|  |
| --- |
| REGISTRATION REPORT  **Part B**  Section 6  Mammalian Toxicology  Detailed summary of the risk assessment |
| Product code: ADM.09250.H.1.A  Product name(s): **2,4-D 95 SP**  Chemical active substance:  2,4-dichlorophenoxy acetic acid, 80.4% or 804 g/Kg |
| Central Zone  Zonal Rapporteur Member State: Poland |
| CORE ASSESSMENT  (authorization) |
| Applicant: XXXX  Sponsor: XXXX  Submission date: March 2023  Evaluation date: December 2023  MS Finalisation date: March 2024 |

Version history

|  |  |
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| When | What |
| March 2023 | 1st applicant version |
| December 2023 | Version evaluated by zRMS PL |
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|  |  |

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# Mammalian Toxicology (KCP 7)

## Summary

Table 6.1‑1: Information on ADM.09250.H.1.A/2,4-D 95 SP \*

|  |  |
| --- | --- |
| Product name and code | 2,4-D 95 SP/ADM.09250.H.1.A |
| Formulation type | Soluble Powder [Code: SP] |
| Active substance(s) (incl. content) | 2,4-dichlorophenoxy acetic acid; 80.4% or 804 g/Kg |
| Function | Herbicide |
| 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 ADM.09250.H.1.A/2,4-D 95 SP 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 ADM.09250.H.1.A/2,4-D 95 SP according to Regulation (EC) No 1272/2008

|  |  |
| --- | --- |
| Hazard class(es), categories | Acute Tox. 4  ~~Eye Dam. 1~~  STOT SE 3 |
| Hazard pictograms or Code(s) for hazard pictogram(s) | ~~GHS05~~  GHS07 |
| Signal word | Warning, ~~Danger~~ |
| Hazard statement(s) | H302-Harmful if swallowed  ~~H318-Causes serious eye damage~~  H335-~~STOT SE 3~~ May cause respiratory irritation |
| Precautionary statement(s) | P102-Keep out of reach of children  P261- Avoid breathing dust/spray  P264-Wash hands thoroughly after handling  P270-DO not eat, drink or smoke when using this product.  ~~P280-Wear protective gloves and eye protection/face protection.~~  P301+P312- IF SWALLOWED: Call a POISON CENTER/doctor.  ~~P302+P352-IF ON SKIN: Wash with plenty of water and soap.~~  ~~P305+P351+P338-IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.~~  P304+P340-IF INHALED: Remove person to fresh air and keep comfortable for breathing.  P405-Store locked up.  P501-Dispose of contents/container to an approved waste disposal plant. |
| Additional labelling phrases | To avoid risks to man and the environment, comply with the instructions for use. [EUH401] |
| Repeated exposure may cause skin dryness or cracking [EUH066] |

Table 6.1‑3: Summary of risk assessment for operators, workers, residents and bystanders for ADM.09250.H.1.A/2,4-D 95 SP

|  | Result | PPE/Risk mitigation measures |
| --- | --- | --- |
| Operators | Acceptable | Workwear (arms, body and legs covered), gloves and face mask/respiratory protection (FP2, P2 and similar) during mixing/loading.  Workwear (arms, body and legs covered) and gloves during application. |
| Workers | Acceptable | Workwear (arms, body and legs covered) |
| Residents | Acceptable | None |
| Bystanders | Acceptable | None |

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

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

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 a.s./ha   a) a.s. 1 b) a.s. 2 | Water L/ha  min./max. | Operator | Worker | Residents | Bystander |
| 1. | Spring Wheat (BBCH 15-25) | F | Overall, Broadcast foliar spray  LCTM | 1 | a) 0.750 | 200-300 | - | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032 | R | A | A | A |

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

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

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

Explanation for column 10 “Acceptability of exposure assessment”

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

Data gaps

No data gaps.

## 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)

|  | (2,4-dichlorophenoxy) acetic acid |
| --- | --- |
| Common Name | 2,4-D |
| CAS-No. | 94-75-7 |
| Classification and proposed labelling | |
| With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended) –  Harmonised classification - Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) | Hazard classess, categories: Acute Tox. 4\*, Eye Dam. 1, Skin Sens. 1 and STOT SE 3  Codes for hazard pictograms: GHS05, GHS07  Signal word: Danger, ~~Warning~~  Hazard statements:  H302 ‘Harmful if swallowed’  H318 ‘Causes serious eye damage’  H317 ‘May cause an allergic skin reaction’  H335 ‘May cause respiratory irritation’  ~~EUH066 ‘Repeated exposure may cause skin dryness or cracking’~~ |
| Additional C&L proposal | None |
| Agreed EU endpoints | |
| AOEL systemic | 0.02 mg/kg bw/d (not corrected for oral absorption) |
| Reference | EFSA Conclusion (2014) |
| Conditions to take into account/critical areas of concern with regard to toxicology | |
| According to EFSA Conclusion (2014) for 2,4-D | None |

## Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for ADM.09250.H.1.A/2,4-D 95 SP 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 and are described in detail in Appendix 2. The formulation toxicity studies provided were generated in 2011 to support registration outside of the EU, thus are provided for information only.  In accordance with paragraph 69 of [2019/C 229/01 Commission Notice — Technical Guidelines on Data Protection according to Regulation (EC) No 1107/2009](https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Feur-lex.europa.eu%2Flegal-content%2FEN%2FTXT%2FPDF%2F%3Furi%3DOJ%3AC%3A2019%3A229%3AFULL%26from%3DEN&data=05%7C01%7CJoshua.Fernandes%40erm.com%7Cd7a63e00b2bf493b4d8808daf4758036%7Cf2fe6bd39c4a485bae69e18820a88130%7C0%7C0%7C638091082774020155%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=3Q0ATDV6lFtYZ4eJbIdiqgZh6%2B4SefF9jBINxP4AQz8%3D&reserved=0), full details of product classification using the calculation method are given in Part C, and outcomes reported below.

Table 6.3‑1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for ADM.09250.H.1.A/2,4-D 95 SP

| Type of test, species, model system (Guideline) | Result | Acceptability | Classification  (acc. to the criteria in Reg. 1272/2008) | Reference |
| --- | --- | --- | --- | --- |
| Acute oral toxicity: ~~ATE calculation~~ Rat, (OECD 423 (2001) | LD50>300 – <2000 mg/kg bw | Yes | Acute Tox. 4, H302 | Satyavani G., 2011a |
| Acute dermal toxicity: ~~ATE calculation~~ Rat, (OECD 402 (1987) | Not acutely toxic  LD50>2000mg/kg bw | Yes | None | Satyavani G., 2011b |
| Acute inhalation toxicity: ~~ATE calculation~~ Rat, (OECD 403 (2009) | Not acutely toxic  LC50>1.36 mg/L air/4h | Yes | None | Jagan Mohan Rao, P., 2011 |
| Skin irritation: ~~additivity calculation~~ Rabbit (OECD 404 (2002)) | Non-irritant | Yes | None | Satyavani G., 2011c |
| Eye irritation: ~~additivity calculation~~ Rabbit (OECD 405 (2002)) | Mild-irritant | Yes | ~~H318~~ None | Satyavani G., 2011d |
| Skin sensitisation: ~~additivity calculation~~ guinea pig (OECD 406 (1992), Buehler (3 inductions) | Non-sensitising | **No** | None - based on no classification for skin sesnsitisation of a.s. 2,4-D (according to EFSA Journal 2014;12(9):3812) | Satyavani G., 2011e |
| Supplementary studies for combinations of plant protection products | No data – not required | | | |

Table 6.3‑2: Additional toxicological information relevant for classification/labelling of ADM.09250.H.1.A/2,4-D 95 SP

|  | 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)\* | 2,4-dichlorophenoxy acetic acid (80.4% (w/w)) | Acute Tox. 4, H302  Eye Dam. 1, H318  STOT SE 3, H335 | EFSA conclusion (EFSA Journal 2014;12(9):3812) | Acute Tox. 4, H302  ~~Eye Dam. 1, H318~~  STOT SE 3, H335 |
| Further toxicological information | No data – not required | EUH066 | EFSA Journal 2014;12(9):3812 | EUH066 |

\*Material safety data sheet by the applicant

## Toxicological Evaluation of Groundwater Metabolites

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

## Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in ADM.09250.H.1.A/2,4-D 95 SP are presented in the following table.

Table 6.5‑1: Dermal absorption rates for active substances in ADM.09250.H.1.A/2,4-D 95 SP

|  | 2,4-dichlorophenoxy acetic acid | |
| --- | --- | --- |
|  | Value | Reference |
| Concentrate | 0.40% | New study reported in Appendix 2 |
| Dilution  (1:300) | 3.50% | New study reported in Appendix 2 |

### 

### Justification for proposed values – 2,4-D

Proposed dermal absorption rates for 2,4-D are based on dermal absorption study conducted with ADM.09250.H.1.A/2,4-D 95 SP. The study results are summarised in the following table. A full summary of study on the dermal absorption of formulation have not previously been evaluated within an EU peer review process are described in detail in Appendix 2.

Table 6.5‑3: Summary of the results of submitted dermal absorption studies for 2,4-D

| Test | Concentrate | Spray dilution  (1:300) | Formulation in study | Acceptability of study | Justification provided on representativity of study formulation for current product | Acceptability of justification | Reference\* |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *In vitro* (human) | 0.40% | 3.50% (1:300) | ADM.09250.H.1.A / 2,4-D 95 SP | Yes | Yes (see Appendix A 2.10) - dermal absorption study conducted with current product ADM.09250.H.1.A / 2,4-D 95 SP | Justification accepted. Endpoint can be used for current product | Hassler, S. 2022 |

\* indicates that a study has not been reviewed at EU level

## 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 | ADM.09250.H.1.A/2,4-D 95 SP |
| Formulation type | SP |
| Category | Herbicide |
| Active substance(s) (incl. content) | **2,4-D**  804 g/kg |
| AOEL systemic | 0.02 mg/kg bw/d |
| Inhalation absorption | 100% |
| Oral absorption | 100% |
| Dermal absorption | Concentrate: 0.40%  Dilution: 3.5% (3 g/L)  (Based on product (formulation)) |

### 

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

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

Justification

The GAP identified in Table 6.1‑4 is deemed to be critical for operators, residents and workers

### Operator exposure (KCP 7.2.1)

#### Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substance during application of ADM.09250.H.1.A/2,4-D 95 SP according to the critical use is presented in Table 6.6‑2. The outcome of the estimation is presented in Table 6.6‑3 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6‑2: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Field crops (max. 0.9328 product/ha, (2,4-D acid)) |
| Model(s) | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032  calculator version: ~~v 0.3.22~~ 1.0.1 |

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

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | 2,4-dichlorophenoxy acetic acid | |
| Model data | Level of PPE | Total absorbed dose  (mg/kg/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to field crops | | | |
| Application rate | | 1 x 0.750 kg a.s./ha | |
| **Spray application** (AOEM**;** 75th percentile)  Body weight: 60 kg | Work wear (arms, body and legs covered) M/L and A | 0.2 | ~~770~~ 874 |
| Work wear (arms, body and legs covered) + gloves M/L and A  + ~~gloves and~~ face mask (FP2, P2 and similar) M/L | 0.02 | ~~94.9~~ 86.7 |

#### 

#### Measurement of operator exposure

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

### Worker exposure (KCP 7.2.3)

#### Estimation of worker exposure

Table 6.6‑4 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with ADM.09250.H.1.A/2,4-D 95 SP according to the critical use. Outcome of the estimation is presented in Table 6.6‑5 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6‑4: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Field crops (max. 0.9328 product/ha, (2,4-D acid)) |
| Model | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032  calculator version: v 0.3.22 |

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

|  |  | 2,4-dichlorophenoxy acetic acid | |
| --- | --- | --- | --- |
| Model data | Level of PPE | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Inspection, irrigation / Outdoor  Outdoor  Work rate: 2 hours/day  DT50: 30 days  DFR: 3 µg/cm2/kg a.s./ha  Interval between treatments: 365 days | | | |
| Number of applications and application rate | | 1 x 0.750 kg a.s./ha | |
| Body weight: 60 kg | Potential  TC: 12500 cm2/person/h | 0.04 | 197 |
| Work wear (arms, body and legs covered)  TC: 1400 cm2/person/h | 0.004 | 22.1 |
| Work wear (arms, body and legs covered) and gloves  TC: 1250 cm2/person/h | 0.004 | 19.7 |

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

#### Measurement of worker exposure

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

### Resident and bystander exposure (KCP 7.2.2)

#### Estimation of resident and bystander exposure

For 2,4-dichlorophenoxy acetic acid no acute acceptable operator exposure value (AAOEL, RVAAS) has been set on EU-level until now. Thus, no acute exposure calculations are required: According to Commission Guidance Document SANTE-10832-2015 rev. 1.7 (24.01.2017) no bystander exposure assessments can be performed with the OPEX model where no AAOEL has been set. Additionally, for active substances with no potential acute systemic toxicity, exposure assessments for residents also covers bystander exposure (EFSA Journal 2022;20(1):7032).

Table 6.6‑6 shows the exposure model(s) used for estimation of resident and bystander exposure to 2,4-dichlorophenoxy acetic acid. The outcome of the estimation is presented in Table 6.6‑7 (longer term resident exposure). Detailed calculations are in Appendix 3.

Table 6.6‑6: Exposure models for intended uses

|  |  |
| --- | --- |
| Critical use(s) | Field crops (max. 0.9328 product/ha, (2,4-D acid)) |
| Model | Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2022;20(1):7032  calculator version: ~~v 0.3.22~~ 1.0.1 |

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

|  |  | 2,4-dichlorophenoxy acetic acid | |
| --- | --- | --- | --- |
| Model data |  | Total absorbed dose (mg/kg bw/day) | % of systemic AOEL |
| Tractor mounted boom spray application outdoors to field crops  Buffer zone: 2-3 m  Drift reduction technology: No  DFR: 3 µg/cm2/kg a.s./ha  Interval between treatments: 365 days | | | |
| Application rate | | 1 x 0.750 kg a.s./ha | |
| Resident child  Body weight: 10 kg | Drift (95th perc.) | 0.004 | ~~21.5~~ 21.6 |
| Vapour (95th perc.) | ~~0.01~~ 0.0008 | ~~60~~ 4 |
| Deposits (95th perc.) | ~~0.0009~~ 0.001 | ~~4.5~~ 5.3 |
| Re-entry (95th perc.) | 0.005 | 26.6 |
| Sum (mean) | ~~0.02~~ 0.008 | ~~96.3~~ 40.9 |
| Resident adult  Body weight: 60 kg | Drift (95th perc.) | 0.001 | 5.1 |
| Vapour (95th perc.) | ~~0.004~~ 0.0003 | ~~20.3~~ 1.4 |
| Deposits (95th perc.) | 0.0002 | 1.1 |
| Re-entry (95th perc.) | 0.003 | 14.8 |
| Sum (mean) | ~~0.007~~ 0.003 | ~~35.2~~ 16.3 |

#### 

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

Since the resident and/or bystander exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for 2,4-dichlorophenoxy acetic acid will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

### Combined exposure

Not relevant. The product contains only one active substance.

1. Lists of data considered in support of the evaluation

Tables considered not relevant can be deleted as appropriate.

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

List of data submitted by the applicant and relied on

| Data point | Author(s) | Year | Title Company Report No.  Source (where different from company) GLP or GEP status Published or not | Vertebrate study Y/N | Owner |
| --- | --- | --- | --- | --- | --- |
| KCP 7.1.1 | Satyavani, G. | 2011a | Acute Oral Toxicity Study with Pielik 95 SP in Wistar Rats 90014608 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.1.2 | Satyavani, G. | 2011b | Acute Dermal Toxicity Study with Pielik 95 SP in Wistar Rats 90014609 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.1.3 | Jagan Mohan Rao, P. | 2011 | Pielik 95 SP: Acute inhalation toxicity study in Wistar rats 90014488 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.1.4 | Satyavani, G. | 2011c | Acute Dermal irritation/corrosion of Pielik 95 SP in New Zealand White Rabbits 90014610 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.1.5 | Satyavani, G. | 2011d | Acute Eye Irritation/Corrosion of Pielik 95 SP in New Zealand White Rabbits 90014611 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.1.6 | Satyavani, G. | 2011e | Skin Sensitization potential of Pielik 95 SP in Guinea Pig 90014612 International Institute of Biotechnology and Toxicology (IIBAT), Padappai - 601 301, Kancheepuram District, Tamil Nadu, India. GLP Unpublished | Y | Adama |
| KCP 7.3/01 | Hassler, S. | 2022 | 2,4-D sodium salt monohydrate – *In vitro* percutaneous penetration of [14C]2,4-D sodium salt monohydrate formulated as 2,4-D 95 SP (ADM.09250.H.1.A) through human skin membranes  20220212  Innovative Environmental Services (IES) Ltd., Benkenstrasse 260, 4108 Witterswil, Switzerland  GLP  Unpublished | N | Adama |

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 |
| --- | --- | --- | --- | --- | --- |
| - | - | - | - | - | - |
|  |  |  |  |  |  |

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

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

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

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

1. Detailed evaluation of the studies relied upon

* 1. Statement on bridging possibilities

The studies presented within Appendix 2 have been performed on ADM.09250.H.1.A \ 2,4-D 95 SP. No bridging of data has been required.

|  |  |
| --- | --- |
| Comments of zRMS: | Acceptable - ‘Pielik 95 SP’ is the trade name of ADM.09250.H.1.A / 2,4-D 95 SP |

* 1. Acute oral toxicity (KCP 7.1.1)

|  |  |
| --- | --- |
| Comments of zRMS: | Study is acceptable; conducted according to recent guidelines.  Based on results of the study the oral LD50 is >300 and <2000 mg/kg bw/d, therefore the formulation ADM.09250.H.1.A / Pielik 95 SP should be classified as Acute Tox. 4, H302 under the criteria of CLP Regulation. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.1 |
| Report | Acute Oral Toxicity Study with Pielik 95 SP in Wistar Rats  Satyavani G., 2011a  90014608 |
| Guideline(s) | OECD Test Guideline 423 (2001) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | Pielik 95 SP (Batch No. 56) |
| **Species** | Rat, Crl:WI |
| **No. of animals (group size)** | 3 rats (female) / group |
| **Dose(s)** | 300 and 2000 mg/kg bw |
| **Exposure** | Once by gavage |
| **Vehicle/Dilution** | Distilled water |
| **Post exposure observation period** | 14 days |
| **Remarks** | None |

**Results and discussions**

**Table A 1: Results of acute oral toxicity study in rats of Pielik 95 SP**

| **Dose (mg/kg bw)** | **Toxicological results \*** | **Duration of signs** | **Time of death** | **LD50 (mg/kg bw) (14 days)** |
| --- | --- | --- | --- | --- |
| Female rats | | | | |
| 300 (step 1) | 0/0/3 | - | Study termination | > 300 |
| 300 (Step 2) | 0/0/3 | - | Study termination | > 300 |
| 2000 (Step 3) | 3/3/3 | Day 0 | Day 0 | < 2000 |

\* 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 Pielik 95 SP**

|  |  |
| --- | --- |
| **Mortality** | None of the animals treated with 300 mg/kg bw died during the entire experiment period.  All animals died within 4 hours after adimistration of 2000 mg/kg bw dose. |
| **Clinical signs** | No clinical signs of toxicity were observed in the animals after administration of 300 mg/kg bw for the entire observation period.  All animals treated with 2000 mg/kg bw exhibited catalepsy at 1 hour and 2 hour after dose administration. |
| **Body weight** | Body weight and body weight gain was considered to be normal during the experimental period for animals after administration of 300 mg/kg bw. |
| **Macroscopic examination** | The necropsies performed at the end of the study revealed no macroscopic findings. |

**Conclusion**

Under the experimental conditions, the acute oral LD50 of Pielik 95 SP determined is > 300 – 2000 mg/kg bw in female Wistar rats, with LD50 cut off value 500 mg/kg bw. Thus, Pielik 95 SP is to be classified as Acute Tox. Oral, Category 4 (H302: harmful if swallowed) according to Regulation (EC) No. 1272/2008.

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

|  |  |
| --- | --- |
| Comments of zRMS: | Study is acceptable; conducted according to recent guideline (at the time of conducting the study).  Based on results of the study the dermal LD50 of the product ADM.09250.H.1.A / Pielik 95 SP is >2000 mg/kg bw/d in rats, therefore no classification is required for acute dermal toxicity under the criteria of CLP Regulation. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.2 |
| Report | Acute Dermal Toxicity Study with Pielik 95 SP in Wistar Rats  Satyavani, G., 2011b  90014609 |
| Guideline(s) | OECD 402 (1987) |
| Deviations | None |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | Pielik 95 SP (Batch No. 56) |
| **Species** | Rat, Crl:WI |
| **No. of animals (group size)** | 10 rats, 5 male and 5 female |
| **Dose(s)** | 2000 mg/kg bw |
| **Exposure** | 24 hours (dermal, semi-occlusive) |
| **Vehicle/Dilution** | Distilled water |
| **Post exposure observation period** | 14 days |
| **Remarks** | None |

**Results and discussions**

**Table A 3: Results of acute dermal toxicity study in rats of Pielik 95 SP**

| **Dose (mg/kg bw)** | **Toxicological results \*** | **Duration of signs** | **Time of death** | **LD50 (mg/kg bw) (14 days)** |
| --- | --- | --- | --- | --- |
| Male rat | | | | |
| 2000 | 0/0/5 | - | Study termination | >2000 |
| Female rat | | | | |
| 2000 | 0/0/5 | - | Study termination | >2000 |

\* 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 Pielik 95 SP**

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

**Conclusion**

Under the experimental conditions, the dermal LD50 of Pielik 95 SP is greater than 2000 mg/kg bw in male and female Wistar rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Acute inhalation toxicity (KCP 7.1.3)

|  |  |
| --- | --- |
| Comments of zRMS: | Study is acceptable; conducted according to recent guideline.  Based on results of the study the inhalation LC50 of the product ADM.09250.H.1.A / Pielik 95 SP is > 1.36 mg/L air/4h (maximum attainable concentration) in rats, therefore no classification is required for acute inhalation toxicity under the criteria of CLP Regulation. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.3 |
| Report | Pielik 95 SP: Acute inhalation toxicity study in Wistar rats  Jagan Mohan Rao P., 2011  90014488 |
| Guideline(s) | OECD 403 (2009) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | Pielik 95 SP (Batch No. 56) |
| **Species** | Rat, Crl:WI |
| **No. of animals (group size)** | 6 rats (3 male and 3 female) |
| **Concentration(s)** | 1.36 mg/L air |
| **Exposure** | 4 hours (nose only) |
| **Vehicle/Dilution** | None |
| **Post exposure observation period** | 14 days |
| **Remarks** | None |

**Results and discussions**

**Table A 5: Concentration(s) and exposure conditions**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **Maximum achievable mean concentration  (mg/L air)** | **Mean Mass Median Aerodynamic Diameter**  **MMAD \* (µm)** | **Geometric Standard Deviation**  **GSD \*\* (µm)** |
| 1 | 1.36 | 3.54 | 2.49 |

\* MMAD = Mass Median Aerodynamic Diameter

\*\* GSD = Geometric Standard Deviation

**Table A 6: Results of acute inhalation toxicity study in rats of Pielik 95 SP**

| **Concentration (mg/L air)** | **Toxicological results \*** | **Duration of signs** | **Time of death** | **LC50 (mg/L air) (14 days)** |
| --- | --- | --- | --- | --- |
| Male rats | | | | |
| 1.36 | 0/0/3 | 0 | Study termination | > 1.36 |
| Female rats | | | | |
| 1.36 | 0/0/3 | 0 | Study termination | > 1.36 |

\* 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 Pielik 95 SP**

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

**Conclusion**

Under the experimental conditions, the inhalation 4 hour nose only LC50 of Pielike 95 SP is greater than 1.36 mg/L air in male and female Wistar rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

* 1. Skin irritation (KCP 7.1.4)

|  |  |
| --- | --- |
| Comments of zRMS: | Study is acceptable; conducted according to recent guideline (at the time of conducting the study).  None of the animals showed any skin reaction after treatment with test material  Based on results of the study in rabbits, product ADM.09250.H.1.A / Pielik 95 SP is not a skin corrosive/irritant, therefore no classification is required for skin corrosion/irritation under the criteria of CLP Regulation. |

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

|  |  |
| --- | --- |
| Reference | KCP 7.1.4 |
| Report | Acute Dermal irritation/corrosion of Pielik 95 SP in New Zealand White Rabbits  Satyavani G., 2011c  90014610 |
| Guideline(s) | OECD 404 (2002) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | Pielik 95 SP (Batch No. 56) |
| **Species** | Rabbit, New Zealand White |
| **No. of animals (group size)** | 3 (female) |
| **Initial test using one animal** | Yes |
| **Exposure** | 500 mg (4 hours, semi-occlusive) |
| **Vehicle/Dilution** | Distilled water |
| **Post exposure observation period** | 3 days |
| **Remarks** | None |

**Results and discussions**

**Table A 8: Skin irritation of Pielik 95 SP**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Animal No.** |  | **Scores after treatment \*** | | | | **Mean scores (24-72 h)** | **Reversible (day)** |
| **1 h** | **24 h** | **48 h** | **72 h** |
| 1352 | Erythema  Oedema | 0  0 | 0  0 | 0  0 | 0  0 | 0  0 | -  - |
| 1353 | Erythema  Oedema | 0  0 | 0  0 | 0  0 | 0  0 | 0  0 | -  - |
| 1354 | 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. |
| **Body weight:** | Body weight and body weight gain was considered to be normal. |

**Conclusion**

Under the experimental conditions, Pielik 95 SP 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: | Study is acceptable; conducted according to recent guideline (at the time of conducting the study).  Test material tested on 3 female rabbits exhibited ocular lesions of: <1 for corneal opacity and iritis, <2 for conjunctival redness and oedema, calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material. In all animals, effects on the cornea, iris or conjunctiva were fully reversed within the observation period. Based on results of the study in rabbits, the product ADM.09250.H.1.A / Pielik 95 SP should not be classified for eye damage/irritation under the criteria of CLP Regulation. |

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

|  |  |
| --- | --- |
| Reference | KCP 7.1.5 |
| Report | Acute Eye Irritation/Corrosion of Pielik 95 SP in New Zealand White Rabbits  Satyavani G., 2011d  90014611 |
| Guideline(s) | OECD Test Guideline 405 (2002) |
| Deviations | No |
| GLP | Yes |
| Acceptability | Yes |

**Materials and methods**

|  |  |
| --- | --- |
| Test material (Lot/Batch No.) | Pielik 95 SP (Batch No. 56) |
| Species | Rabbit, New Zealand White |
| No. of animals (group size) | 3 (female) |
| Initial test using one animal | Yes |
| Exposure | 0.1 g applied to the conjunctival sac  (Treated eye: left eye, control: right eye) |
| Irrigation (time point) | 24 hours after test item application |
| Vehicle/Dilution | None |
| Post exposure observation period | 9 days |
| Remarks | None |

**Results and discussions**

**Table A 9: Eye irritation of Pielik 95 SP**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Animal No.** |  | **Scores after treatment \*** | | | | | | **Mean scores (24-72 h)** | **Reversible (day)** |
| **1 h** | **24 h** | **48 h** | **72 h** | **7 d** | **9 d** |
| 1355 | Corneal opacity  Area of cornea involved  Iritis  Redness conjunctivae  Chemosis conjunctivae  Discharge conjunctivae | 0  0  0  1  2  1 | 0  0  0  1  1  1 | 1  3  0  2  1  1 | 1  3  0  2  0  0 | 1  1  0  1  0  0 | 0  0  0  0  0  0 | 0.67  2.00  0.00  1.67  0.67  0.67 | 9  9  -  8  3  3 |
| 1356 | Corneal opacity  Area of cornea involved  Iritis  Redness conjunctivae  Chemosis conjunctivae  Discharge conjunctivae | 0  0  0  1  2  1 | 0  0  0  1  2  0 | 1  3  0  2  1  0 | 1  3  0  2  0  0 | 1  1  0  1  0  0 | 0  0  0  0  0  0 | 0.67  2.00  0.00  1.67  1.00  0.00 | 9  9  -  8  3  1 |
| 1357 | Corneal opacity  Area of cornea involved  Iritis  Redness conjunctivae  Chemosis conjunctivae  Discharge conjunctivae | 0  0  0  1  2  1 | 0  0  0  1  2  1 | 0  0  0  1  2  0 | 1  2  0  2  1  0 | 1  1  0  1  0  0 | 0  0  0  0  0  0 | 0.33  0.67  0.00  1.33  1.67  0.33 | 8  8  -  8  4  2 |

\* scores in the range of:

0 to 4 for cornea opacity, area of cornea involved and chemosis

0 to 3 for redness and discharge of conjunctivae

0 to 2 for iritis

|  |  |
| --- | --- |
| **Clinical signs:** | The test animals exhibited conjunctival (redness, chemosis and discharge) and corneal (opacity) lesions. In one animal the ocular lesions cleared on the 8th day (animal 1357) whereas in the other two animals, the ocular lesions cleared on the 9th day (animals 1355 and 1356). |
| **Body weight:** | Body weight and body weight gain was considered to be normal. |

**Conclusion**

Under the experimental conditions, Pielik 95 SP is considered mildly irritating to eyes. However, Pielik 95 SP does not require to be classified for eye irritation according to Regulation (EC) No. 1272/2008.

* 1. Skin sensitisation (KCP 7.1.6)

|  |  |
| --- | --- |
| Comments of zRMS: | According to the study report (Satyavani G., 2011e) the test substance was moistened with minimum volume of distilled water and tested as a paste in range finding and main study (for induction and challenge exposure). However the known concentrations of solutions of the solid test material in suitable vehicle should be used in the range finding study. Only liquid test substances can be applied undiluted, according to OECD guideline 406 (Buehler test method).  A sensitization response in reliability check with Mercaptobenzothiazole was observed in 20% of animals tested, however no information on concentration of the sensitiser and vehicle used in reliability check was reported. Probably, undissolved Mercaptobenzothiazole was tested. Therefore the study is not considered reliable and is not used to assess the sensitising potential of the product ADM.09250.H.1.A / Pielik 95 SP. |

* + 1. Study 1

|  |  |
| --- | --- |
| Reference | KCP 7.1.6 |
| Report | Skin Sensitization potential of Pielik 95 SP in Guinea Pigs  Satyavani G., 2011e  90014612 |
| Guideline(s) | OECD 406 (1992) |
| Deviations | ~~No~~ Yes, see comment, above. |
| GLP | Yes |
| Acceptability | ~~Yes~~. No |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |
| --- | --- |
| **Test material (Lot/Batch No.)** | Pielik 95 SP (Batch No. 56) |
| **Species** | Guinea pig, Dunkin Hartley |
| **No. of animals (group size)** | 30 males (treatment: 20 animals, control: 10 animals) |
| **Dose(s)** | Range finding study: 500 and 2000 mg/~~kg bw~~ patch  Induction exposure: 2000mg/patch  Challenge exposure: 500mg/patch |
| **Exposure** | 6 hours (topical induction, occlusive)  Repeated application on days 0, 7 and 14 |
| **Vehicle/Dilution** | Distilled water |
| **Post exposure observation period** | 30 hours and 54 hours |
| **Realiability check** | Mercaptobenzothiazole. Topical application: induction: 750mg, Challenge: 250mg  Performed not concurrently, but in the 4-5 months prior to study conduct (in the months of Jan - Feb 2011). A sensitization response was observed in 20% of animals tested. |
| **Remarks** | None |

**Results and discussions**

**Table A 10: Results of skin sensitisation study of Pielik 95 SP**

|  | 24 hours | 48 hours | Total number of animals affected |
| --- | --- | --- | --- |
|  | After challenge | |  |
| Pielik 95 SP | 0/20\* | 0/20\* | 0 |
| Test vehicle control group - distilled water | 0/10\* | 0/10\* | 0 |
| Positive control - Mercaptobenzothiazole | 2 (scores of 1, 2) /10\* | 2 (scores of 1, 1) /10\* | 2 |

\* Number of animals with positive dermal response (scores of 1-3) /number of animals in dose group

|  |  |
| --- | --- |
| **Clinical signs:** | No clinical signs of toxicity were observed. |
| **Body weight:** | Body weight and body weight gain was considered to be normal. |

**Conclusion**

Under the experimental conditions, Pielik 95 SP is a 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)

Not relevant.

* 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 – 2,4-D sodium salt monohydrate in ADM.09250.H.1.A /2,4-D 95 SP

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

|  |  |
| --- | --- |
| Comments of zRMS: | Study is accepted. The dermal penetration of 2,4-D (as sodium salt monohydrate) formulated as product 2,4-D 95 SP (ADM.09250.H.1.A) through human dermatomed skin was determined *in vitro*. The amount of applied dose penetrating within 24 hours was determined to be 2.35%±1.54% (mean ± standard deviation) and 0.34%±0.08% for the formulation concentrate and the 1:300 spray dilution, respectively. The dermal penetration estimates to be used for the operator worker, resident and bystander exposure assessment were set at 3.5% and 0.4% for the formulation concentrate and the 1:300 spray dilution based on the EFSA guidance criteria |

|  |  |
| --- | --- |
| Reference: | KCP 7.3/01 |
| Report | Hassler S., 2022,  2,4-D sodium salt monohydrate – In vitro percutaneous penetration of [14C]2,4-D sodium salt monohydrate formulated as 2,4-D 95 SP (ADM.09250.H.1.A) through Human Skin Membranes |
| Guideline(s): | OECD 428 (2004); EC No. 440/2008 (2008), Method B.45; Sanco/222/2000/Rev. 7 (2004) |
| Deviations: | No |
| GLP: | Yes (certified laboratory) |
| Acceptability: | Yes, study considered acceptable |
| Duplication  (if vertebrate study) | No |

**Materials and methods**

|  |  |  |
| --- | --- | --- |
| **Test material** | Name (Lot/Batch No.) | 2,4-D sodium monohydrate, [ring-U- 14C⦌ (Batch XXVII/50/A/1) |
|  | Test preparation | Radioformulation |
| Specific activity | 4869 KBq/mg |
| Radiochemical purity | 99.71% |
| Product | Name (Lot/Batch No.) | 2,4-D 95 SP (containing 2,4-D sodium salt monohydrate, CAS No. 7084-86-8)  (Batch 2111140274) |
| Company code | ADM.09250.H.1.A |
| Concentration a.s. | 950 g/~~L~~ kg |
| Formulation type | Soluble powder (SP) |
| Blank product | Name (Lot/Batch No.) | None |
| Concentration a.s. | Not applicable |

|  |  |  |
| --- | --- | --- |
| **Test system** |  |  |
| Diffusion cell | Cell type | Flow |
| (if dynamic) Flow rate | 3mL/h |
| Exposed skin area | ~~1.8 x 1.8 cm~~ 1cm2 |
| Cover | Open |
| Membrane | Skin type | Dermatomed |
| Skin thickness range | 400 µm |
| Skin donors age | 19-55 years |
| Skin donors sex | Female |
| Location | Abdomen (4) and breast (2) |
| Source | Cosmetic surgery |
| Integrity test | [3H]-Water |
| Receptor | Receptor medium | Phosphate buffered saline (PBS) |
| Solubility in receptor medium | Yes. |
| Sample Time | Exposure time | 8 hours |
| Observation time | 24 hours |
| Sampling | Sample intervals | 0-8 hours: 1 hour intervals  8-24 hours: 2 hours inervals |
| Washing |  | At the end of the exposing period, i.e. 8 hours after the start of exposure, with a mild shower gel solution |
| Final Procedure | Tape stripping | Yes |
| TS1-2 analysed separately | Yes |

|  |  |  |
| --- | --- | --- |
| **Tested doses** | Formulation A2  (commercial product 1:1) | Formulation A1  (dilution ratio of 1:300) |
| Target concentration [g/L] | 590 | 3 |
| Area dose [µg/cm²] | 5556 | 32.5 |
| Total dose [dpm/cell] | 1,776,793 ± 4.1% | 1,017,210 ± 0.4% |
| Specific activity [kBq/ml] | 3078 | 1664 |
| No. of donors | 6 | 5 |
| No of cells used/valid cells\* | 9/9 | 9/9 |
| Remarks: The dosing regime is considered to mimic realistic exposure conditions. The high dose level reflects the commercial product (950 g 2,4-D sodium salt monohydrate /kg commercial product), applied in form of an aqueous paste 1:1 (wetted to assure appropriate skin contact and mimic sweat), accounting for a 1.18159 conversion factor from 2,4-D sodium salt to 2,4-D acid. The low dose reflects the concentration recommended for use, i.e. 3 g 2,4-D sodium salt monohydrate/L (1 kg commercial product/ha in 300 L water, according to a dilution ratio of 1:300. | | |

\* Justification for excluded cells, if applicable

**Results and discussions**

**Table A 11: *In-vitro* dermal penetration of 2,4-D formulated as 2,4-D 95 SP through human skin - Recovery data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose group** | | Formulation A2  Dilution 1:1 | Formulation A1  Dilution 1:300 |
| Exposure period | | 8 hours | |
| Target concentration | [g/L] | 590 | 3 |
| Target dose | [µg/cm²] | 5900 | 30 |
| Mean actual applied dose | [µg/cm²] | 5556 | 32.5 |
|  | | Recovery [%] | |
|  | | Mean ± SD | |
| **Dislodgeable dose** | | | |
| e.g. Skin washing after 8 h | | 100.37 ±3.04 | 93.64 ±5.33 |
| e.g. Terminal skin washing (24 h) | | 0.01 ±0.01 | 2.21 ±2.22 |
| Donor chamber wash | | <0.01 | 0.09 ±0.16 |
| **Dose associated to skin** | | | |
| Tape strips 1 + 2 | | 0.02 ±0.02 | 1.18 ±1.25 |
| Tape strips 3 – n=10 | | 0.02 ±0.01 | 0.91 ±0.82 |
| Exposed skin | | <0.01 | 0.18 ±0.24 |
| **Absorbed dose** | | 0.34 ±0.08 | 1.26 ±0.77 |
| Receptor fluid | | 0.34 ±0.08 | 1.24 ±0.76 |
| Receptor chamber wash | | <0.01 | 0.02 ±0.04 |
| **Total recovery1** | | 100.77 ±3.07 | 99.49 ±0.91 |
| Absorption essentially complete at end of study (>75% absorption within half the study duration) [%Absorption at t0.5] 2 | | Yes [within 12h: 97% ±3%] | Yes [within 12h: 82% ±17%] |
| If no:  Absorption estimates  = absorbed dose + exposed skin + tape strips 3-n=10 | | N/A | 2.35 ±1.54 |
| If yes:  Absorption estimates = absorbed dose + exposed skin | | 0.34 ±0.08 | N/A |
| Absorption estimate normalised3 | | N/A | N/A |
| Multiplication factor added to the SD (k) | | 0.77 (n=9) | 0.77 (n=9) |
| SD \* k | | 0.08\*0.77 | 1.54\*0.77 |
| Relevant absorption estimate | | 0.40 | 3.5 |
| **Absorption estimates used for risk assessment4** | | **0.4** | **3.5** |
| 1 Values may not calculate exactly due to rounding of figures  2 In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2017;15(6):4873) the radioactivity in the second tape-strip pool (3rd to nth tape strip) is considered potentially absorbable if less than 75% of the absorption occurred in the first half of the study. 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 Relevant absorption estimate was rounded to the required number of significant figures.  N/A: not applicable | | | |

**Remarks**

None.

**Conclusion/endpoint:**

Following topical application of [14C]2,4-D sodium salt monohydrate (formulated as 2,4-D 95 SP), applied to human skin *in vitro*, the total absorption of 2,4-D sodium salt monohydrate through human skin membrane was 1.45% and 0.34% of the applied dose for the tested field dilution and for the undiluted commercial product, respectively.

The values to be used in the risk assessment are 3.5% and 0.40% for the field dilution (3 g/L) and for the undiluted commercial product (590 g/L), respectively.

* 1. Other/Special Studies

Not relevant.

1. Exposure calculations
   1. Operator exposure calculations (KCP 7.2.1.1)
      1. Calculations for 2,4-D

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Formulation type** | Wettable powder, soluble powder | **Name of active substance** | 2,4-d (2,4-dichlorophenoxy acetic acid 80.4%) |
| **Concentration of active substance [g a.s./l or kg]** | 590 | **Crops** | Field crops |
| **Area treated [ha/day]** | 50 | **Application method** | Downward spraying |
| **Dermal absorption [%] (concentrate)** | 0.4 | **Application technique** | Vehicle-mounted |
| **Dermal absorption [%] (dilution)** | 5.72363041700736 | **Indoor/outdoor** | Outdoor |
| **Oral absorption [%]** | 100 | **Drift reduction [%]** | 0 |
| **Inhalation absorption [%]** | 100 | **Type of cultivation** | Normal |
| **Body weight (kg)** | 60 |  |  |
| **AOEL [mg/kg bw/day]** | 0.02 |  |  |
| **AAOEL [mg/kg bw]** |  |  |  |

zRMS: Input data - concentration of active substance in PPP of 804 g/kg is used (instead of 590 g a.s./L, see table above)

|  |  |  |  |
| --- | --- | --- | --- |
| **Formulation type** | Wettable powder, soluble powder | **Name of active substance** | 2,4-d |
| **Concentration of active substance [g a.s./l or kg]** | **804** | **Crops** | Field crops |
| **Area treated [ha/day]** | 50 | **Application method** | Downward spraying |
| **Dermal absorption [%] (concentrate)** | 0.4 | **Application technique** | Vehicle-mounted |
| **Dermal absorption [%] (dilution)** | **4.20016800672027** | **Indoor/outdoor** | Outdoor |
| **Oral absorption [%]** | 100 | **Drift reduction [%]** | 0 |
| **Inhalation absorption [%]** | 100 | **Type of cultivation** | Normal |
| **Body weight (kg)** | 60 |  |  |
| **AOEL [mg/kg bw/day]** | 0.02 |  |  |
| **AAOEL [mg/kg bw]** |  |  |  |

Table A 13: Estimation of longer term operator exposure towards 2,4-D according to EFSA guidance 2022

| **Activity** | **Systemic exposure per body part** | **With workwear** | **With workwear + PPE/RPE** |
| --- | --- | --- | --- |
| **Mixing and loading  (µg/kg bw per day)** | *Hand protection* | *None* | *Protected hands* |
| **Hands exposure** | **19.7** | **0.4** |
| *Body protection* | *Workwear* | *Workwear* |
| **Body exposure** | **1.4** | **1.4** |
| *Head protection* | *None* | *Fp2, p2 and similar* |
| **Head exposure** | **0.3** | **0.2** |
| *Inhalation protection* | *None* | *Fp2, p2 and similar* |
| **Inhalation exposure** | **128** | **12.8** |
| **Application  (µg/kg bw per day)** | *Hand protection* | *None* | *None* |
| **Hands exposure** | **3.9** | **3.9** |
| *Body protection* | *Workwear* | *Workwear* |
| **Body exposure** | **0.06** | **0.06** |
| *Head protection* | *None* | *None* |
| **Head exposure** | **0.1** | **0.1** |
| *Inhalation protection* | *None* | *None* |
| **Inhalation exposure** | **0.09** | **0.09** |
| **Total** | Total systemic exposure [mg/kg bw per day] | 0.2 | 0.02 |
| % of AOEL | 770 | 94.9 |

**zRMS: Per body part - Short term exposure (OPEX calculator version: 1.0.1)**

| **Activity** | **Systemic exposure per body part** | **With workwear** | **With workwear + PPE/RPE** |
| --- | --- | --- | --- |
| **Mixing and loading  (µg/kg bw per day)** | *Hand protection* | *None* | *Protected hands* |
| **Hands exposure** | **24.1** | **0.5** |
| *Body protection* | *Workwear* | *Workwear* |
| **Body exposure** | **1.7** | **1.7** |
| *Head protection* | *None* | *Fp2, p2 and similar* |
| **Head exposure** | **0.4** | **0.3** |
| *Inhalation protection* | *None* | *Fp2, p2 and similar* |
| **Inhalation exposure** | **145** | **14.5** |
| **Application  (µg/kg bw per day)** | *Hand protection* | *None* | *Protected hands* |
| **Hands exposure** | **3.9** | **0.2** |
| *Body protection* | *Workwear* | *Workwear* |
| **Body exposure** | **0.06** | **0.06** |
| *Head protection* | *None* | *None* |
| **Head exposure** | **0.1** | **0.1** |
| *Inhalation protection* | *None* | *None* |
| **Inhalation exposure** | **0.1** | **0.1** |
| **Total** | Total systemic exposure [mg/kg bw per day] | 0.2 | 0.02 |
| % of AOEL | 874 | 86.7 |

* 1. Worker exposure calculations (KCP 7.2.3.1)
     1. Calculations for 2,4-D

Table A 14: Input parameters considered for the estimation of worker exposure

|  |  |  |  |
| --- | --- | --- | --- |
| **Indoor/outdoor** | Outdoor | **AOEL [mg/kg bw/day]** | 0.02 |
| **Re-entry activity** | Inspection, irrigation | **Dermal transfer coefficient - Total potential exposure [cm²/h]** | 12500 |
| **Crops** | Field crops | **Dermal transfer coefficient - Arm, body and legs covered [cm²/h]** | 1400 |
| **Application method** | Downward spraying | **Dermal transfer coefficient - Hands, arm, body and legs covered [cm²/h]** | 1250 |
| **Application technique** | Vehicle-mounted | **Dermal transfer coefficient - Hands covered, no workwear [cm²/h]** |  |
| **Max. application rate of the product [l or kg/ha]** | 0.9328 | **DFR refined worker [µg/cm² foliage per kg a.s./ha]** | 3 |
| **Max. no. of applications** | 1 | **DT50 foliar worker [days]** | 30 |
| **Interval between multiple applications [days]** | NA |  |  |
| **Multiple application factor** | 1 |  |  |
| **Body weight (kg)** | 60 |  |  |
| **Name of active substance** | 2,4-d (2,4-dichlorophenoxy acetic acid 80.4%) |  |  |
| **Dermal absorption [%] (dilution)** | ~~5.72363041700736~~  4.2 |  |  |
| **Inhalation absorption [%]** | 100 |  |  |
| **Time [hours per day]** | 2 |  |  |

Table A 15: Estimation of longer term worker exposure towards 2,4-D according to EFSA guidance 2022

| **Exposure route** | **Description** | **Potential** | **Workwear** | **Workwear and gloves** | **Gloves** |
| --- | --- | --- | --- | --- | --- |
| Dermal | Systemic dermal exposure [mg a.s. per day] | 2.4 | 0.3 | 0.2 | NA |
| Inhalation | Systemic inhalation exposure [mg a.s. per day] |  |  |  | NA |
| Total | Total systemic exposure [mg a.s. per day] | 2.4 | 0.3 | 0.2 | NA |
| Total systemic exposure [mg/kg bw per day] | 0.04 | 0.004 | 0.004 | NA |
| % of AOEL | 197 | 22.1 | 19.7 | NA |

* 1. Resident and bystander exposure calculations (KCP 7.2.2.1)
     1. Calculations for 2,4-D

Table A 16: Estimation of longer term resident exposure towards 2,4-D according to EFSA guidance 2022

| **Model data** | **Level of PPE** | **Total absorbed dose [mg/kg bw per day]** | **% of systemic AOEL** |
| --- | --- | --- | --- |
| Season: Not relevant  Buffer zone: 2-3 m  Drift reduction technology: 0 %  Interval between treatments: NA  Minimum volume of water: 200 l | | | |
| **2,4-d (2,4-dichlorophenoxy acetic acid 80.4%)** | Number of applications and application rate: 1 x 0.550352 kg a.s./ha  Dermal absorption: 5.72363041700736 %  DFR: 3 µg/cm² foliage per kg a.s./ha  DT50: 30 days | | |
| Resident child  Body weight: 10 kg | Drift (75th perc.) | 0.004 | 21.5 |
| Vapour (75th perc.) | 0.01 | 60 |
| Deposits (75th perc.) | 0.0009 | 4.5 |
| Re-entry (75th perc.) | 0.005 | 26.6 |
| Sum (mean) | 0.02 | 96.3 |
| Resident adult   Body weight: 60 kg | Drift (75th perc.) | 0.001 | 5.1 |
| Vapour (75th perc.) | 0.004 | 20.3 |
| Deposits (75th perc.) | 0.0002 | 1.1 |
| Re-entry (75th perc.) | 0.003 | 14.8 |
| Sum (mean) | 0.007 | 35.2 |

**zRMS: Estimation of longer term resident exposure towards 2,4-D according to EFSA guidance 2022 – using the application rate: 0.7499712 kg a.s./ha** (instead of 0.550352 kg a.s./ha, see table above) - **OPEX calculator version: 1.0.1**

| **Model data** | **Level of PPE** | **Total absorbed dose [mg/kg bw per day]** | **% of systemic AOEL** |
| --- | --- | --- | --- |
| Season: Not relevant  Buffer zone: 2-3 m  Drift reduction technology: 0 %  Interval between treatments: NA  Minimum volume of water: 200 l | | | |
| **2,4-d** | Number of applications and application rate: 1 x **0.7499712** kg a.s./ha  Dermal absorption: 4.20016800672027 %  DFR: 3 µg/cm² foliage per kg a.s./ha  DT50: 30 days | | |
| Resident child  Body weight: 10 kg | Drift (75th perc.) | 0.004 | 21.6 |
| Vapour (75th perc.) | 0.0008 | 4 |
| Deposits (75th perc.) | 0.001 | 5.3 |
| Re-entry (75th perc.) | 0.005 | 26.6 |
| **Sum (mean)** | **0.008** | **40.9** |
| Resident adult   Body weight: 60 kg | Drift (75th perc.) | 0.001 | 5.1 |
| Vapour (75th perc.) | 0.0003 | 1.4 |
| Deposits (75th perc.) | 0.0002 | 1.1 |
| Re-entry (75th perc.) | 0.003 | 14.8 |
| **Sum (mean)** | **0.003** | **16.3** |

**zRMS’s exposure assessment for operator, worker, resident and bystander for product: 2,4-D 95 SP, according to OPEX version: 1.0.1:**



* 1. Combined exposure calculations

Not relevant. The product contains only one active substance.

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

No studies relied upon.