

# New Knowledge on Allergen Thresholds

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# Current Situation

- Clinical oral challenges have clearly documented that each food-allergic individual has a threshold dose below which they will not experience an adverse reaction – HUMAN DATA
- The distribution of individual threshold doses can be used to establish population thresholds that would estimate the percentage of allergic consumers who would be predicted to react to any specific dose of the allergenic food
- The science is solid

# Exquisite Sensitivity of Some Food-Allergic Individuals

- Trace amounts of the offending food will trigger reactions
- **BUT IT IS NOT ZERO!!**
- **SEVERE RXNS DO NOT OCCUR AT LOW DOSES!**

# Current Situation

- Public health authorities have not established regulatory action levels or thresholds for any of the allergenic foods
- Labeling laws/regulations in many countries impose a de facto zero threshold for labeling
- **The zero threshold approach is disadvantageous to all stakeholders!!**

# Implications of Zero

- Food-allergic consumers:
  - have a diminished quality of life due to limited food choices
  - are faced with a proliferation of PAL
  - live with a constant fear of experiencing a severe, life-threatening reaction
  - attempt to make personal risk decisions based on interpretation of PAL statements
  - many choose to consumer some PAL products

# Implications of Zero

- Public health authorities:
  - Spend time chasing zero and thus may miss situations that present biggest risk
  - Fail to recognize that many actions have no public health benefit
  - End up with a Reportable Food Registry where undeclared allergens are the #1 reason for recalls but questionable risks
  - Foster or even encourage use of PAL

# Implications of Zero

- Physicians/Allergists:
  - must deal with scared and frustrated patients – if you treat all of them the same, then they all believe that they are the most sensitive
  - have no simple approach to identifying the most sensitive patients or way to give them differential advice even if they could
  - many advise at least some patients to ignore PAL

# Implications of Zero

- Food industry:
  - cannot achieve nor prove zero
  - cannot trust that any detectable level of allergen by any method would not be considered as a regulatory violation
  - reluctant to set corporate threshold levels without regulatory guidance
  - makes heavy use of PAL statements
  - limited ability to select best analytical methods



# Implications of Zero

- Analytical test methods industry:
  - incentive exists to continue to pursue ever more sensitive methods; “zero” keeps getting less
  - no need to reach agreement on harmonization of test methods so lack of standardization on reporting units, standards, validation criteria, etc.
  - test methods have unfortunately become a major obstacle to threshold adoption

# What Does the Food-Allergic Consumer See?



# Precautionary Labeling for Allergenic Foods: Use and interpretation by various stakeholders?



Carnauba Wax.

**ALLERGY INFORMATION:**

**Consumers with food allergies or other sensitivities, please review the ingredients carefully.**

All ingredients are wheat free, gluten free, nut free, peanut free, and trans-fat free. All mixes are packaged on equipment that process wheat, milk, egg, soy, and sulfiting agents. May contain traces of peanuts and tree nuts.

Major allergens: milk and egg.

May contain soy.

# Precautionary Labeling for Allergenic Foods (PAL)

- PAL is quite candidly a mess
- PAL does not serve allergic consumers well
- Because PAL is not truly risk-based
- PAL is confusing to consumers
- PAL serves the food industry better than consumers because it allows them to identify potential risks without really having to assess the risk
- PAL serves public health authorities very well because they can avoid difficult risk management decisions

# Precautionary Labeling for Allergenic Foods

## FDA Criteria

- Voluntary statements that can be used communicate potential risk to allergic consumers
- Must adhere to general labeling law expectation: statements must be truthful and not misleading
- Unofficially, promoting the use of expanded use of PAL

# Precautionary Labeling for Allergenic Foods

## FARRP Criteria

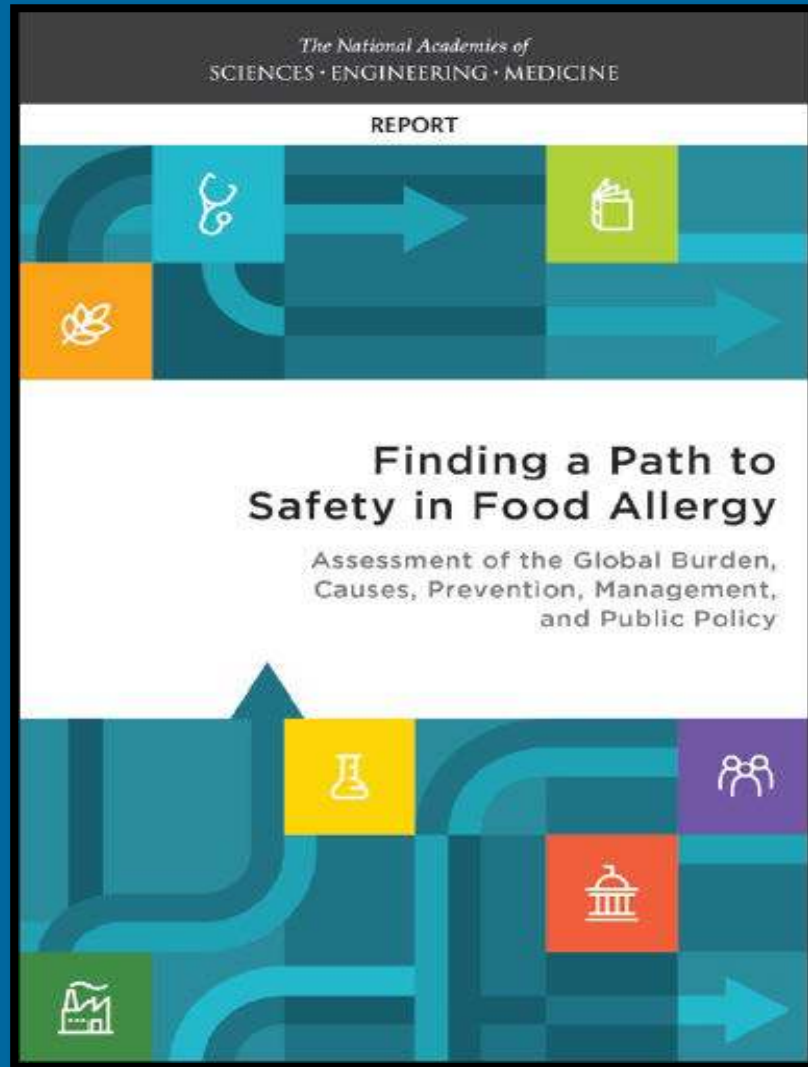
- Voluntary statements that can be used communicate potential risk to allergic consumers
- Use “May Contain” or other similar labeling strategies judiciously and **ONLY** in situations where contamination is:
  1. Documented
  2. Sporadic
  3. Uncontrollable **AND**
  4. Potentially Hazardous

# Is There a Better Way Forward?





*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE



Finding a Path  
to Safety in  
Food Allergy  
*Highlights of the  
Consensus Report*

# IMPROVE POLICIES AND PREVENTION OF SEVERE REACTIONS

## **The committee recommends that**

- **the Codex Alimentarius Commission and public health authorities in individual countries decide on a periodic basis about which allergenic foods should be included in their priority lists based on scientific and clinical evidence of regional prevalence and severity of food allergies as well as allergen potency**

## **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**



# The Science of Thresholds

# Food Allergen Thresholds

- Clinical data exist on individual threshold doses for various allergenic foods from oral challenges conducted for diagnosis, threshold trials, and immunotherapy trials – published and unpublished
- FARRP and TNO collaborate to develop a continuously updated dataset of individual thresholds
- Dose-distribution modeling can be performed to determine population thresholds which could be used as basis for Reference Doses



# 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

# VITAL Dataset Progress

Assembled and evaluated clinical data on all possible priority allergenic foods

- Peanut
- Milk
- Egg
- Hazelnut

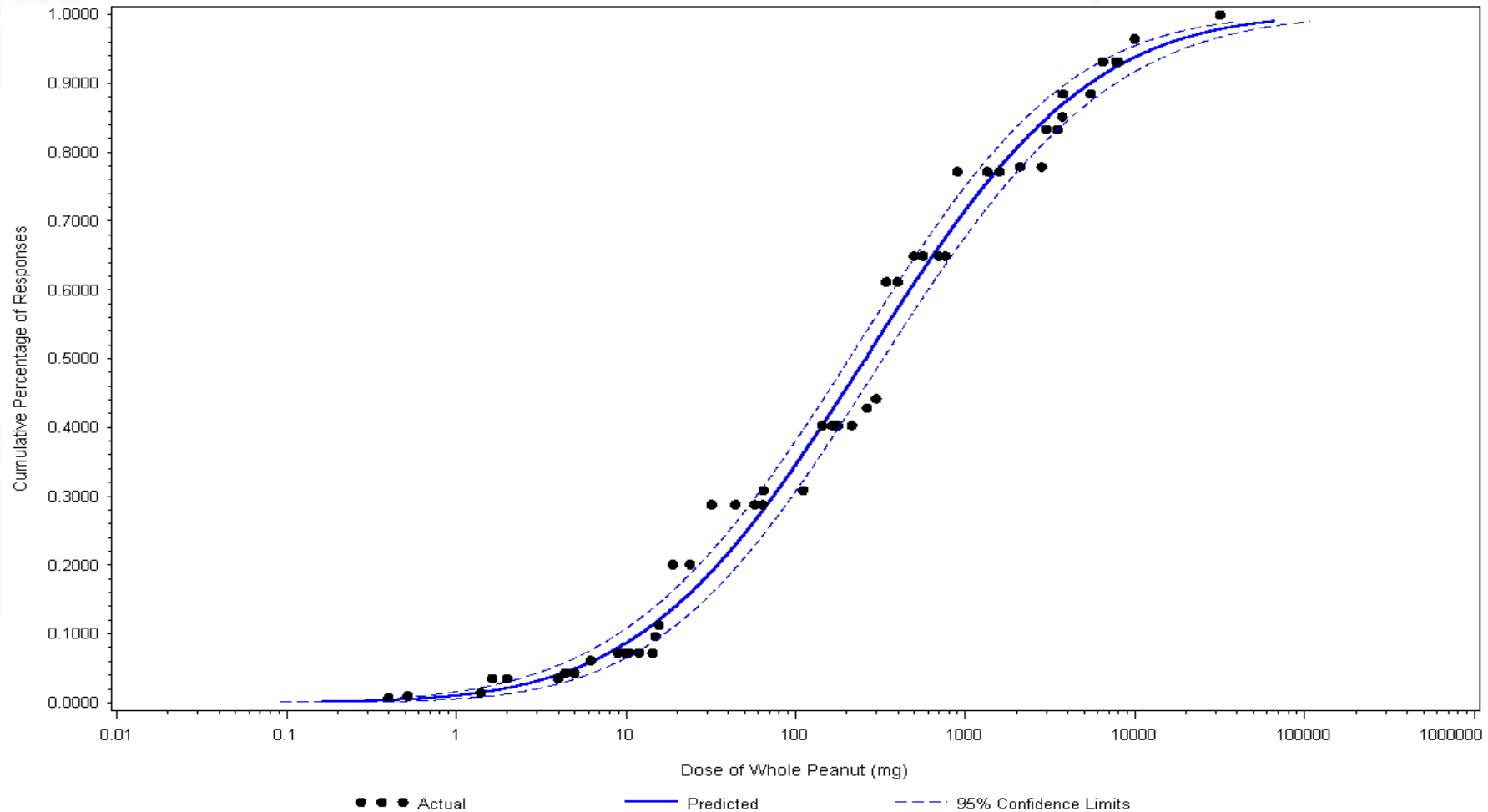
- Soybean
- Wheat
- Cashew
- Mustard
- Lupine
- Sesame seed
- Shrimp

- Celery
- Fish

# 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
<b>Total</b>	<b>1844</b>	<b>1434</b>	<b>3278</b>

# Log-Normal Population Distribution (expressed as whole peanut)



# Statistical Dose-Distribution Modeling

- Fit threshold data to parametric models using SAS LIFEREG (v 9.1) procedures (log-normal, log-logistic, and Weibull)
- Calculate the ED values for the sampled population with confidence intervals and select appropriate reference doses
- VITAL (Australia) uses ED01 or 95% lower confidence interval of ED05
- The accuracy of threshold estimates depends upon the population sampled, the number of subjects, and the statistical approach used

# VITAL Scientific Expert Panel Recommendations - 2012

Allergen	mg Protein Level
Peanut	0.2
Milk	0.1
Egg	0.03
Hazelnut	0.1
Soy	1.0
Wheat	1.0
Cashew	2.0
Mustard	0.05
Lupin	4.0
Sesame	0.2
Shrimp	10.0
Celery	n/a
Fish	n/a

# Dose of Peanuts Causing Reactions in Peanut-Allergic Individuals



<b>0.2mg</b> (0.05 mg)	<b>0.4mg</b> (0.1 mg)	<b>1.0mg</b> (0.25 mg)	<b>5.0mg</b> (1.25 mg)	<b>25mg</b> (6.25 mg)	<b>100mg</b> (25 mg)	<b>400mg</b> (100 mg)
<b>Lowest Eliciting Dose in mg whole peanut (mg peanut protein)</b>						
<b>Percent of Peanut-Allergic Population That Would React To Dose</b>						
<b>0.3%</b>	<b>1%</b>	<b>4.25%</b>	<b>14%</b>	<b>30%</b>	<b>50%</b>	

Ballmer-Weber and Hourihane

# Emerging Consensus on VITAL Reference Doses

- FDA (2006) indicated that probabilistic dose-distribution modeling was the best approach to use to establish thresholds
- EuroPrevall Workshop (2009) agreed with that approach
- VITAL (Australian Allergy Bureau) used that approach in 2011 to first establish Reference Doses



# Emerging Consensus on VITAL Reference Doses

- ILSI-Europe endorsed use of VITAL Reference Doses in 2014
- U.S. National Academies of Science, Engineering & Medicine endorsed the VITAL approach in their report of November, 2016

# Why Don't We Have Food Allergen Reference Doses?

- Widespread (but unsubstantiated) concern that very low doses provoke severe allergic reactions
- Are the threshold data representative of the entire population with allergy to that particular food?

Severity, age, geographic origin, form of food?

- The choice of parametric dose-distribution model and the failure of VITAL to use the most conservative model (Weibull)

FARRP & TNO are pursuing model averaging

# Why Don't We Have Food Allergen Reference Doses?

- Do the results of controlled clinical challenges parallel reactions that occur in the community?

iFAAM data released soon

- Could the dose escalation approach used in clinical challenges promote temporary desensitization?

Just completed one-shot peanut study to be published soon in *J Allergy Clin Immunol*

- Uncertainty factors: uncontrolled asthma, coexistent illness, stress, alcohol intake, exercise, etc.



RESEARCH

Open Access

# Peanut Allergen Threshold Study (PATs): validation of eliciting doses using a novel single-dose challenge protocol

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# Peanut Allergen Threshold Study (PATs) Objectives

- To validate the predicted ED05 (log-normal) for peanut used by VITAL Scientific Expert Panel
- To determine if any of the dose-distribution models (log normal, log logistic or Weibull) were predictive
- To assess safety of a single dose clinical challenge
- To assess severity of reactions at ED05 dose

# Peanut Allergen Threshold Study (PATs)

- Recruit 375 “unselected” consecutive patients in three centres (Cork, Boston, Melbourne)
- Anaphylaxis not an exclusion criterion
- Reaction or + challenge in last 2 yrs or “definitively high” SPT/splgE
- Agreed stop criteria – objective symptoms only
- Record all observations – subjective and objective

# Peanut Allergen Threshold Study (PATs) Results

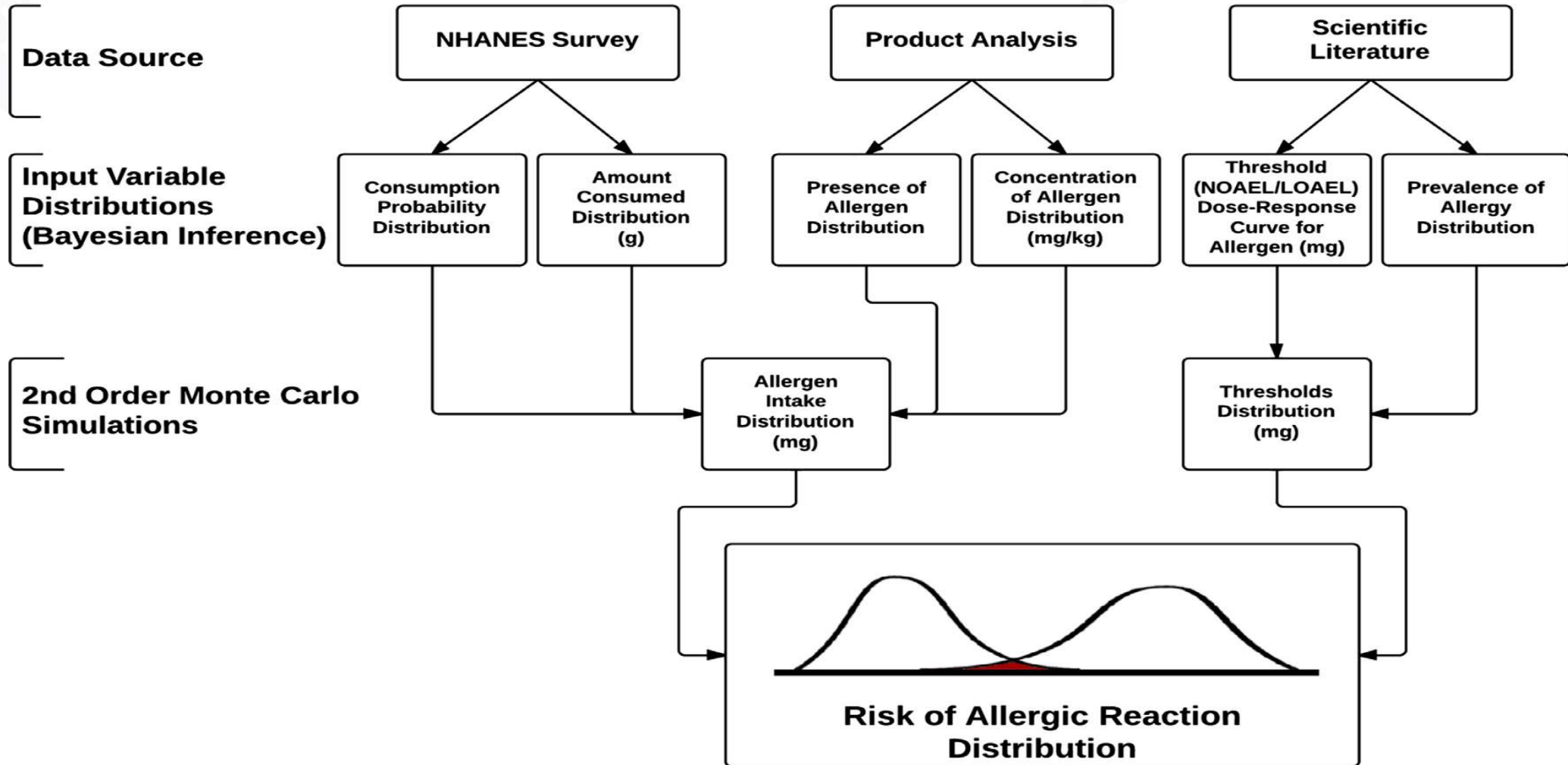
- 2.3% (8 subjects) reacted at ED05 so original prediction was too conservative. Why?
- Log normal and log logistic models are best predictors; cannot recommend Weibull model
- Single dose challenges are safe and single dose approach could be used to develop a clinical approach to identify the most sensitive patients
- No severe reactions occurred at ED05

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# Quantitative Risk Assessment



# QRA – The Inputs

- Threshold dose-distributions: solid, validated especially for peanut, milk, egg, hazelnut
- Food consumption estimates (mean, 90%, 95%): excellent in U.S.; USDA NHANES database
- Analytical estimates of allergen residues: commercial ELISA methods available for many allergenic foods but not often validated with naturally incurred standards; have variable calibrators with questionable adjustment factors

# Improved Allergen Risk Assessment Circa 2016

- Quantitative risk assessment is emerging as an approach to guide labeling, recalls, and ACPs
- Not yet widely adopted
- But we have human threshold data from allergic consumers
- Reliable analytical data can be obtained with caution
- Reliable consumption information exists in some countries
- These form the elements of QRA



[www.farrp.org](http://www.farrp.org)