DER Composers for Registrant e-Submission of Study Data Summaries

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Vision for PRIA process improvement

- DER Composers have been developed for systematic capture of rat pharmacokinetic and metabolism study data
- Using the same approach, EPA would develop DER Composers to facilitate electronic capture of registrant-submitted toxicity data
- Upon pesticide registration, data would be made available through public databases
Developing DER Composers

Objective:
- improve efficiency in data summary and submission
- maximize electronic data transfer to minimize data errors
- facilitate QA of data
- autopopulate Agency knowledge-bases to improve PRIA workflow;
  - getting data in the hands of the risk assessor more efficiently
  - spend less time compiling data and more time assessing
DER Composers

• Use DER Composers for livestock or rat metabolism data submission as recommended by OECD Working Group on Pesticides, MetaPath Users Group working with OECD Secretariat

• Use DER Composers for EDSP T1S data submission
Computational Tools
for Metabolism Research and Risk Assessment

MetaPath
a metabolism pathways database and data evaluation tools

DER Composer
a software template for efficient data entry to facilitate:
- creation of draft Data Evaluation Records (DER) for risk assessor evaluations of OPP metabolism studies
- auto-population of submitted data into MetaPath
Assessment Team (Lead Toxicologist and Risk Assessors) review the Toxicology Profile using summary information in draft DER and refer to Study File as appropriate.

Proposed MetaPath/DER Composer use in OPP workflow:

- Residues Of Concern Knowledgebase Subcommittee (ROCKS) Registrant produces draft DER (doc file) and XML for a ‘new’ chemical using DER Composer (rat metabolism, livestock residues, plant residues, environmental degradates).

- ‘new’ chemical xml (after QA) is added to MetaPath database.

- MetaPath tools used to assess common metabolites for Proposed Residue Definitions for inclusion in Risk Assessment and Tolerance Expression recorded in draft DER.

- ROCKS Hazard Assessors pre-meet before full committee meeting to discuss team proposal and consider metabolites of potential hazard concern (using MetaPath and/or other (Q)SAR tools for predictions) summarized in draft DER.

- ROCKS Committee Reviews the team’s proposal and renders an Expert opinion/recommendation(s); draft DER updated and decision finalized and reported in final DER.

- Draft DER
DER Composer

Developed around Pharmacokinetic & Metabolism, and Nature of the Residue harmonized guidelines:

1) OPPTS 870.7485 (85-1) Rat Metabolism
2) OPPTS 860.1300 Nature of Residues in Animals

• Data entered in DER Composers can output as:
  – *.xml file for direct data import into MetaPath
  – *.doc file draft Data Evaluation Record to record OPP decisions

• Efficient standardized data entry

• Facilitates electronic data submission and e-population of new data into MetaPath into the future
OECD/OPP Guideline document used as framework for DER Composer development

870.7485 (85-1) Rat Metabolism & PK

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test compound:
   - Radioactively labeled material: [indicate position of radioactive label, eg. [Phenyl-U-14C] XX]
   - Radiochemical purity:
   - Specific activity:
   - Lot batch #:

2. Vehicle and/or positive control: [when appropriate], Lot/Batch #, Purity

3. Test animals:
   - Species:
   - Strain:
   - Age/weight at study initiation:
   - Source:
   - Housing:
   - Diet:
   - Water:
   - Environmental conditions:
     - Temperature: °C
     - Humidity: %
     - Air changes: /hr
     - Photoperiod: hr dark/hr light
   - Acclimation period:

4. Preparation of dosing solutions:

B. STUDY DESIGN AND METHODS:

1. Group arrangements:
   - Animals were assigned [note how assigned, e.g., random, briefly describe groups as needed] to the test groups noted in Table 1.
TABLE 1: Dosing groups for pharmacokinetic studies for (biological) [dosage form of study drug is RECOMMENDED] *Additional text groups are used e.g. pilot study, dermal exposure, inhalation exposure or binary distribution etc. Include these in the table.

<table>
<thead>
<tr>
<th>Test group</th>
<th>Dose of labeled material (mg/kg)</th>
<th>Number test</th>
<th>Remarks (e.g. time of sacrifice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Dosing and sample collection: (briefly describe dosing methods and sample collection)

a. Pharmacokinetic studies: [give details of experiments including what was sampled (urine, feces, tissue, cage washes, bile, if appropriate) and when and how often.]

b. Metabolite characterization studies: [What was collected for identification, when and from how many animals (samples pooled or not, method type for identification (e.g., GCMS or TLC)].

3. Statistics: [List parameters that were analyzed and the statistical methods used; include a statement that the Reviewer considers the analyses used to be appropriate. If inappropriate, provide alternative rationale.]

II. RESULTS:

A. PHARMACOKINETIC STUDIES:

1. Preliminary experiment: (if applicable) [Briefly describe results]

2. Absorption: [Briefly describe absorption, may include an optional table relating excretion of radioactivity (in urine, feces, etc.) to sampling time]

3. Tissue distribution (include groups that are applicable; describe distribution patterns for each treatment group. Some form of Table 2 is recommended, if data are available.)

TABLE 2: Distribution of radioactivity in rat tissues/organ after administration of C14-labeled Compound XXV

<table>
<thead>
<tr>
<th>Tissue/organ</th>
<th>Oral dose</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ 1</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>Organ 2</td>
<td></td>
<td></td>
<td>Male</td>
</tr>
</tbody>
</table>

* Data obtained from pages (insert page numbers) in the study report.

[Write a brief narrative of the contents of Table 2 under the following 4 headings:]

B. METABOLITE CHARACTERIZATION STUDIES:

[Give the metabolites identified, include percent of radioactive dose given, where they were identified, when if applicable, how they were identified if applicable, how much parent was present in the excreta. Some form of Table 3 is recommended. When available, include summary of metabolic pathways and figures available. Mention which are major vs. minor pathways. Include the regimens postulated pathway as a figure or attachment, preferably electronic.]

TABLE 3: Recovery of radioactivity in tissues and excreta of rats after administration of C14-labeled Compound XXV

<table>
<thead>
<tr>
<th>Percent of radioactive dose recovered</th>
<th>Oral dose</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Expired air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartilage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cage wash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4. Metabolite profile in excreta of rats dosed with C-14 labeled Compound XY-a

<table>
<thead>
<tr>
<th>Compound</th>
<th>Oral dose</th>
<th>Percent of administered dose</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female (If Applicable)</td>
<td>Male (If Applicable)</td>
<td>Male (If Applicable)</td>
</tr>
<tr>
<td>Parent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identified metabolite 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identified metabolite 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total identified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unidentified metabolite X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unidentified metabolite Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unidentified at origin or at some band</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total unidentifed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total accounted for</td>
<td>100</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Lost unaccounted for a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* Data obtained from pages (insert page #) in the study report.
* Total accounted for = (Total identified) + (Total unidentified)
* 100 - (Total accounted for)

II. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

B. REVIEWER COMMENTS:

Give overall summary tying together all the above data, discussing differences from study author's opinion, deficiencies.

C. STUDY DEFICIENCIES:

List each deficiency (distinguishing between major and minor ones) with the data required to resolve the deficiency. If no data can be provided to satisfy the deficiency, indicate impact on regulatory decision.
The 'General Info' screen corresponds to the first page of an OPP rat metabolism Data Evaluation Record (DER).

Important step to set reference in order to generate tables.

Note the OPP and OECD guideline numbers.

DER Composer – Data Entry Screen for ‘General Info’
OECD/OPP Guideline document used as framework for DER Composer development
870.7485 (85-1) Rat Metabolism & PK

DER Template

DER Composer entry screen
DER Composer data entry screen

DER *.doc file

NAME OF TECHNICAL PC Code: Metabolism (oral absorption) / Page 1 of 2
OPPTS 870.7485[85-1], OECD 417

EPA Reviewer: J Jones
Signature
Date 8-14-2007

EPA Secondary Reviewer: R Kolanczyk
Signature
Date 8-14-2007

EPA WAM: PV Shah
Branch Chief
Date 8-14-2007

STUDY TYPE: Metabolism rat; OPPTS 870.7485[85-1], OECD 417
PC CODE: 64001
SUBMISSION NO.: 99999999

TEST MATERIAL: Phenol
IUPAC/SYSTEMATIC NAME: Phenol
SYNONYMS: Hydroxybenzene, phenolic acid, benzene, carbolic acid, phenol

SPONSOR: Acme Industrial, Frankfort Germany
EXECUTIVE SUMMARY:
This is a test. A narrative section should be placed here.

COMPLIANCE: This is a test. A narrative section should be placed here.
**MetaPath – ‘General Info’**

References:

Parent structure:
- PC code: 64001
- CASNo: 000108-95-2
- Chemical name: phenol
- Test compound: phenol
- IUPAC name: phenol
- Batch/Lot: 00002
- Purity: 98.5 - 98.5 %
- Contaminants: none listed
- Description: colorless solid, sweeterry color
### Materials and Methods

**Part A: Materials.**

Chemical structure can be drawn with 2D structure drawing package, or from imported SMILES string. Include radio-label in naming convention.

**Radiolabelled test material:**

- **Phenol ring-U-14C**
  - **Radiolabelled purity:** 95.5%
  - **Specific activity:** 1.00 μCi/mg
  - **Lot/batch #:** 2014

**Non-Radiolabelled test material:**

- **Phenol**
  - **Description:** Colorless solid, sweet tarry color
  - **Lot/batch #:** 00002
  - **Purity:** 98.5%
  - **Contaminants:** None listed
  - **CAS # of TGAI:** 100-96-2

**2. Vehicle and/or positive control**

Phenol ring-U-14C was suspended in 0.5% Tragacanth solution. No positive controls were utilized in any of the experiments.

**3. Test animals**
DER Composer - getting chemical structure input

1) Use Drawing Package (re: 2-D Editor Manual provided)

2) Apply SMILES String (e.g., SMILES file for pesticides)

SMILES = simplified molecular input line entry specification

2-D structure described by ASCII string
**MetaPath - Materials & Methods info for parent chemical**

**Summary**

**References:**

**Parent structure:**
- **PC code:** 64001
- **CasNo:** 000108-95-2
- **Chemical name:** phenol
- **Test compound:** phenol
- **IUPAC name:** phenol
- **Batch/Lot:** 00002
- **Purity:** 99.5 - 99.5%
- **Contaminants:** none listed
- **Description:** colorless solid, sweetery color
Appendix Table 1:
Systematic capture of treatment group parameters for:
- autopopulation of DER Table 1
- Specifies treatments, i.e., M,F; dose level & duration; excretion route, etc., as ‘Highlight Treatment Group’ feature in MetaPath

Appendix Table 2:
- Chemical structures of parents and metabolites entered as SMILES strings;
- Connectivity between parent and each metabolite (i.e., the metabolism pathway) is specified here
MetaPath - Highlight Treatment Group Feature

Chemical structure:

CAS: 000108-95-2, phenol

[Diagram of chemical structure]

Treatment group:
- Rat, male, in vivo, urine, oral, viscer
- Reference:

Subjects:
- Species: Rat
- Gender: Male (5 subjects)
- Weight: Between 200 – 225 grams (male)
- Age: Between 7 – 12 weeks old
- Housing: Water
- Housing: During experimental period, rats were maintained individually in metabolism cages
- Diet: Altromin 1324 or 9439 Long-Life Diet 21 days started at 16 hrs prior to dosing
- Water: 4% water ad libitum

Environment conditions:
- Temperature: Between 18 – 23°C
- Humidity: Between 25 – 70%
- Air changes: 10-15/hr
- Photosynthetic: 12 hrs light/12 hrs dark
- Acclimation period: 2 weeks

In vivo In vitro:
- In vivo
- Exptl. details: Not reported

Sampling / analytical:
- Samples matrix: Urine
- Sample times (fasted): 4, 8, 24, 48 hrs
Appendix Table 1:
Systematic capture of treatment group parameters for:
- autopopulation of DER Table 1
- Specifies treatments, i.e., M,F; dose level & duration; excretion route, etc., as ‘Highlight Treatment Group’ feature in MetaPath

Appendix Table 2:
- Chemical structures of parents and metabolites entered as SMILES strings;
- Connectivity between parent and each metabolite (i.e., the metabolism pathway) is specified here
Tables are built for Pharmacokinetic and Metabolite Characterization data.

Pre-populated with row & column headers as defined in Appendices; this info is used in MetaPath to associate which metabolites were found under which experimental conditions; e.g., if a cell in this table reports a number for a metabolite, then the metabolite will be shown as detected in that treatment (dose level; gender group) in MetaPath if selected in “Highlight Treatment Group.”
## Table vs. Urinary metabolites (% of dose over 24 or 48 hrs) of Phenol-ring-UL-14C following oral dosing to rats

<table>
<thead>
<tr>
<th>Compound</th>
<th>1 mg/kg males</th>
<th>1 mg/kg females</th>
<th>10 mg/kg males</th>
<th>10 mg/kg females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinone</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>catechol</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>phenol</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>phenolglucuronide</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>hydroquinone sulfate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>catechol sulfate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>L-4,5-benzoquinol (a)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

### Total Identified

<table>
<thead>
<tr>
<th>% Identified</th>
<th>1 mg/kg males</th>
<th>1 mg/kg females</th>
<th>10 mg/kg males</th>
<th>10 mg/kg females</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>% Identified</th>
<th>1 mg/kg males</th>
<th>1 mg/kg females</th>
<th>10 mg/kg males</th>
<th>10 mg/kg females</th>
</tr>
</thead>
</table>

### Total Urinary Recovery

<table>
<thead>
<tr>
<th>% Recovered</th>
<th>1 mg/kg males</th>
<th>1 mg/kg females</th>
<th>10 mg/kg males</th>
<th>10 mg/kg females</th>
</tr>
</thead>
</table>

### LOST/ACCOUNTED

<table>
<thead>
<tr>
<th>% Lost</th>
<th>1 mg/kg males</th>
<th>1 mg/kg females</th>
<th>10 mg/kg males</th>
<th>10 mg/kg females</th>
</tr>
</thead>
</table>

### Summary

- **Total Identified**: 10
- **Total Urinary Recovery**: 10
- **LOST/ACCOUNTED**: 0
MetaPath displays study details for each Treatment Group from Materials & Methods and Appendix 1 of DER Composer.
## IV. APPENDIX

### APPENDIX 1: Experimental protocol for metabolism studies of phenylpyrazole-1-14C in rat for MRID 2245687

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>No.</th>
<th>Date Assayed</th>
<th>Latency</th>
<th>Type</th>
<th>Strain</th>
<th>Experiment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>3</td>
<td>2.34</td>
<td>single</td>
<td>7.4 x</td>
<td>dros</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>4</td>
<td>3.27</td>
<td>single</td>
<td>4.5 x</td>
<td>dros</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>5</td>
<td>2.98</td>
<td>single</td>
<td>6.8 x</td>
<td>dros</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>6</td>
<td>2.38</td>
<td>single</td>
<td>4.8 x</td>
<td>dros</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>7</td>
<td>2.34</td>
<td>single</td>
<td>4.6 x</td>
<td>dros</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### APPENDIX 2: Metabolism Inventory: Table of rat exposed to phenylpyrazole-1-14C

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td><img src="https://example.com/phenol.png" alt="Phenol Structure" /></td>
<td>1</td>
</tr>
<tr>
<td>Alcohol</td>
<td><img src="https://example.com/alcohol.png" alt="Alcohol Structure" /></td>
<td>2</td>
</tr>
<tr>
<td>Benzyl</td>
<td><img src="https://example.com/benzyl.png" alt="Benzyl Structure" /></td>
<td>3</td>
</tr>
<tr>
<td>Phenolates</td>
<td><img src="https://example.com/phenolates.png" alt="Phenolates Structure" /></td>
<td>4</td>
</tr>
</tbody>
</table>
Part B: Study Design and methods.

Analytical method details can be captured as text, or more systematically in a Table.

From Appendix 1 - Auto-population of DER Table 1 Group Arrangements

Text box for narrative

Analytical method details can be captured as text, or more systematically in a Table.
Text boxes are included for addition of explanatory information as typically found in DERs

A.) filled in by registrant

B.) & C). Filled in later by OPP to summarize their assessment

This information is captured in DER (*.doc file) but not in MetaPath
DER Composers

• This presentation uses examples from DER Composers for livestock or rat metabolism with the corresponding MetaPath database.

• DER Composers will be used for EDSP T1S data submission with data going to EDSP databases
Designing Computational Tools: Metabolism Pathways (MetaPath) Expert System for Pesticide Registrant Submitted Health & Ecological Effects Data

Partnership between EPA, Office of Pesticide Programs (OPP) and EPA, ORD, NHEERL & NERL, PMRA Health Canada:

NHEERL, MED - Duluth, MN  
  P. Schmieder, R. Kolanczyk

NERL, ERD - Athens, GA  
  J. Jones

Cooperative Agreement with:  
  Laboratory of Mathematical Chemistry (LMC), Bourgas University, Bourgas, Bulgaria  
  O. Mekenyan

OPP, Health Effects Division (HED):  
  M. Manibusan, C. Olinger, R. Kent

OPP - Residues Of Concern Knowledge-bases Sub-committee (ROCKS)

PMRA, Health Canada:  
  L. Croteau, M. Gerrits
Ask Tom Steeger for demonstration of DER Composer software

THANKS!