USDA

United States Department of Agriculture

One Team, One Purpose

Food Safety and Inspection Service

Protecting Public Health and Preventing Foodborne Illness

Identification and Prioritization of Chemical Hazards in Animal Products Monitored by the U. S. National Residue Program

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Food Safety and Inspection Service:

- Intro
  - Food Safety and Inspection Service
  - Chemical Prioritization
  - Chemicals of Concern Priority Ranking
  - National Residue Program – Restructuring
  - Chemical Hazard Identification
  - Mathematical Modeling
- Public Health-Based Model
- Latent Variable Model
- Public Health Based vs Latent Variable
- Conclusion

Food Safety and Inspection Service (FSIS)

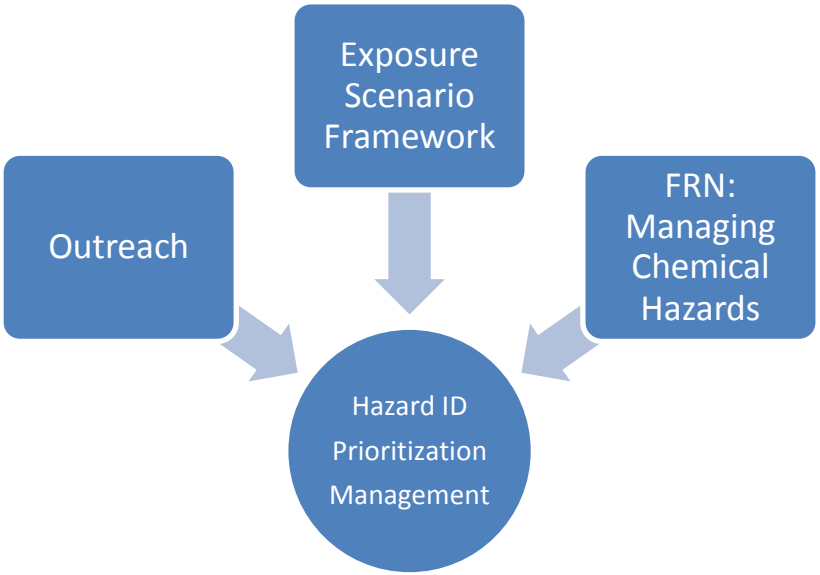
The Food Safety and Inspection Service (FSIS) is the public health agency in the U.S. Department of Agriculture (USDA) and is responsible for ensuring that meat, poultry, and processed egg products are safe, wholesome, and accurately labeled.

Food Safety and Inspection Service:

Chemical Prioritization

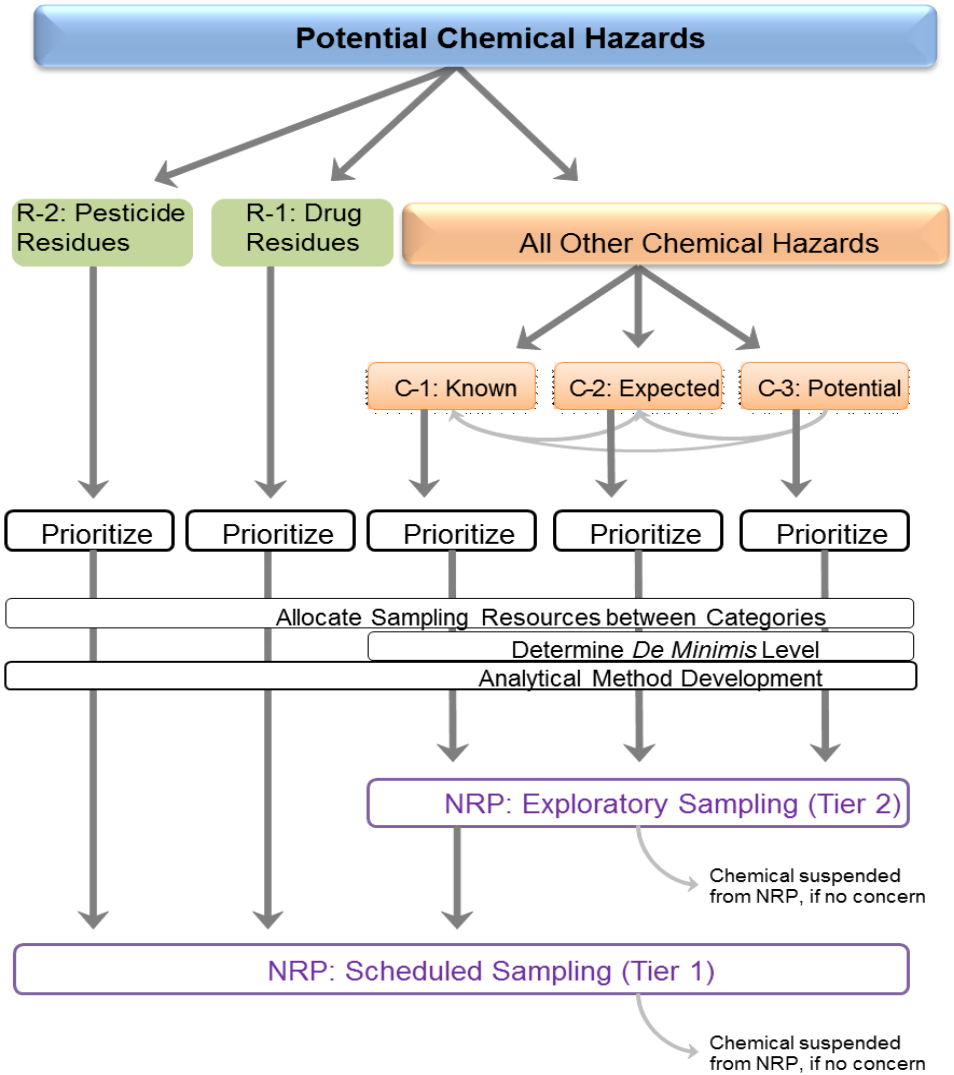
- Chemical identification provides a framework which allows us to systematically evaluate and determine if there's a potential risk to develop an adverse health outcome from exposure to chemicals that might be present in FSIS-regulated food.

- Prioritization allows us to determine which chemicals might present a higher risk of developing an adverse health outcome than others.



Food Safety and Inspection Service:

Current Work - "Binning" Schematic



C-1: Known – Chemicals detected previously by FSIS, but not in NRP.

C-2: Expected – Chemicals detected in foods by other countries or known to be present in food products.

C-3: Potential – Chemicals listed under TSCA (EPA), Substance Priority List (ATSDR), Toxic Release Inventory (EPA).

Prioritization model could be adjusted to specific bins and/or laboratory resources in conjunction with a prior review of the variables.

Food Safety and Inspection Service:

Chemicals of Concern Priority Ranking

- Prior to 2012:
  - A complex ranking system was developed by the members of Surveillance Advisory Team (SAT) and incorporated in the Blue Book.
  - The ranking was based on a 4-point scale
  - Members of the SAT scored chemicals of concern based on a number of factors
  - Such factors include:
    - FSIS Historical Testing Info
    - Regulatory Concern
    - Lack of FSIS Testing Info
    - Pre-slaughter Interval
    - Bio-concentration Factor
    - Endocrine Disruption
    - Toxicity

Food Safety and Inspection Service:

Limitations of Chemical Ranking System

1. Countless list of chemicals and metabolites

2. Data complexity
   - The breadth of data needed for each chemical

3. Testing capabilities as a rate-limiting step
   - Single residue method (Pre- MRM)

Food Safety and Inspection Service:

National Residue Program – Restructuring

- FSIS announcement of restructuring of NRP - July 2012 http://www.fsis.usda.gov/wps/wcm/connect/96433e1b-d3b6-42b0-93a8-f0beee77e520/2012-0012.pdf?MOD=AJPERES
  - Multi-residue chemical methods
    - Multi-Residue Method (MRM) (53+) and Pesticide (108) method
  - Significant expansion of the number of analytes screened
  - Chemicals of concern can be readily added to MRM and/or Pesticide method* (based on chemical structure and volatility)

Food Safety and Inspection Service:

Chem Hazard Identification

- With the new methods and the labs increased in capabilities:

"A pure scientific-based risk-ranking model is needed in order to incorporate chemicals of public health concern which are not being analyzed for by the NRP."

Food Safety and Inspection Service:

Mathematical Models

- A FSIS workgroup has been looking at two proposed models for chemical ranking:

1. Public Health-based model

2. Latent Variable model

* For this initial review we are going to focus on pesticides*

Public Health-Based Model

Food Safety and Inspection Service:

Public Health-Based Model

- This is a revamp of the model used in the past blue book.
- Based a 6-point scale (4- point scale in previous ranking)

$$\textit{Relative public health} = \textit{Exposure} \times \textit{Toxicity}$$

- Factors:
  - Exposure
    - Bioavailability (BA) Factor (L)
    - Usage Data* (S)
  - Toxicity
    - Chronic dietary toxicity (%cPAD) (T)
    - Carcinogenicity (C)

Food Safety and Inspection Service:

Exposure – Bioavailability Factor (L)

- The bioavailability (BA) variable has been adopted from the previously proposed ranking model (NRP Blue book 99-07).

6= log K_{ow} greater than 5

5= log K_{ow} between 4 and 5

4= log K_{ow} between 3 and 4

3= log K_{ow} between 2 and 3

2= log K_{ow} between 1 and 2

1= log K_{ow} less than 1

Food Safety and Inspection Service:

Exposure - Usage Data (S)

- U.S. Geological Survey (USGS) published a paper containing the Estimated Annual Agricultural Pesticide use for Counties of the US (08-12).
- Contained annual county-level pesticide for 423 herbicides, insecticides, and fungicides applied to agricultural crops grown in the conterminous United States during 2008–12
- Data in Kg used

6= Greater than 25,000 kg
5= Between 20,000 and 25,000 kg
4= Between 15,000 and 20,000 kg
3= Between 10,000 and 15,000 kg
2= Between 1,000 and 10,000 kg
1= Less than 1,000 kg

Food Safety and Inspection Service:

Toxicity - Chronic Dietary Toxicity (T)

- Based on EPA calculation of population adjusted dose (PAD)
- Example: Piperonyl Butoxide (PBO)

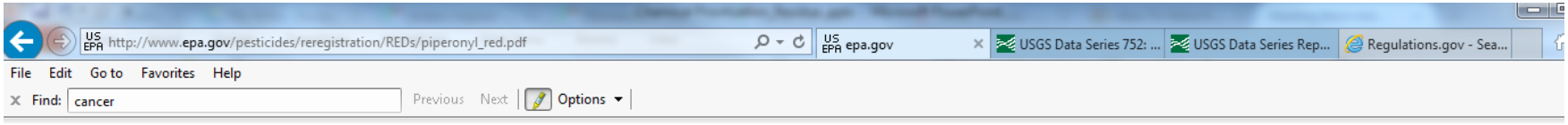


Table 4: Endpoints for Assessing Occupational and Residential Risks for PBO

Exposure Scenario	Dose, Uncertainty Factors (UFs), and Safety Factors (SFs)	Population Adjusted Dose (PAD) or Target Margin of Exposure (MOE)	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= 15.5 mg/kg/day UF = 100 (inter- and intra-species UF) FQPA SF = 1X Total UF = 100 Chronic RfD = 0.16 mg/kg/day	cPAD = $\frac{\text{chronic RfD}}{\text{FQPA SF}}$ cPAD = 0.16 mg/kg/day	Chronic oral toxicity study, dogs LOAEL = 52.8 mg/kg/day based on decrease in body weight gain, and increases in alkaline phosphatase activity, liver weight and hepatocellular hypertrophy (MRID: 42926001, 42926002)
	NOAEL= 89 mg/kg/day		Two generation reproduction study,

Food Safety and Inspection Service:

Toxicity - Chronic dietary toxicity (T)

- Based on EPA calculation of population adjusted dose (PAD)

$$Exposure = Consumption\left(\frac{kg_{food}}{kg/bw/day}\right) \times Residue\left(\frac{mg_{pesticide}}{kg_{food}}\right)$$

$$\%cPAD = \frac{Exposure\left(\frac{mg}{kg/bw/day}\right)}{cPAD\ or\ ADI\left(\frac{mg}{kg/bw/day}\right)} \times 100$$

$$\%cPAD = \frac{Consumption\left(\frac{kg_{food}}{kg/bw/day}\right) \times Residue\left(\frac{mg_{pesticide}}{kg_{food}}\right)}{cPAD\ or\ ADI\left(\frac{mg}{kg/bw/day}\right)} \times 100$$

Categorical distribution of the % cPAD

6= If greater than 100%

5= If between 75 and 100%

4= If between 50 and 75%

3= If between 10 and 50%

2= If between 1 and 10%

1= If less than 1%

Food Safety and Inspection Service:

Toxicity - Carcinogenicity Potential (C)

- EPA published Annual Cancer Report (Oct. 2014)
  - Chemicals Evaluated for Carcinogenic Potential

- Annual cancer Report

6=	Group A - Suggestive Carcinogenic to humans
5=	Group B - Probable Carcinogenic to Humans
4=	Group C - Possible Carcinogenic to Humans
3=	Group D - Not Classifiable
2=	Group E - Evidence of Non-carcinogenicity for Humans
1=	Not Likely to Be Carcinogenic to Humans

Food Safety and Inspection Service:

Public Health-Based Model

- Factors:
  - Exposure
    - Bioavailability Factor (L)
    - Usage Data* (S)
  - Toxicity
    - Chronic dietary toxicity (%cPAD) (T)
    - Carcinogenicity (C)

$$\textbf{\textit{Relative public health}} = \textbf{\textit{Exposure}} \times \textbf{\textit{Toxicity}}$$

$$\textbf{\textit{Relative public health}} = \left(\frac{L + 2S}{3}\right) \times \left(\frac{T + C}{2}\right) = \textbf{\textit{Rank}}$$

Food Safety and Inspection Service:

Ranking of Pesticides using Public Health Model

488 Pesticides
(Domestic and International)

Columns:

- Chemical #
- Chemical Names
- EPA ranking
- Bio concentration Factor (L)
- Usage Data* (S)
- Toxicity (oral %PAD) (T)
- Carcinogenicity (C)

3	#	Chemicals	BA (kow)(L)	Usage(U)	Tox. New (Mean)	Carcinogenic Potential	Rank
4	296	mancozeb	2	6	3	5	18.7
5	017	aldrin	6	1	6		16.0
6	108	cyhalothrin- lambda	6	6	2	3	15.0
7	350	pendimethalin	6	6	1	4	15.0
8	161	diuron	3	3	3	6	13.5
9	441	Tembotrione	3	3	3	6	13.5
10	059	carbaryl (1-Naphthol)	3	6	1	4	12.5
11	080	chlorothalonil	3	6	1	4	12.5
12	085	Chlorpyrifos oxon	3	6	3	2	12.5
13	131	dicamba	3	6	2	3	12.5
14	394	propiconazole	3	6	1	4	12.5
15	043	bifenthrin	6	3	2	4	12.0
16	174	esfenvalerate	6	6	2	2	12.0
17	086	Chlorpyrifos-methyl oxon	2	6	3	2	11.7
18	228	flumethrin	6	2	6	1	11.7
19	472	tribufos (DEF)	6	2	3	4	11.7
20	063	carbophenothion	6	1	4		10.7
21	010	acetochlor	3	3	1	6	10.5
22	046	boscalid	3	3	1	6	10.5
23	091	clodinafop-propargyl	3	2	3	6	10.5
24	293	malathion	3	3	1	6	10.5
25	001	2,4-D (2,4-Dichlorophenoxyacetic acid)	3	6	2	2	10.0
26	083	chlorpyrifos	3	6	2	2	10.0
27	084	chlorpyrifos methyl	3	6	3	1	10.0
28	111	cypermethrin (all isomers)	6	2	2	4	10.0

Latent Variable Model

Food Safety and Inspection Service:

Latent Variable Model

Latent Variable Model

- Statistical model that relates a set of variables to a set of latent variables

- There is no data for the latent risk variable which is the dependent variable in the model

- The latent variable is inferred from the data in the independent variables

- Note: **this is entirely different than fitting the model to the data which statisticians typically do by either simplifying the model (delete parameters or employ transformations, etc.) or moving on to other models with different probability distribution assumptions.**

Food Safety and Inspection Service:

Latent Variable Model

- The Latent Risk Model is a Non-Linear Model that is Linear in the parameters

$Y = m X + b$,

- Y is dependent,
- X is independent,
- m is the slope and b is the intercept

$\text{Logit}(Pi) = Xj + bi$,

- There are **j** chemicals and **i** category levels of risk for each risk attribute
- **bi**'s are averaged over all chemicals because there is only one estimated risk level per chemical

Food Safety and Inspection Service:

Latent Variable Risk Model

- Data from Public-Health Based model
- 6-point scale
- Factors:
    - Bioavailability (L)
    - Usage Data* (S)
    - Chronic dietary toxicity (%cPAD) (T)
    - Carcinogenicity (C)

Food Safety and Inspection Service:

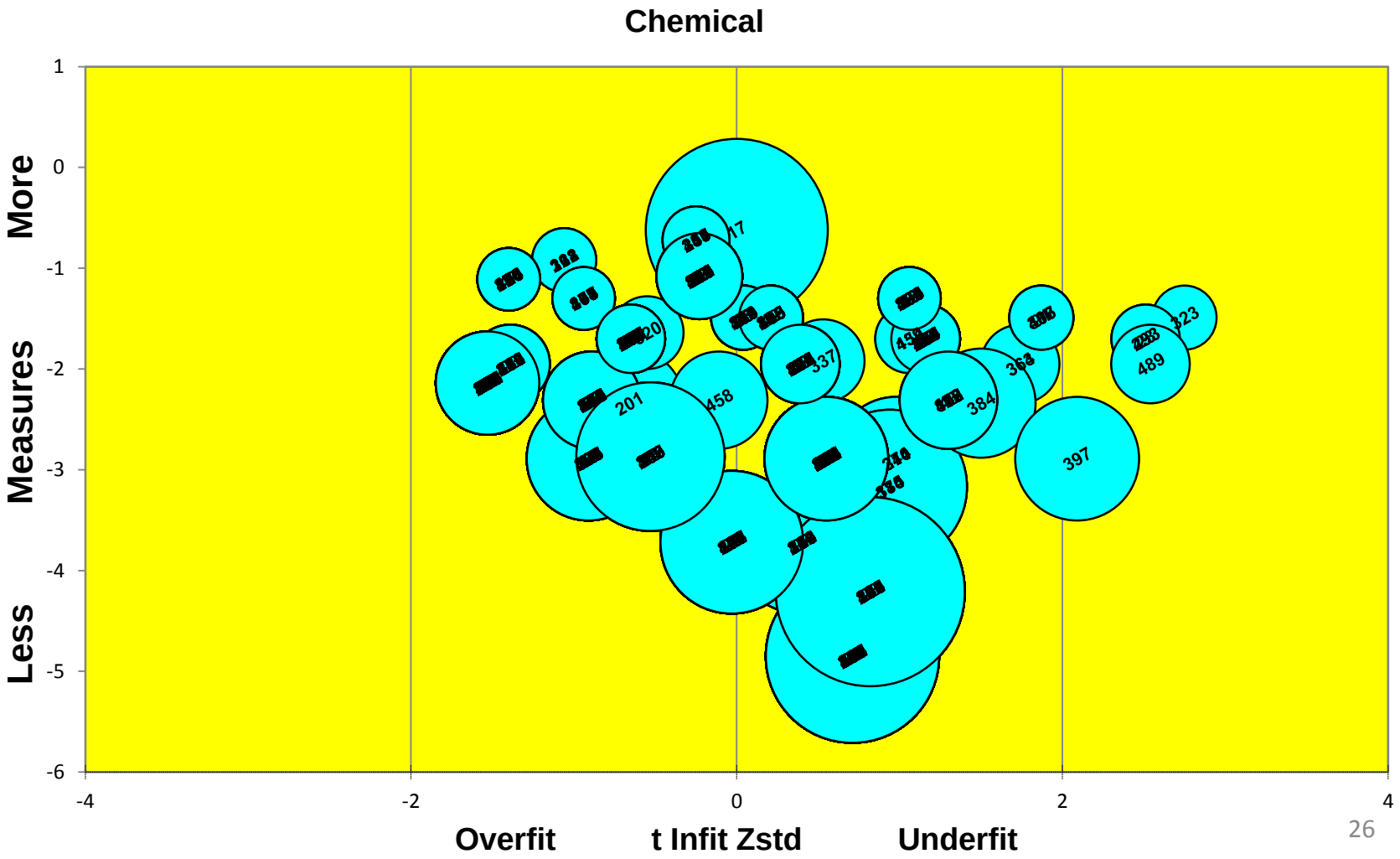
Latent Variable Model

#	Chemicals	Latent_Rank
017	aldrin	1
203	Fenoxaprop ethyl	2
217	flonicamid	3
285	isoxaben	4
330	Nitrapyrin	5
353	Penthiopyrad	6
441	Tembotrione	7
118	daminozide	8
262	haloxyfop	9
048	bromadiolone	10
049	bromophos	11
063	carbophenothion	12
068	chlordane	13
069	chlordane cis	14
070	chlordane trans	15
119	DDD	16
120	DDD o,p'	17
122	DDE o,p'	18
123	DDE p,p'	19
151	dimoxystrobin	20
173	EPTC (S-Ethyl dipropylthiocarbamate)	21
185	ethoxysulfuron	22
255	furathiocarb	23
264	Heptachlor epoxide (cis&trans) or (B+A)	24
312	methoprene	25

- The top 25 chemicals ranked using the Latent Variable Model
- Aldrin is observed to be ranked high on the Latent Variable Model, but Mancozeb is ranked #77.

Food Safety and Inspection Service:

Latent Risk Model Statistical Evaluation



Food Safety and Inspection Service:

Public Health Based vs Latent Variable

- Comparison between the two proposed models.
- There are a few chemicals that were close in ranking:
  - Aldrin
  - Diuron
  - Carbophenothion

3	#	Chemicals	EPA	PH_Rank	Latent_Rank
4	296	mancozeb		1	77
5	017	aldrin	H	2	1
6	108	cyhalothrin- lambda		3	42
7	350	pendimethalin		4	51
8	161	diuron	L	5	7
9	441	Tembotrione		6	54
10	059	carbaryl (1-Naphthol)	HH	7	105
11	080	chlorothalonil	HH	8	168
12	085	Chlorpyrifos oxon		9	172
13	131	dicamba		10	183
14	394	propiconazole	M	11	320
15	043	bifenthrin	HH	12	72
16	174	esfenvalerate	H	13	248
17	086	Chlorpyrifos-methyl oxon	M	14	291
18	228	flumethrin		15	321
19	472	tribufos (DEF)	H	16	422
20	063	carbophenothion	H	17	12
21	010	acetochlor		18	45
22	046	boscalid	HH	19	47
23	091	clodinafop-propargyl		20	70
24	293	malathion	L	21	137

Food Safety and Inspection Service:

Public Health Based vs Latent Variable

- Top 100 chemicals in comparison to EPA ranking

Public Health Based Model

EPA Ranking	# EPA Ranking	# in PH_Rank
HH	33	17
H	40	17
M	48	9
L	82	12

Latent Variable Risk Model

EPA Ranking	# EPA Ranking	# in Latent_Rank
HH	33	12
H	40	15
M	48	4
L	82	13

- Of the top 100
  - PH_Model - 31 of the chemicals are screened under Pesticide method
  - Latent_Model - 27 of the chemicals are screened under Pesticide method
- Latent Model allows the incorporation of chemicals which we do not have complete data available
  - (ex; Allethrin which could not be incorporated in PH model (2 out of 4 variables available) was able to ranked under Latent Model

Food Safety and Inspection Service:

Conclusion

- The models are intended to provide a list of priority chemicals of concern related to food safety that could impact public health through consumption

- The models will allow the agency to allocate resource to high priority chemicals of concern

- FSIS is currently considering the pros and cons of the two models

Food Safety and Inspection Service:

What's Next?

- Peer review
  - EPA
  - FDA
- Optimize the pesticide list
- Compile relevant data for the Veterinary drug and other drugs.
- Run the both model on Veterinary drugs

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- Peer review
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