B.7.1 Metabolism, Distribution, and Expression of Residues in Plants

(Annex IIA 6.2; Annex IIIA, 8.2)

This dossier is submitted in support of uses of [active ingredient] on [target crops]. To cover the categories of [crop types; i.e., fruiting vegetables, leafy vegetables, root vegetable, etc.], studies on the metabolism of [active ingredient] have been performed in [crops].

### B.7.1.1 [Crop 1]

**Document ID:** MRID No.

PMRA No.

**Report:** Report Citation

**Guidelines:** EPA OCSPP Harmonized Test Guideline 860.1300 Nature of the Residue - Plants, Livestock (August 1996)  
PMRA Regulatory Directive Dir98-02 – Residue Chemistry Guidelines, Section 2 -Nature of the Residue - Plants, Livestock  
OECD Guideline 501 Metabolism in Crops (January 2007)

**GLP Compliance:** [No or Significant] deviations from regulatory requirements were reported which would have an impact on the validity of the study. [If “Significant,” then explain below the deficiencies and their impact on the acceptability of the study]

**Acceptability:** The study [is/is not] considered scientifically acceptable. [If not acceptable, then explain why below]

**Evaluator:** [Name of regulatory person who reviewed the study]

**EXECUTIVE SUMMARY**

The metabolism of [active ingredient] was investigated in [crop] following applications (specify type of application) with [14C specify radiolabel]-[active ingredient] (specific activity: xx Bq/mg) formulated as [specify formulation] at a maximum seasonal application rate of [xx lb ai/A (yy g ai/ha)]. Applications were performed at [growth stages]. Include details of testing environment (i.e., outdoor test plots, greenhouse, etc.). [Crop matrices] were harvested with a preharvest interval (PHI) of [xx] days.

[Briefly summarize extraction procedures and analytical methods used to identify metabolites.]

[Crop] samples were stored frozen for a maximum of [xx] days/months between collection and analysis. Storage stability of [active ingredient] was demonstrated in [crop] for up to [xx] days/months in the study. [The metabolite profiles in the chromatograms obtained from the first and second HPLC analysis were similar for [crop matrix] samples, thus demonstrating the stability of the analytes of interest in [crop] commodities for up to zz months of frozen storage. or Given that samples were stored frozen for less than 6 months, storage stability data are not required.]

[Briefly summarize radioactivity in plant parts (absorption/distribution/disposition), extractability, and recoveries/accountabilities.]

[Indicate whether the parent or metabolite(s) was (were) found to be the predominant residue(s) (include ppm equivalents and corresponding % TRR/crop matrix). Indicate whether any other metabolites were identified and if any were present at concentrations >0.1 ppm and/or >10% TRR.]

[Summarize the metabolic pathway.]

The metabolic pathway of [active ingredient] in [crop] involves/proceeds via…

[Include this section only if the "GLP Compliance" prompt above is answered "Significant deviations from regulatory requirements were reported."]

**COMPLIANCE**

The following deviations from GLP requirements were reported: [list].

[Include this section only if the "Acceptability" prompt above is answered "The study is not considered scientifically acceptable."]

**STUDY DEFICIENCIES**

Under the conditions and parameters used in the study, the data are classified as scientifically unacceptable. [Explain the deficiencies and their impact on the acceptability of the study.] The study [can or cannot] be upgraded by submission of additional information; if “can be,” then list the additional data required.

**I. Materials and Methods**

**A. Materials**

**1. Test Material**

|  |  |
| --- | --- |
| **Table B.7.1.1-1. [Active Ingredient] Nomenclature.** | |
| **Common name** |  |
| **Identity** | [CAS Chemical Name] |
| **CAS no.** |  |
| **Company experimental name** |  |
| **Other synonyms (if applicable)** |  |
| **Lot/Batch #** |  |
| **Radiochemical purity** | a-label: xx% |
| b-label: xx% |
| **Specific activity as received** | a-label: xx mCi/mmol (xx mCi/mg) |
| b-label: xx mCi/mmol (xx mCi/mg) |
| **Specific activity of the formulated test substance** | a-label: xx mCi/mmol (xx mCi/mg) |
| b-label: xx mCi/mmol (xx mCi/mg) |
| **Position of radiolabels**  [Insert structures] | |

**2. Test Crop**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table B.7.1.1-2. Crop Information.** | | | | |
| Crop/Crop Group | Variety | Growth Stage at Application | Growth Stage at Harvest | Harvested  Commodities |
|  |  |  |  |  |
|  |  |  |  |  |

**3. Soil Type**

[List soil type and discuss physicochemical properties in Table B.7.1.1-3 if relevant to metabolism in the crop (primarily for soil-applied test substance.)]

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table B.7.1.1-3. Soil Physicochemical Properties.** | | | | | | | |
| Soil Type | pH | OM % | Sand % | Silt % | Clay % | Moisture Holding Capacity (at 1/3 bar) | CEC  (meg/100 g) |
|  |  |  |  |  |  |  |  |

OM = organic matter, CEC = cation-exchange capacity.

**B. STUDY DESIGN**

**Experimental Conditions**

[Briefly describe how the plants were grown (i.e., outdoor, greenhouse, etc.).]

|  |  |
| --- | --- |
| **Table B.7.1.1-4. Use Pattern Information.** | |
| Chemical name |  |
| Application method |  |
| Application rate |  |
| Number of applications |  |
| Timing of applications |  |
| PHI |  |

**Sampling**

[Briefly describe how samples were taken, parts sampled, how samples were handled after harvesting (shipment, storage, etc.), and any preparation that was done prior to extraction.]

**Extraction and Analysis**

[If available, then include a flowchart of the extraction and fractionation schemes.]

[Briefly describe the extraction, fractionation and hydrolysis strategies for each tissue including solvents used (ratios), the order of their use, the extraction procedures employed (i.e., blending, maceration, Soxhlet, etc.) and other extraction techniques.]

[Briefly describe procedures used to release bound and conjugated residues (i.e., acid, base, or enzyme hydrolysis, exhaustive extraction, etc.). Has the petitioner justified the use of severe conditions (e.g., strong acid hydrolysis in the presence of heat, etc.).]

**Identification and Characterization**

[Briefly describe the methods used for identification/characterization of the residues (LSC, TLC, GLC, HPLC, etc.). If applicable, then very briefly describe difficulties with methods that fail to elucidate the nature of the residues or bound residues as in lignin, cellulose, protein solubilization methodologies.]

**II. RESULTS AND DISCUSSION**

**A. Total Radioactive Residues**

**Quantitation**

[Briefly describe methods for determining TRR values.]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table B.7.1.1-5. TRR in [Crop Matrices].** | | | | |
| Matrix | A-label | | B-label | |
| %TRR | ppm | %TRR | ppm |
|  |  |  |  |  |
|  |  |  |  |  |

**B. Extraction, Characterization, and Distribution of Residues**

**Extraction and characterization of residues in [crop]**

**A label:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table B.7.1.1-6. Distribution of the Parent and the Metabolites in Plant Matrices Following Application of [A label] Radiolabeled [Active Ingredient] at [Rate].** [Note: Add rows to the table as needed to accommodate the fractionation/characterization scheme. Create additional Tables B.7.1.1-x as needed to accommodate additional radiolabel positions. Alternatively, if only 1 or 2 matrices are included in study, then the columns of this table could be modified to accommodate the additional radiolabel positions.] | | | | | | |
| Metabolite Fraction | Matrix 1 | | Matrix 2 | | Matrix 3 | |
| (TRR = xx ppm) | | (TRR = xx ppm) | | (TRR = xx ppm) | |
| %TRR | ppm | %TRR | ppm | %TRR | ppm |
| Surface wash |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Organosoluble |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Aqueous soluble |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Etc. (e.g. PES) |  |  |  |  |  |  |

**B label:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table B.7.1.1-7. Distribution of the Parent and the Metabolites in Plant Matrices Following Application of [B label] Radiolabeled [Active Ingredient] at [Rate].** [Note: Add rows to the table as needed to accommodate the fractionation/characterization scheme. Create additional Tables B.7.1.1-x as needed to accommodate additional radiolabel positions. Alternatively, if only 1 or 2 matrices are included in study, then the columns of this table could be modified to accommodate the additional radiolabel positions.] | | | | | | |
| Metabolite Fraction | Matrix 1 | | Matrix 2 | | Matrix 3 | |
| (TRR = xx ppm) | | (TRR = xx ppm) | | (TRR = xx ppm) | |
| %TRR | ppm | %TRR | ppm | %TRR | ppm |
| Surface wash |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Organosoluble |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Aqueous soluble |  |  |  |  |  |  |
| [Add a row for each identified compound] |  |  |  |  |  |  |
| [Unidentified compound] |  |  |  |  |  |  |
| Etc. (e.g. PES) |  |  |  |  |  |  |

**C. Storage Stability of Residues**

[Discuss whether the petitioner demonstrated that residues are stable during storage.]

|  |  |  |  |
| --- | --- | --- | --- |
| **Table B.7.1.1-8. Summary of Storage Conditions.** | | | |
| Matrix  (RAC or Extract) | Storage Temperature  (°C) | Actual Study Duration (days or months) | Interval of Demonstrated Storage Stability  [specify crop/matrix if different]  (days/months) |
|  |  |  |  |
|  |  |  |  |

**D. Identity of Residues in [Crop]**

**A label:**

[Briefly summarize the metabolites found in each matrix.]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table B.7.1.1-9. Summary of Characterization and Identification of Radioactive Residues in Plant Matrices Following Application of [A label] Radiolabeled [Active ingredient] at [Rate].** [Note: Create additional Tables B.7.1.1-x as needed to accommodate additional radiolabel positions. Alternatively, if only 1 or 2 matrices are included in study, then the columns of this table could be modified to accommodate the additional radiolabel positions.] | | | | | | |
| Compound | Matrix 1 | | Matrix 2 | | Matrix 3 | |
| % TRR | ppm | % TRR | ppm | % TRR | ppm |
| [Parent] |  |  |  |  |  |  |
| [Metabolite 1] |  |  |  |  |  |  |
| [Metabolite 2] |  |  |  |  |  |  |
| [Metabolite 3] |  |  |  |  |  |  |
| [Metabolite 4] |  |  |  |  |  |  |
| Total extractable  (Aqueous + organic) |  |  |  |  |  |  |
| Total identified |  |  |  |  |  |  |
| Total unidentified |  |  |  |  |  |  |
| Total bound residues (PES) |  |  |  |  |  |  |
| % Accountability  Total (ppm)/TRR (ppm) \* 100 |  |  |  |  |  |  |

PES = post-extraction solids.

**B label:**

[Briefly summarize the metabolites found in each matrix. Are there any major differences between labels?]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table B.7.1.1-10. Summary of Characterization and Identification of Radioactive Residues in Plant Matrices Following Application of [B label] Radiolabeled [Active ingredient] at [Rate].** [Note: Create additional Tables B.7.1.1-x as needed to accommodate additional radiolabel positions. Alternatively, if only 1 or 2 matrices are included in study, then the columns of this table could be modified to accommodate the additional radiolabel positions.] | | | | | | |
| Compound | Matrix 1 | | Matrix 2 | | Matrix 3 | |
| % TRR | ppm | % TRR | ppm | % TRR | ppm |
| [Parent] |  |  |  |  |  |  |
| [Metabolite 1] |  |  |  |  |  |  |
| [Metabolite 2] |  |  |  |  |  |  |
| [Metabolite 3] |  |  |  |  |  |  |
| [Metabolite 4] |  |  |  |  |  |  |
| Total extractable  (Aqueous + organic) |  |  |  |  |  |  |
| Total identified |  |  |  |  |  |  |
| Total unidentified |  |  |  |  |  |  |
| Total bound residues (PES) |  |  |  |  |  |  |
| % Accountability  Total (ppm)/TRR (ppm) \* 100 |  |  |  |  |  |  |

PES = post-extraction solids.

**E. Proposed Metabolic Pathway**

[Briefly describe the metabolic pathway and reactions (i.e., oxidation, hydrolysis, etc.).]

**Figure B.7.1.1. Proposed Metabolic Profile of [Active ingredient] in [Crop].**

[Insert metabolic profile]

|  |  |  |
| --- | --- | --- |
| **Table B.7.1.1-11. Identification of Compounds from Metabolism Study (both proposed and found).** | | |
| Common Name/Code  [Figure B.7.1.1 ID No.] | Chemical Name | Chemical Structure |
|  |  |  |
|  |  |  |
|  |  |  |

**III. CONCLUSIONS**

The [crop] metabolism study is considered scientifically [acceptable or unacceptable]. [Briefly, summarize the results of the submitted plant metabolism studies such as: routes or pathways, mechanisms involved and extent/degree of metabolism observed, nature, amount, and distribution of TRR in the plant tissues. Conclusion should be very high level.]

**REFERENCES**

[Cite references for other metabolism studies (if applicable). Include the EPA MRID# and PMRA# of both the study and the review (if available).]

### B.7.1.2 [Crop 2]

**Document ID:** MRID No.

PMRA No.

**Report:** Report Citation

**Guidelines:** EPA OCSPP Harmonized Test Guideline 860.1300 Nature of the Residue – Plants, Livestock (August 1996)  
PMRA Regulatory Directive Dir98-02 – Residue Chemistry Guidelines, Section 2 -Nature of the Residue - Plants, Livestock  
OECD Guideline 501 Metabolism in Crops (January 2007)

**GLP Compliance:** [No or Significant] deviations from regulatory requirements were reported which would have an impact on the validity of the study. [If “Significant,” then explain below the deficiencies and their impact on the acceptability of the study]

**Acceptability:** The study [is/is not] considered scientifically acceptable. [If not acceptable, then explain why below]

**Evaluator:** [Name of regulatory person who reviewed the study]

**[Repeat previous sections, modify as appropriate.]**

Template Version – February 2016