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

BACKGROUND

- 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

See https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects for additional information

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.

REVIEW OF ENHANCED DATA 2010-2015

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.

REVIEW OF ENHANCED DATA 2010-2015

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

PILOT

- 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

- 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

PILOT

- 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

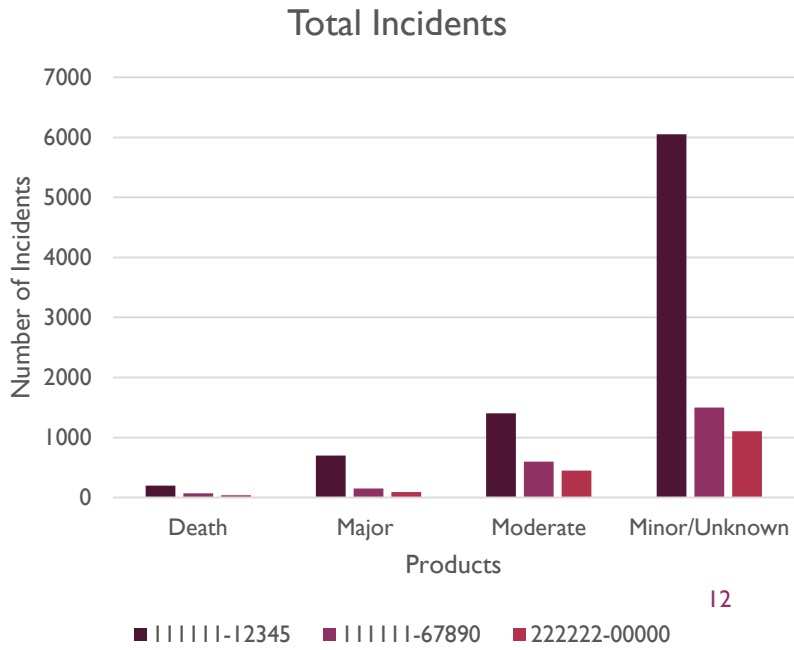
Review total incidents:

- 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)

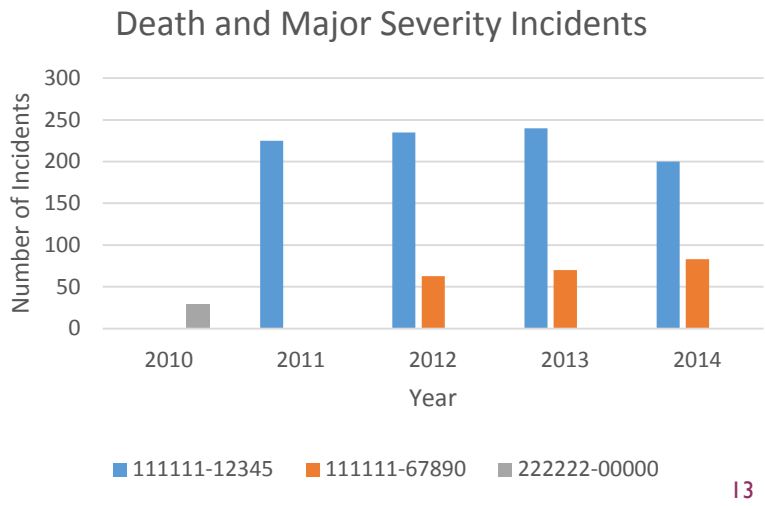
EPA Reg. No.	Death	Major	Moderate	Minor/UNK	Total
111111-12345*	200	700	1400	6050	8350
111111-67890	70	150	600	1500	2320
222222-00000	37	90	450	1102	1679



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)

EPA Reg. No.	Year	Death	Major	Moderate	Minor/UNK	Total
111111-12345*	2011	50	175	420	1813	2458
	2012	60	175	375	1215	1825
	2013	40	200	280	1362	1882
	2014	50	150	325	1660	2185
111111-67890	2012	13	50	250	350	663
	2013	25	45	125	325	520
	2014	18	65	225	340	648
222222-00000	2010	10	20	80	222	332



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.

LEVEL 2: REPORTING ODDS RATIO (ROR)

- Example of ROR results

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

Among reported cases:

- **The odds of death + major incident for <u>Product A</u> 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

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

Among reported cases:

- **The odds of death + major incident for <u>Product B</u> 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

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

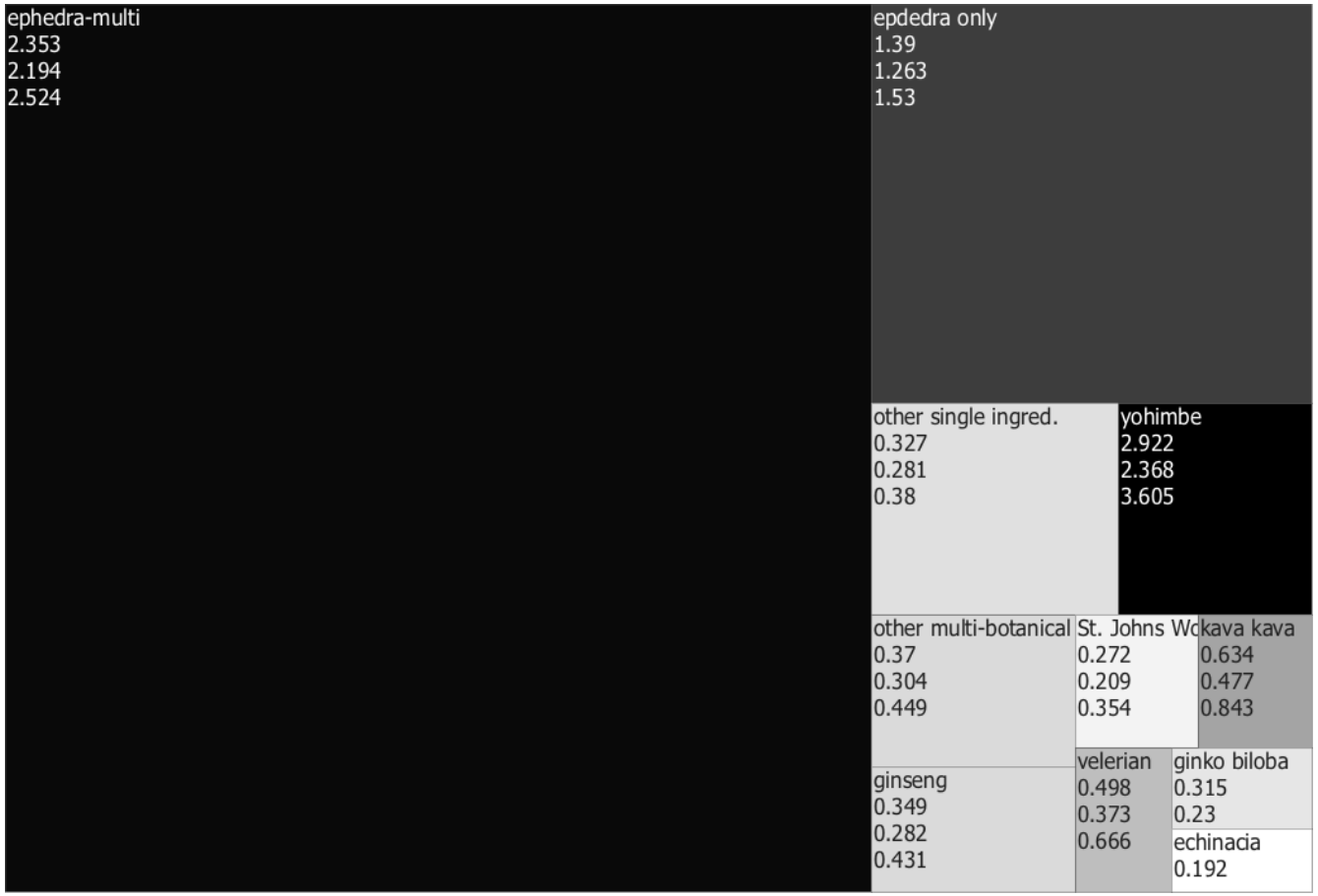
Among reported cases:

- **The odds of death + major incident for <u>Product C</u> 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

Reference: Watson *et al*. (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.

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 X 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

Outcome	Comparison	IRR (95% C.I.)
Death + major	Product A vs. All other products (not A)*	2.59 (2.29, 2.94)
	Product B vs. All other products (not B)	0.64 (0.56, 0.74)
	Product C vs. All other products (not C)	0.34 (0.28, 0.41)

An IRR > 1 indicates the incident rate of the product is greater than the incident rate of all other products

LEVEL 4: INCIDENT RATE RATIO BY PRODUCT, ACTIVE INGREDIENT, OR SYMPTOM

- 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:

Outcome	Comparison	IRR (95% C.I.)
Death + major	Active Ingredient X vs. All other active ingredients (not X)	1.70 (1.63, 1.85)
	Active Ingredient Y vs. All other active ingredients (not Y)	0.42(0.32, 0.58)
	Active Ingredient Z vs. All other products (not Z)	0.30 (0.21, 0.47)

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) :

Outcome	Comparison	IRR (95% C.I)
Blindness	Product A vs. All other products (not A)	1.26 (1.18, 1.48)
	Product B vs. All other products (not B)	0.45(0.36, 0.60)
	Product C vs. All other products (not C)	0.16 (0.10, 0.28)

Outcome	Comparison	IRR (95% C.I)
Convulsion	Product A vs. All other products (not A)	1.56 (1.43, 1.73)
	Product B vs. All other products (not B)	0.52(0.41, 0.76)
	Product C vs. All other products (not C)	0.26 (0.18, 0.40)

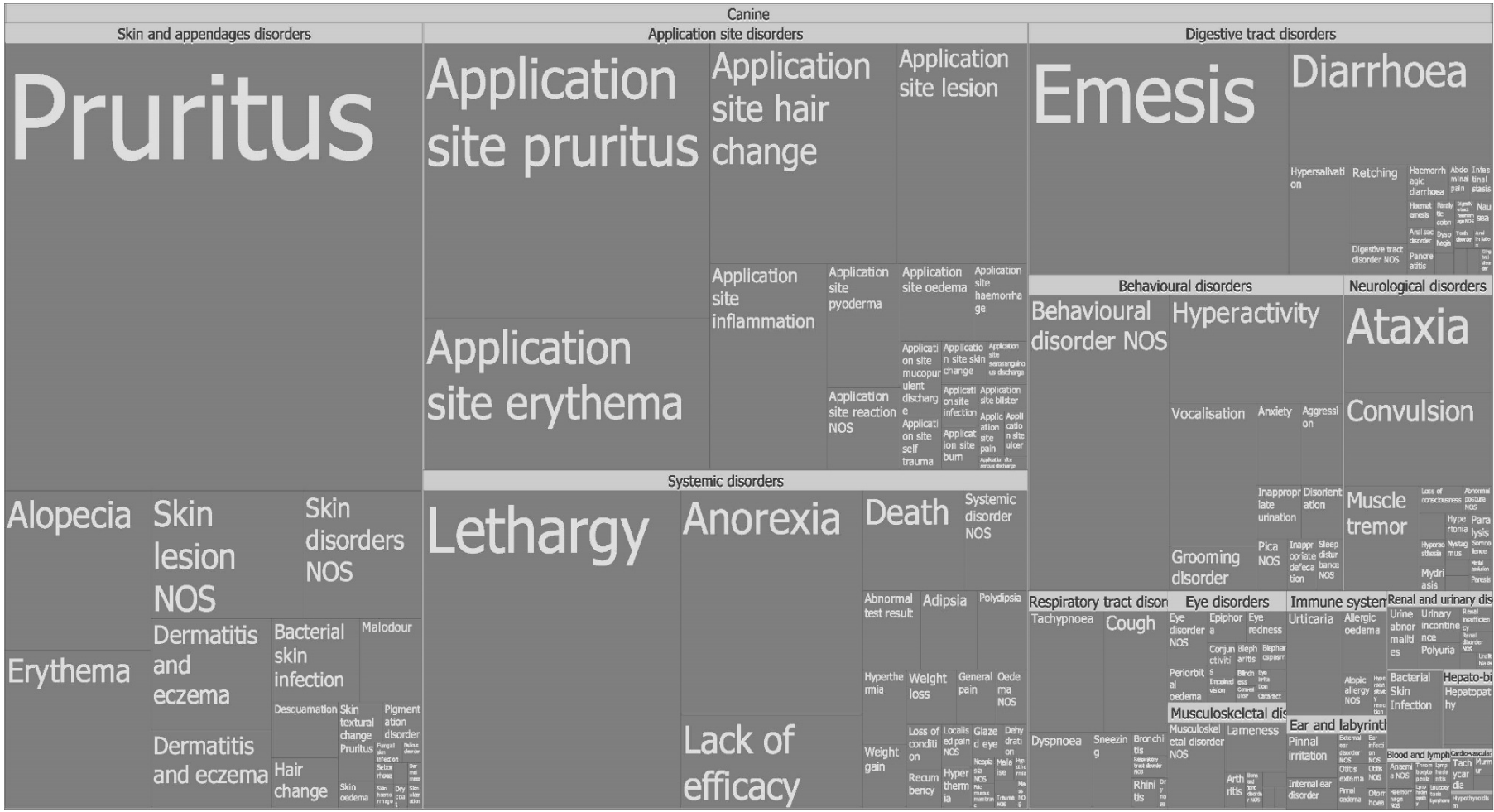
Outcome	Comparison	IRR (95% C.I)
Pruritis	Product A vs. All other products (not A)	1.65 (1.48, 1.76)
	Product B vs. All other products (not B)	0..40 (0.28, 0.79)
	Product C vs. All other products (not C)	0.21 (0.13, 0.56)

An IRR > 1 indicates the incident rate of the product is greater than the incident rate of all other products

LEVEL 4: INCIDENT RATE RATIO BY PRODUCT, ACTIVE INGREDIENT, OR SYMPTOM

- 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

THE DEVELOPMENT OF THE SPOT-ON INCIDENT DATA TEMPLATE

- 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

OVERVIEW OF SPOT-ON INCIDENT AND SALES DATA REPORTING TEMPLATES

- 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

NEXT STEPS

- 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

SUPPLEMENTAL ATTACHMENT

Data from: Watson, William A. *et al.* (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.

- 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.

Table 1
Hazard factor analysis and risk ratio for botanical products reported to TESS from 1993 through 2002

Product category	Cases with known outcomes	Hazard factor/ 1000 known outcomes	Rate ratio (95% CI)
Yohimbe	367	416.7	2.08 (1.59–2.80)
Ephedra (multi-ingredient)	10,690	267.1	1.33 (1.27–1.40)
Ephedra only	2604	250.0	1.25 (1.11–1.40)
Kava Kava	406	137.9	0.69 (0.48–0.97)
Valerian	464	112.1	0.56 (0.39–0.078)
Other multi-botanical products	1293	88.2	0.44 (0.35–0.054)
Ginseng	1140	83.3	0.42 (0.32–0.52)
Other single ingredient products	2363	82.1	0.41 (0.34–0.48)
Ginkgo biloba	564	74.5	0.37 (0.25–0.52)
St. John's Wort	910	65.9	0.33 (0.24–0.43)
Echinacea	699	47.2	0.24 (0.15–0.33)
Total	21,500	200.23	1.00 (0.96–1.04)

Hazard factor calculation: (moderate outcomes + major outcomes + deaths) / number of cases with known outcomes (from Woolf et al., 2003).

SUPPLEMENTAL ATTACHMENT

Herbal	known cases	HF/1000	RR	A	B	C	D	**OR**	OR, LCB	OR, UCB
yohimbe	367	416.7	2.081107	153	214	4152	16981	2.92	2.37	3.61
ephedra-multi	10690	267.1	1.333966	2855	7835	1450	9360	2.35	2.19	2.52
epdedra only	2604	250	1.248564	651	1953	3654	15242	1.39	1.26	1.53
kava kava	406	137.9	0.688708	56	350	4249	16845	0.63	0.48	0.84
velerian	464	112.1	0.559856	52	412	4253	16783	0.50	0.37	0.67
other multi-botanical	1293	88.2	0.440493	114	1179	4191	16016	0.37	0.30	0.45
ginseng	1140	83.3	0.416022	95	1045	4210	16150	0.35	0.28	0.43
other single ingred.	2363	82.1	0.410028	194	2169	4111	15026	0.33	0.28	0.38
ginko biloba	564	74.5	0.372072	42	522	4263	16673	0.31	0.23	0.43
St. Johns Wort	910	65.9	0.329122	60	850	4245	16345	0.27	0.21	0.35
echinacia	699	47.2	0.235729	33	666	4272	16529	0.19	0.13	0.27

Data from: Watson, W.A. *et al.* (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.

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