



# **Draft Assessment Report**

## **Evaluation of Active Substances**

Plant Protection Products

Prepared according to **Regulation (EC) 1107/2009**  
as it applies in Great Britain

### **Elemental iron**

#### **Volume 3 – B.6 (PPP) – Final Bite**

Great Britain

January 2024

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## Version History

| When          | What  |
|---------------|---|
| November 2021 | Initial DAR   |
| February 2022 | Updated post Expert Committee on Pesticides (ECP) Independent Scientific Advice (ISA) (November 2021 meeting) |
| January 2024  | Updates made after comments from the applicant  |

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## **B.6. TOXICOLOGY AND METABOLISM DATA AND ASSESSMENT OF RISKS FOR HUMANS**

The representative product, Final-Bite® (product code 0402206), is a Ready-to-Use Bait (RB) containing 10 g of active substance/kg (1 % w/w). The proposed representative use of Final-Bite is on various crops as a molluscicide.

### **B.6.1. ACUTE TOXICITY OF PLANT PROTECTION PRODUCT**

In order to meet the requirements for toxicological information on the representative product, the applicant has followed a tiered approach, taking into consideration the Regulations 1107/2009, 284/2013 and CLP Reg. EC No. 1272/2008. Information on the acute toxicity and other hazard properties of all components has been obtained from the SDS (Safety Data Sheets) provided by the applicant. For further details please see volume 4, section C.1.3.

Regarding the acute oral, dermal and inhalation toxicity of Final Bite, adequate information is available in the submitted SDSs, therefore the relevant toxicological data requirements for the representative product have been addressed by applying the calculation method of Regulation (EC) No 1272/2008 to its components. For the remaining endpoints of skin/eye irritation and skin sensitisation potential, the applicant has submitted data, in line with the guidance provided in the relevant OECD IATA for each hazard.

The applicant has addressed the information requirements as follows:

- Acute oral and dermal toxicity: There are no acute toxicity studies for the oral or dermal routes of exposure and the assessment is conducted using the ingredient information on the SDSs (calculation method for acute toxicity).
- Acute inhalation toxicity: An acceptable waiver based on Section 7.1.3 of Regulation 284/2013 has been provided;
- Eye and dermal irritation: The potential for eye and skin corrosivity/irritancy was assessed using ingredient information and a battery of validated *in vitro* studies (OECD 431, 439, 492 and 437);
- Skin sensitisation: *In vitro* studies were found impractical, owing to insolubility of the material, and due to insufficient data on the provided SDSs, an *in vivo* Local Lymph Node Assay (LLNA; OECD 442B) was conducted.

Additionally, the applicant states further vertebrate data have been generated for global registration purposes and can be made available upon request. However, these data are in contravention of Article 62, Regulation (EC) No. 1107/2009 and are not included in the current HSE evaluation.

**Table 6.1-1: Summary of acute toxicity studies conducted with Final Bite**

| Reference                        | Method                                  | Result                           | Classification<br>(Reg (EC) No. 1272/2008) |
|----------------------------------|---|----------------------------------|--|
| Acute oral                       | Calculation method                      | n/a                              | No Classification                          |
| Acute dermal                     | Calculation method                      | n/a                              | No Classification                          |
| Acute inhalation                 | Waiver and calculation method           | n/a                              | No Classification                          |
| Skin irritation -<br>Ref: 177930 | <i>In vitro</i> skin corrosion OECD 431 | Non corrosive to EpiDerm™ tissue | Category 2 (H315); causes skin irritation  |

Table 6.1-1: Summary of acute toxicity studies conducted with Final Bite

| Reference                            | Method                                   | Result   | Classification<br>(Reg (EC) No. 1272/2008) |
|--------------------------------------|--|--|--|
| Skin irritation -<br>Ref: 177931     | <i>In vitro</i> skin irritation OECD 439 | Irritant to EpiDerm™ tissue, shown by decreased cell viability |  |
| Eye irritation –<br>Ref: 177932      | <i>In vitro</i> eye irritation OECD 492  | Irritant to EpiOcular™ tissue, either Cat 1 or Cat 2           | C  |
| Eye irritation –<br>Ref: 177932      | <i>In vitro</i> eye irritation OECD 437  | Irreversible effects on opacity and permeability               |  |
| Skin sensitisation -<br>Ref: U-17291 | LLNA-BrdU in mice                        | Not sensitising  | No Classification                          |

**B.6.1.1. Oral**

The representative formulation, Final Bite, contains no ingredients relevant to the calculation of an oral ATEmix. Therefore, Final Bite should not be classified for oral toxicity according to Reg (EC) No. 1272/2008.

**B.6.1.2. Dermal**

The representative formulation, Final Bite, contains no ingredients relevant to the calculation of a dermal ATEmix. Therefore, Final Bite should not be classified for dermal toxicity according to Reg (EC) No. 1272/2008.

**B.6.1.3. Inhalation**

The representative formulation Final Bite is a dry granular product and contains one ingredient classified for acute inhalation toxicity Category 4. However, the applicant has demonstrated that less than 1 % of the granular particles present with a diameter of < 50 µm, and hence it is reasonable to waive the characterisation of the acute inhalation toxicity profile of the formulation.

Furthermore, the single co-formulant - relevant to the calculation of an inhalation ATEmix – is present at just ■■■ % w/w, meaning that the representative product Final Bite should not be classified for inhalation toxicity according to Reg (EC) No. 1272/2008.

**B.6.1.4. Skin irritation**

The representative formulation, Final Bite, was tested in an *in vitro* skin corrosion test (OECD 431) and an *in vitro* skin irritation test (OECD 431). In both test methods, the induction of cytotoxicity provides an indication of the potential of the formulation to cause damage to human skin cells.

|                                      |  |           |
|--------------------------------------|--|-----------|
| <b>Study</b>                         | <b><i>In vitro</i> Skin Corrosion: Human Skin Model Test (EpiDerm™) with Final Bite-0402206. Study Report 177930</b> |           |
| <b>Reference</b>                     | CP 7.1.4/01: [REDACTED] (2018), Applicant ref R-39093  |           |
| <b>Test substance</b>                | Final Bite – Blue 2.5 mm, 0402206, Batch KM8017420OH   |           |
| <b>Guideline</b>                     | OECD 431   | GLP : Yes |
| <b>Date performed</b>                | 10 Nov 2018 – 8 Dec 2018   |           |
| <b>Test facility</b>                 | Eurofins Munich  |           |
| <b>Deviations from the guideline</b> | None   |           |
| <b>Study Acceptable</b>              | Yes.   |           |

#### *Materials and Methods:*

The corrosive properties of Final Bite was investigated in an OECD 431 guideline-compliant study, using a validated reconstituted human epidermis model (EpiDerm™). There were no deviations from the guideline, and all the main components of the skin corrosivity test method (Annex 2, OECD 431) were clearly reported. The commercially-sourced tissue samples were supplied with acceptable quality control evidence – there were no concerns over the morphology, reproducibility or viability of the tissues as supplied to the laboratory.

In the main experiment, 25 mg of Final Bite was manually ground to a powder and topically applied to EPI-200 EpiDerm™ tissues, in duplicate per each exposure time (3 and 60 min). In order to confirm study validity, negative (distilled water) and positive (8 N potassium hydroxide) cultures were set up in parallel. After either 3 or 60 minute exposure periods, the test article and controls were removed by PBS-rinsing x 20 and the MTT viability test was immediately performed in full compliance with Annex 2, OECD 431. For each tissue insert, 3 x 200 µL aliquots of the MTT assay extract were measured for MTT-formazan using standard (OD) absorbance at  $570 \pm 30$  nm.

In addition to the positive and negative in-study controls, freeze-killed controls were included and pre-experiments were performed to assess the potential for interference within the MTT assay. The non-specific MTT formation (% NSMTT) was evaluated by incubating Final Bite with 1 ml of MTT medium for 60 minutes before the OD was measured. Since the test item is blue in colour and absorbed light at  $570 \pm 30$  nm, the non-specific colour (NSC<sub>living</sub>) interference of the test article was also checked by incubating 25 mg of Final Bite with two additional living control tissues per exposure period (3 and 60 min), without the MTT-stain. Appropriate controls were used in both pre-experiments.

The cut-off % cell viability values distinguishing corrosive from non-corrosive in accordance with CLP Reg (EC) No 1272/2008 are defined as follows:

**Table 6.1.4/01-1 Prediction model for the EpiDerm *in vitro* skin corrosivity test method**

| Mean tissue viability                               | Prediction to be considered |
|---|-----------------------------|
| < 50 % after 3 min exposure                         | Corrosive                   |
| ≥ 50 % after 3 min AND < 15% after 60 min exposure  |                             |
| ≥ 50 % after 3 min AND ≥ 15 % after 60 min exposure | Non-corrosive               |

#### *Results:*

The study met the acceptability criteria listed within Annex 2 of OECD 431 – including the specific criteria for tissue viability of concurrent positive and negative controls and a prescribed low coefficient of variation for negative and Final Bite tissues replicates (i.e. for tissues in the range of 20 -100 % mean cell viability, CV of viability must be ≤ 30 %). The historical control data were provided in the study report and confirm that the positive and negative control mean values are within the HCD boundaries (see Table 5 of the study report for further details).

The pre-experiments supporting the MTT assay confirmed there was no potential for either direct reduction of MTT to MTT-formazan by Final Bite, nor any interference by the coloured test material in the absence of MTT (NSMTT = 0 %; NSC<sub>living</sub> 0.1 and 0.2 % at 3 or 60 mins respectively, which is lower than the recommended cut-off limit of 5 %). The low values of the NSC<sub>living</sub> confirm that despite the blue colour of Final Bite in either water

or isopropanol solution, the EpiDerm™ tissues were not stained by the test article. Therefore, no corrections for colorimetric interference in the MTT assay were required in this *in vitro* skin corrosion test.

The cytotoxicity results demonstrate that the mean relative tissue viability was within the bounds of what is considered to be non-cytotoxic. Relative tissue viabilities were greater than the cut-off limits of 50 % (81.4 %) and  $\geq 15$  % (100.1 %) at 3 and 60 min exposure periods respectively, meaning that no triggers for corrosivity were triggered.

**Table 6.1.4/01-2 Tissue viability at 3 and 60 minutes; Final Bite *in vitro* skin corrosivity test**

| Exposure time                          | Replicate | Mean OD <sub>570</sub> ± SD<br>(n=3; blank corrected) | Mean OD <sub>570</sub> ± SD<br>(replicates 1+2) | Mean rel.<br>tissue viability<br>% | CV<br>% |
|--|-----------|---|---|------------------------------------|---------|
| 3 min                                  |           |   |   |                                    |         |
| Negative control<br>(H <sub>2</sub> O) | 1         | 1.801 ± 0.060   | 1.755 ± 0.065                                   | 100                                | 3.7     |
|  | 2         | 1.709 ± 0.055   |   |                                    |         |
| Final Bite                             | 1         | 1.398 ± 0.086   | 1.428 ± 0.043                                   | 81.4                               | 3.0     |
|  | 2         | 1.459 ± 0.051   |   |                                    |         |
| Positive control<br>(8N KOH)           | 1         | 0.095 ± 0.026   | 0.101 ± 0.010                                   | 5.8                                | 9.5     |
|  | 2         | 0.108 ± 0.026   |   |                                    |         |
| 60 min                                 |           |   |   |                                    |         |
| -ve control<br>(H <sub>2</sub> O)      | 1         | 1.707 ± 0.038   | 1.761 ± 0.077                                   | 100                                | 4.4     |
|  | 2         | 1.815 ± 0.075   |   |                                    |         |
| Final Bite                             | 1         | 1.725 ± 0.049   | 1.763 ± 0.054                                   | 100.1                              | 3.1     |
|  | 2         | 1.801 ± 0.059   |   |                                    |         |
| +ve control<br>8N KOH)                 | 1         | 0.029 ± 0.026   | 0.052 ± 0.033                                   | 3.0                                | 62.5    |
|  | 2         | 0.075 ± 0.026   |   |                                    |         |

#### Conclusions:

The test article showed no corrosive effects under the conditions of this study. Final Bite should not be classified for skin corrosion according to Reg (EC) No. 1272/2008..

However, in order to address the data requirement of skin irritation and following the OECD integrated approach to testing and assessment (IATA), the applicant has provided an *in vitro* skin irritation study on Final Bite, which is summarised below.

|                                      |   |           |
|--------------------------------------|---|-----------|
| <b>Study</b>                         | <b><i>In vitro</i> Skin irritation: Human Skin Model Test (EpiDerm™) with Final Bite-0402206. Study Report No. 177931</b> |           |
| <b>Reference</b>                     | CP 7.1.4/02: (2018a), Applicant ref R-39094   |           |
| <b>Test substance</b>                | Final Bite – Blue 2.5 mm, 0402206, Batch KM8017420OH  |           |
| <b>Guideline</b>                     | OECD 439  | GLP : Yes |
| <b>Date performed</b>                | 10 Nov 2018 – 24 Nov 2018   |           |
| <b>Test facility</b>                 | Eurofins Munich   |           |
| <b>Deviations from the guideline</b> | None  |           |
| <b>Study Acceptable</b>              | Yes   |           |

#### Materials and Methods:

The dermal irritation potential of Final Bite was investigated in an OECD 439 guideline-compliant study, using a validated reconstituted human epidermis model (EpiDerm™). There were no deviations from the guideline, and all the main components of the skin corrosivity test method (Annex 3, OECD 439) were clearly reported. The commercially-sourced tissue samples were supplied with acceptable quality control evidence – there were no concerns over the morphology, reproducibility or viability of the tissues as supplied to the laboratory.

In the main experiment, 25 mg of Final Bite was manually ground to a powder and topically applied to EPI-200 EpiDerm™ tissues, in triplicate for a 60 min exposure time. In order to confirm study validity, negative (PBS) and positive (5 % SDS) cultures were run concurrently. After 60 min, the test article was removed by PBS-rinsing x 15, replaced with fresh medium and the tissues were allowed to recover for 42 h. This post-treatment recovery incubation period allows for the manifestation of clear cytotoxicity and recovery from weak, non-specific cytotoxicity. After the post-incubation period, the MTT viability test was performed. For each tissue insert, 2 x 200 µL aliquots of the MTT assay extract were measured for MTT-formazan using standard (OD) absorbance at  $570 \pm 30$  nm.

In addition to the positive and negative in-study controls, freeze-killed controls were included and pre-experiments were performed to assess the potential for interference within the MTT assay. The non-specific MTT formation (% NSMTT) was evaluated by incubating Final Bite with 1 ml of MTT medium for 60 minutes before the OD was measured. Since the aqueous test item is blue in colour and absorbed light at  $570 \pm 30$  nm, the non-specific colour (NSC<sub>living</sub>) interference of the test article was also assessed by incubating 25 mg of Final Bite with two additional living control tissues, without the MTT-stain. Appropriate controls were used in both pre-experiments.

The cut-off % value distinguishing classification from non-classification in accordance with CLP Reg (EC) No 1272/2008 is defined below:

**Table 6.1.4/02-1 Prediction model for the EpiDerm *in vitro* skin irritation test method**

| Mean tissue viability | Prediction to be considered |
|-----------------------|-----------------------------|
| ≤ 50 %                | Category 1 or Category 2    |
| > 50 %                | Non-irritant                |

**Results:**

The study met the acceptability criteria listed within Annex 3 of OECD 439 – including specific criteria for mean tissue viability of concurrent SDS positive control, OD<sub>570</sub> of the PBS negative control, and a low variation between replicates (SD ≤ 18 %). The historical control data were provided in the study report and confirm that the positive and negative control mean values are within the HCD boundaries (see Table 4 of the study report for further details).

The pre-experiments supporting the MTT assay confirmed there was no potential for either direct reduction of MTT to MTT-formazan by Final Bite, nor any interference by the coloured test material in the absence of MTT (NSMTT = 0 %; NSC<sub>living</sub> 0.13 %). Therefore, no corrections for colorimetric interference in the MTT assay were required in this *in vitro* skin irritation test.

The cytotoxicity results demonstrate that the mean relative skin tissue viability was below 50 %, confirming that the criteria for applying classification were met.



**Table 6.1.4/02-2 Tissue viability; Final Bite *in vitro* skin irritation test**

| Exposure time                 | Replicate | Mean OD <sub>570</sub><br>(blank corrected) | Mean OD <sub>570</sub> ± SD<br>(3 replicates) | Mean rel.<br>tissue viability<br>± SD % |
|-------------------------------|-----------|---|---|---|
| Negative control<br>(PBS)     | 1         | 1.842                                       | 1.792 ± 0.090                                 | 100 ± 5                                 |
|                               | 2         | 1.687                                       |   |   |
|                               | 3         | 1.846                                       |   |   |
| Final Bite                    | 1         | 0.549                                       | 0.618 ± 0.158                                 | 34.5 ± 8.8                              |
|                               | 2         | 0.507                                       |   |   |
|                               | 3         | 0.799                                       |   |   |
| Positive control<br>(5 % SDS) | 1         | 0.044                                       | 0.032 ± 0.016                                 | 1.8 ± 0.9                               |
|                               | 2         | 0.038                                       |   |   |
|                               | 3         | 0.013                                       |   |   |

**Conclusions:**

Under the conditions of this *in vitro* skin irritation study, the test article, Final Bite, showed irritant effects and warrants classification for dermal irritation in accordance with Regulation (EC) No. 1272/2008. However since this test method cannot discriminate between category 1 and category 2 classifications, it must be incorporated into a weight of evidence analysis, presented below.

**Overall conclusion on dermal effects of the preparation ‘Final Bite’**

Considering the overall *in vitro* database, and with reference to paragraph 36 of OECD TG 439, since the test article Final Bite, was found to be non-corrosive (based on OECD TG 431) and shows tissue viability ≤ 50 % in the present OECD TG 439 test method, in accordance with Regulation (EC) No. 1272/2008, skin irritant category 2 is justified (H315).

*Applicant: Same proposal*

**B.6.1.5. Eye irritation**

The representative formulation, Final Bite, was tested in two *in vitro* eye irritation tests (OECD 492 and OECD 437). It is currently accepted that there are no *in vitro* or *ex-vivo* test methods which can identify reversible eye effects i.e. those that would be classified under Reg (EC) No. 1272/2008 for eye effects category 2. Nevertheless, the approach taken by the applicant is consistent with a “bottom-up” approach endorsed by the OECD IATA (2017) for serious eye damage and irritation. The information provided by the applicant is considered to have adequately fulfilled the information requirements of Reg. (EC) No. 284/2013.

|                                      |   |           |
|--------------------------------------|---|-----------|
| <b>Study</b>                         | <b><i>In vitro</i> Eye Irritation: Ocular Irritation Assay using the EpiOcular™ Human Tissue Model with Final Bite-0402206. Study report 177932</b>   |           |
| <b>Reference</b>                     | CP 7.1.5/01: (2018b), Applicant ref R-39096   |           |
| <b>Test substance</b>                | Final Bite – Blue 2.5 mm, 0402206, Batch KM80174200H  |           |
| <b>Guideline</b>                     | OECD 492  | GLP : Yes |
| <b>Date performed</b>                | 10 Nov 2017 –1 Dec 2017   |           |
| <b>Test facility</b>                 | Eurofins Munich   |           |
| <b>Deviations from the guideline</b> | None  |           |
| <b>Study Acceptable</b>              | Yes. <ul style="list-style-type: none"> <li>It appears that due to the mixture of Final Bite in distilled water being blue in appearance, a pre-check for colour interference using living-tissue controls should have been included in the main test. The missing pre-check means that it is not possible to quantify the non-specific colour interference within the test system. However, the omission does not compromise the conclusions of the study because the results of the test are « positive » for hazard identification and any correction for colour interference would not alter the conclusion.</li> </ul> |           |

|  |   |
|--|---|
|  | <ul style="list-style-type: none"> <li>A pre-check for colour interference using isopropanol solvent was not performed, as should have been the case for a coloured solid coloured test substance.</li> </ul> |
|--|---|

#### *Materials and Methods:*

In order to clarify if Final Bite may be considered for classification for ocular irritancy, the potential to induce cytotoxicity in a reconstructed human cornea-like epithelium model (EpiOcular™) was investigated in an OECD 492 test method. The scientific basis being that any compound which induces serious eye damage or irritation, will induce cytotoxicity in the corneal epithelium and/or conjunctiva (OECD IATA, 2017). There were no major deviations from the guideline, and all the main components of the test method (Annex 2, OECD 492) were reported. The commercially-sourced tissue samples were supplied with acceptable quality control evidence – there were no concerns over the morphology, reproducibility or viability of the tissues as supplied to the laboratory.

In the main experiment, Final Bite was manually ground to a fine powder and 50 mg was placed onto the apical surface of the acclimatised EpiOcular™ tissue, in duplicate. In order to confirm study validity, negative (distilled water) and positive (methyl acetate) cultures were run concurrently. After 6 h, the test article and control substances were removed by extensive rinsing with PBS, replaced with fresh medium and the tissues were allowed to recover for 18 h. This post-treatment recovery incubation period allows for the manifestation of clear cytotoxicity and recovery from weak, non-specific cytotoxicity. After the post-incubation period, the standard MTT viability test was performed. For each tissue insert, 2 x 200 µL aliquots of the MTT assay extract were measured for MTT-formazan using standard (OD) absorbance at  $570 \pm 30$  nm.

In addition to the positive and negative in-study controls, a pre-check was performed to assess the potential for direct interference within the MTT viability assay. The non-specific MTT formation (% NSMTT) was evaluated by incubating 50 mg Final Bite with 1 ml of MTT medium for 3 h before a visual check was performed.

The cut-off % value distinguishing non-classification in accordance with CLP Reg (EC) No 1272/2008 is defined below:

**Table 6.1.5/01-1 Prediction model for the EpiOcular™ *in vitro* eye irritation method**

| Mean tissue viability | Prediction to be considered |
|-----------------------|-----------------------------|
| ≤ 60 %                | category 1 or category 2    |
| > 60 %                | No category assigned        |

#### *Results:*

The study met the acceptability criteria listed within Annex 2 of OECD 492 – including specific criteria for mean tissue viability of the positive control (< 50 %), OD<sub>570</sub> of the PBS negative control (between 0.8 and 2.5), and a low variation between replicate viabilities (< 20 %). The historical control data were provided in the study report and confirm that the positive and negative control mean values are within the HCD boundaries (see Table 4 of the study report for further details).

The pre-experiment supporting the MTT assay confirmed there was no potential for direct reduction of MTT to MTT-formazan by Final Bite because the mixture did not turn blue in colour.

The cytotoxicity results demonstrate that the mean relative viability of reconstructed human cornea-like epithelium tissue following exposure to Final Bite was below 60 %, confirming that it is not possible to assign “no classification” to the test formulation.

**Table 6.1.5/01-2 Tissue viability; Final Bite *in vitro* EpiOcular™ eye irritation test**

| Exposure time                          | Replicate | Mean OD <sub>570</sub><br>(blank corrected) | Mean OD <sub>570</sub> ± SD | Mean rel.<br>tissue viability<br>± SD % |
|--|-----------|---|-----------------------------|---|
| Negative control<br>(H <sub>2</sub> O) | 1         | 1.833                                       | 1.776 ± 0.07                | 100 ± 6.3                               |
|  | 2         | 1.720                                       |                             |   |
| Final Bite                             | 1         | 0.058                                       | 0.071 ± 0.01                | 4.0 ± 1.5                               |
|  | 2         | 0.084                                       |                             |   |
| Positive control<br>(methyl acetate)   | 1         | 0.320                                       | 0.340 ± 0.02                | 19.1 ± 2.3                              |
|  | 2         | 0.360                                       |                             |   |

**Conclusions:**

Under the conditions of this *in vitro* eye irritation study in reconstructed human cornea-like epithelium, the test article showed irritant effects and it is not possible to assign a “no category” classification to Final Bite. Since it is not possible to discriminate between eye irritation/reversible effects on the eye (Cat 2) and serious eye damage/irreversible effects on the eye (Cat 1) using this test method, further testing is required.

| Study                         | Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay with Final Bite-0402206 Study Report 177936   |           |
|-------------------------------|---|-----------|
| Reference                     | CP 7.1.5/02: (2018), Applicant ref R-39095  |           |
| Test substance                | Final Bite – Blue 2.5 mm, 0402206, Batch KM8017420OH  |           |
| Guideline                     | OECD 437  | GLP : Yes |
| Date performed                | 4 Dec 2017 – 6 Dec 2017   |           |
| Test facility                 | Eurofins Munich   |           |
| Deviations from the guideline | None  |           |
| Study Acceptable              | <p>Yes. Sufficient scientific justification for open-chamber method is provided. Only the method of application differs between the test article (open-chamber) and the two controls (closed-chamber application method); after dosing an open-chamber cornea, it is converted to a closed-chamber for the exposure period.</p> <p>The study author states that all corneas underwent a 2 h post-exposure incubation before assessing opacity and permeability; however, according to OECD 437, for solids, this additional incubation step was not required. Overall, since the solid was moistened and the controls were acceptable, this is not considered to have adversely impacted upon the study validity.</p> |           |

**Materials and Methods:**

The ocular hazard of the representative formulation, Final Bite, was estimated as function of its ability to induce opacity and increased permeability in an isolated bovine cornea in an OECD 437 guideline-compliant study.

The assay was conducted with isolated corneas obtained from cattle freshly slaughtered on the test day. The study report contains sufficient details on the collection of the eyes and the subsequent preparation of the corneas into the test chambers. All corneas were equilibrated with media on both the anterior and posterior sides for an hour after mounting into the test chambers and a pre-test opacity measurement was recorded. Following the equilibration period, the media was removed from the anterior chamber and replaced with the test article (Final Bite, 750 mg) or the 750 µl of either positive (20 % w/v imidazole in 0.9 % NaCl) or negative (0.9 % NaCl) control.

The test was performed on a total of 3 corneas per dosing group, for specific measurements of opacity and permeability in order to generate an *in vitro* irritancy score (IVIS).

Due to the insoluble nature of Final Bite (in 0.9 % NaCl), the test article was applied directly onto the corneal surface assembled into an open-chamber method and moistened with 0.9 % NaCl.

Opacity: After a 4 h exposure period at 32°C, the test article and controls were removed by rinsing at least 3 times with media containing phenol red (standard indicator of alkali and acids), followed by a final rinse with phenol red-free media, once the corneal surface was free of test substance. The anterior chamber was refilled with fresh media and the illuminance measurement was performed using an opacitometer to obtain final opacity readings.

Permeability: After the illuminance measurement was performed, the media was replenished, 1 mL of a 5 mg/mL sodium fluorescein dye solution was added to the anterior chamber and the corneas were incubated for 90 minutes at 32°C. The amount of dye penetrating through to the posterior chamber media was then measured by UV/VIS spectrophotometry at 490 nm (OD<sub>490</sub>).

The *in vitro* irritation score (IVIS) = Mean opacity value + (15 x mean permeability OD<sub>490</sub> value)

The IVIS cut-off values for identifying a test chemical as causing serious eye damage (CLP Reg 1272/2008 Cat 1) or non-classification are defined below:

**Table 6.1.5/02-1 Prediction model for the BCOP *ex-vivo* eye hazard method**

| Mean IVIS     | Prediction to be considered |
|---------------|-----------------------------|
| ≤ 3           | No category                 |
| > 55          | Category 1                  |
| 3 < IVIS ≤ 55 | No prediction possible      |

**Results:**

The study met the acceptability criteria for the positive control in relation to the HCD and the negative control resulted in an IVIS score of well below 3. See original study report table 5 for positive control HCD which confirms that the *in vitro* irritation score obtained with the positive control falls within the two SD of the current historical mean.

All replicates per treatment group yielded unequivocal results and the IVIS scores for Final Bite indicate that this preparation causes eye damage. The scores are presented below.

**Table 6.1.5/02-2 Opacity, permeability and IVIS scores; Final Bite *in vitro* BCOP test method**

| Exposure group                    | Cornea replicate | Opacity (corrected) | Mean opacity ± SD | Permeability (OD <sub>490</sub> ) | Mean permeability ± SD (OD <sub>490nm</sub> ) | IVIS   |
|-----------------------------------|------------------|---------------------|-------------------|-----------------------------------|---|--------|
| Negative control (0.9 % NaCl)     | 1                | 0.04                | 0.18 ± 0.25       | 0.010                             | 0.012 ± 0.002                                 | 0.35   |
|                                   | 2                | 0.04                |                   | 0.013                             |   |        |
|                                   | 3                | 0.47                |                   | 0.012                             |   |        |
| Final Bite                        | 1                | 137.79              | 107 ± 27.74       | -0.008                            | -0.004 ± 0.004                                | 106.93 |
|                                   | 2                | 83.97               |                   | 0.000                             |   |        |
|                                   | 3                | 99.23               |                   | -0.006                            |   |        |
| Positive control (20 % imidazole) | 1                | 70.35               | 80.12 ± 10.67     | 1.284                             | 1.488 ± 0.297                                 | 102.44 |
|                                   | 2                | 78.50               |                   | 1.351                             |   |        |
|                                   | 3                | 91.51               |                   | 1.828                             |   |        |

**Conclusions:**

Under the conditions of this *in vitro* study, the test article, Final Bite, showed irreversible eye effects and warrants classification in accordance with Regulation (EC) No. 1272/2008 as causing serious eye damage category 1 (H318).

**Overall conclusion on ocular effects of the preparation ‘Final Bite’**

Final Bite was tested in two *in vitro* OECD test methods with reliable, results produced from both studies. Neither OECD 492 nor OECD 437 allow identification of eye irritants which would be classified as a category 2 eye irritant, however the information requirements of Reg (EC) No. 1107/2009 are fulfilled by the applicant's dossier which followed a “bottom-up” approach (OECD IATA, 2017).

In an OECD 492 study performed with reconstructed human cornea-like epithelium, exposure to Final Bite induced a decrease in tissue viability – an indication of eye damage and eye irritation and confirming that the test compound requires classification in category 1 or 2 for this hazard. In the subsequent OECD 437 study, exposure of Final Bite to excised bovine corneas induced significant opacity and permeability, resulting in a IVIS confirming the serious eye damage’ (category 1) potential for the formulation.

Considering the overall *in vitro* database generated with OECD test methods 437 and 492, sufficient evidence exists to support classification of Final Bite in accordance with Reg (EC) No. 1272/2008 as ‘causes serious eye damage, category 1 (H318).

*Applicant: Same proposal*

#### B.6.1.6. Skin sensitization

There is insufficient information on this hazard endpoint presented in the submitted SDS for the co-formulants within the representative formulation. Therefore, it is not possible to reliably establish the potential for skin sensitisation based on the conventional (calculation) method. In order to fulfil this specific information point, the applicant has attempted to generate *in vitro* data in accordance with the adopted OECD 442B, 442C and 442E guidelines (applicant references CP 7.1.6/01 - 03). However, it was technically impossible to perform these methods due to insolubility of the Final Bite preparation in the required solvents. Therefore, the performance of the OECD 442B LLNA is both scientifically justified and supported by the EU regulatory requirements.

|                                      |   |           |
|--------------------------------------|---|-----------|
| <b>Study</b>                         | <b>Skin Sensitisation Study of Final Bite-0402206 by Local Lymph Node Assay (BrdU-ELISA Method) in Mice. Study Report No. U-17291</b> |           |
| <b>Reference</b>                     | CP 7.1.6/01, [REDACTED] (2018), Applicant ref R-39456   |           |
| <b>Test substance</b>                | Final Bite – Blue 2.5 mm, 0402206, Batch KM8017420OH  |           |
| <b>Guideline</b>                     | OECD 442B   | GLP : Yes |
| <b>Date performed</b>                | 15 Feb 2018 – 20 Apr 2018   |           |
| <b>Test facility</b>                 | [REDACTED]  |           |
| <b>Deviations from the guideline</b> | None  |           |
| <b>Study Acceptable</b>              | Yes   |           |

The aim of this study was to determine the skin sensitisation potential of the representative formulation, Final Bite, following dermal exposure.

##### *Materials and methods:*

In an OECD 442B guideline-compliant study, 5 female CBA/CaOlaHsd mice per group were dosed with Final Bite at 10 %, 25 % and 50 % w/v. Concurrent negative vehicle control (acetone: olive oil 4:1 v/v) and positive control (25 % eugenol in vehicle) were included as concurrent controls. The test concentrations were chosen on the basis of a pre-experiment in which the highest soluble concentration of Final Bite was found to be 50 % w/v, at which point no adverse dermal reactions were noted.

The Final Bite preparations and controls were applied at a rate of 25 µl/ear on Days 1,2 and 3. Bodyweights and clinical observations were recorded. On Day 5, all animals were administered 0.5 ml BrdU via the i.p route. On Day 6, the animals were sacrificed and the auricular lymph nodes of both sides were isolated into PBS for determination of cellular proliferation. The mean BrdU Labelling Index was determined for each group using a commercial kit and the mean Stimulation Index (SI) derived for each treatment group and the positive control relative to the negative vehicle control group.

##### *Results:*

No clinical signs of toxicity or mortality were evident in the mice of either control or treatment groups. There was no erythema, or statistically or biologically significant increased ear thickness (compared to Day 1) observed on the ears of any mice of the treatment or control groups, confirming that the study was not confounded by irritation. All animals gained body weight when compared to the pre-dose body weights.

The mean SI values were 1.2, 1.5 and 1.4 at concentrations of 10 %, 25 % and 50 % w/v Final Bite, compared to the vehicle control group. These values are below the cut-off of 1.6 for identifying a positive skin response) and were not accompanied by a dose-response. The concurrent positive control was 3.8, confirming the acceptance criteria of the study.

##### *Conclusions:*



Under the conditions of this *in vivo* LLNA study, the test item was shown to have no sensitising properties. Therefore, the representative formulation, Final Bite, should not be classified for skin sensitisation in accordance with Reg. (EC) No. 1272/2008.

#### **B.6.1.7. Supplementary studies on the plant protection product**

Not required.

#### **B.6.1.8. Supplementary studies for combinations of plant protection products**

Not required.

### **B.6.2. DERMAL ABSORPTION**

The applicant has presented a reasoned case to support the proposed dermal absorption estimate of 10 % for elemental iron in all uses of the representative product, Final Bite. No experimental data on the dermal absorption potential of elemental iron in the representative formulation have been submitted. The representative product, Final-Bite®, is a Ready to Use Bait (RB) containing 10 g of active substance/kg (1 % w/w), intended for use on various crops, without further dilution. A single dermal absorption value is required for non-dietary risk assessment of the representative use.

#### ***Applicability of EFSA 2017 guidance default values for elemental iron:***

A rigid application of the EFSA 2017 <sup>1</sup>dermal absorption guidance leads to the categorisation of ‘Final Bite’ as an “other” formulation type and at 1 % elemental iron w/w, it would also be viewed as a “dilution”, resulting in a default value of 70 % (EFSA 2017; SCoPAFF 2017). The applicant has submitted the following justification, outlining the rationale for deviation from the prescribed EFSA 2017 default value (70 %), towards a lower dermal absorption estimate (10 %):

The refined dermal absorption default values in the EFSA guidance on dermal absorption (EFSA 2017a) are based on dermal absorption data collected by industry (Aggarwal et al. 2014; Aggarwal et al. 2015) and other data collected by BfR (compare comments in EFSA 2017c), i.e. the German Federal Institute for Risk Assessment. The database is publically available along with the guidance. It includes three ready-to-use bait (RB) products at concentrations of 0.061, 0.768 and 52 g/kg with a maximum dermal absorption cell value of 1.02%. The maximum value for the lower concentrated products is 0.91%. Other bait products included pellet baits and wax blocks with even lower concentrations and lower dermal absorption values. While it is statistically not appropriate to use maximum values, it gives us an indication about the appropriateness of the suggested 70%. The default value grouping is not based on scientific but on practical considerations of having “not too many default values” (Chiusolo 2017; EFSA 2017b). There is no insoluble metallic active substance in the database and a prediction based on the data by using the default values has to be regarded as being out of domain. *N.B.: elemental iron is insoluble in water and organic solvents.*

The HSE agrees with the applicant, in that a dearth of relevant values in the supporting database means that expert judgement must be applied whilst applying the EFSA 2017 dermal absorption guidance to substances not strictly within the applicability domain, and in the case of elemental iron in Final Bite, a default value of 70 % is not appropriate. In order to support the use of 10 % as a pragmatic dermal absorption estimate, the known physiological characteristics and physicochemistry of elemental iron are given further consideration below:

#### ***Physicochemistry and physiological characteristics of elemental iron following dermal exposure to Final Bite:***

<sup>1</sup> EFSA2017, EFSA 2017a: EFSA guidance on dermal absorption (2017); EFSA2017b: pers comms at Info session on applications, EFSA, Parma Sept 2017

In considering the physicochemistry of Final Bite, it is noted that the formulation is nearly dust-free and is insoluble in either pH neutral aqueous or organic solvents. The applicant has proposed that Final Bite is very similar to a solid concentrate, for which a 10 % default is presented in the EFSA 2017 guidance. Due to the large particle size of the nearly dust-free, partitioning into the lipid matrix of cellular membranes is implausible for elemental iron from dermal exposure to Final Bite, and further passive penetration to the systemic environment is not expected.

The EFSA 2017 dermal absorption guidance allows the use of oral absorption value as a surrogate for dermal absorption in a limited range of circumstances, primarily because ADME characteristics of active substances within products and especially human data are usually not available. This is different for elemental iron under consideration, for which the gastrointestinal absorption is well characterized in humans as an active, tightly controlled process (Lynch, S. *et al.*, 2018). It is also known that whilst there is no actively-controlled iron excretion process in the human body, there are several known passive excretion pathways of ionic iron, one of them being desquamation (Lynch *et al.* 2018; Milstone, L.M., 2004).

Furthermore, due to its poor solubility, negligible oxidation of elemental iron to either  $\text{Fe}^{2+}$  or  $\text{Fe}^{3+}$  is expected following topical exposure at a skin sweat pH of approximately 4.2-6.5 (██████████ *et al.*, 2010a; ██████████ *et al.*, 2014). As a result of the presumed lack of generation of these more bioavailable forms upon topical exposure to the PPP, the use of human oral absorption data (50 %; DAR Doc 3CA\_B6.1) to derive a dermal absorption estimate is not considered appropriate.

***Conclusion and proposal for dermal absorption value of elemental iron following dermal exposure to Final Bite:***

Based on the well-known ADME characteristics of iron in the human body, in the zerovalent form, it seems unlikely that any significant penetration of biologically inactive elemental iron following dermal exposure to Final Bite will occur. In conclusion, and in line with previous EFSA conclusions for dermal absorption of  $\text{Fe}^{2+}$  from a generally more bioavailable EC formulation type, and  $\text{Fe}^{3+}$  from a comparable RB formulation type, a precautionary **dermal absorption estimate of 10 %** is considered to be a justified and pragmatic proposal to account for dermal penetration of ionic species released from elemental iron particulate matter.

### **B.6.3. AVAILABLE TOXICOLOGICAL DATA RELATING TO CO-FORMULANTS**

Acceptable SDS have been submitted for all of the co-formulants listed in Vol 4, section C.1.3. Any co-formulants classified for acute toxicity, skin and eye irritation and skin sensitisation have been considered above.

In addition to these effects, Final Bite contains a co-formulant (present at ██████ % w/w) classified for STOT-RE Category 2 (respiratory tract) and a co-formulant (present at ██████ % w/w) classified for STOT-SE3 (respiratory irritation). However, these levels are below the generic concentration limits (10 % and 20 % respectively), and classification for these hazards is not triggered.

No classification for acute toxicity by either the oral, dermal or inhalation routes is warranted. The step-wise combined evidence, generated in line with the OECD IATAs on skin corrosion/irritation (OECD IATA 2014) and eye damage/irritation (OECD 2017) indicates that the representative formulation Final Bite requires classification for dermal and ocular irritant effects under Reg (EC) No. 1272/2008. A mouse LLNA-BrdU confirms that the formulation presents no evidence for dermal sensitisation potential.

### **OVERALL TOXICOLOGICAL CLASSIFICATION OF THE REPRESENTATIVE FORMULATION FINAL BITE IN ACCORDANCE WITH REG. (EC) NO. 1272/2008**

**Skin Irritation Category 2; H315 (Causes skin irritation)**

**Eye Irritation Category 1; H318 (Causes serious eye damage)**

### **B.6.4. EXPOSURE DATA**

The representative formulation, 'Final Bite', is a Ready-to-Use Bait (RB) containing 10 g of elemental iron/kg (1% w/w). It is used as a professional molluscicide for slug and snail control on various edible and non-edible crops. A summary of the application parameters pertinent to operator, worker, resident and bystander exposure assessment

for ‘Final Bite’ are presented in Table B.6.4-1. Table B.6.4-2 presents the toxicological endpoints used to estimate systemic exposure to elemental iron and the classification of ‘Final Bite’ for human health effects.

Estimates of operator, worker, bystander and resident exposure were conducted in line with the EFSA guidance (EFSA Journal 2014;12(10):3874) and the respective calculator (Version: 30 March 2015). It is noted that the product ‘Final Bite’ contains elemental iron that has no significant acute toxicity and/or the potential to exert effects after a single dose and hence in this instance an acute exposure risk assessment is not required. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days.

Table B.6.4-1: Summary of ‘Final Bite’ application parameters pertinent to the operator, bystander, resident and worker exposure assessment

| <b>‘Final Bite’</b>                        |   |
|--|---|
| <b>Formulation type</b>                    | Ready-to-Use Bait (RB) containing 10 g/kg (1% w/w) iron   |
| <b>Use</b>                                 | Molluscicide for slug and snail control on various edible and non-edible crops indoors and outdoors |
| <b>Application method</b>                  | Vehicle-mounted broadcast and manual granule application  |
| <b>Max individual dose</b>                 | 8 kg of product/ha (0.08 kg a.s./ha)  |
| <b>Max total dose</b>                      | 48 kg/ha product (0.48 kg a.s./ha)  |
| <b>Max number of applications per year</b> | 6 per crop  |
| <b>Interval between applications</b>       | 5 days  |
| <b>Latest time of application</b>          | No restriction  |
| <b>Vapour pressure</b>                     | Negligible volatility   |

Table B.6.4-2: Summary of ‘Final Bite’ toxicological endpoints and classification for human health effects

| <b>‘Final Bite’</b>           |  |
|-------------------------------|--|
| <b>Systemic AOEL</b>          | 0.4 mg/kg bw/day   |
| <b>Dermal absorption</b>      | 10 % product (ready-to-use)  |
| <b>Oral absorption</b>        | 50 %   |
| <b>Inhalation absorption</b>  | 100 %  |
| <b>Product classification</b> | Skin Irritation 2; H315 (Causes skin irritation)<br>Eye Irritation 1; H318 (Causes serious eye damage) |

#### B.6.4.1. Operator exposure

Exposure was calculated for application of ‘Final Bite’ through vehicle mounted broadcast application and manual application assuming the use of standard work clothing. The product is to be applied to soil around and under rows of crops therefore the ‘bare soil’ scenario has been used in the operator exposure calculations. In the original PHED studies supporting granular application in the EFSA Calculator operators wore normal workwear and gloves during mixing and loading application. The EFSA Calculator includes an estimate of potential exposure, assuming the calculated potential exposure is 100 times higher than the actual exposure estimates from the PHED studies. The EFSA Calculator provides an option for the use of certified protective coveralls, this is the actual potential exposure value from the PHED studies with the use of normal workwear (arms, body & legs covered).

The EFSA Calculator does not include calculations for operator exposure indoors, and for granule application it is considered that exposure indoors would be equivalent to exposure outdoors. A summary of the estimated long term exposures is provided in Table B.6.4.1-1 and Table B.6.4.1-2 with outputs from the EFSA Calculator provided in Appendix 1, estimate 1 and 2.



Table B.6.4.1-1: EFSA calculator estimates of long-term exposure to elemental iron for operators applying ‘Final Bite’ through vehicle mounted broadcast application

|  |  | Elemental Iron                  |                    |
|--|--|---------------------------------|--------------------|
| Model data   | Level of PPE                                   | Total absorbed dose (mg/kg/day) | % of systemic AOEL |
| Scenario: Bare soil / Outdoor / Broadcast application / Vehicle-mounted<br>Formulation type: Granule<br>Work rate: 50 ha<br>Season: Not relevant |  |                                 |                    |
| Application rate   |  | 0.08 kg a.s./ha                 |                    |
| Granule application (PHED model; 75 <sup>th</sup> percentile)<br>Body weight: 60 kg  | Workwear (arms, body & legs covered) M/L and A | 0.0028                          | 0.71%              |

The estimated long-term operator exposure to elemental iron is calculated to be within acceptable limits and equal to 1% of the AOEL for an operator that applies the product ‘Final Bite’ without using PPE.

Table B.6.4.1-2: EFSA calculator estimates of long-term exposure to elemental iron for operators applying ‘Final Bite’ through manual application

|   |  | Elemental Iron                  |                    |
|---|--|---------------------------------|--------------------|
| Model data  | Level of PPE                                   | Total absorbed dose (mg/kg/day) | % of systemic AOEL |
| Scenario: Bare soil / Outdoor / Manual application / Manual<br>Formulation type: Granule<br>Work rate: 1 ha<br>Season: Not relevant |  |                                 |                    |
| Application rate  |  | 0.08 kg a.s./ha                 |                    |
| Granule application (PHED model; 75 <sup>th</sup> percentile)<br>Body weight: 60 kg   | Workwear (arms, body & legs covered) M/L and A | 0.3902                          | 97.56%             |

The estimated long-term operator exposure to elemental iron is calculated to be within acceptable limits and equal to 98% of the AOEL for an operator that applies the product ‘Final Bite’ without using PPE

#### Local effects risk assessment

As summarised in Volume 1 Section 2.6.13, there is limited evidence from literature that inhalation of particulate carbonyl elemental iron powder may lead to lung overload and local toxicity. The evidence is not extensive and comes from a single publication. The endpoints from this study were not carried forward to derive a quantitative non-dietary reference value. Given that no reference value was set for local effects, no higher tier non-dietary risk assessment has been performed.

#### Classification of ‘Final Bite’

The product ‘Final Bite’, is classified for human health effects as eye irritant Category 1 and skin irritant Category 2, hence the following PPE is required: suitable protective clothing (coveralls), suitable protective gloves and face protection (faceshield) when handling the product.

#### B.6.4.2. Bystander and resident exposure

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

Bystander and resident exposure is not expected from the proposed indoor use of 'Final Bite' therefore no assessment has been carried out.

##### Exposure to surface deposits from drift of granules

For outdoor application of granular plant protection products, it is considered that dermal exposure from surface deposits could occur, therefore, an assessment of systemic longer term exposure to residents has been performed using the EFSA model based on the assumption of 3% drift of granules for broadcast and manual applications. In line with the EFSA guidance a Turf Transferable Residue (TTR) value of 1% applicable for products applied as granules is used in the exposure calculations. An estimate of exposure from the vapour pathway has not been calculated as elemental iron is classified as negligible volatility. The spray drift and dermal exposure from dislodgeable foliar residues from entry into treated crops exposure pathways are not considered relevant for the application of granules. Elemental iron is inherently stable as it cannot be chemically (or bio-) degraded therefore it cannot be transformed into related degradation products or metabolites therefore, a half-life value (DT<sub>50</sub>) of 1000 days is assumed in the calculation so that residue decline is not taken account. A summary of the estimated long-term exposure and comparison with the AOEL is provided in the Table B.6.4.2-1 with outputs from the EFSA calculator provided in Appendix 1, estimate 3.

Table B.6.4.2-1: EFSA calculator estimate of longer term exposure of residents to elemental iron for the proposed use of 'Final Bite' through vehicle mounted broadcast application

|   |                                   | Elemental Iron                        |                    |
|---|-----------------------------------|---------------------------------------|--------------------|
| Model data  | Exposure                          | Total absorbed dose<br>(mg/kg bw/day) | % of systemic AOEL |
| Scenario: Bare soil / Outdoor / Broadcast application of granules / Vehicle-mounted<br>Formulation type: Granule<br>Buffer zone: 2-3 m<br>Drift reduction technology: not applicable<br>DT <sub>50</sub> : 1000 days<br>TTR: 1%<br>Oral absorption: 50%<br>Season: not applicable |                                   |                                       |                    |
| Number of applications and application rate:  |                                   | 6 x 0.08 kg a.s./ha                   |                    |
| Resident child<br>Body weight: 10 kg  | Deposits (75 <sup>th</sup> perc.) | 0.0001                                | 0.03%              |
| Resident adult<br>Body weight: 60 kg  | Deposits (75 <sup>th</sup> perc.) | <0.0001                               | 0.01%              |

An acceptable longer term exposure of residents to elemental iron is predicted for an unprotected child and adult for the surface deposits pathway for which exposure is estimated to be 0.03% (child) and 0.01% (adult) of the AOEL for elemental iron respectively.

##### Exposure to children from direct ingestion of granules

For products applied as granules there is a potential for oral exposure to children from direct ingestion of granules.

##### *Ingestion of granules*

'Final Bite' is a small blue ready-for-use bait, therefore, there is the potential for oral exposure via ingestion of the product by children who may enter treated areas soon after the product has been applied. In this case, exposure cannot be predicted using the EFSA Calculator, therefore, a reverse exposure calculation is considered appropriate. A reverse exposure risk assessment has been conducted to determine the unacceptable exposure (>100% of the AOEL of elemental iron) to a child through ingestion of the product.

Table B.6.4.3-1: Estimate of child exposure to elemental iron through ingestion of granules for the proposed use of 'Final Bite' on various edible and non-edible crops

| <b>Steps in calculating child exposure through ingestion of granules in areas treated with 'Final Bite'.</b> |  |
|--|--|
| 1  | 'Final Bite' has a granule diameter of 2.5 mm and with a product bulk density of 0.7806 g/cm <sup>3</sup> , on this basis, product weight is approximately 6.4 mg per granule (Volume 3, B.2.)   |
| 2  | Following a single application of the product at the proposed application rate of 8 kg product/ha (0.8 g product/m <sup>2</sup> ), the number of granules on the soil surface is calculated to be equal to $0.8/0.0064 = 125$ granules/m <sup>2</sup> . Assuming a 3% drift of granules into neighbouring gardens, the number of granules would be equal to $125 \times 3\% = 3.75$ granules/m <sup>2</sup> , rounded to 4 granules/m <sup>2</sup> . |
| 3  | On the basis that the product contains 1% w/w of elemental iron, the amount of the active substance in one granule is equivalent to $6.4 \text{ mg} \times 0.01 = 0.064 \text{ mg a.s./granule}$   |
| 3  | Based upon the AOEL of elemental iron of 0.4 mg/kg bw/day and assuming a child body weight of 10 kg, an acceptable ingestion rate of 4 mg elemental iron per child/day is calculated   |
| 4  | The number of granules corresponding to unacceptable child resident exposure via ingestion of the product is calculated as $4 \text{ mg a.s.} / 0.064 \text{ mg a.s./granule} = 62.5$ granules. This value is rounded to 63 granules   |

Based on the reverse reference calculation, the number of granules corresponding to unacceptable exposure to a child resident through ingestion of the product is equal to 63 granules. Given that the estimate of the number of granules on the surface of the garden through drift of the product is 4 granules/m<sup>2</sup> it is considered highly unlikely that a child resident would ingest this amount of product. Therefore the risk of ingestion of granules by a child resident is considered acceptable.

#### B.6.4.3. Worker exposure

Worker re-entry exposure to dislodgeable foliar residues is regarded as being negligible in the context of use of granular plant protection products. However, it is considered that in the case of plant protection products applied to bare soil, workers could be exposed to the active substance via handling of the treated soil. An assessment of worker exposure for handling soil has therefore been performed based upon consideration of hand soil loading for workers and soil adherence to skin, as referenced in Appendix F in the EFSA guidance on pesticides exposure assessment of operators, workers, residents and bystanders (EFSA Journal 2014; 12(10):3874).

The following long-term worker exposure assessment has been carried out to address potential exposure to workers handling bare soil treated with 'Final Bite' where exposure to soil-borne residues occurs in the absence of contact with treated foliage. Estimates of potential dermal exposure can be derived by considering the concentration of the active substance in the treated soil, together with soil dermal adherence data and a default hand soil loading value of 0.44 mg/cm<sup>2</sup> for workers. The EFSA guidance also outlines the following assumptions which can be used in the worker exposure assessments: the distribution of the product is limited to the top 5 cm layer of soil; soil density is 1.5 g/cm<sup>3</sup>; 100% of the applied dose reaches the soil surface. Based upon the above recommendations made in the EFSA guidance, long-term exposure for workers handling bare soil is estimated considering the potential accumulation of residues in accordance with the critical GAP for 'Final Bite' (6 x 0.08 kg elemental iron/ha) and has been carried out as follows:

Table B.6.4.3-2: Estimate of worker exposure (dermal) to elemental iron for the proposed use of 'Final Bite' on various edible and non-edible crops

| <b>Steps in calculating worker (dermal) exposure resulting from handling soil treated with 'Final Bite'.</b> |  |
|--|--|
| 1  | The maximum individual dose of elemental iron is 0.08 kg a.s./ha which is equivalent to: 80,000 mg elemental iron/ha or 8 mg elemental iron/m <sup>2</sup> .   |
| 2  | If it is assumed that the product is distributed in the top 5 cm of soil (EFSA Guidance, 2014), then the application rate corresponds to: 160 mg elemental iron/m <sup>3</sup> (following a single application). |

|   |   |
|---|---|
| 3 | Following 6 applications of the product (in accordance with the critical GAP) the worst-case soil concentration of elemental iron will be 960 mg elemental iron/m <sup>3</sup> .<br>(Note – since the active substance is an element, no degradation (DT <sub>50</sub> ) has been assumed in this instance).                  |
| 3 | If it is assumed that the soil density is 1.5 g/cm <sup>3</sup> equivalent to 1500 kg/m <sup>3</sup> (EFSA Guidance, 2014), then the amount of elemental iron in the soil corresponds to: 960 mg elemental iron / 1500 kg soil, equivalent to 0.64 mg elemental iron/kg soil, equivalent to 0.00064 mg elemental iron/g soil. |
| 4 | Assuming that the average surface area of a worker's hands of 820 cm <sup>2</sup> (EFSA guidance, 2014), and a soil retention of 0.44 mg/cm <sup>2</sup> (EFSA Guidance, 2014) then the amount of soil retained on a worker's hands will be 361 mg of soil.   |
| 5 | 361 mg of soil will contain: 0.361 g soil * 0.00064 mg elemental iron/g = 0.00023104 mg elemental iron. Therefore, workers will be (dermally) exposed to 0.00023 mg elemental iron.   |
| 6 | Using a worst-case 10% dermal absorption value for elemental iron, this corresponds to worker exposure to 0.000023 mg elemental iron.   |
| 7 | Based upon a default worker body weight of 60 kg (EFSA Guidance, 2014) the estimated worker exposure will be: 0.000023 mg elemental iron/ 60 kg bw = 0.00000038 mg/kg bw/day  |
| 8 | Therefore, worker exposure corresponds to 0.0001% of the AOEL (0.4 mg/kg bw/day) for elemental iron.  |

The systemic longer term exposure for a worker is calculated to be equivalent to <1% of the AOEL for elemental iron for a worker without PPE. The predicted exposure to a re-entry worker is within acceptable limits.

### B.6.5. EXPOSURE AND RISK ASSESSMENT

A non-dietary human exposure risk assessment for elemental iron has been conducted based on the representative product 'Final Bite' containing 10 g/kg (1% w/w) elemental iron. The product is used as a molluscicide for outdoor and indoor edible and non-edible crops. Exposure was estimated using the EFSA guidance (EFSA Journal 2014;12(10):3874) and the respective calculator. The exposure risk assessment was conducted using a dermal absorption for the ready to use product of 10%. Elemental iron does not have significant acute toxicity or the potential to exert toxic effects after a single exposure, therefore no acute risk assessment is required. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Thus, long-term exposure assessment also covers acute exposure assessment.

#### B.6.5.1. Operator exposure

The operator exposure assessment indicates that the proposed uses of 'Final Bite' through vehicle mounted broadcast application will result in acceptable systemic operator exposure equal to 0.71% of the AOEL for elemental iron for an operator that applies the product wearing normal workwear (arms, body and legs covered) and no PPE. For the proposed uses of 'Final Bite' through manual application an acceptable systemic operator exposure is calculated to be equal to 98% of the AOEL for elemental iron for an operator that applies the product wearing normal workwear (arms, body and legs covered) and no PPE. For granule application it is considered that exposure indoors would be equivalent to exposure outdoors. A higher tier local effects risk assessment for exposure via the inhalation route indicates that for the proposed use of 'Final Bite' exposure is equal to 2% of the AOEL for elemental iron for an operator that applies the product without PPE. It is noted that due to the classification of the representative product 'Final Bite' for human health effects, the following PPE is required for operators: suitable protective clothing (coveralls), suitable protective gloves and face protection (face shield) when handling the product.

#### B.6.5.2. Bystander and resident exposure

The longer term exposure assessment to residents indicates that the proposed outdoor uses of 'Final Bite' will result in an acceptable risk of exposure to an unprotected adult and child. The longer term exposure to residents is acceptable for the surface deposits pathway at 0.03% (child) and 0.01% (adult) of the AOEL for elemental iron respectively. An assessment of exposure to child from ingestion of 'Final Bite' granules has been conducted. The number of granules a child would have to ingest to result in adverse health effects is calculated to be approximately 63 granules. It is considered improbable that a child resident would ingest this amount of product, as such, the risk from ingestion of granules is considered to be acceptable.

Elemental iron does not have significant acute toxicity or the potential to exert toxic effects after a single exposure, therefore no bystander risk assessment is required. Resident/bystander exposure is not expected from the proposed indoor use of 'Final Bite'.

#### B.6.5.3. Worker exposure

Worker re-entry exposure to dislodgeable foliar residues is regarded as being negligible in the context of use of granular plant protection products. An assessment of worker exposure has been undertaken for workers handling treated soil. For the proposed uses of 'Final Bite' the worker exposure is predicted to be equal to <1% of the AOEL for elemental iron for a worker without PPE which is within acceptable limits.

#### Conclusion

The operator, bystander, resident and worker risk assessment demonstrates an acceptable risk of exposure to elemental iron under conditions of intended uses of the representative product 'Final Bite', thus a safe use can be concluded.

#### B.6.6. REFERENCES RELIED ON

| Data Point                                    | Author(s) | Year | Title<br>Company<br>Report No.<br>Source (where<br>different from<br>company)<br>GLP or GEP<br>status<br>Published or<br>not                                      | Vertebrate<br>study<br>Y/N | Data<br>protection<br>claimed<br>Y/N | Justification<br>if data<br>protection is<br>claimed | Owner | Previous<br>evaluation |
|---|-----------|------|---|----------------------------|--------------------------------------|--|-------|------------------------|
| CP<br>7.1.4/01<br>Acute<br>skin<br>irritation | ██████    | 2018 | <i>In vitro</i> Skin<br>Corrosion:<br>Human Skin<br>Model Test<br>(EpiDerm™)<br>with Final Bite-<br>0402206. Study<br>Report 177930<br>GLP<br>Unpublished         | N                          | Y                                    | New data for<br>a new plant<br>protection<br>product | ADAMA | None                   |
| CP<br>7.1.4/02<br>Acute<br>skin<br>irritation | ██████    | 2018 | <i>In vitro</i> Skin<br>irritation:<br>Human Skin<br>Model Test<br>(EpiDerm™)<br>with Final Bite-<br>0402206. Study<br>Report No.<br>177931<br>GLP<br>Unpublished | N                          | Y                                    | New data for<br>a new plant<br>protection<br>product | ADAMA | None                   |
| CP<br>7.1.5/01<br>Acute eye<br>irritation     | ██████    | 2018 | <i>In vitro</i> Eye<br>Irritation:<br>Ocular Irritation<br>Assay using the<br>EpiOcular™  | N                          | Y                                    | New data for<br>a new plant<br>protection<br>product | ADAMA | None                   |

| Data Point                          | Author(s)              | Year | Title<br>Company Report No.<br>Source (where different from company)<br>GLP or GEP status<br>Published or not   | Vertebrate study<br>Y/N | Data protection claimed<br>Y/N | Justification if data protection is claimed | Owner | Previous evaluation |
|-------------------------------------|------------------------|------|---|-------------------------|--------------------------------|---|-------|---------------------|
|                                     |                        |      | Human Tissue Model with Final Bite-0402206. Study report 177932 GLP Unpublished   |                         |                                |   |       |                     |
| CP 7.1.5/02<br>Acute eye irritation | ██████                 | 2018 | Screening for the Eye Irritancy Potential using the Bovine Corneal Opacity and Permeability Assay with Final Bite-0402206 Study Report 177936 GLP Unpublished | N                       | Y                              | New data for a new plant protection product | ADAMA | None                |
| CP 7.1.6/01                         | ██████                 | 2018 | Skin Sensitisation Study of Final Bite-0402206 by Local Lymph Node Assay (BrdU-ELISA Method) in Mice.   | Y                       | Y                              | New data for a new plant protection product | ADAMA | None                |
| CP 7.3                              | Lynch S. <i>et al.</i> | 2018 | Biomarkers of Nutrition for Development (BOND)-Iron Review. The Journal of nutrition. Published   | N                       | N                              | -   | -     | N                   |
| CP 7.3                              | Milestone L. M.        | 2004 | Epidermal desquamation. Journal of dermatological science. 36:131-140 Published   | N                       | N                              | -   | -     | N                   |

## APPENDIX 1: EXPOSURE MODELLING

### Estimate 1: EFSA Calculator estimate of operator exposure for application of ‘Final Bite’ via tractor mounted broadcast application, no PPE

#### Model Input

|  |  |
|--|--|
| Substance name   | Elemental iron   |
| Product name   | Final Bite   |
| Reference value non acutely toxic active substance (RVNAS) | 0.4 mg/kg bw/day   |
| Reference value acutely toxic active substance (RVAAS)     | mg/kg bw/day   |
| Crop type  | Bare soil  |
| Substance properties                                       |  |
| Formulation type   | Granules, fine granules  |
| Minimum volume water for application (liquids)             | L/ha   |
| Maximum application rate of active substance               | 0.08 kg a.s. /ha   |
| 50% Dissipation Time DT50                                  | 30 days  |
| Initial Dislodgeable Foliar Residue                        | 3 µg/cm <sup>2</sup> of foliage/kg a.s. applied/ha                         |
| Dermal absorption of product                               | 10.00%   |
| Dermal absorption of in-use dilution                       | 10.00%   |
| Oral absorption of active substance                        | 50.00%   |
| Inhalation absorption of active substance                  | 100.00%  |
| Vapour pressure of active substance                        | low volatile substances having a vapour pressure of <5*10 <sup>-3</sup> Pa |
| Scenario   |  |
| Indoor or Outdoor application                              | Outdoor  |
| Application method   | Broadcast application of granules  |
| Application equipment                                      | Vehicle-mounted  |
| Buffer strip   | 2-3 m  |
| Number of applications                                     | 6  |
| Interval between multiple applications                     | 5 days   |
| Season (upward spraying orchards only)                     | not relevant   |

**Operator exposure for granular applications**

|                                      |                                   |                        |
|--------------------------------------|-----------------------------------|------------------------|
| Application rate of active substance | 0.08 kg a.s./ha                   | <i>I_AppRate</i>       |
| Assumed area treated                 | 50 ha/day                         | <i>d_AreaTreated</i>   |
| Amount of active substance applied   | 4 kg a.s./day                     | <i>I_AmountAS</i>      |
| Dermal absorption of the product     | 10.00%                            | <i>I_AbsorpProduct</i> |
| Dermal absorption of in-use dilution | 10.00%                            | <i>I_AbsorInuse</i>    |
| Formulation type                     | Granules, fine granules           |                        |
| Indoor or Outdoor application        | Outdoor                           |                        |
| Application method                   | Broadcast application of granules |                        |
| Application equipment                | Vehicle-mounted                   |                        |

  

| Mixing and loading | Exposure values      | mg exposure/kg a.s. mixed and loaded |                          | Reference          | Comment   |
|--------------------|----------------------|--------------------------------------|--------------------------|--------------------|---|
|                    |                      | 75 <sup>th</sup> centile             | 95 <sup>th</sup> centile |                    |   |
|                    | Hands                | 0.0015                               | 0.0069                   | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a 'worst case' reduction factor of 1% for gloves/coverall |
|                    | Body                 | 0.0162                               | 0.0427                   | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a 'worst case' reduction factor of 1% for gloves/coverall |
|                    | Inhalation           | 0.0208                               | 0.0784                   | PHED               |   |
|                    | Protective Equipment | Choose item                          |                          | Penetration factor |   |
|                    | Gloves               | None                                 |                          |                    | Protection for granules exposure is based on measured values  |
|                    | Body PPE             | Certified protective coverall        |                          |                    |   |
|                    | RPE                  | None                                 |                          | 1                  |   |
|                    |                      |                                      |                          |                    |   |

  

| Application | Exposure values      | mg exposure/kg a.s. applied   |                          | Reference          | Comment   |
|-------------|----------------------|-------------------------------|--------------------------|--------------------|---|
|             |                      | 75 <sup>th</sup> centile      | 95 <sup>th</sup> centile |                    |   |
|             | Hands                | 0.0004                        | 0.0013                   | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a 'worst case' reduction factor of 1% for gloves/coverall |
|             | Body                 | 0.0047                        | 0.0151                   | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a 'worst case' reduction factor of 1% for gloves/coverall |
|             | Inhalation           | 0.0012                        | 0.0045                   | PHED               |   |
|             | Protective Equipment | Choose item                   |                          | Penetration factor |   |
|             | Gloves               | None                          |                          |                    | Protection for granules exposure is based on measured values  |
|             | Body PPE             | Certified protective coverall |                          |                    |   |
|             | RPE                  | None                          |                          | 1                  |   |
|             |                      |                               |                          |                    |   |

**1. Total**

|  | Without RPE/PPE | With RPE/PPE |  |
|--|-----------------|--------------|--|
| Longer term  |                 |              |  |
| Total systemic exposure from mixing, loading and application (mg a.s./day)                     | 0.9997666       | 0.1707942    |  |
| Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day) | 0.0166628       | 0.0028466    |  |
| % of RVNAS   | 4.17%           | 0.71%        |  |
| Acute  |                 |              |  |
| Total systemic exposure from mixing, loading and application (mg a.s./day)                     | 2.9691607       | 0.6802422    |  |
| Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day) | 0.0494860       | 0.0113374    |  |
| % of RVAAS   | #DIV/0!         | #DIV/0!      |  |



## 2. Longer term exposure

## 2.1 Mixing and loading

|                                  | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                  |
|----------------------------------|----------------------------------|---------------------------------------|--|
| Without                          |                                  |                                       |  |
| Hands                            | 0.0581075                        | 0.0009685                             | $D14*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Body                             | 0.6495738                        | 0.0108262                             | $D15*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Inhalation                       | 0.0832407                        | 0.0013873                             | $D16*i\_AmoutAS*i\_AbsorpInhalation$     |
| Sum                              | 0.7909220                        | 0.0131820                             |  |
| With RPE/PPE (as selected above) |                                  |                                       |  |
| Hands                            | 0.0581075                        | 0.0009685                             | $D14*i\_AmoutAS*i\_AbsorpProduct$        |
| Body                             | 0.0064957                        | 0.0001083                             | $D15*i\_AmoutAS*i\_AbsorpProduct$        |
| Inhalation                       | 0.0832407                        | 0.0013873                             | $D16*i\_AmoutAS*i\_AbsorpInhalation*F20$ |
| Sum                              | 0.1478440                        | 0.0024641                             |  |

## 2.2

## Application

|                                  | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                  |
|----------------------------------|----------------------------------|---------------------------------------|--|
| Without RPE/PPE                  |                                  |                                       |  |
| Hands                            | 0.0163303                        | 0.0002722                             | $D25*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Body                             | 0.1877721                        | 0.0031295                             | $D26*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Inhalation                       | 0.0047422                        | 0.0000790                             | $D27*i\_AmoutAS*i\_AbsorpInhalation$     |
| Sum                              | 0.2088446                        | 0.0034807                             |  |
| With RPE/PPE (as selected above) |                                  |                                       |  |
| Hands                            | 0.0163303                        | 0.0002722                             | $D25*i\_AmoutAS*i\_AbsorpInuse$          |
| Body                             | 0.0018777                        | 0.0000313                             | $D26*i\_AmoutAS*i\_AbsorpInuse$          |
| Inhalation                       | 0.0047422                        | 0.0000790                             | $D27*i\_AmoutAS*i\_AbsorpInhalation*F31$ |
| Sum                              | 0.0229502                        | 0.0003825                             |  |

## 3. Acute exposure

## 3.1 Mixing and loading

|                                  | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                  |
|----------------------------------|----------------------------------|---------------------------------------|--|
| Without                          |                                  |                                       |  |
| Hands                            | 0.2753496                        | 0.0045892                             | $E14*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Body                             | 1.7061779                        | 0.0284363                             | $E15*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Inhalation                       | 0.3137257                        | 0.0052288                             | $E16*i\_AmoutAS*i\_AbsorpInhalation$     |
| Sum                              | 2.2952532                        | 0.0382542                             |  |
| With RPE/PPE (as selected above) |                                  |                                       |  |
| Hands                            | 0.2753496                        | 0.0045892                             | $E14*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Body                             | 0.0170618                        | 0.0002844                             | $E15*100*i\_AmoutAS*i\_AbsorpProduct$    |
| Inhalation                       | 0.3137257                        | 0.0052288                             | $E16*i\_AmoutAS*i\_AbsorpInhalation*F20$ |
| Sum                              | 0.6061371                        | 0.0101023                             |  |

## 3.2

## Application

|                                  | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                  |
|----------------------------------|----------------------------------|---------------------------------------|--|
| Without RPE/PPE                  |                                  |                                       |  |
| Hands                            | 0.0500152                        | 0.0008336                             | $E25*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Body                             | 0.6058611                        | 0.0100977                             | $E25*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Inhalation                       | 0.0180312                        | 0.0003005                             | $E26*i\_AmoutAS*i\_AbsorpInhalation$     |
| Sum                              | 0.6739075                        | 0.0112318                             |  |
| With RPE/PPE (as selected above) |                                  |                                       |  |
| Hands                            | 0.0500152                        | 0.0008336                             | $E25*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Body                             | 0.0060586                        | 0.0001010                             | $E26*100*i\_AmoutAS*i\_AbsorpInuse$      |
| Inhalation                       | 0.0180312                        | 0.0003005                             | $E27*i\_AmoutAS*i\_AbsorpInhalation*F31$ |
| Sum                              | 0.0741051                        | 0.0012351                             |  |

### Estimate 2: EFSA Calculator estimate of operator exposure for application of ‘Final Bite’ via manual application, no PPE

#### Operator exposure for granular applications

|                                      |                                |                 |
|--------------------------------------|--------------------------------|-----------------|
| Application rate of active substance | 0.08 kg a.s./ha                | i_AppRate       |
| Assumed area treated                 | 1 ha/day                       | d_AreaTreated   |
| Amount of active substance applied   | 0.08 kg a.s./day               | i_AmountAS      |
| Dermal absorption of the product     | 10.00%                         | i_AbsorpProduct |
| Dermal absorption of in-use dilution | 10.00%                         | i_AbsorInuse    |
| Formulation type                     | Granules, fine granules        |                 |
| Indoor or Outdoor application        | Outdoor                        |                 |
| Application method                   | Manual application of granules |                 |
| Application equipment                | Manual                         |                 |

  

| Mixing and loading | Exposure values      | mg exposure/kg a.s. mixed and loaded |                          | Reference          | Comment   |
|--------------------|----------------------|--------------------------------------|--------------------------|--------------------|---|
|                    |                      | 75 <sup>th</sup> centile             | 95 <sup>th</sup> centile |                    |   |
|                    | Hands                | 0.0000                               | 0.0000                   | PHED               | Value for application is for combination of mixing&loading and application  |
|                    | Body                 | 0.0000                               | 0.0000                   | PHED               | Value for application is for combination of mixing&loading and application  |
|                    | Inhalation           | 0.0000                               | 0.0000                   | PHED               | Value for application is for combination of mixing&loading and application  |
|                    | Protective Equipment | Choose item                          |                          | Penetration factor |   |
|                    | Gloves               | None                                 |                          |                    | Protection for granules exposure is based on measured values  |
|                    | Body PPE             | Certified protective coverall        |                          |                    |   |
|                    | RPE                  | None                                 |                          | 1                  |   |
| Application        | Exposure values      | mg exposure/kg a.s. applied          |                          | Reference          | Comment   |
|                    |                      | 75 <sup>th</sup> centile             | 95 <sup>th</sup> centile |                    |   |
|                    | Hands                | 28.5320                              | 94.3636                  | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a ‘worst case’ reduction factor of 1% for gloves/coverall |
|                    | Body                 | 68.8708                              | 253.4433                 | PHED               | Exposure value originally included use of PPE, calculated potential exposure is 100 times higher assuming a ‘worst case’ reduction factor of 1% for gloves/coverall |
|                    | Inhalation           | 0.4677                               | 1.5251                   | PHED               |   |
|                    | Protective Equipment | Choose item                          |                          | Penetration factor |   |
|                    | Gloves               | None                                 |                          |                    | Protection for granules exposure is based on measured values  |
|                    | Body PPE             | Certified protective coverall        |                          |                    |   |
|                    | RPE                  | None                                 |                          | 1                  |   |

#### 1. Total

|  | Without RPE/PPE | With RPE/PPE |  |
|--|-----------------|--------------|--|
| Longer term  |                 |              |  |
| Total systemic exposure from mixing, loading and application (mg a.s./day)                     | 77.9596281      | 23.4139916   |  |
| Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day) | 1.2993271       | 0.3902332    |  |
| % of RVNAS   | 324.83%         | 97.56%       |  |
| Acute  |                 |              |  |
| Total systemic exposure from mixing, loading and application (mg a.s./day)                     | 278.3675653     | 77.6404394   |  |
| Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day) | 4.6394594       | 1.2940073    |  |
| % of RVAAS   | #DIV/0!         | #DIV/0!      |  |

## 2.2

## Application

|   | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                   |
|---|----------------------------------|---------------------------------------|---|
| <b>Without RPE/PPE</b>                  |                                  |                                       |   |
| Hands                                   | 22.8256069                       | 0.3804268                             | $D25*100*i\_AmountAS*i\_Absorplnuse$      |
| Body                                    | 55.0966025                       | 0.9182767                             | $D26*100*i\_AmountAS*i\_Absorplnuse$      |
| Inhalation                              | 0.0374186                        | 0.0006236                             | $D27*i\_AmountAS*i\_Absorplnhalation$     |
| Sum                                     | 77.9596281                       | 1.2993271                             |   |
| <b>With RPE/PPE (as selected above)</b> |                                  |                                       |   |
| Hands                                   | 22.8256069                       | 0.3804268                             | $D25*i\_AmountAS*i\_Absorplnuse$          |
| Body                                    | 0.5509660                        | 0.0091828                             | $D26*i\_AmountAS*i\_Absorplnuse$          |
| Inhalation                              | 0.0374186                        | 0.0006236                             | $D27*i\_AmountAS*i\_Absorplnhalation*F31$ |
| Sum                                     | 23.4139916                       | 0.3902332                             |   |

## 3. Acute exposure

## 3.1 Mixing and loading

|   | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                   |
|---|----------------------------------|---------------------------------------|---|
| <b>Without</b>                          |                                  |                                       |   |
| Hands                                   | 0.0000000                        | 0.0000000                             | $E14*100*i\_AmountAS*i\_Absorplnuse$      |
| Body                                    | 0.0000000                        | 0.0000000                             | $E15*100*i\_AmountAS*i\_Absorplnuse$      |
| Inhalation                              | 0.0000000                        | 0.0000000                             | $E16*i\_AmountAS*i\_Absorplnhalation$     |
| Sum                                     | 0.0000000                        | 0.0000000                             |   |
| <b>With RPE/PPE (as selected above)</b> |                                  |                                       |   |
| Hands                                   | 0.0000000                        | 0.0000000                             | $E14*100*i\_AmountAS*i\_Absorplnuse$      |
| Body                                    | 0.0000000                        | 0.0000000                             | $E15*100*i\_AmountAS*i\_Absorplnuse$      |
| Inhalation                              | 0.0000000                        | 0.0000000                             | $E16*i\_AmountAS*i\_Absorplnhalation*F20$ |
| Sum                                     | 0.0000000                        | 0.0000000                             |   |

## 3.2

## Application

|   | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula                                   |
|---|----------------------------------|---------------------------------------|---|
| <b>Without RPE/PPE</b>                  |                                  |                                       |   |
| Hands                                   | 75.4908877                       | 1.2581815                             | $E25*100*i\_AmountAS*i\_Absorplnuse$      |
| Body                                    | 202.7546727                      | 3.3792445                             | $E25*100*i\_AmountAS*i\_Absorplnuse$      |
| Inhalation                              | 0.1220050                        | 0.0020334                             | $E26*i\_AmountAS*i\_Absorplnhalation$     |
| Sum                                     | 278.3675653                      | 4.6394594                             |   |
| <b>With RPE/PPE (as selected above)</b> |                                  |                                       |   |
| Hands                                   | 75.4908877                       | 1.2581815                             | $E25*100*i\_AmountAS*i\_Absorplnuse$      |
| Body                                    | 2.0275467                        | 0.0337924                             | $E26*100*i\_AmountAS*i\_Absorplnuse$      |
| Inhalation                              | 0.1220050                        | 0.0020334                             | $E27*i\_AmountAS*i\_Absorplnhalation*F31$ |
| Sum                                     | 77.6404394                       | 1.2940073                             |   |

## Estimate 3: EFSA Calculator estimate of resident exposure (longer term)

|   |  |                          |                                    |  |
|---|--|--------------------------|------------------------------------|--|
| Croptype  | Bare soil  |                          |                                    |  |
| Application method  | Broadcast application of granules  |                          |                                    |  |
| Application equipment   | Vehicle-mounted  |                          |                                    | <i>i_AppEquip</i>                          |
| Formulation type  | Granules, fine granules  |                          |                                    | <i>i_FormVal</i>                           |
| Buffer strip  | 2-3 m  |                          |                                    | <i>i_Buffer</i>                            |
| Application rate of the product   | 0.08 kg a.s./ha  |                          |                                    | <i>i_AppRate</i>                           |
| Concentration of active substance (in-use dilution for liquid applications) | #DIV/0! kg a.s./kg   |                          |                                    | <i>d_ConcAS</i>                            |
| Dermal absorption of product  | 10.00%   |                          |                                    | <i>i_AbsorpProduct</i>                     |
| Dermal absorption of in-use dilution  | 10.00%   |                          |                                    | <i>i_AbsorpInuse</i>                       |
| Oral absorption   | 50.00%   |                          |                                    | <i>i_AbsorpOrallnuse</i>                   |
| Dislodgeable foliar residue ( <i>i_AppRate</i> * <i>i_DFR</i> )             | 0.24 µg a.s./cm <sup>2</sup>   |                          |                                    | <i>d_DFR</i>                               |
| Vapour pressure of in-use dilution  | low volatile substances having a vapour pressure of <5*10 <sup>-3</sup> Pa |                          |                                    | <i>i_Volat</i>                             |
| Concentration in air  | 0.001 mg/m <sup>3</sup>  |                          |                                    | <i>d_AirCon</i>                            |
| Resident dermal spray drift exposure 75th percentile - adult                | NA ml spray dilution/person  |                          |                                    |  |
| Resident dermal spray drift exposure 75th percentile - child                | NA ml spray dilution/person  |                          |                                    |  |
| Resident inhal. spray drift exposure 75th percentile - adult                | NA ml spray dilution/person  |                          |                                    |  |
| Resident inhal. spray drift exposure 75th percentile - child                | NA ml spray dilution/person  |                          |                                    |  |
| Resident dermal spray drift exposure mean - adult                           | NA ml spray dilution/person  |                          |                                    |  |
| Resident dermal spray drift exposure mean - child                           | NA ml spray dilution/person  |                          |                                    |  |
| Resident inhal. spray drift exposure mean - adult                           | NA ml spray dilution/person  |                          |                                    |  |
| Resident inhal. spray drift exposure mean - child                           | NA ml spray dilution/person  |                          |                                    |  |
| Exposure duration dermal  | 2 hours  |                          |                                    | <i>d_ReExpDur</i>                          |
| Exposure duration inhalation  | 24 hours   |                          |                                    | <i>d_ReExpDurInhal</i>                     |
| Exposure duration entry into treated crops                                  | 0.25 hours   |                          |                                    | <i>d_ExpDurTreatCrop</i>                   |
| Light clothing adjustment factor  | 18.0%  |                          |                                    | <i>d_ClothAF</i>                           |
| Breathing rate adult  | 0.23 m <sup>3</sup> /day/kg  |                          |                                    | <i>d_BreathRAD</i>                         |
| Breathing rate child (1-3 year old)   | 1.07 m <sup>3</sup> /day/kg  |                          |                                    | <i>d_BreathRCh</i>                         |
| Drift percentage on surface (75th percentile)                               | 3.00%  |                          |                                    |  |
| Drift percentage on surface (mean)  | 3.00%  |                          |                                    |  |
| Turf transferable residues percentage                                       | 1.00%  |                          |                                    | <i>d_Turf</i>                              |
| Transfer coeff. of surface deposits-adult                                   | 7300 cm <sup>2</sup> /hour   |                          |                                    | <i>d_ReTCAd</i>                            |
| Transfer coeff. of surface deposits-child (1-3 year old)                    | 2600 cm <sup>2</sup> /hour   |                          |                                    | <i>d_ReTCh</i>                             |
| Saliva extraction percentage  | 50.00%   |                          |                                    | <i>d_SalExt</i>                            |
| Surface area of hands mouthed   | 20 cm <sup>2</sup>   |                          |                                    | <i>d_AreaHM</i>                            |
| Frequency of hand to mouth activity   | 9.5 events/hour  |                          |                                    | <i>d_ReFreqHM</i>                          |
| Ingestion rate for mouthing of grass per day                                | 25 cm <sup>2</sup>   |                          |                                    | <i>d_MouthGrass</i>                        |
| Dislodgeable residues percentage transferability for object to mouth        | 20.00%   |                          |                                    | <i>d_DRP</i>                               |
| Transfer coefficient for entry into treated crops (75th percentile) - ad    | 7500 cm <sup>2</sup> /h  |                          |                                    | <i>d_TcEntryAd</i>                         |
| Transfer coefficient for entry into treated crops (75th percentile) - chi   | 2250 cm <sup>2</sup> /h  |                          |                                    | <i>d_TcEntryCh</i>                         |
| Transfer coefficient for entry into treated crops (mean) - adult            | 5980 cm <sup>2</sup> /h  |                          |                                    | <i>d_TcEntryAd</i>                         |
| Transfer coefficient for entry into treated crops (mean) - child            | 1794 cm <sup>2</sup> /h  |                          |                                    | <i>d_TcEntryCh</i>                         |
| <b>1. Total</b>   |  |                          |                                    |  |
| <b>1.1 1-3 year old child</b>   |  |                          |                                    |  |
|   | Spray drift (75th percentile)  | Vapour (75th percentile) | Surface deposits (75th percentile) | Entry into treated crops (75th percentile) |
| Total systemic exposure (mg a.s./day)                                       | NA   | 0.0107000                | 0.0012349                          | NA   |
| Total systemic exposure per kg body weight (mg a.s./day/kg)                 | NA   | 0.0010700                | 0.0001235                          | NA   |
| % of RVNAS  |  | 0.27%                    | 0.03%                              |  |
| <b>1.2 Adult</b>  |  |                          |                                    |  |
|   | Spray drift  | Vapour                   | Surface deposits                   | Entry into treated crops                   |
| Total systemic exposure (mg a.s./day)                                       | NA   | 0.0138000                | 0.0020843                          | NA   |
| Total systemic exposure per kg body weight (mg a.s./day/kg)                 | NA   | 0.0002300                | 0.0000347                          | NA   |
| % of RVNAS  |  | 0.06%                    | 0.01%                              |  |

| 2. Resident exposure 75th Percentile |                                  |                                       |   |   |
|--------------------------------------|----------------------------------|---------------------------------------|---|---|
|                                      | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula   | Comments  |
| 1-3 year old child                   |                                  |                                       |   |   |
| Spray drift                          |                                  |                                       | $((C16^*i\_Absorplnuse*(1-d\_ClothAF))+C18)*d\_ConcAS$  | NA for application of granules  |
| Vapour                               | 0.0107000                        | 0.0010700                             | $d\_AirCon*d\_BreathRCh*d\_BwChild$   |   |
| Surface deposits                     |                                  |                                       |   |   |
| Dermal                               | 0.0007424                        | 0.0000742                             | $((i\_AppRate/100)*C29*d\_Turf*d\_ReTCCh*d\_ReExpDur*MAX((i\_AbsorpProduct\_i\_Absorplnuse)*d\_MAF*IF(i\_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)))$ |   |
| Hand to mouth                        | 0.0001356                        | 0.0000136                             | $((i\_AppRate/100)*C29*d\_Turf*d\_SalExt*d\_AreaHM*d\_ReFreqHM*d\_ReExpDur*i\_AbsorpOrallnuse*d\_MAF$   |   |
| Object to mouth                      | 0.0003569                        | 0.0000357                             | $((i\_AppRate/100)*C29*d\_DRP*d\_MouthGrass*i\_AbsorpOrallnuse*d\_MAF$  |   |
| Entry into treated crops             |                                  |                                       |   |   |
| Dermal                               |                                  |                                       |   | NA for application of granules since calculation is same as for worker exposure and have no worker exposure for application of granules |
| Hand to mouth                        |                                  |                                       | $((i\_AppRate/100)*d\_Turf*d\_MAF*d\_SalExt*d\_AreaHM*d\_ReFreqHM*d\_ReExpDur*i\_AbsorpOrallnuse$   | Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.                  |
| Object to mouth                      |                                  |                                       | $((i\_AppRate/100)*d\_DRP*d\_MouthGrass*i\_AbsorpOrallnuse*d\_MAF$  | Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.                  |
| Adult                                |                                  |                                       |   |   |
| Spray drift                          |                                  |                                       | $(C15^*i\_Absorplnuse*(1-d\_ClothAF))+C17)*d\_ConcAS$   | NA for application of granules  |
| Vapour                               | 0.0138000                        | 0.0002300                             | $d\_AirCon*d\_BreathRAD*d\_BwAdult$   |   |
| Surface deposits (dermal)            | 0.0020843                        | 0.0000347                             | $((i\_AppRate/100)*C30*d\_Turf*d\_ReTCAd*d\_ReExpDur*i\_AbsorpProduct*d\_MAF$   |   |
| Entry into treated crops (dermal)    |                                  |                                       |   | NA for application of granules since calculation is same as for worker exposure and have no worker exposure for application of granules |
| 3. Summing of exposure pathways mean |                                  |                                       |   |   |
|                                      | Systemic exposure [mg a.s. /day] | Systemic exposure [mg a.s./kg bw/day] | Formula   | Comments  |
| 1-3 year old child                   |                                  |                                       |   |   |
| Spray drift                          |                                  |                                       | $((C20^*i\_Absorplnuse*(1-d\_ClothAF))+C22)*d\_ConcAS$  | NA for application of granules  |
| Vapour                               | 0.0107000                        | 0.0010700                             | $d\_AirCon*d\_BreathRCh*d\_BwChild$   |   |
| Surface deposits                     |                                  |                                       |   |   |
| Dermal                               | 0.0007424                        | 0.0000742                             | $((i\_AppRate/100)*C30*d\_Turf*d\_ReTCCh*d\_ReExpDur*MAX((i\_AbsorpProduct\_i\_Absorplnuse)*d\_MAF*IF(i\_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)))$ |   |
| Hand to mouth                        | 0.0001356                        | 0.0000136                             | $((i\_AppRate/100)*C30*d\_Turf*d\_SalExt*d\_AreaHM*d\_ReFreqHM*d\_ReExpDur*i\_AbsorpOrallnuse*d\_MAF$   |   |
| Object to mouth                      | 0.0003569                        | 0.0000357                             | $((i\_AppRate/100)*C30*d\_DRP*d\_MouthGrass*i\_AbsorpOrallnuse*d\_MAF$  |   |
| Entry into treated crops             |                                  |                                       |   |   |
| Dermal                               |                                  |                                       |   | NA for application of granules since calculation is same as for worker exposure and have no worker exposure for application of granules |
| Hand to mouth                        |                                  |                                       | $((i\_AppRate/100)*i\_d\_Turf*d\_MAF*d\_SalExt*d\_AreaHM*d\_ReFreqHM*d\_ReExpDur*i\_AbsorpOrallnuse$  | Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.                  |
| Object to mouth                      |                                  |                                       | $((i\_AppRate/100)*i\_d\_DRP*d\_MouthGrass*i\_AbsorpOrallnuse*d\_MAF$   | Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.                  |
| Adult                                |                                  |                                       |   |   |
| Spray drift                          |                                  |                                       | $((C19^*i\_Absorplnuse*(1-d\_ClothAF))+C21)*d\_ConcAS$  | NA for application of granules  |
| Vapour                               | 0.0138000                        | 0.0002300                             | $d\_AirCon*d\_BreathRAD*d\_BwAdult$   |   |
| Surface deposits (dermal)            | 0.0020843                        | 0.0000347                             | $((i\_AppRate/100)*C30*d\_Turf*d\_ReTCAd*d\_ReExpDur*MAX((i\_AbsorpProduct\_i\_Absorplnuse)*d\_MAF*IF(i\_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)))$ |   |
| Entry into treated crops (dermal)    |                                  |                                       |   | NA for application of granules since calculation is same as for worker exposure and have no worker exposure for application of granules |