Assessing Risks of Exposure to Allergens from Foods

Joe Baumert, Ph.D.
Co-Director
Food Allergy Research & Resource Program
University of Nebraska

The National Academies of Science
Institute of Medicine – Food Allergy Workshop
September 1, 2015
Current Situation

- 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 is acutely aware of allergens
  - However there is little or no guidance on action levels/thresholds so extensive use of precautionary labeling (“may contain”) currently exists
Disadvantages of Zero Threshold Approach

- Food-allergic consumers have diminished quality of life due to limited food choices

- Healthcare professionals need to advise scared and frustrated patients
  - Very difficult since precautionary labeling is not consistently used
  - Advice varies from one healthcare professional to the next

- Food industry (some companies, not all!) focuses attention on zero and sometimes misses the big picture pertaining to overall food safety
Moving Toward a Finite Threshold Concept

- Clinical threshold studies have shown that allergic individuals can tolerate ingestion of small amounts of their offending allergen
  - Clinical data are emerging that could allow the establishment of consensus thresholds/action levels
  - Consensus is emerging in U.S., EU, and Australia to support establishment of thresholds/action levels
    - Discussed by stakeholder groups including food industry, regulators, patient organizations, healthcare professionals

- Objective is to improve the quality of life of food-allergic consumers with the establishment of finite threshold approach
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
Risk Assessment

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

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
Input Parameters:

- Clinical threshold data from low-dose food challenges
  - *Note: data from food-allergic individuals rather than extrapolation from animal models as in classical toxicological approaches*

- Exposure Assessment
  - Food intake
  - Level of contamination
Secondary Input Parameters

- Prevalence of the Food Allergy
- Market Share for Specific Product in Category
- Number of Packages of Food Manufactured
- Propensity to Buy Advisory Labeled Products
Assumptions are Necessary

- Assumptions on consumption, purchasing habits, and prevalence of allergy are required for some forms of risk characterization
- The assumptions made for each simulation vary by the way you want to express risk
Expressions of Risk

- **User Population Risk**
  - Assumes everyone is allergic and consumes the product

- **Allergic Population Risk**
  - Assumes everyone is allergic but a specific percent (%) consume the product

- **Overall Population Risk**
  - Assumes a percent (%) of people are allergic and a specific percent (%) consume the product
Quantitative Risk Assessment

Data Source
- NHANES Survey
- Product Analysis
- Scientific Literature

Input Variable Distributions (Bayesian Inference)
- Consumption Probability Distribution
- Amount Consumed Distribution (g)
- Presence of Allergen Distribution
- Concentration of Allergen Distribution (mg/kg)
- Threshold (NOAEL/LOAEL) Dose-Response Curve for Allergen (mg)
- Prevalence of Allergy Distribution

2nd Order Monte Carlo Simulations

Risk of Allergic Reaction Distribution

© 2015
End of Simulation: 1 of 5 simulations had a predicted reaction but computer runs up to 5 million simulations.
Determination of Individual Threshold Doses

- Data from low-dose double-blind, placebo controlled food challenges (DBPCFCs) have become increasingly available in recent years
  - Published and unpublished threshold data from diagnostic evaluations, threshold studies and immunotherapy trials are now available
- Statistical dose-distribution modeling of individual reactive doses can be used to establish population thresholds for individual food allergens
Peanut Threshold Population Distribution (expressed as mg peanut protein)

Cumulative Dose of Protein (mg)

- Log-Normal
- Log-Logistic
- Weibull

© 2015
Dose of Peanuts Causing Reactions in Peanut-Allergic Individuals

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

0.4 mg peanut is the eliciting dose of the most sensitive peanut-allergic patient reported in the published clinical literature.

Ballmer-Weber and Hourihane
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
Extended threshold literature review

- Peanut, 750
- Milk, 351
- Egg, 206
- Hazelnut, 202
- Soy, 80
- Wheat, 40
- Cashew, 31
- Mustard, 33
- Sesame, 21
- Shrimp, 48
- Celery, 39
- Fish, 19
- Lupin, 24
Dose Distributions for Various Food Allergens: Not all food allergens are created equal
Exposure Assessment

- Exposure assessment has 2 main components:
  - Food intake (amount and frequency)
  - Level of contamination in the food (and frequency)

- Both of these factors can be used in food allergy risk assessment to generate an allergen intake distribution
  - Quantitative risk assessment such as probabilistic modelling can be used to statistically predict the probability of an allergic reaction occurring

- Accurate exposure assessment is an important component of the overall risk assessment
  - Must ensure that the consumption data is reflective of the entire population of consumers
  - Contamination data must be carefully calculated or analytically assessed
Exposure Assessment: Food Intake Data

- Based on e.g. 7 days dietary record, 2 days dietary record, 24 h recall, portion/serving size
  - The primary goal is to gather nutritional data and data on consumption patterns of the general population

- Different levels of detail
  - Intake per day
  - Intake per meal/eating occasion
  - Food groups (e.g. Bread)
    - Wheat bread
      - Wheat bread with fat containing kernels
        » Brand name
Exposure Assessment: Food Intake Data Relevant for Food Allergy

- Intake data are based on the general population with an unknown proportion of food allergic individuals.

- It is assumed if a food allergic person eats a certain food the portion size and frequency of consumption will not differ from a non allergic person.

- We don’t know if this assumption is correct.
Exposure Assessment: Using Contamination Data

- The concentration of allergenic food residue (or protein from the allergenic source) can be determined either by calculation or by quantitative analysis.

- Quantitative analysis commonly conducted on ingredients or finished food products that may contain an unintended allergenic residue.
  - Ideally the analytical method used to determine the concentration of the unintended allergic residue would detect proteins from the allergenic source.
    - Total protein
    - A certain protein fraction from the allergenic source (e.g. casein)
    - A specific allergen (e.g. Ara h 2 from peanut)
Analytical Methods

• Quantitative Methods:
  • Enzyme Linked Immunosorbent Assay (ELISA)
  • Polymerase Chain Reaction (PCR)
  • Mass Spec Methods (LC-MS/MS)
  • Surface Plasmon Resonance (SPR)

• Qualitative Methods:
  • Lateral Flow Devices (ELISA LFD)
  • General Protein Tests
  • ATP/Bioluminescence Tests
Selection of an Appropriate Methods is Not Trivial

• What do you want to measure?
  • Select appropriate detection system according to major components in the product
    ▪ Example: Milk
      ➢ Total Milk
      ➢ β-lactoglobulin
      ➢ Casein

• What protein source is used as the standard in the method?

• What units are the results reported in?
  • Example: ppm casein or ppm NFDM
Example of Quantitative Risk Assessment: Peanut in Nutrition Bars

- 197 nutrition bars with advisory labeling for peanut were analyzed for the presence of peanut.
  - 11.1% contained detectable levels of peanut
  - Concentrations ranging from 2.5 to 26,000 ppm whole peanut (0.00025% - 2.6%)

## Peanut Advisory Labeled Nutrition Bars: Results

<table>
<thead>
<tr>
<th>Simulation Results</th>
<th>Mean Predicted Reactions</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction Probability in User Population</td>
<td>7.4 per 1,000</td>
<td>1.9</td>
</tr>
<tr>
<td>Reaction Probability in Peanut Allergic Population</td>
<td>2.3 per 100,000</td>
<td>0.6</td>
</tr>
<tr>
<td>Reaction Probability in Overall Population</td>
<td>1.8 per 10,000,000</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Conclusion: Nutrition bars bearing precautionary allergen labeling do pose a risk to peanut-allergic individuals and should be avoided by this sensitive population of consumers.

Peanut Advisory Labeled Nutrition Bars: A Risky Product

User Risk: 7.4 ± 1.9 Reactions per 1,000 Peanut-Allergic Individuals

Conclusions

• QRA provides an in-depth analysis not available with previous methods
  – Integrates variability and uncertainty of inputs into the risk assessment model for a more realistic estimate of potential risk

• QRA is flexible and applicable to a wide range of scenarios

• QRA enables risk assessors to make an informed decision based on the true risk of a product
Areas of Additional Work

- Fill the existing voids (almond, walnut, etc.)

- Attempt to find additional useful data on foods where low numbers of data points exist
  - EuroPrevall threshold data, FARRP/TNO data mining efforts, iFAAM* data gap analysis

- European Commission iFAAM project
  - Threshold data for walnut
  - Single-dose studies for hazelnut, milk, egg
  - Evaluate and develop quantitative risk assessment models

- The peanut single-dose experiments (discrete dose with ED$_{05}$ in three different countries (Ireland, USA, Australia)

*iFAAM – Integrated Approaches to Food Allergen and Allergy Management – European Commission funded project*
Areas of Additional Work

● Analytical methodology
  – Reference materials needed for standardization
  – Further evaluation and improvement of analytical methods for detection of some processed forms of allergens (e.g. hydrolysed proteins)

● Consumption
  – Evaluate the consumption patterns of food allergic individuals
  – Mirabel study in France is currently studying consumption patterns of peanut allergic individuals
    • Will this data resemble patterns for other food allergic individuals?
  – Do consumption surveys vary significantly between different geographic regions
    • iFAAM project is evaluating this for 3 European countries.
    • Further research should expand this evaluation to other countries throughout the world
Acknowledgements

- Steve Taylor, Ph.D.
- Dave Marx, Ph.D.
- Jamie Kabourek
- Ben Remington, Ph.D.
- Geert Houben, Ph.D.
- Astrid Kruizinga
- Marty Blom, Ph.D.
- Barbara Petersen, Ph.D.
- Rene Crevel, Ph.D.
- Heather Leslie
Thank You for Your Attention

Joe Baumert, Ph.D.
Food Allergy Research & Resource Program
Department of Food Science & Technology
University of Nebraska
jbaumert2@unl.edu