Quantitative Food Allergen Risk Assessment

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Current Status of Regulatory 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
The Zero Risk/Zero Threshold Paradigm

Exposure Dose is always greater than 0

• Zero risk/zero threshold approach is unsustainable operationally and statistically

• A transparent, science-based risk assessment and management process is needed moving forward
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

• 2006 FDA Threshold Working Group also concluded that a quantitative risk assessment approach to establishment of thresholds/actions levels provided the most robust information on population-based health hazard assessment
Emerging Consensus on Thresholds/Reference Doses

- VITAL 2.0 (Allergy Bureau of Australia and New Zealand) Reference Doses were underpinned by use of quantitative (probabilistic) risk assessment

- ILSI-Europe endorsed use of VITAL Reference Doses in 2014

- iFAAM utilized the same threshold data for development of Tier 1 and Tier 2 risk assessment models

- U.S. National Academies of Science, Engineering & Medicine endorsed the VITAL approach in their report of November, 2016

- Several countries have proposed the use of reference doses/action levels to evaluate the risk of unintended allergen presence
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

• Risk assessments can evaluate the risk on an individual or population basis
Comparing Exposure Doses Versus Patient Eliciting Doses (Thresholds) to Estimate the Potential for a Reaction to Occur

1. Estimated Exposure

Consumption quantity (g) x Detected levels of protein residue from the allergenic source (µg/g)

2. Patient Eliciting Threshold

mg amount of protein from the allergenic source that results in a reaction
Which Product Provides the Greater Exposure Risk?

<table>
<thead>
<tr>
<th>Product</th>
<th>Peanut Protein (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product 1</td>
<td>10 ppm</td>
</tr>
<tr>
<td>Product 2</td>
<td>4.17 ppm</td>
</tr>
<tr>
<td>Product 3</td>
<td>0.84 ppm</td>
</tr>
</tbody>
</table>
Which Product Provides the Greater Exposure Risk?

• Product 1:
  10 ppm Peanut Protein (µg/g)

75th Percentile Consumption of Spices:
20g per eating occasion

• Product 2:
  4.17 ppm Peanut Protein (µg/g)

75th Percentile Consumption of Biscuits:
48g per eating occasion

• Product 3:
  0.84 ppm Peanut Protein (µg/g)

75th Percentile Consumption of a Composite Dish:
237g per eating occasion
Which Product Provides the Greater Exposure Risk?

- Product 1: 20g pepper x 10 µg/g = 200 µg peanut protein (0.2 mg)

- Product 2: 48g biscuit x 4.17 µg/g = 200 µg peanut protein (0.2 mg)

- Product 3: 237g lasagna x 0.84 µg/g = 200 µg peanut protein (0.2 mg)

VITAL 2.0 Reference Dose = 0.2 mg peanut protein
Population-Based Quantitative (Probabilistic) Risk Assessment (QRA)

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
- Allergen Intake Distribution (mg)
- Thresholds Distribution (mg)

Risk of Allergic Reaction Distribution
Key Components of a Risk Assessment: Primary Input Parameters:

• Understanding where UAP may occur
  ➢ Understand your vulnerabilities
  ➢ Tracking allergens

• 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/consumption (g; quantity & frequency)
  ➢ Level of allergen cross-contact (μg/g or ppm; & frequency)
Exposure Assessment

• Exposure assessment has 2 main components:
  ➢ Food consumption (g)
  ➢ Level of allergen cross-contact in the food
    (µg/g or ppm protein from the allergenic source)

• 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
  ➢ Cross-contact data must be carefully calculated or analytically assessed
Exposure Assessment: Food Consumption Data

• Consumption data can be gleaned from dietary surveys or recommended portion sizes
  - 7 days dietary record, 2 days dietary record, or 24 hour recall
    - The primary goal is to gather nutritional data and data on consumption patterns – reflects the organisation of data

• Different levels of detail in dietary surveys
  - Intake per day or intake per meal/eating occasion
  - Food groups (e.g. Bread)
    - Wheat bread
      - Whole grain wheat bread, white bread
      - Brand name
Exposure Assessment: Food Consumption Data

• Must ensure that the consumption estimates are reflective of the entire population of consumers
  ➢ portion size
  ➢ mean (average) consumption amount
  ➢ P75 of food consumption distribution
  ➢ maximum consumption amount (very conservative)
Exposure Assessment: 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 (rather than DNA or ATP)

  ➢ There are important differences in target proteins that are detected and report units

    ➢ (ppm WHAT???)
      - Commodity (e.g. NFDM)
      - Total protein from the allergenic source (e.g. total milk protein)
      - A certain protein fraction from the allergenic source (e.g. casein or whey)
      - A specific allergen (e.g. α-casein or β-lactoglobulin)
Expressions of Risk

• **User 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
Population-Based Quantitative (Probabilistic) Risk Assessment (QRA)

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2nd Order Monte Carlo Simulations
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- Thresholds Distribution (mg)

Risk of Allergic Reaction Distribution
QRA Approach (Risk in the Population)

- Calculate risk of predicted allergic reaction during a single eating occasion (%)
Quantitative Risk Assessment Examples
Risk Assessment Example 1
RTE Popcorn
# Calculation of Milk Protein in Ready-To-Eat Popcorn

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% Milk protein in flavor</th>
<th>% Flavor in slurry</th>
<th>% Milk protein in slurry</th>
<th>Milk protein in slurry (ppm)</th>
<th>% Slurry on popcorn</th>
<th>% Protein in formula</th>
<th>ppm allergen in formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butter Flavor</td>
<td>0.000250%</td>
<td>5.0%</td>
<td>0.000012500%</td>
<td>0.13</td>
<td>16.00%</td>
<td>0.000002%</td>
<td>0.020000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serving Size (g)</th>
<th>Allergen protein per serving (g)</th>
<th>Allergen protein per serving (mg)</th>
<th>VITAL 2.0 Reference Dose for milk (mg)</th>
<th>Amount of product achieving VITAL 2.0 Reference Dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>0.000001</td>
<td>0.00062</td>
<td>0.1</td>
<td>5,000.00</td>
</tr>
<tr>
<td>76</td>
<td>0.000002</td>
<td>0.001526</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases</th>
<th>Bags per Case</th>
<th>Bags affected</th>
<th>Servings per bag</th>
<th>Servings affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,500</td>
<td>12</td>
<td>42,000</td>
<td>2.5</td>
<td>105,000</td>
</tr>
</tbody>
</table>
Quantitative Risk Assessment
Consumption Analysis

Popcorn Consumption Estimates Using the 2003-2010 NHANES Dietary Surveys

<table>
<thead>
<tr>
<th>Food Product Category</th>
<th># of Individuals Who Reported Consuming the Product Category</th>
<th>Estimated % of U.S. Population that Consume the Product Category</th>
<th>Consumption Estimates Per Eating Occasion (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
<tr>
<td>Ready-To-Eat Popcorn</td>
<td>500</td>
<td>1.5%</td>
<td>30</td>
</tr>
</tbody>
</table>
Population-Based Quantitative (Probabilistic) Risk Assessment (QRA)

Data Source
- NHANES Survey
- Product Analysis
- Scientific Literature

Input Variable Distributions (Bayesian Inference)
- Consumption Probability Distribution
- Amount Consumed Distribution (g)
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- Concentration of Allergen Distribution (mg/kg)
- Threshold (NOAEL/LOAEL) Dose-Response Curve for Allergen (mg)
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2nd Order Monte Carlo Simulations
- Allergen Intake Distribution (mg)
- Thresholds Distribution (mg)

Risk of Allergic Reaction Distribution
Quantitative Risk Assessment Results

RTE Popcorn_QRA_SEO_0.02ppm Milk Protein

Individual thresholds predicted to have a reaction in simulation (mg protein)

Reaction: ++ + 1

Average Consumption Amount (g Popcorn)

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# Quantitative Risk Assessment of the RTE Popcorn that Contains 0.02 ppm Milk Protein Residue.

<table>
<thead>
<tr>
<th>Product</th>
<th>Allergen Analyzed in Risk Assessment</th>
<th>ppm in Protein in Finished Product</th>
<th>User Risk</th>
<th>Milk Allergic Population</th>
<th>Overall Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTE Popcorn</td>
<td>Milk</td>
<td>ppm Milk Protein</td>
<td># of Reactions per # of Milk Allergic Users (%)</td>
<td># of Reactions per # of Milk Allergic Consumers (%)</td>
<td># of Reactions per # of Individuals in the U.S. (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.02 ppm</td>
<td>8.0 per 10 million (0.00008%)</td>
<td>1.3 per 100 million (0.0000013%)</td>
<td>1.3 per 10 billion (0.000000013%)</td>
</tr>
</tbody>
</table>

*User Risk: assumes that all individuals consuming RTE popcorn are milk-allergic which is a very conservative assumption and likely overestimates the true risk of allergic reaction occurring upon consumption of these products.

**Milk Allergic Population: assumes that 1.5% of the milk-allergic individuals consume RTE popcorn on any given eating occasion.

***Overall Population: assumes that 1.0% of the population is milk-allergic and 1.5% consume RTE popcorn on any given eating occasion.

The most sensitive 1% of the milk allergic population would need to consume 5 kg of popcorn during a single eating occasion to reach their threshold dose. This is 58x the consumption of the 99% reported consumption of the 99 percentile consumers.
Risk Assessment Example 2
Cheese Cracker
## Risk Assessment Example 2

### Cheese Cracker

**Calculation of Peanut Protein in Cheese Cracker**

ppm Peanut Protein in Cracker: 5 ppm peanut protein

<table>
<thead>
<tr>
<th>Serving Size (g)</th>
<th>Allergen protein per serving (g)</th>
<th>Allergen protein per serving (mg)</th>
<th>VITAL Reference Dose for protein (mg)</th>
<th>Amount of product achieving VITAL 2.0 Reference Dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.0002</td>
<td>0.2</td>
<td>0.2</td>
<td>40</td>
</tr>
<tr>
<td>80</td>
<td>0.0004</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quantitative Risk Assessment

Consumption Analysis

Cheese Cracker Consumption Estimates Using the 2003-2010 NHANES Dietary Surveys

<table>
<thead>
<tr>
<th>Food Product Category</th>
<th># of Individuals Who Reported Consuming the Product Category</th>
<th>Estimated % of U.S. Population that Consume the Product Category</th>
<th>Consumption Estimates Per Eating Occasion (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
<tr>
<td>Cheese Cracker</td>
<td>189</td>
<td>0.57%</td>
<td>37</td>
</tr>
</tbody>
</table>
Population-Based Quantitative (Probabilistic) Risk Assessment (QRA)

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- Prevalence of Allergy Distribution

2nd Order Monte Carlo Simulations
- Allergen Intake Distribution (mg)
- Thresholds Distribution (mg)

Risk of Allergic Reaction Distribution
Quantitative Risk Assessment Results
## Quantitative Risk Assessment of the Cheese Cracker that Contains 5 ppm Peanut Protein Residue.

<table>
<thead>
<tr>
<th>Product</th>
<th>Allergen Analyzed in Risk Assessment</th>
<th>ppm in Protein in Finished Product</th>
<th>User Risk</th>
<th>Peanut Allergic Population</th>
<th>Overall Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese Cracker</td>
<td>Peanut</td>
<td>ppm Peanut Protein</td>
<td># of Reactions per # of Peanut Allergic Users (%)</td>
<td># of Reactions per # of Peanut Allergic Consumers (%)</td>
<td># of Reactions per # of Individuals in the U.S. (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 ppm</td>
<td>4 per 1000 (0.4%)</td>
<td>3.2 per 100,000 (0.0032%)</td>
<td>3.2 per 10 million (0.000032%)</td>
</tr>
</tbody>
</table>

*User Risk: assumes that all individuals consuming cheese crackers are peanut-allergic which is a very conservative assumption and likely overestimates the true risk of allergic reaction occurring upon consumption of these products.

**Peanut Allergic Population: assumes that 1% of the peanut-allergic individuals consume cheese crackers on any given eating occasion.

***Overall Population: assumes that 1.0% of the population is peanut-allergic and 0.57% consume cheese crackers on any given eating occasion.
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
  ➢ Can also be used to inform deterministic/safety assessment (Tier 1) approaches

• QRA enables risk assessors to make an informed decision based on the true risk of a product
Thank You For Your Attention

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