 |
| **Purity:** | Nominal 167 g/L fluquinconazole and 31.2 g/L prochloraz |
| **Stability of test compound:** | Stable for the duration of the study |

**Study Design and Methods**

**Field Phase dates:** 23 August 2007 to 14 September 2007

**Experimental dates:** 23 August 2007 to 19 December 2007

**Study Description**

39 operators were monitored between 23 August 2007 and 14 September 2007.

The purpose of this study was to generate operator exposure data during the mixing/loading/calibration, bagging of treated seed and cleaning of seed treatment equipment at static sites in Germany (6 sites), United Kingdom (4 sites) and France (1 site) following treatment with a fungicide nominally containing 167 g/L fluquinconazole and 31.2 g/L prochloraz (34 g/L as copper chloride complex) using batch or continuous flow seed treatment equipment. The recommended use rate of the product is 4.5 L per tonne of seed, equivalent to 751.5 g fluquinconazole and 140.4 g prochloraz per tonne of seed.

The three main phases of seed treatment were followed in this study, namely the mixing/loading/ calibration, bagging of treated seed and cleaning of seed treatment equipment.

Dermal exposure was measured by operators wearing standardised whole-body outer and inner dosimeters. For the bagging activities, each operator wore dosimeters consisting of a long sleeved jacket and long trousers (100% cotton), long sleeved vest and long-johns (100% cotton). The nitrile gloves were made available for the operators (worn at the discretion of the operator when touching contaminated surfaces). For the cleaning activities, each operator wore the same dosimeters as the bagging activities in addition to an impermeable coverall (‘Tyvek’) and impermeable gloves (nitrile), which were worn throughout the cleaning activities.

Head exposure was measured by face/neck wipes.

Actual hand exposure was measured by the handwash procedure. Protective gloves, worn in accordance with label recommendations, were analysed for the determination of potential hand exposure.

Inhalation exposure was measured by means of personal air sampling pumps connected to an IOM sampling cassette with glass fibre filter located in the operator’s breathing zone.

All samples collected were analysed for residues of fluquinconazole and prochloraz.

Inner and outer dosimeters, Tyvek, face/neck wipes and nitrile gloves were cut into small pieces and placed into glass vessels and extracted with methanol. Air sampling filters were extracted with acetone. All extracts were diluted for the determination of fluquinconazole and prochloraz by HPLC-MS/MS.

Hand wash solutions were directly analysed by HPLC-MS/MS.

**Results – Prochloraz**

Since all mean field fortification recoveries for prochloraz were within the range 92 to 106% operator exposure results have not been corrected. Where a residue below the limit of quantification (LOQ) has been found a value of 0.5 × LOQ has been reported and used in summary calculations. The following table gives a summary of the residues of test item on each dosimeter for each operator. Actual dermal exposure is calculated by summing residues from inner dosimeters, hand wash and face/neck wipe specimens. Potential inhalation exposure is the residues measured in the breathing zone based upon a ventilation rate of 14 L/min for tasks. All field fortified recovery samples for prochloraz gave recoveries ≥ 92%.

Table A 25: Determined Residues of prochloraz during bagging (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| Body Weight (kg) | 75.00 | 83.70 | 84.00 | 88.70 | 109.0 | 97.30 | 76.20 | 100.0 | 105.2 | 105.1 | 100.7 |
| Exposure time (min) | 284.0 | 426.0 | 403.0 | 408.0 | 398.0 | 458.0 | 265.0 | 460.0 | 402.0 | 285.0 | 285.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| Arms | 78.90 | 6.870 | 45.30 | 21.75 | 208.5 | 175.5 | 228.0 | 14.79 | 5.070 | 169.5 | 5.145 |
| Legs | 50.00 | 5.120 | 62.80 | 11.12 | 114.8 | 182.0 | 136.4 | 24.76 | 8.120 | 125.2 | 5.000 |
| Torso | 101.0 | 13.80 | 108.0 | 28.08 | 206.2 | 178.8 | 286.0 | 52.68 | 11.67 | 240.0 | 20.04 |
| TOTAL | 229.9 | 25.79 | 216.1 | 60.95 | 529.5 | 536.3 | 650.4 | 92.23 | 24.86 | 534.7 | 30.19 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| Arms | 11.48 | 0.770 | 3.150 | 0.405 | 9.660 | 32.55 | 27.51 | 2.625 | 1.358 | 15.82 | 1.204 |
| Legs | 7.792 | 0.824 | 2.160 | 0.629 | 6.144 | 33.60 | 8.800 | 1.448 | 0.824 | 4.304 | 0.356 |
| Torso | 20.68 | 1.515 | 4.336 | 1.440 | 29.22 | 32.75 | 13.17 | 4.981 | 2.417 | 11.17 | 0.751 |
| TOTAL | 39.95 | 3.109 | 9.646 | 2.474 | 45.02 | 98.90 | 49.48 | 9.054 | 4.599 | 31.29 | 2.311 |
| **Handwash** | | | | | | | | | | | |
| Measured | 34.22 | 5.910 | 71.50 | 10.45 | 94.80 | 232.6 | 115.7 | 20.28 | 20.15 | 193.1 | 23.26 |
| TOTAL | 34.22 | 5.910 | 71.50 | 10.45 | 94.80 | 232.6 | 115.7 | 20.28 | 20.15 | 193.1 | 23.26 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 2.805 | 0.201 | 2.819 | 0.100 | 2.749 | 3.421 | 11.16 | 1.353 | 0.261 | 0.907 | 0.186 |
| TOTAL | 2.805 | 0.201 | 2.819 | 0.100 | 2.749 | 3.421 | 11.16 | 1.353 | 0.261 | 0.907 | 0.186 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | 5.008 | NA | NA | 2936 | 616.0 | 63.60 | NA | 38.56 | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 0.556 | 0.297 | 0.390 | 0.150 | 0.287 | 0.544 | 1.820 | 0.337 | 0.262 | 0.380 | 0.025 |
| TOTAL | 0.556 | 0.297 | 0.390 | 0.150 | 0.287 | 0.544 | 1.820 | 0.337 | 0.262 | 0.380 | 0.025 |

Table A 26: Determined Residues of prochloraz during bagging (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| Body Weight (kg) | 90.00 | 118.0 | 63.20 | 80.50 | 63.00 | 81.00 | 65.60 | 90.10 | 81.30 | 71.00 | 97.70 |
| Exposure time (min) | 288.0 | 463.0 | 177.0 | 177.0 | 270.0 | 226.0 | 138.0 | 265.0 | 267.0 | 274.0 | 383.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| Arms | 62.10 | 52.50 | 1.065 | 6.960 | 8.190 | 5.895 | 0.065 | 15.75 | 47.55 | 8.430 | 10.61 |
| Legs | 33.36 | 45.60 | 1.664 | 2.656 | 5.880 | 9.840 | 0.122 | 40.00 | 59.20 | 7.360 | 17.84 |
| Torso | 117.0 | 163.5 | 2.632 | 3.500 | 10.34 | 8.976 | 0.120 | 145.9 | 54.08 | 20.48 | 30.20 |
| TOTAL | 212.5 | 261.6 | 5.361 | 13.12 | 24.41 | 24.71 | 0.307 | 201.7 | 160.8 | 36.27 | 58.65 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| Arms | 19.39 | 21.98 | 0.310 | 0.131 | 1.281 | 0.587 | 0.056 | 3.031 | 14.77 | 1.260 | 1.547 |
| Legs | 4.200 | 19.52 | 0.189 | 0.232 | 0.363 | 0.277 | 0.036 | 1.736 | 1.368 | 0.283 | 1.400 |
| Torso | 6.172 | 10.00 | 0.390 | 0.255 | 0.991 | 1.553 | 0.084 | 28.82 | 14.95 | 3.097 | 5.826 |
| TOTAL | 29.76 | 51.50 | 0.889 | 0.617 | 2.635 | 2.417 | 0.176 | 33.59 | 31.09 | 4.640 | 8.773 |
| **Handwash** | | | | | | | | | | | |
| Measured | 406.0 | 281.4 | 4.867 | 2.294 | 2.688 | 8.070 | 0.050 | 243.9 | 48.20 | 3.380 | 34.20 |
| TOTAL | 406.0 | 281.4 | 4.867 | 2.294 | 2.688 | 8.070 | 0.050 | 243.9 | 48.20 | 3.380 | 34.20 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 3.573 | 9.512 | 0.156 | 0.100 | 0.112 | 0.100 | n.d. | 4.362 | 4.895 | 1.949 | 0.608 |
| TOTAL | 3.573 | 9.512 | 0.156 | 0.100 | 0.112 | 0.100 | n.d. | 4.362 | 4.895 | 1.949 | 0.608 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | NA | NA | NA | NA | 3.800 | NA | NA | NA | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 0.319 | 5.280 | 0.014 | 0.010 | 0.107 | 0.058 | 0.006 | 0.033 | 0.050 | 0.353 | 0.090 |
| TOTAL | 0.319 | 5.280 | 0.014 | 0.010 | 0.107 | 0.058 | 0.006 | 0.033 | 0.050 | 0.353 | 0.090 |

Table A 27: Summary of Field Results – prochloraz bagging

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| **Actual Dermal Exposure (µg/hr)** | 16.263 | 1.298 | 12.506 | 1.915 | 21.492 | 43.87 | 39.93 | 4.002 | 3.732 | 47.429 | 5.423 |
| **Potential Inhalation Exposure (µg/hr)** | 0.822 | 0.293 | 0.406 | 0.158 | 0.311 | 0.499 | 2.885 | 0.308 | 0.274 | 0.561 | 0.036 |
| **Active Substance handled (kg/day)** | 4.914 | 3.941 | 10.73 | 3.941 | 11.65 | 9.126 | 4.914 | 10.73 | 3.941 | 12.08 | 12.08 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

Table A 28: Summary of Field Results – prochloraz bagging

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| **Actual Dermal Exposure (µg/hr)** | 91.525 | 44.377 | 2.004 | 1.021 | 1.207 | 2.808 | 0.099 | 63.812 | 18.917 | 2.183 | 6.828 |
| **Potential Inhalation Exposure (µg/hr)** | 0.466 | 4.790 | 0.033 | 0.023 | 0.167 | 0.109 | 0.019 | 0.053 | 0.079 | 0.541 | 0.099 |
| **Active Substance handled (kg/day)** | 12.08 | 10.73 | 6.880 | 6.880 | 4.423 | 7.020 | 3.189 | 9.316 | 9.316 | 4.423 | 11.65 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

Table A 29: Determined Residues of prochloraz during cleaning (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 38 | 39 | 45 | 48 | 40 | 43 | 44 | 47 |
| Body Weight (kg) | 76.20 | 90.00 | 109.0 | 105.2 | 65.60 | 81.00 | 96.80 | 100.1 |
| Exposure time (min) | 33.00 | 20.00 | 9.000 | 15.00 | 26.00 | 16.00 | 7.000 | 13.00 |
| **Inner dosimeter (representing the skin)** | | | | | | | | |
| arms | 10.64 | 3.122 | 1.274 | 0.105 | 0.095 | 0.203 | 0.395 | 25.83 |
| legs | 2.560 | 3.296 | 24.56 | 0.089 | 0.242 | 0.088 | 0.165 | 3.952 |
| torso | 4.846 | 2.737 | 15.56 | 0.235 | 0.183 | 0.378 | 1.664 | 2.582 |
| TOTAL | 18.05 | 9.155 | 41.40 | 0.429 | 0.519 | 0.669 | 2.223 | 32.36 |
| **Handwash** | | | | | | | | |
| Measured | 18.90 | 24.50 | 138.0 | 13.80 | 0.542 | 0.824 | 1.090 | 13.90 |
| TOTAL | 18.90 | 24.50 | 138.0 | 13.80 | 0.542 | 0.824 | 1.090 | 13.90 |
| **Face/neck wipes** | | | | | | | | |
| Measured | 21.00 | 14.04 | 8.503 | 0.155 | 0.050 | 0.269 | 0.725 | 2.053 |
| TOTAL | 21.00 | 14.04 | 8.503 | 0.155 | 0.050 | 0.269 | 0.725 | 2.053 |
| **Residues in air sampling tubes** | | | | | | | | |
| Measured | 0.696 | 0.314 | 0.980 | 2.864 | 0.103 | 0.258 | 0.084 | 0.054 |
| TOTAL | 0.696 | 0.314 | 0.980 | 2.864 | 0.103 | 0.258 | 0.084 | 0.054 |

Table A 30: Summary of field results - prochloraz cleaning

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 38 | 39 | 45 | 48 | 40 | 43 | 44 | 47 |
| **Actual Dermal Exposure (µg/operation)** | 57.95 | 47.69 | 187.9 | 14.384 | 1.111 | 1.762 | 4.038 | 48.32 |
| **Potential Inhalation Exposure (µg/operation)** | 4.872 | 2.195 | 6.860 | 20.05 | 0.720 | 1.806 | 0.588 | 0.381 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

Table A 31: Determined Residues of prochloraz during mixing/loading/calibration (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedure | Pre-mix | | | | | Dry-couple | | | |
| Operator Number | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| Body Weight (kg) | 84.00 | 76.20 | 65.60 | 105.2 | 89.10 | 100.1 | 96.80 | 81.00 | 70.10 |
| Exposure time (min) | 10.00 | 25.00 | 32.00 | 32.00 | 459.0 | 6.000 | 3.000 | 2.000 | 2.000 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | |
| arms | 0.236 | 3.870 | 0.094 | 22.95 | 253.5 | 0.459 | 0.193 | 0.642 | 0.169 |
| legs | 1.832 | 18.16 | n.d. | 6.120 | 244.8 | 0.852 | 0.159 | 0.404 | 0.198 |
| torso | 14.200 | 6.960 | n.d. | 369.0 | 634.4 | 0.714 | 0.120 | 1.888 | 0.040 |
| TOTAL | 16.268 | 28.99 | 0.094 | 398.1 | 1133 | 2.025 | 0.472 | 2.934 | 0.407 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | |
| arms | 0.109 | 2.884 | 0.050 | 0.173 | 21.77 | 1.624 | 0.076 | 0.110 | 0.103 |
| legs | 0.178 | 1.194 | 0.026 | 0.254 | 12.08 | 1.034 | 0.097 | 0.103 | 0.129 |
| torso | 0.442 | 1.039 | 0.077 | 0.941 | 51.93 | 2.206 | 0.236 | 1.060 | 0.264 |
| TOTAL | 0.729 | 5.117 | 0.153 | 1.368 | 85.78 | 4.864 | 0.409 | 1.274 | 0.496 |
| **Handwash** | | | | | | | | | |
| Measured | 6.080 | 7.310 | n.d. | 1.490 | 109.9 | 5.34 | 0.538 | 0.455 | 0.200 |
| TOTAL | 6.080 | 7.310 | n.d. | 1.490 | 109.9 | 0.534 | 0.538 | 0.455 | 0.200 |
| **Face/neck wipes** | | | | | | | | | |
| Measured | 0.364 | 1.357 | n.d. | 0.104 | 15.21 | 0.500 | 0.099 | 0.050 | 0.050 |
| TOTAL | 0.364 | 1.357 | n.d. | 0.104 | 15.21 | 0.500 | 0.099 | 0.050 | 0.050 |
| **Residues in air sampling tubes** | | | | | | | | | |
| Measured | 0.002 | 0.008 | 0.005 | 0.012 | 0.400 | 0.001 | n.d. | n.d. | n.d. |
| TOTAL | 0.002 | 0.008 | 0.005 | 0.012 | 0.400 | 0.001 | n.d. | n.d. | n.d. |

Table A 32: Summary of Field Results – prochloraz mixing/loading/calibration

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| **Actual Dermal Exposure (µg/operation)** | 7.173 | 13.784 | 0.153 | 2.962 | 210.9 | 10.704 | 1.046 | 1.779 | 0.746 |
| **Potential Inhalation Exposure (µg/operation)** | 0.015 | 0.057 | 0.033 | 0.082 | 2.800 | 0.007 | n.d. | n.d. | n.d. |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

**Conclusions - Prochloraz**

The study is considered to provide suitable data for the estimation of operator exposure for the tasks of bagging and equipment cleaning during the treatment of seed.

**Results - Fluquinconazole**

Since all mean field fortification recoveries for fluquinconazole were greater than 98% operator exposure results have not been corrected. Where a residue below the limit of quantification (LOQ) has been found a value of 0.5 × LOQ has been reported and used in summary calculations.

The following table gives a summary of the residues of test item on each dosimeter for each operator.

Actual dermal exposure is calculated by summing residues from inner dosimeters, hand wash and face/neck wipe specimens. Potential inhalation exposure is the residues measured in the breathing zone based upon a ventilation rate of 14 L/min for tasks.

All field fortified recovery samples for fluquinconazole, gave recoveries greater than 98%.

Table A 33: Determined Residues of fluquinconazole during bagging (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| Body Weight (kg) | 75.00 | 83.70 | 84.00 | 88.70 | 109.00 | 97.30 | 76.20 | 100.00 | 105.20 | 105.10 | 100.70 |
| Exposure time (min) | 284.0 | 426.0 | 403.0 | 408.0 | 398.0 | 458.0 | 265.0 | 460.0 | 402.0 | 285.0 | 285.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| Arms | 66.45 | 42.75 | 196.5 | 113.000 | 831.00 | 211.50 | 333.00 | 75.60 | 41.3 | 289.50 | 18.00 |
| Legs | 76.4 | 36.5 | 282.4 | 77.600 | 397.60 | 211.6 | 105.60 | 105.60 | 57.2 | 327.60 | 14.0 |
| Torso | 98.36 | 101.9 | 529 | 152.000 | 636.00 | 231.20 | 518.4 | 270.0 | 86.32 | 810.0 | 71.44 |
| TOTAL | 241.2 | 181 | 1008 | 342.60 | 1864.60 | 654.3 | 957 | 451 | 185 | 1427.1 | 103.5 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| Arms | 9.520 | 5.334 | 7.140 | 2.198 | 30.59 | 48.58 | 25.90 | 12.11 | 10.99 | 47.67 | 1.218 |
| Legs | 5.920 | 5.624 | 8.560 | 3.944 | 14.56 | 23.84 | 7.384 | 6.352 | 5.296 | 8.080 | 0.7952 |
| Torso | 11.430 | 8.480 | 8.888 | 7.244 | 55.54 | 30.340 | 22.500 | 23.300 | 17.880 | 24.12 | 1.2050 |
| TOTAL | 26.87 | 19.44 | 24.59 | 13.39 | 100.69 | 102.8 | 55.78 | 41.76 | 34.17 | 79.87 | 3.218 |
| **Handwash** | | | | | | | | | | | |
| Measured | 35.060 | 68.100 | 317.600 | 87.500 | 575.000 | 244.000 | 191.600 | 111.600 | 180.700 | 873.000 | 61.970 |
| TOTAL | 35.060 | 68.100 | 317.600 | 87.500 | 575.000 | 244.000 | 191.600 | 111.600 | 180.700 | 873.000 | 61.970 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 2.493 | 1.34 | 16.69 | 0.983 | 9.988 | 4.109 | 30.380 | 9.512 | 2.501 | 3.294 | 0.250 |
| TOTAL | 2.493 | 1.34 | 16.69 | 0.983 | 9.988 | 4.109 | 30.380 | 9.512 | 2.501 | 3.294 | 0.250 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | 37.12 | NA | NA | 16040 | 2024 | 140.8 | NA | 213.2 | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 1.8 | 1.208 | 2.000 | 0.864 | 1.3 | 0.397 | 6.48 | 1.752 | 1.44 | 1.728 | 0.076 |
| TOTAL | 1.8 | 1.208 | 2.000 | 0.864 | 1.3 | 0.397 | 6.48 | 1.752 | 1.44 | 1.728 | 0.076 |

Values in italics are < LOQ. Half the LOQ is taken for the calculations

Table A 34: Determined Residues of fluquinconazole during bagging (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| Body Weight (kg) | 90.00 | 118.00 | 63.20 | 80.50 | 63.00 | 81.00 | 65.60 | 90.10 | 81.30 | 71.00 | 97.70 |
| Exposure time (min) | 288.0 | 463.0 | 177.0 | 177.0 | 270.0 | 226.0 | 138.0 | 265.0 | 267.0 | 274.0 | 383.0 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | | | |
| Arms | 283.50 | 307.50 | 1.191 | 11.910 | 42.9 | 33.600 | 0.669 | 61.350 | 73.050 | 45.450 | 36.000 |
| Legs | 109.60 | 234.4 | 2.356 | 8.280 | 31.480 | 44.800 | 3.600 | 32.400 | 69.200 | 40.400 | 40.800 |
| Torso | 466.40 | 888.00 | 6.572 | 9.876 | 52.960 | 48.040 | 2.444 | 621.600 | 55.720 | 106.100 | 84.400 |
| TOTAL | 859.5 | 1429.9 | 10.119 | 30.066 | 127.340 | 126.440 | 6.713 | 715.350 | 197.970 | 191.950 | 161.200 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | | | |
| Arms | 64.89 | 105.7 | 0.4580 | 0.3920 | 5.859 | 1.967 | 0.4330 | 5.040 | 1.260 | 4.088 | 3.136 |
| Legs | 7.336 | 86.40 | 0.2080 | 0.3730 | 1.528 | 1.280 | 1.382 | 1.400 | 0.544 | 0.8080 | 2.712 |
| Torso | 19.250 | 47.080 | 0.6860 | 0.5930 | 4.4710 | 3.3690 | 1.4070 | 88.06 | 2.2360 | 10.6100 | 10.380 |
| TOTAL | 91.48 | 239.2 | 1.352 | 1.358 | 11.86 | 6.616 | 3.222 | 94.50 | 4.040 | 15.51 | 16.23 |
| **Handwash** | | | | | | | | | | | |
| Measured | 1868.000 | 1779.000 | 19.530 | 4.534 | 14.140 | 67.530 | 2.370 | 1222.000 | 110.000 | 17.120 | 56.400 |
| TOTAL | 1868.000 | 1779.000 | 19.530 | 4.534 | 14.140 | 67.530 | 2.370 | 1222.000 | 110.000 | 17.120 | 56.400 |
| **Face/neck wipes** | | | | | | | | | | | |
| Measured | 15.200 | 63.92 | *0.5* | *0.5* | 0.675 | 0.500 | 0.250 | 7.187 | 1.362 | 15.080 | 1.044 |
| TOTAL | 15.200 | 63.92 | *0.5* | *0.5* | 0.675 | 0.500 | 0.250 | 7.187 | 1.362 | 15.080 | 1.044 |
| **Nitrile Gloves** | | | | | | | | | | | |
| TOTAL | NA | NA | NA | NA | NA | 23.44 | NA | NA | NA | NA | NA |
| **Residues in air sampling tubes** | | | | | | | | | | | |
| Measured | 1.36 | 27.52 | 0.056 | 0.038 | 0.584 | 0.33 | 0.035 | 0.126 | 0.154 | 2.008 | 0.363 |
| TOTAL | 1.36 | 27.52 | 0.056 | 0.038 | 0.584 | 0.33 | 0.035 | 0.126 | 0.154 | 2.008 | 0.363 |

Values in italics are <LOQ. Half the LOQ is taken for the calculations

Table A 35: Summary of Field Results – fluquinconazole bagging

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 6 | 7 | 4 | 14 | 15 | 16 | 17 | 19 | 20 | 21 | 22 |
| **Actual Dermal Exposure (µg/hr)** | 13.610 | 12.518 | 53.431 | 14.981 | 103.369 | 45.965 | 62.890 | 21.244 | 32.443 | 201.298 | 13.776 |
| **Potential Inhalation Exposure (µg/hr)** | 2.662 | 1.191 | 2.084 | 0.912 | 1.407 | 0.364 | 10.270 | 1.600 | 1.504 | 2.547 | 0.112 |
| **Active Substance handled (kg/day)** | 26.300 | 21.11 | 57.41 | 21.11 | 62.370 | 48.850 | 26.30 | 57.410 | 21.11 | 64.630 | 64.630 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

Table A 36: Summary of Field Results – fluquinconazole bagging

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 23 | 24 | 1 | 3 | 5 | 8 | 10 | 11 | 13 | 18 | 25 |
| **Actual Dermal Exposure (µg/hr)** | 411.391 | 269.819 | 7.248 | 2.167 | 5.927 | 19.818 | 2.540 | 299.703 | 25.933 | 10.447 | 11.541 |
| **Potential Inhalation Exposure (µg/hr)** | 1.983 | 24.964 | 0.133 | 0.090 | 0.908 | 0.613 | 0.107 | 0.200 | 0.242 | 3.078 | 0.398 |
| **Active Substance handled (kg/day)** | 64.63 | 57.410 | 36.820 | 36.82 | 23.670 | 37.580 | 17.070 | 49.86 | 49.860 | 23.670 | 62.370 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/hr (at a breathing rate of 14 L/min).

Table A 37: Determined Residues of fluquinconazole during cleaning (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Operator Number | 38 | 39 | 45 | 48 | 40 | 43 | 44 | 47 |
| Body Weight (kg) | 76.20 | 90.00 | 109.00 | 105.20 | 65.60 | 81.0 | 96.80 | 100.10 |
| Exposure time (min) | 33.00 | 20.00 | 9.00 | 15.00 | 26.00 | 16.00 | 7.0 | 13.00 |
| **Inner dosimeter (representing the skin)** | | | | | | | | |
| arms | 10.57 | 8.400 | 6.118 | 1.127 | 0.5215 | 0.7504 | 1.554 | 21.91 |
| legs | 1.968 | 9.760 | 92.00 | 0.576 | 1.896 | 0.4312 | 0.4448 | 11.04 |
| torso | 7.0980 | 10.240 | 35.840 | 1.9050 | 1.6130 | 1.2770 | 1.49500 | 2.2830 |
| TOTAL | 19.64 | 28.40 | 134.0 | 3.608 | 4.031 | 2.459 | 3.494 | 35.23 |
| **Handwash** | | | | | | | | |
| Measured | 13.700 | 53.100 | 717.000 | 109.000 | 3.880 | 4.630 | 2.81 | 51.300 |
| TOTAL | 13.700 | 53.100 | 717.000 | 109.000 | 3.880 | 4.630 | 2.81 | 51.300 |
| **Face/neck wipes** | | | | | | | | |
| Measured | 37.93 | 75.98 | 43.040 | 1.125 | 0.571 | 1.008 | 3.816 | 8.746 |
| TOTAL | 37.93 | 75.98 | 43.040 | 1.125 | 0.571 | 1.008 | 3.816 | 8.746 |
| **Residues in air sampling tubes** | | | | | | | | |
| Measured | 0.912 | 1.252 | 4.8 | 0.042 | 0.804 | 1.06 | 0.432 | 0.079 |
| TOTAL | 0.912 | 1.252 | 4.8 | 0.042 | 0.804 | 1.06 | 0.432 | 0.079 |

Values in italics are < LOQ. Half the LOQ is taken for the calculations

Table A 38: Summary of Field Results – fluquinconazole cleaning

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 38 | 39 | 45 | 48 | 40 | 43 | 44 | 47 |
| **Actual Dermal Exposure (µg/operation)** | 71.266 | 157.480 | 893.998 | 113.733 | 8.482 | 8.097 | 10.120 | 95.279 |
| **Potential Inhalation Exposure (µg/operation)** | 6.38 | 8.76 | 33.60 | 0.29 | 5.63 | 7.420 | 3.02 | 0.553 |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

Table A 39: Determined Residues of fluquinconazole during mixing/loading/calibration (all values in µg/sample)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Procedure | Pre-mix | | | | | Dry-couple | | | |
| Operator Number | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| Body Weight (kg) | 84.0 | 76.2 | 65.6 | 105.2 | 89.1 | 100.1 | 96.8 | 81.0 | 70.1 |
| Exposure time (min) | 10 | 25 | 32 | 32 | 459 | 6 | 3 | 2 | 2 |
| **Outer Dosimeter – cotton work jacket and trousers** | | | | | | | | | |
| arms | 1.002 | 0.99 | 0.51 | 144.20 | 112.2 | 0.150 | 0.150 | 3.420 | 1.308 |
| legs | 8.56 | 11.720 | 4.520 | 39.48 | 135.2 | 1.120 | n.d. | 2.072 | 0.200 |
| torso | 71.32 | 3.408 | 2.412 | 1782 | 246.8 | 0.836 | n.d. | 14.68 | n.d. |
| TOTAL | 80.88 | 16.12 | 7.45 | 1965.7 | 494.2 | 2.106 | 0.150 | 20.17 | 1.508 |
| **Inner dosimeter (representing the skin)** | | | | | | | | | |
| arms | 0.537 | 0.262 | 0.266 | 1.792 | 8.470 | 0.482 | *0.035* | 0.507 | *0.035* |
| legs | 0.968 | 0.270 | 1.856 | 1.704 | 5.032 | 0.606 | *0.040* | 0.429 | *0.040* |
| torso | 2.575 | 0.157 | 1.061 | 4.610 | 21.06 | 0.899 | *0.090* | 1.128 | 0.146 |
| TOTAL | 4.080 | 0.689 | 3.183 | 8.106 | 34.56 | 1.987 | 0.165 | 2.064 | 0.221 |
| **Handwash** | | | | | | | | | |
| Measured | 25.200 | 0.995 | 1.300 | 15.300 | 103.4 | 3.860 | *0.250* | 2.390 | *0.250* |
| TOTAL | 25.200 | 0.995 | 1.300 | 15.300 | 103.4 | 3.860 | *0.250* | 2.390 | *0.250* |
| **Face/neck wipes** | | | | | | | | | |
| Measured | 1.705 | *0.250* | *0.250* | 0.900 | 6.218 | *0.250* | *0.250* | *0.250* | n.d. |
| TOTAL | 1.705 | *0.250* | *0.250* | 0.900 | 6.218 | *0.250* | *0.250* | *0.250* | n.d. |
| **Residues in air sampling tubes** | | | | | | | | | |
| Measured | *0.005* | *0.005* | *0.062* | 0.076 | 0.147 | n.d. | n.d. | n.d. | n.d. |
| TOTAL | *0.005* | *0.005* | *0.062* | 0.076 | 0.147 | n.d. | n.d. | n.d. | n.d. |

Values in italics are < LOQ. Half the LOQ is taken for the calculations

Table A 40: Summary of Field Results – fluquinconazole mixing/loading/calibration

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Operator Number** | 27 | 28 | 33 | 34 | 36 | 31 | 26 | 32 | 35 |
| **Actual Dermal Exposure (µg/operation)** | 30.985 | 1.934 | 4.733 | 24.306 | 144.18 | 6.097 | 0.665 | 4.704 | 0.471 |
| **Potential Inhalation Exposure (µg/operation)** | 0.035 | 0.035 | 0.434 | 0.529 | 1.029 | n.d. | n.d. | n.d. | n.d. |

Actual Dermal Exposure (ADE) = Sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.

Potential Inhalation Exposure (PIE) = Residues measured in the breathing zone expressed as µg/operation (at a breathing rate of 14 L/min).

**Conclusions - Fluquinconazole**

The study is considered to provide suitable data for the estimation of operator exposure for the tasks of bagging and equipment cleaning during the treatment of seed.

**Overall Conclusions**

Dermal and inhalation exposure to prochloraz and fluquinconazole during mixing/loading/calibration, bagging and cleaning was calculated using the 75th percentile of the measured data (Table A 33). During the mixing/loading/calibration tasks, inhalation exposure was not measured for all operators. This left just five data points, which was not suitable for calculating an exposure value.

Table A 41: Measured values used to calculate operator exposure during seed treatment

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Estimated Total Systemic Exposurea (mg/kg bw/day) | | | |
| Active substance | TASK | PPE (gloves) | 60 kg body weight | | 70 kg body weight | |
| Empiricalb | Parametricb | Empiricalb | Parametricb |
| Metalaxyl-M | Bagging (25 kg bags) | No | 0.00006 | **0.00007** | 0.00005 | **0.00006** |
| Cleaning | Yes | **0.00028** | 0.00027 | **0.00024** | 0.00023 |
| Fludioxonil | Bagging (25 kg bags) | No | **0.00035** | 0.00034 | **0.00030** | 0.00029 |
| Cleaning | Yes | 0.00061 | **0.00073** | 0.00052 | **0.00062** |
| Azoxystrobin | Bagging (25 kg bags) | No | **0.00014** | 0.00014 | **0.00012** | 0.00012 |
| Cleaning | Yes | 0.00061 | **0.00073** | 0.00052 | **0.00062** |
| Thiabendazole | Bagging (25 kg bags) | No | 0.00016 | **0.00017** | 0.00014 | **0.00014** |
| Cleaning | Yes | 0.00014 | **0.00015** | 0.00012 | **0.00013** |

(a) Inhalation exposure values from prochloraz study have been adjusted to 20.83 L/min.

(b) prochloraz study values (75th percentile).

1. Findlay, aM.L., Chester, G., Mallyon B. Worker Exposure During Treatment of Seed with ‘Baytan’. Report No. RJ 1621B. 12th December 1994. [↑](#footnote-ref-2)
2. Leplay, M.A., Vergnon, JC., Zell, S. Worker Exposure During Treatment of Wheat Seed With ‘Germinate Double’. Report No. 93002 HI 557/037/95. [↑](#footnote-ref-3)
3. Chester, G., Wiseman, M., Pontal, P-G., Worker Exposure During Seed Treatment and Sowing of Treated Seed in the UK and France: An Overview. Zeneca Agrochemicals, Fernhurst, Haslemere. Report No. TMF 4896. The data are property of the Seed-TROPEX Group of which Syngenta is a member. [↑](#footnote-ref-4)
4. EFSA Panel on Plant Protection Products and their Residues (PPR); Scientific Opinion on Preparation of a Guidance Document on Pesticide Exposure Assessment for Workers, Operators, Bystanders and Residents. EFSA Journal 2010;8(2):1501. [65 pp.]. doi:10.2903/j.efsa.2010.1501. Available online: www.efsa.europa.eu [↑](#footnote-ref-5)
5. Findlay, M., Chester G. - Worker Exposure During Sowing of Treated Seed with ‘Baytan’. Report No. WER001, issued 3 February 1995. [↑](#footnote-ref-6)
6. Leplay, M.A. - Worker Exposure During Drilling of Wheat Seed Treated With Germinate Double. Report No. 93003 HI 5/42, issued March 1995. [↑](#footnote-ref-7)