Advances in Food Allergen Threshold and Quantitative Risk Assessment

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USDA Public Meeting:

Preventing Undeclared Allergens:

A Strategic Approach to Reducing Recalls

March 16, 2017

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Current Status of Thresholds

- Public health authorities have not established regulatory action levels for any of the allergenic foods
  - With the exception of Japan (10 µg/g protein limit for labeling)
- Labeling laws/regulations in many countries impose a zero threshold for source labeling of ingredients
- Food industry and regulators are acutely aware of allergens
  - How much allergenic residue is too much OR how clean is clean enough?? (Remember it is impossible to assure zero risk with anything in life)
    - With little or no guidance on action levels/thresholds, extensive use of precautionary labeling ("may contain") currently exists

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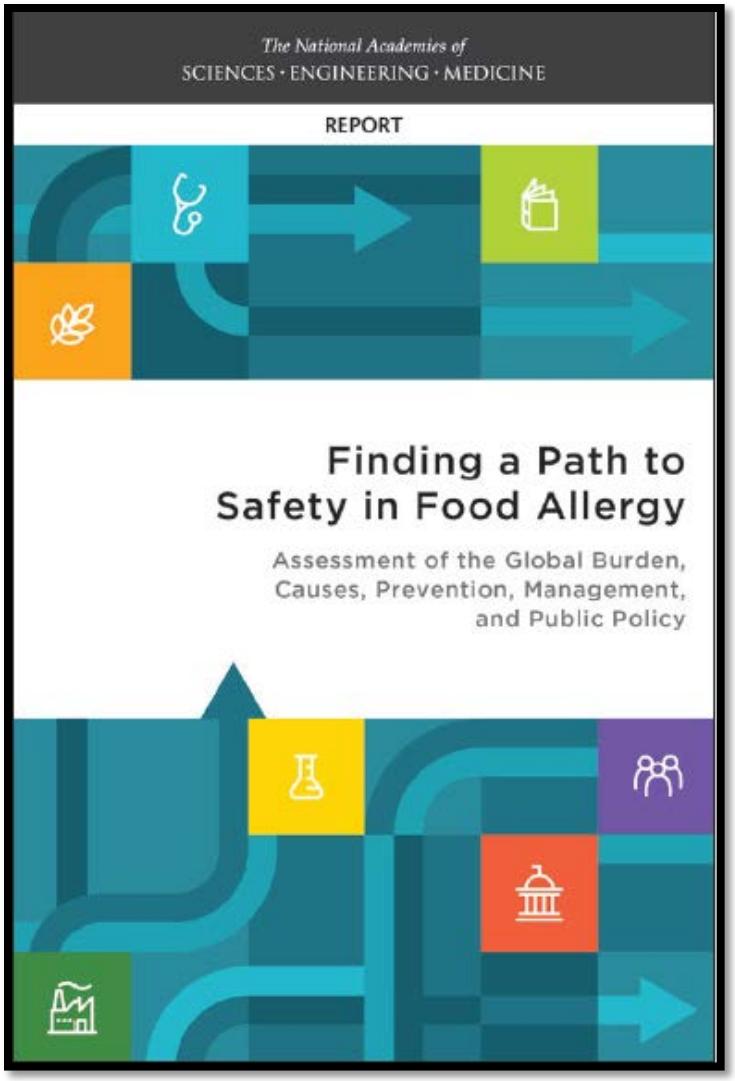

Safety in Food Allergy

- *Highlights of the Consensus Report*

The committee recommends that:

- **the Food and Drug Administration makes its decisions about labeling exemptions for ingredients derived from priority allergenic sources based on a quantitative risk assessment framework**

POLICIES REGARDING LABELING OF PACKAGED FOODS

- **…the food manufacturing industry, the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) work cooperatively to replace the Precautionary Allergen Labeling system for low-level allergen contaminants with a new risk-based labeling approach, such as the VITAL program used in Australia and New Zealand**

POLICIES REGARDING LABELING OF PACKAGED FOODS

A Risk-Based Labeling Approach

- **FDA and USDA should establish Reference Doses (thresholds) for allergenic foods, where possible**
- **Sufficient clinical data on thresholds exist for peanut, milk, egg, certain tree nuts (hazelnut, cashew), soybean, wheat, fish and crustacean shellfish (shrimp) to establish Reference Doses**
- **With Reference Doses, foods should have PAL only when exposure would result in doses above the Reference Dose level**
- **FDA should restrict allowable PAL statements to one phrase**
- **FDA and USDA should educate consumers and health care providers on the meaning of PAL statements**

Do We Have Sufficient Data to Determine Population Dose-Response Thresholds for Allergenic Foods?

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Allergic Patients Present with Different Levels of Sensitivity

0.2mg	0.4mg	1.0mg	5.0mg	25mg	100mg	400mg
(0.05 mg)	(0.1 mg)	(0.25 mg)	(1.25 mg)	(6.25 mg)	(25 mg)	(100 mg peanut protein)

*0.4 mg peanut (0.1 mg peanut protein) is the eliciting dose of the most sensitive peanut-allergic patient reported in the published clinical literature

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Food Allergen Thresholds

- Clinical data exist on individual threshold doses of various allergenic foods from oral challenges conducted for diagnosis, threshold trials, and immunotherapy trials – published and unpublished

- These data are unique and can be used as a central input in risk assessment
  - with food allergies we have HUMAN DATA from sensitive individuals
- FARRP and TNO collaborate to develop a continuously updated dataset of individual thresholds

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FARRP-TNO Threshold Methodological Approach

- Criteria for inclusion:
  - Published studies or unpublished clinical data
  - Food-allergic by history or other factors
  - DBPCFC (+open challenge for infants)
  - Description of NOAEL and/or LOAEL (if dosing regimen provided, then can determine NOAEL from LOAEL)
  - Data on individual patients
  - Objective symptoms @ doses

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FARRP-TNO Dataset Progress

Assembled and evaluated clinical data on all possible priority allergenic foods

- Peanut
- Milk
- Egg
- Hazelnut

- Soybean
- Wheat
- Cashew
- Mustard
- Lupine
- Sesame seed
- Shrimp

- Celery
- Fish

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FARRP-TNO Food Allergen Threshold Database

Allergenic Source	Included in 2012 VITAL Analysis	New Published or Clinic Threshold Data	Total
Peanut	750	452	1202
Milk	351	100	451
Egg	206	176	382
Hazelnut	202	209	411
Soy Flour	51	3	54
Soy Milk	29	4	33
Wheat	40	57	97
Cashew	31	214	245
Mustard	33	0	33
Lupine	24	1	25
Sesame	21	19	40
Shrimp	48	27	75
Celeriac*	39	43	82
Fish*	19	29	48
Buckwheat**		26	26
Walnut**		74	74
Total	**1844**	**1434**	**3278**

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Statistical Dose-Distribution Modeling

- Individual threshold data fitted to parametric models using the SAS LIFEREG procedure
  - Data fitted to Log-Normal, Log-Logistic and Weibull distributions
  - No biological rationale to prefer 1 model over another
  - All 3 models were evaluated for goodness of fit to the actual clinical data when considering the appropriate eliciting dose value (ED_p)
- Data was modelled on the basis of both discrete and cumulative dosing
  - Data also evaluated for children and adults separately where sufficient data existed

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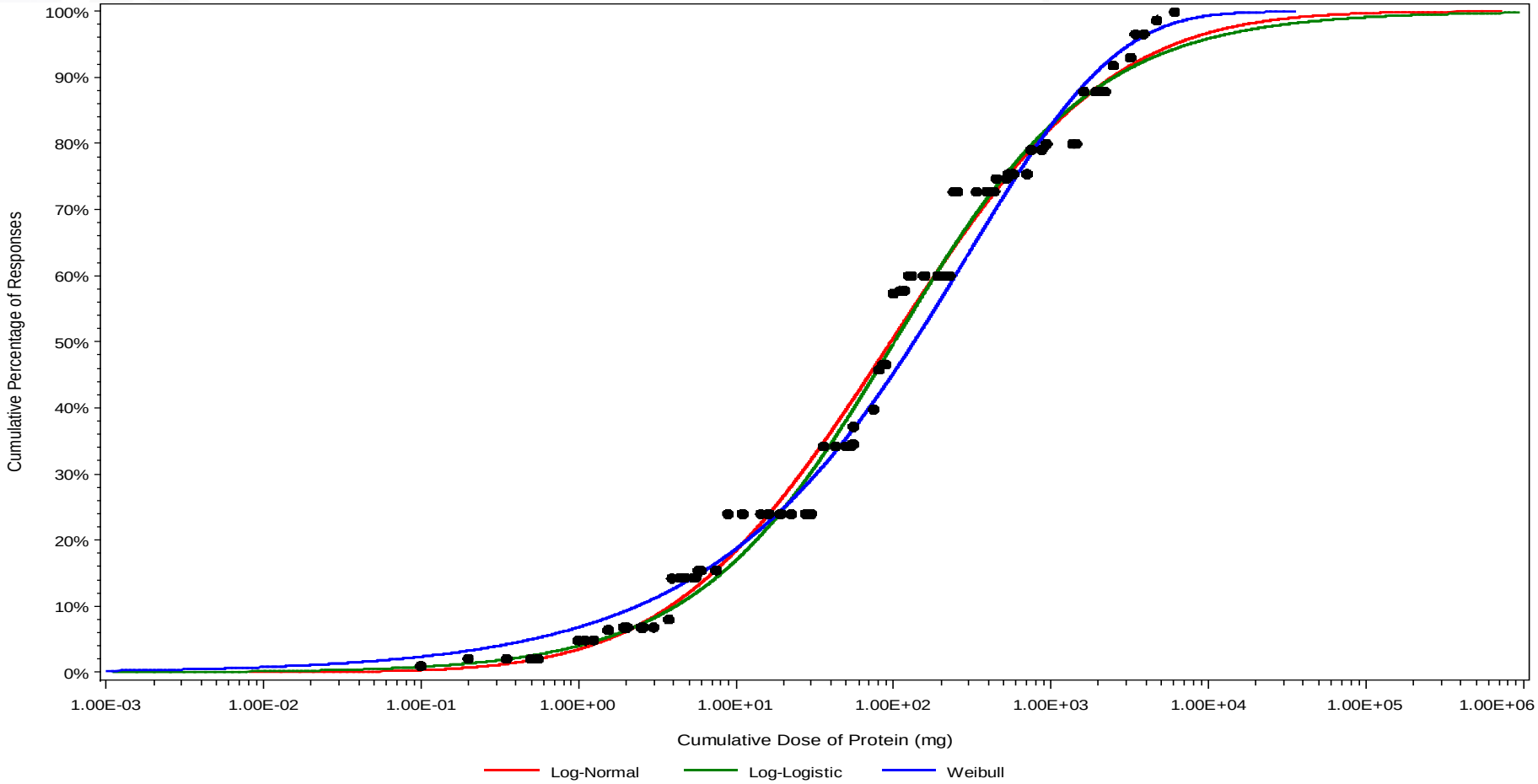
Peanut Threshold Population Distribution (expressed as mg peanut protein)



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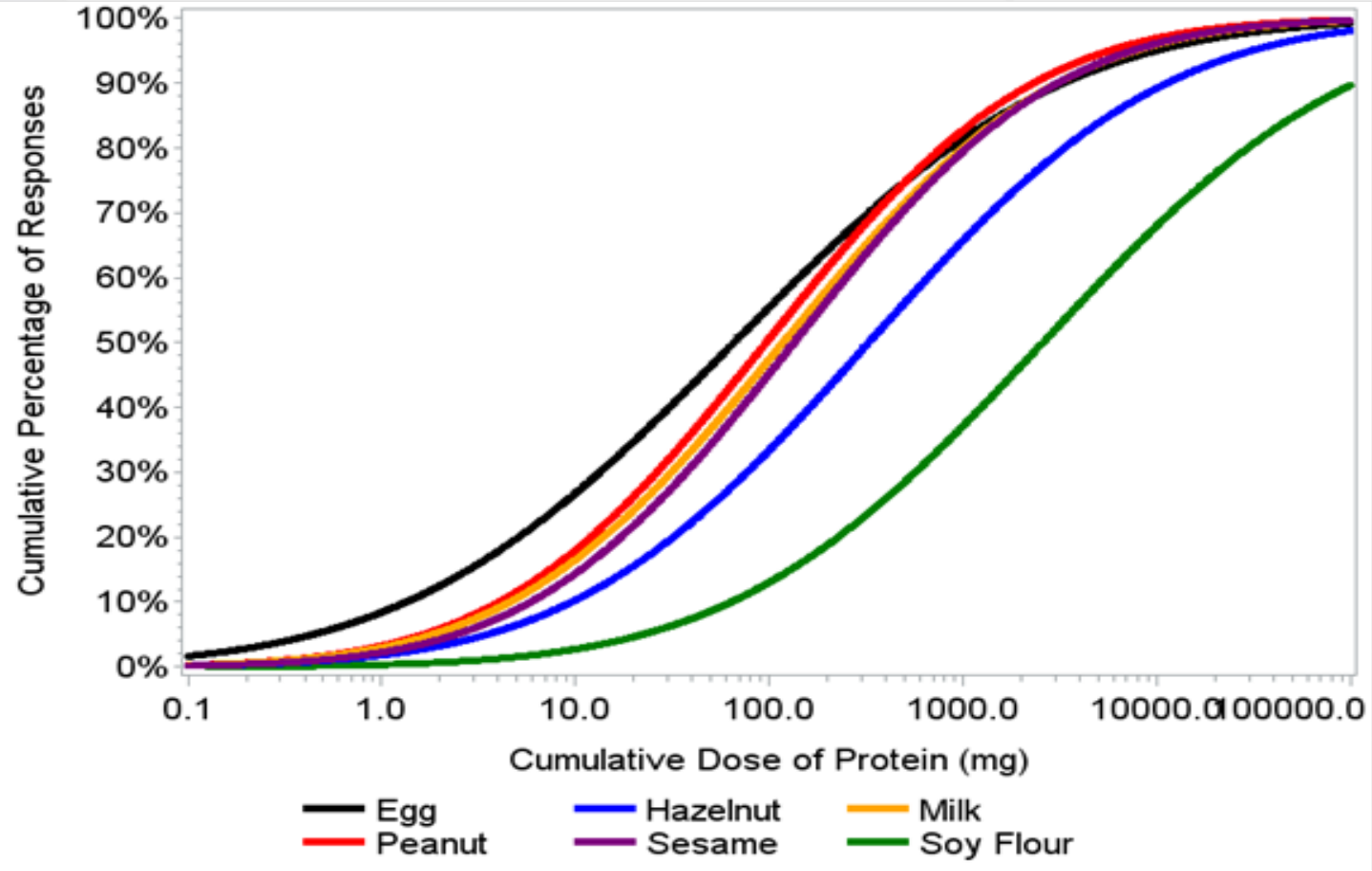
Dose Distributions for Various Food Allergens: Not all food allergens are created equal



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Validating Population Dose-Distribution Models: Peanut Allergy Threshold Study (PATS)

Accepted Manuscript

Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in peanut allergic children

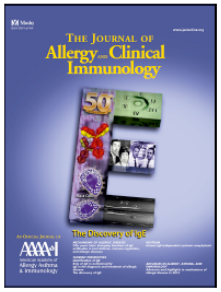
Jonathan O'B. Hourihane, MD, DM, Katrina J. Allen, MD, PhD, Wayne G. Shreffler, MD, PhD, Gillian Dunngalvin, PhD, Julie A. Nordlee, MS, Giovanni A. Zurzolo, PhD, Audrey DunnGalvin, PhD, Lyle C. Gurrin, PhD, Joseph L. Baumert, PhD, Steve L. Taylor, PhD

PII: S0091-6749(17)30324-X

DOI: 10.1016/j.jaci.2017.01.030

Reference: YMAI 12664

To appear in: *Journal of Allergy and Clinical Immunology*



- Objectives:
  - To validate the predicted ED05 (log-normal) for peanut used by VITAL Scientific Expert Panel
  - To assess severity of reactions at ED05 dose
- Recruited 378 "unselected" consecutive patients in three centres (Cork, Boston, Melbourne)

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Single dose challenge
a new risk assessment paradigm

- 2.1% met the predetermined objective criteria vs. 5% predicted
  - Potential selection bias toward more highly sensitive subjects used to model the dose-distribution curves since the data was recorded at tertiary allergy clinics??
  - Objective criteria in these studies used to establish the LOAEL not has stringent as the criteria used in PATS (i.e. single sneeze, cough, or hive considered objective)??
- Log-normal distribution seems to be reasonable and appropriately conservative for use in the estimation of EDs for peanut
  - The even more conservative Weibull distribution should not be used
- Safe; all reactions mild in peanut single dose challenge
  - Interpretable in same way as routine OFC
  - Easy to prepare and perform single dose OFC
  - Most useful for very anxious patients and parents

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Statistical Dose-Distribution Modeling

- Currently collaborating with TNO (B. Remington, G. Houben, W. Blom), Indiana University (K. Shao), and NIOSH (M. Wheeler) to perfect the use of model averaging on interval-censored data
- Will then apply model averaging approach using multiple models to the allergen threshold databases
- Removes subjectivity from model selection but must still weight data from various models to goodness of fit with the actual data

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Can Thresholds Support Labeling and Risk Assessment Decisions?

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Development of Risk Assessment Approaches for Food Allergens

- 2007 workshop on risk assessment approaches – EuroPrevall, ILSI-EU and UK FSA
  1. Safety Assessment Approach
  2. Benchmark Dose (BMD) and Margin of Exposure (MoE) Approach
  3. Probabilistic Approach
- Workshop concluded that the BMD/MoE and probabilistic approaches had the most merit
  - Rely upon low-dose extrapolation from dose-distributions of clinical thresholds rather than a single point estimate

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Risk Assessment

- a function of the exposure dose (mg of protein from the allergenic source) compared to the threshold dose (mg of protein from the allergenic source)

Exposure Dose < Threshold Dose = no predicted reaction
Exposure Dose ≥ Threshold Dose = a predicted reaction

- Quantitative risk assessment can evaluate the risk on an individual or population basis

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Input Parameters:

SERVING SIZE

Grams of food

INPUT 1:
Consumption data

CONTAMINATION LEVEL

Level of peanut protein residue in food (mg/kg)

INPUT 2:
Contamination levels

POPULATION THRESHOLD

Milligrams peanut protein

INPUT 3:
Threshold data

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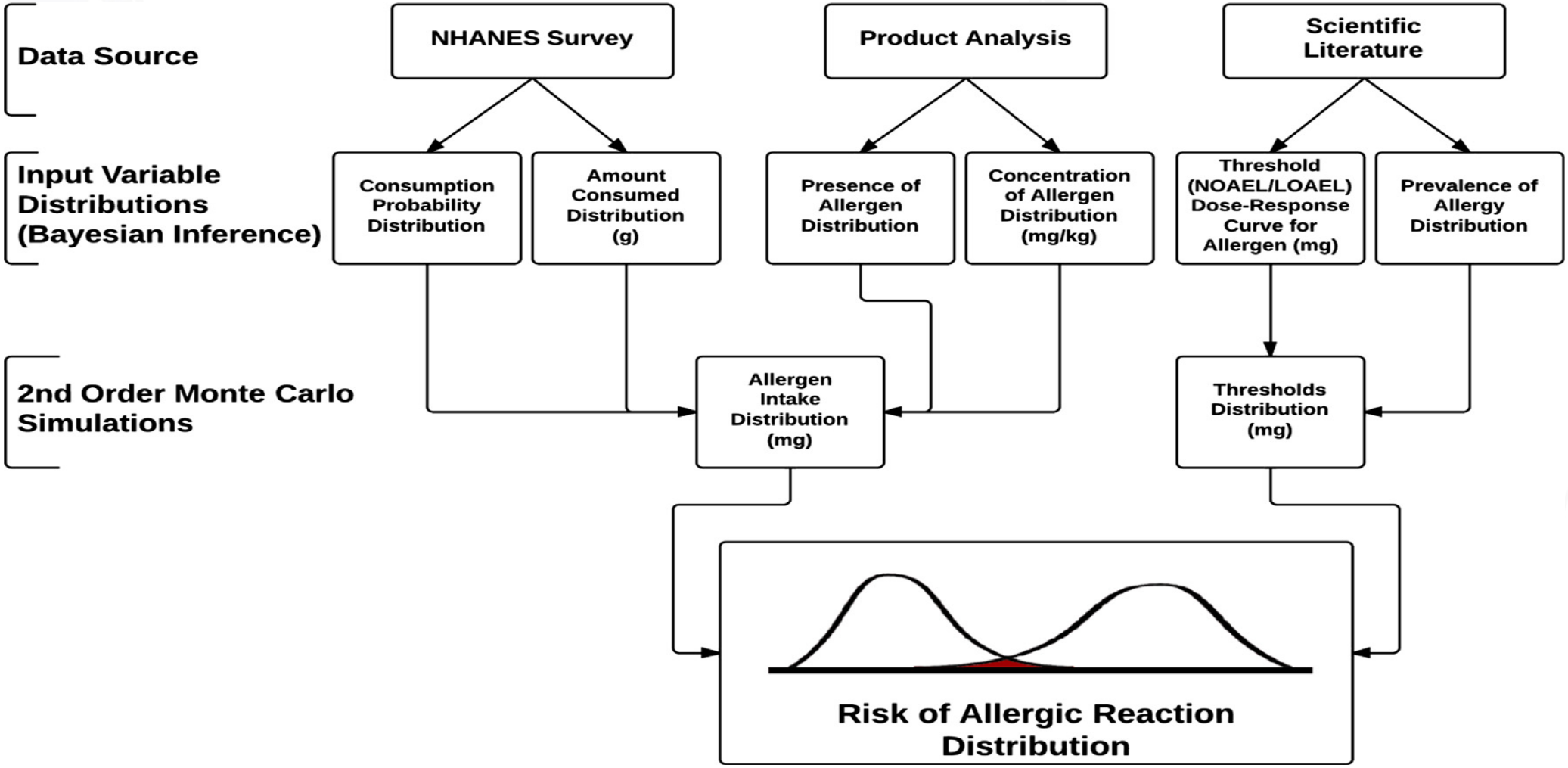
Quantitative Risk Assessment (QRA)



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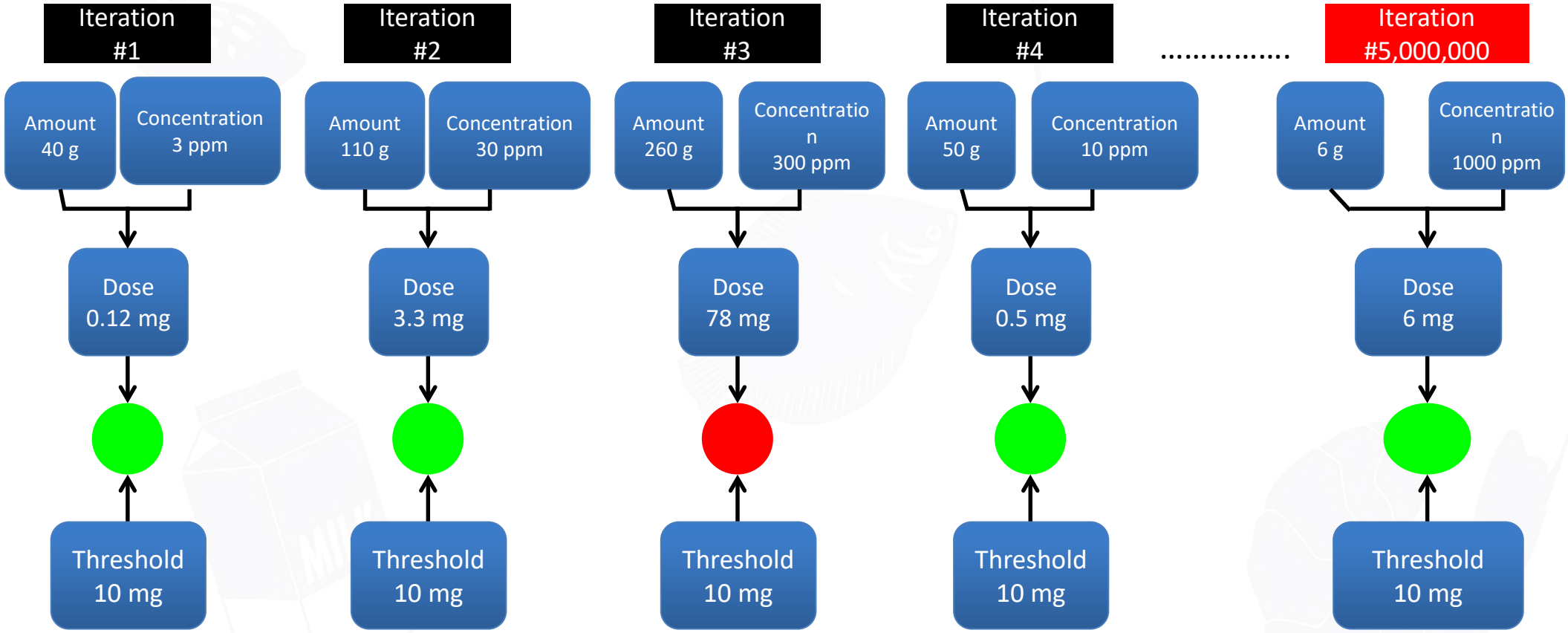
QRA Approach



- Calculate risk of predicted allergic reaction during a single eating occasion (%)

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VITAL* Scientific Expert Panel and the ILSI-EU**: From Thresholds to Action Levels Expert Group

- Utilized threshold data collected by FARRP and TNO on 13 priority food allergens
- Both groups agreed to use the same dataset and the same reference dose recommendations based on conservative dose estimates for each allergic population
  - Groups both consisted of multiple stakeholder groups which debated accepted levels of risk

*VITAL – Voluntary Incidental Trace Allergen Labeling Program
**ILSI-EU – International Life Sciences Institute - Europe

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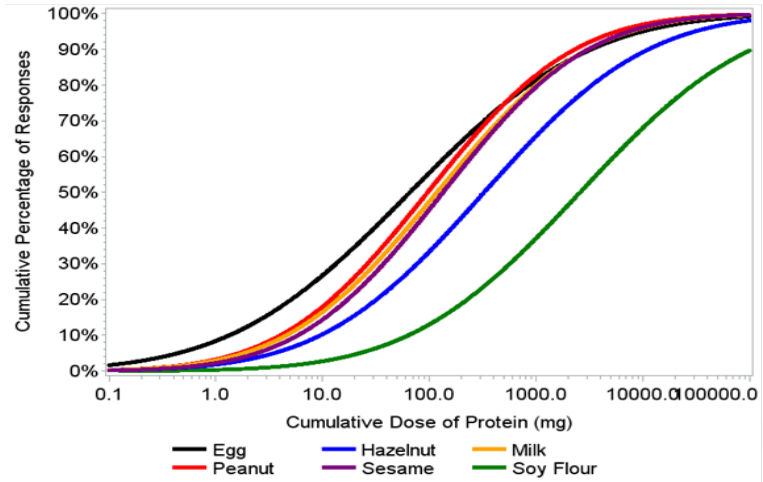
VITAL® Reference Doses

Allergen	mg Protein Level
Peanut	0.2
Milk	0.1
Egg	0.03
Hazelnut	0.1
Soy	1.0
Wheat	1.0
Sesame	0.2
Crustacean shellfish	10.0
Mustard	0.05
Other Tree Nuts	0.1



- Based upon the ED_{01} for peanut, milk egg and hazelnut
- Based upon the 95% LCI of ED_{05} for the remaining 5 allergens
- Other tree nuts based upon the hazelnut reference dose

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VITAL® - A Risk Assessment Tool

- Used to assess the impact of allergen cross contact
- Uses an action level grid to determine if the presence of residual protein from allergenic substances through cross contact requires precautionary labelling
- Stipulates a consistent precautionary allergen labelling statement – “may be present “
- Aims to avoid indiscriminate use of precautionary labelling and preserve a valuable risk management tool.

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An Example of Using Quantitative Risk Assessment:

The 2014-2015 Peanut in Cumin Story in North America

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Initial Peanut in Cumin Situation

- November 2014 – CFIA conducted a random retail analysis of a taco seasoning product
  - Taco seasoning was positive for peanut (and almond)
- FARRP assisted the company with analysis of retain samples of taco seasoning
  - Concentrations of peanut ranged from 1000 to >5000 ppm peanut using several ELISA kits
  - Individuals ingredients were then analyzed
    - Cumin was found to be positive for peanut (>5000 ppm peanut)
- A recall of taco seasoning and sauce was initiated

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Initial Peanut in Cumin Situation

- Late December 2014 – a second series of FDA and USDA-FSIS recalls initiated involving well over 500 products and 30+ companies
  - Concentrations of peanut ranged from 100 to >5000 ppm peanut (FARRP lab and several other contract labs)
  - Back calculation of positive results in some finished products would lead to levels of 50,000 to 105,000 ppm peanut (5-10% peanut in the cumin!!!)
- Ground cumin from sourced from Turkey was implicated in both instances
- FDA did receive consumer reports of alleged allergic reactions from peanut-allergic individuals

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Initial Peanut in Cumin Situation

- Risk associated with 5000 ppm peanut in cumin
- 5000 ppm peanut (µg/g) x 2% cumin in finished product

  = 100 ppm x 100 g serving of a product

  Exposure dose = 100 mg of peanut

  (25 mg peanut protein)

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The Secondary Cumin Situation

- Since the initial series of recalls involving cumin, many companies are testing for peanut residue in cumin and other spices
- Random low level positives have been found in whole cumin seed with no visible signed of whole or parts of peanut
  - Generally ranging between 5 and 25 ppm peanut
- Due to incidental cross-contact due to agricultural commingling

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The Secondary Cumin Situation

- Are these low level positive results found in whole cumin seed a public health risk?
- Quantitative (Probabilistic) Risk Assessment can provide a thorough, transparent analysis of the potential risk

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Concentration of Peanut in Tacos

Seasoning Product	ppm Peanut in Cumin	% Cumin in Seasoning Blend	ppm Peanut in Seasoning Blend	% Seasoning Blend in Taco Meat (including water)	ppm Peanut in Taco Meat (including water)	Proportion of Meal Component to Total (highlighted item indicates component that includes seasoning in question)	ppm Peanut in Prepared Taco Product
Taco Seasoning	10	8.4	0.84	6.241	0.052	Taco Meat: 35% Tortilla: 45% Lettuce/tomato: 5% Cheese: 10%	0.018
	25	8.4	2.1	6.241	0.131		0.046

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Consumption of Tacos Using the NHANES Dietary Survey

			Daily Consumption Estimates (g)			
Prepared Food Product Category	# of Individuals Who Reported Consuming the Product	Estimated % of U.S. Population that Consume the Product	Average	90th Percentile	95th Percentile	99th Percentile
Tacos	1526	4.63	208	396	489	724

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Quantitative Risk Assessment Results - Tacos

Seasoning Product	ppm Peanut in Cumin	Calculated ppm Peanut in Prepared Product	Prepared Product Category	User Risk	Peanut-Allergic Population Risk	Overall U.S. Population Risk
Taco Seasoning	10	0.018	Tacos	2.8 reactions per 1 million peanut-allergic individuals (0.00028%)	1.3 reactions per 10 million peanut-allergic individuals (0.000013%)	1.0 reaction per 1 billion individuals (0.0000001%)
	25	0.046		1.6 reactions per 100,000 peanut-allergic individuals (0.0016%)	7.6 reactions per 10 million peanut-allergic individuals (0.000076%)	6.1 reactions per 1 billion individuals (0.00000061%)

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Quantitative Risk Assessment Conclusions

- Trace levels of peanut (2.5 to 25 ppm) in **whole cumin** that is used in finished products **do not present a public health risk** based on the clinical threshold information for peanut-allergic individuals
  - At 0.046 ppm peanut, the most sensitive peanut-allergic individual reported in the clinical literature would need to eat 8.6 kg (~18 lbs) of tacos during a single eating occasion.

- Regulatory authorities have NOT established regulatory thresholds/action levels for food allergens
  - Products may be subject to recall despite the extremely low levels in both the cumin and finished products
    - Can quantitative risk assessment be utilized on a case-by-case basis to begin to move away from the current zero threshold/zero risk status quo?

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You have a potential undeclared allergen situation: What do you do??

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Conclusions

- QRA and reference doses could be used advantageously by regulatory authorities to determine:
  - determine which ingredients from allergenic sources need to be labelled by source (FALCPA notifications)
  - curtail excessive use of precautionary labelling
  - determine the degree of risk posed by undeclared allergens in recall situations
  - assess the effectiveness of preventive allergen controls (FSMA)

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Thank You for Your Attention

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