SPOT-ON ENHANCED REPORTING PILOT

WEBINAR

U.S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division and Health Effects Division
June 7, 2016
OVERVIEW

- Background
  - Concern over Spot On Incidents
  - Mitigations
- Review of Enhanced Data 2010-2015
- Pilot Information
- HED’s Analysis Plan and Template
- Timeline
- Next steps
- Q & A
In 2008-2009, a notable increase in the number of reports of adverse health effects from pet spot-on flea and tick control products was identified in EPA’s Incident Data System (IDS).

EPA responded with mitigation measures:

- Label mitigation
- Limitation of CSFs to one formulation
- 2 year time-limited registrations
- Enhanced quarterly incident reporting with corresponding sales data

REVIEW OF ENHANCED DATA 2010-2015

- Appreciable efforts on part of registrants to comply with enhanced incident reporting requirements
- The enhanced reporting was recently compiled by HED into electronic format for analysis
- Several important inconsistencies in the data submissions
- These inconsistencies in the data in effect do not allow for meaningful analysis of the data submissions.
Data Inconsistencies:

- Lack of standard terminology for adverse health effects
- Data Formats
  - Inconsistent among the companies and within the same company over time
  - Different data formats include: PDFs, Excel, Word documents, etc.
  - Cannot include all data into analysis due to some data formats which are unreadable by statistical software
- Incomplete and missing data:
  - No incident counts for some quarters or years
  - Some data files had no EPA Registration Number
  - Some records missing severity, outcome, etc.
Sales Data Issues:

- Companies submitted sales data in reports of PDF files or Word documents
- Many separate files (for many products and many quarters or years)
- Sales data may be global for some companies, but U.S. only for other companies
  - Not necessarily consistent with incident counts
- No sales data for some quarters or years
- Reported total sales data included multiple products
- Cannot include all data into analysis due to some data formats which are unreadable by statistical software
To address the data submission and analysis difficulties, HED created two reporting templates:

- Template for the enhanced spot-on incident data reporting
- Template for spot-on sales data reporting

The enhanced spot-on incident data reporting template standardizes the variables and definitions providing a consistent data format to allow for meaningful statistical analyses.

Sales data template ensures EPA has necessary information on # doses sold for each product (sales data in consistent format)
Pilot Objectives:

- Test a standard template that will facilitate submission of enhanced incident reporting data in a format that can be analyzed in a meaningful way
- Obtain feedback from pilot participants and other interested stakeholders on the feasibility and usability of the template to inform analysis
- Modify the template based on feedback
We are seeking up to 9 volunteer companies/registrants to participate in the pilot.

Participants will:

- Have EPA registered pet spot-on products subject to enhanced reporting requirements.
- Use template to submit incident data and sales information for 1 year (incidents occurring Jan 2016-December 2016).
- Provide feedback on usability and feasibility of format.
- Satisfy the quarterly reporting requirement for said year via participation in the pilot.
WHAT ANALYSES WILL BE DONE USING THE DATA?

- Level 1: Review total and summary of incidents
- Level 2: Reporting Odds Ratio (ROR)
- Level 3: Incident Rate Ratio (IRR)
- Level 4: Signal-based case-by-case review
LEVEL 1: SUMMARY OF NUMBER INCIDENTS

Review total incidents:

- IDS Aggregate query results
  - IDS (Incident Data system) is maintained by OPP and incorporates data submitted by registrants under FIFRA section 6(a)(2), as well as other incidents reported directly to EPA
    - Domestic Animal (Pet) Incidents received from the Registrant are reported in aggregate form on a quarterly basis
      - This data includes the number of incidents reported for quarter, severity of the incidents, products implicated
      - Does not include species or any narrative information regarding exposure scenario or symptoms
  - To detect any signals we need to have a more detailed investigation (i.e. Levels 2+)
LEVEL 1: SUMMARY OF NUMBER INCIDENTS

- Summary can be done by product or active ingredient
  - Which products have large number of incidents?
  - Below is an example table, by product (hypothetical data)

<table>
<thead>
<tr>
<th>EPA Reg. No.</th>
<th>Death</th>
<th>Major</th>
<th>Moderate</th>
<th>Minor/UNK</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>111111-12345*</td>
<td>200</td>
<td>700</td>
<td>1400</td>
<td>6050</td>
<td>8350</td>
</tr>
<tr>
<td>111111-67890</td>
<td>70</td>
<td>150</td>
<td>600</td>
<td>1500</td>
<td>2320</td>
</tr>
<tr>
<td>222222-00000</td>
<td>37</td>
<td>90</td>
<td>450</td>
<td>1102</td>
<td>1679</td>
</tr>
</tbody>
</table>

**Total Incidents**

Number of Incidents

Death | Major | Moderate | Minor/Unknown

Products

- 111111-12345
- 111111-67890
- 222222-00000
LEVEL 1: SUMMARY OF NUMBER INCIDENTS

- Summary can be done by product-year
  - Pattern/trend of number incidents of each product over time
  - Below is an example table (hypothetical data)

<table>
<thead>
<tr>
<th>EPA Reg. No.</th>
<th>Year</th>
<th>Death</th>
<th>Major</th>
<th>Moderate</th>
<th>Minor/UNK</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>111111-12345*</td>
<td>2011</td>
<td>50</td>
<td>175</td>
<td>420</td>
<td>1813</td>
<td>2458</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>60</td>
<td>175</td>
<td>375</td>
<td>1215</td>
<td>1825</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>40</td>
<td>200</td>
<td>280</td>
<td>1362</td>
<td>1882</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>50</td>
<td>150</td>
<td>325</td>
<td>1660</td>
<td>2185</td>
</tr>
<tr>
<td>111111-67890</td>
<td>2012</td>
<td>13</td>
<td>50</td>
<td>250</td>
<td>350</td>
<td>663</td>
</tr>
<tr>
<td></td>
<td>2013</td>
<td>25</td>
<td>45</td>
<td>125</td>
<td>325</td>
<td>520</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>18</td>
<td>65</td>
<td>225</td>
<td>340</td>
<td>648</td>
</tr>
<tr>
<td>222222-00000</td>
<td>2010</td>
<td>10</td>
<td>20</td>
<td>80</td>
<td>222</td>
<td>332</td>
</tr>
</tbody>
</table>
LEVEL 2: REPORTING ODDS RATIO (ROR)

• Using incident database or IDS aggregate query results, we can calculate a Reporting Odds Ratio (ROR) for a given outcome
  • ROR used to compare odds of a given outcome (or event) for one product to odds of (same) outcome to another

• Mathematically:
  • Reporting Odds Ratio (ROR): deaths + majors (as outcome)
    • Odds of deaths+major for Product A = (Number of deaths+major for Product A)/(Number of moderate+minor+unknown for Product A)
    • ROR of a product A = (odds of death+major of product A) / (odds of death+major of pooling all OTHER products (excluding product A))

    -or-

The odds of a death/major outcome (or event) for Product A are 1.27 times (95% CI: 1.12, 1.45) greater than the odds of a death/major outcome for “other than” Product A products.
• Example of ROR results

<table>
<thead>
<tr>
<th>EPA Reg. No.</th>
<th>Product Name</th>
<th>Total cases</th>
<th>Deaths + Majors</th>
<th>ROR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111111-12345</td>
<td>Product A</td>
<td>8350</td>
<td>900</td>
<td>1.27 (1.12, 1.45)</td>
</tr>
<tr>
<td>111111-67890</td>
<td>Product B</td>
<td>2320</td>
<td>220</td>
<td>0.92 (0.79, 1.07)</td>
</tr>
<tr>
<td>222222-00000</td>
<td>Product C</td>
<td>1679</td>
<td>127</td>
<td>0.70 (0.58, 0.84)</td>
</tr>
</tbody>
</table>

Among reported cases:
  o The odds of death + major incident for Product A is 27% higher than that of all other products and it is statistically significant because 95% confidence interval of ROR excludes 1.
LEVEL 2: REPORTING ODDS RATIO (ROR)

• Example of ROR results

<table>
<thead>
<tr>
<th>EPA Reg. No.</th>
<th>Product Name</th>
<th>Total cases</th>
<th>Deaths + Majors</th>
<th>ROR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111111-12345</td>
<td>Product A</td>
<td>8350</td>
<td>900</td>
<td>1.27 (1.12, 1.45)</td>
</tr>
<tr>
<td>111111-67890</td>
<td>Product B</td>
<td>2320</td>
<td>220</td>
<td>0.92 (0.79, 1.07)</td>
</tr>
<tr>
<td>222222-00000</td>
<td>Product C</td>
<td>1679</td>
<td>127</td>
<td>0.70 (0.58, 0.84)</td>
</tr>
</tbody>
</table>

Among reported cases:
  o The odds of death + major incident for Product B is 8% lower but not statistically significantly different than that of all other products because 95% confidence interval of ROR includes 1.
LEVEL 2: REPORTING ODDS RATIO (ROR)

• Example of ROR results

<table>
<thead>
<tr>
<th>EPA Reg. No.</th>
<th>Product Name</th>
<th>Total cases</th>
<th>Deaths + Majors</th>
<th>ROR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111111-12345</td>
<td>Product A</td>
<td>8350</td>
<td>900</td>
<td>1.27 (1.12, 1.45)</td>
</tr>
<tr>
<td>111111-67890</td>
<td>Product B</td>
<td>2320</td>
<td>220</td>
<td>0.92 (0.79, 1.07)</td>
</tr>
<tr>
<td>222222-00000</td>
<td>Product C</td>
<td>1679</td>
<td>127</td>
<td>0.70 (0.58, 0.84)</td>
</tr>
</tbody>
</table>

Among reported cases:

- The odds of death + major incident for **Product C** is 30% lower and statistically significantly different than that of all other products because 95% confidence interval of ROR excludes 1.
LEVEL 2: REPORTING ODDS RATIO (ROR)

Tree plots:
- describe the relative number of reported cases and the ROR among products
- Each rectangle in the figure represents a single product
- Area/size describes the total deaths + major + moderate cases of given product
- Color intensity describes the relative ROR (deaths+majors+moderates) of a product
  - ROR = top number in rectangle
  - 2nd and 3rd numbers are Cis around ROR

See ATTACHMENT for details

LEVEL 3: INCIDENT RATE RATIO (IRR)

- Combining Enhanced Incident Data with Sales Data
- Incident Rate (IR): number of incidents per (e.g.) $10^6$ doses sold or applied
- Incident Rate Ratio (IRR): Ratio of two IRs
  - An IRR > 1 indicates the incident rate of the product is greater than the (blended or pooled) IR of all other products considered together
    - An IRR < 1 indicates that the IR of the product is less than the (blended) IR of all the other products
- Mathematically:
  - IR of product A = (# deaths + # majors)/(# of pet-months “exposure”);
    Where # of pet-months “exposure” = duration of control period per product label $\times$ number of units sold for Product A
  - IRR of Product A = (IR of Product A)/( IR (blended or pooled) for all products OTHER THAN Product A)
**LEVEL 3: INCIDENT RATE RATIO (IRR)**

**Example Table** (hypothetical data):

- **Assume:**
  - each product has 1 million doses in sales
  - duration of use as per product label is
    - 2 months for product A(*);
    - 1 month for product B; and
    - 1 month for product C

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>IRR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death + major</td>
<td>Product A vs. All other products (not A)*</td>
<td>2.59 (2.29, 2.94)</td>
</tr>
<tr>
<td></td>
<td>Product B vs. All other products (not B)</td>
<td>0.64 (0.56, 0.74)</td>
</tr>
<tr>
<td></td>
<td>Product C vs. All other products (not C)</td>
<td>0.34 (0.28, 0.41)</td>
</tr>
</tbody>
</table>

An IRR > 1 indicates the incident rate of the product is greater than the incident rate of all other products.
• IRR of an active ingredient can be estimated, too
  • IRR of an active ingredient = (incident rate of all products with a given active ingredient)/incident rate of all products without the active ingredient)

Example Table:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>IRR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death + major</td>
<td>Active Ingredient X vs. All other active ingredients (not X)</td>
<td>1.70 (1.63, 1.85)</td>
</tr>
<tr>
<td></td>
<td>Active Ingredient Y vs. All other active ingredients (not Y)</td>
<td>0.42 (0.32, 0.58)</td>
</tr>
<tr>
<td></td>
<td>Active Ingredient Z vs. All other products (not Z)</td>
<td>0.30 (0.21, 0.47)</td>
</tr>
</tbody>
</table>

An IRR > 1 indicates the incident rate of the active ingredient is greater than the incident rate of all other active ingredients.
LEVEL 4: INCIDENT RATE RATIO BY PRODUCT, ACTIVE INGREDIENT, OR SYMPTOM

- IRR by specific symptom (e.g., VedDRA), by product can be estimated as well

  Example Table (hypothetical data):

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>IRR (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product A vs. All other products (not A)</td>
<td>1.26 (1.18, 1.48)</td>
</tr>
<tr>
<td></td>
<td>Product B vs. All other products (not B)</td>
<td>0.45 (0.36, 0.60)</td>
</tr>
<tr>
<td></td>
<td>Product C vs. All other products (not C)</td>
<td>0.16 (0.10, 0.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>IRR (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding</td>
<td>Product A vs. All other products (not A)</td>
<td>1.56 (1.43, 1.73)</td>
</tr>
<tr>
<td></td>
<td>Product B vs. All other products (not B)</td>
<td>0.52 (0.41, 0.76)</td>
</tr>
<tr>
<td></td>
<td>Product C vs. All other products (not C)</td>
<td>0.26 (0.18, 0.40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>IRR (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritis</td>
<td>Product A vs. All other products (not A)</td>
<td>1.65 (1.48, 1.76)</td>
</tr>
<tr>
<td></td>
<td>Product B vs. All other products (not B)</td>
<td>0.40 (0.28, 0.79)</td>
</tr>
<tr>
<td></td>
<td>Product C vs. All other products (not C)</td>
<td>0.21 (0.13, 0.56)</td>
</tr>
</tbody>
</table>

An IRR > 1 indicates the incident rate of the product is greater than the incident rate of all other products.
- data signals-canine
  - by symptom
  (VedDRA coded)
Caveats and Reminders Regarding Our Data Analysis

- Signals are signals only –
  - Detected signals are hypotheses only, and do not imply causal relationships
  - Do not replace hands-on clinical review of case reports – medical judgement
  - “Disproportionalities” or SDR (signals of disproportionate reporting)
- Limitations and biases associated with reported data may limit utility
  - In any case, will require cautious interpretation
- Confidentiality
  - Analysis must be done such that a registrant will not be able to use results to derive the sales volume of any other specific registrants
  - In the IRR analysis, we will compare the incident rate of Product A to the incident rate of all other Products together
  - Not compare the incident rate (#incidents/sale volume) of a company A to each of many other registrants separately
Based on previous spot-on incidents submitted to EPA by spot-on registrants

EPA shared the spot-on template and incorporated comments from the following sources:

- Assured-PV (producer of PV Works)
- SafetyCall
- National Pesticide Information Center (NPIC)
- Health Canada PMRA

EPA met with FDA CVM

- Shared the spot-on template and discussed with FDA CVM about their database systems and methodologies of data analysis
- Incorporated their comments into the spot-on template
Variables in the spot-on incident data template

Variables in the spot-on sale data template
TIMELINE

- **June 21, 2016**: deadline to express interest in participation
- **June 28, 2016**: selection of volunteers; participants will be notified
- **July 28, 2016**: optional Q & A conference call
- **August 29, 2016**: submit 1st and 2nd quarter 2016 data using the template
- **Early September 2016**: follow-up webinar for volunteer participants
  - Discussion of template usability and feasibility
- **February 2017**: submit 3rd and 4th quarter data using refined template
Point of contact: Julie Breeden-Alemi, DVM

Email: Breeden-Alemi.Julie@epa.gov using one of the following phrases in the subject line:
- Pilot Spot-On Comment
- Pilot Spot-On Participant
QUESTIONS & COMMENTS

- NOTE: The OR and associated C.I. on the next slide were not present in the original article but were instead calculated by EPA from the data provided.
### SUPPLEMENTAL ATTACHMENT

<table>
<thead>
<tr>
<th>Herbal</th>
<th>known cases</th>
<th>HF/1000</th>
<th>RR</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>OR</th>
<th>OR, LCB</th>
<th>OR, UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>yohimbe</td>
<td>367</td>
<td>416.7</td>
<td>2.081107</td>
<td>153</td>
<td>214</td>
<td>4152</td>
<td>16981</td>
<td>2.92</td>
<td>2.37</td>
<td>3.61</td>
</tr>
<tr>
<td>ephedra-multi</td>
<td>10690</td>
<td>267.1</td>
<td>1.333966</td>
<td>2855</td>
<td>7835</td>
<td>1450</td>
<td>9360</td>
<td>2.35</td>
<td>2.19</td>
<td>2.52</td>
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<tr>
<td>epeddra only</td>
<td>2604</td>
<td>250</td>
<td>1.248564</td>
<td>651</td>
<td>1953</td>
<td>3654</td>
<td>15242</td>
<td>1.39</td>
<td>1.26</td>
<td>1.53</td>
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<td>kava kava</td>
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<td>137.9</td>
<td>0.688708</td>
<td>56</td>
<td>350</td>
<td>4249</td>
<td>16845</td>
<td>0.63</td>
<td>0.48</td>
<td>0.84</td>
</tr>
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<td>velerian</td>
<td>464</td>
<td>112.1</td>
<td>0.559856</td>
<td>52</td>
<td>412</td>
<td>4253</td>
<td>16783</td>
<td>0.50</td>
<td>0.37</td>
<td>0.67</td>
</tr>
<tr>
<td>other multi-botanical</td>
<td>1293</td>
<td>88.2</td>
<td>0.440493</td>
<td>114</td>
<td>1179</td>
<td>4191</td>
<td>16016</td>
<td>0.37</td>
<td>0.30</td>
<td>0.45</td>
</tr>
<tr>
<td>ginseng</td>
<td>1140</td>
<td>83.3</td>
<td>0.416022</td>
<td>95</td>
<td>1045</td>
<td>4210</td>
<td>16150</td>
<td>0.35</td>
<td>0.28</td>
<td>0.43</td>
</tr>
<tr>
<td>other single ingred.</td>
<td>2363</td>
<td>82.1</td>
<td>0.410028</td>
<td>194</td>
<td>2169</td>
<td>4111</td>
<td>15026</td>
<td>0.33</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td>ginko biloba</td>
<td>564</td>
<td>74.5</td>
<td>0.372072</td>
<td>42</td>
<td>522</td>
<td>4263</td>
<td>16673</td>
<td>0.31</td>
<td>0.23</td>
<td>0.43</td>
</tr>
<tr>
<td>St. Johns Wort</td>
<td>910</td>
<td>65.9</td>
<td>0.329122</td>
<td>60</td>
<td>850</td>
<td>4245</td>
<td>16345</td>
<td>0.27</td>
<td>0.21</td>
<td>0.35</td>
</tr>
<tr>
<td>echinacia</td>
<td>699</td>
<td>47.2</td>
<td>0.235729</td>
<td>33</td>
<td>666</td>
<td>4272</td>
<td>16529</td>
<td>0.19</td>
<td>0.13</td>
<td>0.27</td>
</tr>
</tbody>
</table>


NOTE: The OR and associated C.I. were not present in the original article but were instead calculated by EPA from the data provided.