ADVANCES ON RISK ASSESSMENT FOR ALLERGENS IN FOOD: AN OVERVIEW AND SUPPORTING TOOLS

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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
iFAAM Approach to Food Allergen Risk Assessment & Management

- iFAAM = Integrated Food Allergy and Food Allergen Management: a European Commission funded Framework 7 Project
- 32 partners involved in 10 work packages of various aspects
- 4 yr project scheduled for completion in March 2017
iFAAM Approach to Food Allergen Risk Assessment & Management

- Risk Assessment aspect for food industry is the focus of iFAAM Work Package #5
- Conducted through the partners involved in iFAAM Work Package #5 (FARRP, TNO, DTU, ANSES, Hylobates, Unilever)
Objective

To develop a validated tiered risk assessment and evidence-based risk management approach for food allergens in the food chain
Tiered risk assessment in iFAAM

Tier 1 RA as integrated step in the Allergen Tracking process (allergen management)

Process to estimate the possible risks of an unintended allergen presence (UAP)

Perform RA

Outcome RA

Next steps

Tier 1 risk assessment

Exposure below or at a certain risk level

Exposure above a certain risk level

Tier 2 risk assessment

Risk mitigation steps

Estimation risk for allergic reactions
1. Allergen tracking tool:
   Is there a likelihood of cross-contact or contamination with an allergen in the consumer product? **TIER 1**
   - Yes
   - No
   - No action needed

2. Tier 1 RA:
   Exposure > reference dose
   Simple calculation
   - Yes
   - No
   - No action needed

3a. Tier 2 RA: Is risk > Accepted risk?
   Complex analysis with inputs from reference dose, consumption and analytical
   - Yes
   - No
   - No action needed

3b. Risk mitigation measures
Allergen Tracking Tool

Risk assessment procedure :: iFAAM

UAP Identification

Process Vulnerability Assessment
   Allergen Mapping

Tier 1 Risk Assessment

Tier 2 Risk Assessment

Explained in next pictures

Actions Measures

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UAP (Hazard) Identification

How does the allergen enter the facility?

- As an ingredient in ALL recipes:
  - Ensure appropriate “contains” labelling is applied
  - Done

- As an ingredient in some recipes:
  - Process vulnerability assessment
  - Go to Step 2

- UAP in an ingredient:
  - Supplier Issues
  - Consistent? Concentration? Dilution in Recipe?
Tier 1 - a simple risk assessment

Starting points for developing Tier 1 RA

› requires minimal input from users
› be fast with easy accessible data for first estimates
› Inputs: UAP levels (ppm allergen) consumption level estimate (serving size?)

› If **green** then product is safe
› If **red** alerts indicates potential unsafe situation perhaps needing a tier 2 RA, PAL usage, or might point towards some critical steps which can be used in risk management mitigation
iFAAM Tier 1

- Risk = Contamination Level X Exposure
- Establish Reference Doses based upon available data from clinical threshold data
- Use simple exposure estimate such as serving size
- If Exposure Level > Reference Dose, then a hazardous situation is predicted
- Degree of hazard depends on assumptions used for reference dose and consumption
iFAAM WP 5: Actions

- Actions are **not** always labelling or PAL.
- Establishment of Reference Doses is NOT just to control application of PAL.
- Actions might be risk mitigation steps, authority decisions about source labelling exemptions of specific ingredients from allergenic sources, authority decisions about acceptability of commodity comingling, decisions about need for recalls, etc.
The Path Toward Reference Doses

- Clinical oral challenges have clearly documented that each food-allergic individual has a threshold dose below which they will not experience an adverse reaction.
- The distribution of individual threshold doses can be used to establish population thresholds that would predict the percentage of allergic consumers who would be predicted to react to any specific dose of the allergenic food.
- Population thresholds can be used to create Reference Doses.
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!
Approaches to Reference Doses

- Analytical – the limit of detection of a test method
- Deterministic or Safety Assessment Method – from a group of food-allergic individuals, identify the most highly sensitive one (NOAEL), then apply an uncertainty factor
- Risk Assessment Method – model the entire distribution of individual thresholds using parametric dose-distribution models; select an acceptable risk level and use the dose that coincides
Risk Assessment Approach is Best

- Only approach that uses all of the available clinical data
- But it requires the most data to have sufficient confidence
- And the patients whose thresholds are in the distribution must be representative of the whole population with allergies to that food
Risk Assessment Approach is Best

- Endorsed by U.S. Food & Drug Administration
- Selected by EuroPrevall consortium
- Also selected by ILSI-Europe
- Used by Allergen Bureau of Australia & New Zealand to establish reference doses for VITAL
Conclusion Finding 4 – ‘the quantitative risk assessment-based approach provides the strongest, most transparent scientific analyses to establish thresholds for the major food allergens. However, . . the currently available data are not sufficient to meet the requirements of this approach. A research program should be initiated to develop applicable risk assessment tools and to acquire and evaluate the clinical and epidemiological data needed to support the .... approach.”

Do we have or can we create enough data to use this approach? **YES, WE DO**
FARRP/TNO Search for Data

- FARRP began to search published clinical literature for data on individual thresholds for specific allergenic foods based upon low dose oral clinical challenges
- Began with peanuts in 2007
- FARRP also mined unpublished clinical data on individual thresholds from clinics performing low dose oral challenges
- Began with clinic of D. A. Moneret-Vautrin in Nancy France in 2009 on peanut
- TNO (Netherlands) began to mine unpublished clinical data on various foods from Dutch and German clinics in 2009
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
Log-Normal Population Distribution (expressed as whole peanut)
How Much is Too Much?

Milligram amounts!
(ppm concentrations)
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>

Ballmer-Weber and Hourihane
VITAL Reference Dose Approach

- VITAL = Voluntary Incidental Trace Allergen Labeling
- Establish VITAL Scientific Expert Panel
  - Steve Taylor, FARRP (Chair) - USA
  - Joe Baumert, FARRP - USA
  - Geert Houben, TNO - Netherlands
  - Rene Crevel, Unilever – U.K.
  - Simon Brooke-Taylor, Allergen Bureau consultant - Australia
  - Katie Allen, Royal Childrens Hospital - Australia
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

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## Number of Threshold Data Points Gleaned From Publications and Unpublished Clinical Records.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Total No. with Objective Symptoms</th>
<th>Right Censored*</th>
<th>Left Censored**</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>750</td>
<td>132</td>
<td>30</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Milk</td>
<td>351</td>
<td>19</td>
<td>59</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Egg</td>
<td>206</td>
<td>33</td>
<td>24</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>202</td>
<td>67</td>
<td>4</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Soybean</td>
<td>80</td>
<td>28</td>
<td>6</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Wheat</td>
<td>40</td>
<td>1</td>
<td>5</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Cashew</td>
<td>31</td>
<td>16</td>
<td>1</td>
<td>Children</td>
</tr>
<tr>
<td>Mustard</td>
<td>33</td>
<td>10</td>
<td>2</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Lupin</td>
<td>24</td>
<td>7</td>
<td>2</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Sesame</td>
<td>21</td>
<td>1</td>
<td>2</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Shrimp</td>
<td>48</td>
<td>26</td>
<td>0</td>
<td>Adults</td>
</tr>
<tr>
<td>Celery</td>
<td>39</td>
<td>4</td>
<td>15</td>
<td>Children and Adults</td>
</tr>
<tr>
<td>Fish</td>
<td>19</td>
<td>2</td>
<td>6</td>
<td>Children and Adults</td>
</tr>
</tbody>
</table>

*Number of right-censored subjects (NOAEL = highest challenge dose; LOAEL set to infinity).

**Number of left-censored subjects (NOAEL set at zero; LOAEL = lowest challenge dose).

From Food Chem. Toxicol. 63:9-17 (2014)
## 2016 Size of Dataset

<table>
<thead>
<tr>
<th>Allergen</th>
<th># Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>1202</td>
</tr>
<tr>
<td>Milk</td>
<td>451</td>
</tr>
<tr>
<td>Egg</td>
<td>382</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>411</td>
</tr>
<tr>
<td>Soy</td>
<td>54</td>
</tr>
<tr>
<td>Wheat</td>
<td>97</td>
</tr>
<tr>
<td>Cashew</td>
<td>245</td>
</tr>
<tr>
<td>Mustard</td>
<td>33</td>
</tr>
<tr>
<td>Lupin</td>
<td>25</td>
</tr>
<tr>
<td>Sesame</td>
<td>40</td>
</tr>
<tr>
<td>Shrimp</td>
<td>75</td>
</tr>
<tr>
<td>Celery</td>
<td>82</td>
</tr>
<tr>
<td>Fish</td>
<td>48</td>
</tr>
</tbody>
</table>
## VITAL Scientific Expert Panel Recommendations - 2012

<table>
<thead>
<tr>
<th>Allergen</th>
<th>mg Protein Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>0.2</td>
</tr>
<tr>
<td>Milk</td>
<td>0.1</td>
</tr>
<tr>
<td>Egg</td>
<td>0.03</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>0.1</td>
</tr>
<tr>
<td>Soy</td>
<td>1.0</td>
</tr>
<tr>
<td>Wheat</td>
<td>1.0</td>
</tr>
<tr>
<td>Cashew</td>
<td>2.0</td>
</tr>
<tr>
<td>Mustard</td>
<td>0.05</td>
</tr>
<tr>
<td>Lupin</td>
<td>4.0</td>
</tr>
<tr>
<td>Sesame</td>
<td>0.2</td>
</tr>
<tr>
<td>Shrimp</td>
<td>10.0</td>
</tr>
<tr>
<td>Celery</td>
<td>n/a</td>
</tr>
<tr>
<td>Fish</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Estimation of risk from allergenic foods

Safety assessment using data points (deterministic approach)

Tier 1

- Increased level of detail and statistical methods

Safety assessment using distributions (probabilistic approach)

Tier 2

- Point estimates derived from:
  - Reference Dose or other risk estimate
  - Serving size or other estimate of consumption
  - UAP estimate(s)
  - Simple math calculation

- Distribution of:
  - All available data of food challenges
  - All food consumption information
  - (Estimated) UAP levels
  - Advanced statistics

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Tier 2 - a complex risk assessment

Starting points for developing Tier 2 RA

- Requires expert assistance and judgment
- Depends upon risk tolerance of user
- Requires considerable information
- Inputs: UAP levels (ppm allergen)
  - Consumption distribution from national survey
  - Threshold dose distribution
- Determine user risk, allergic population risk and overall population risk (%)
Improved Allergen Risk Assessment Circa 2016

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- Not yet widely adopted
- But we have human threshold data from allergic consumers
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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
- Allergen Intake Distribution (mg)
- Thresholds Distribution (mg)

Risk of Allergic Reaction Distribution

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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; availability in Brazil??
- 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
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Circa 2016

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Impediments to Establishment of Allergen Reference Doses

- Allergic consumers worry about safety of reference doses
- Public health authorities are very cautious about definition of acceptable level of risk and establishment of reference doses
- Food industry has been slow to adopt quantitative risk assessment
- Analytical methods have become a key source of variability and uncertainty
Summary

- Reference doses are the only way to bring some order out of the existing chaos
- Allergic consumers must be willing to accept some small level of risk but its magnitude needs to be explained and clinically demonstrated
- Public health authorities should use reference dose concept to control recalls and PAL usage
- Food industry must use the concept
- Analytical method purveyors must get with the program
A QRA For Peanut in Cumin

- Several recalls occurred in USA in late 2014-2015 due to probable adulteration of peanut into cumin spice (high levels with health risk)
- After the initial series of recalls involving cumin, many companies are testing for peanut residue in cumin and other spices
- Random low level positives (5-25 ppm) were found in whole cumin seed with no visible signs of whole or parts of peanut
- Likely due to incidental cross-contact due to agricultural commingling
The Current 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
## Concentration of Peanut in Tacos

<table>
<thead>
<tr>
<th>Seasoning Product</th>
<th>ppm Peanut in Cumin</th>
<th>% Cumin in Seasoning Blend</th>
<th>ppm Peanut in Seasoning Blend</th>
<th>% Seasoning Blend in Taco Meat (including water)</th>
<th>ppm Peanut in Taco Meat (including water)</th>
<th>Proportion of Meal Component to Total (highlighted item indicates component that includes seasoning in question)</th>
<th>ppm Peanut in Prepared Taco Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taco Seasoning</td>
<td>10</td>
<td>8.4</td>
<td>0.84</td>
<td>6.241</td>
<td>0.052</td>
<td>Taco Meat: 35% Tortilla: 45% Lettuce/tomato: 5% Cheese: 10%</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>8.4</td>
<td>2.1</td>
<td>6.241</td>
<td>0.131</td>
<td></td>
<td>0.046</td>
</tr>
</tbody>
</table>
## Consumption of Tacos Using the NHANES Dietary Survey

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

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# Quantitative Risk Assessment Results - Tacos

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Taco Seasoning</td>
<td>10</td>
<td>0.018</td>
<td>Tacos</td>
<td>2.8 reactions per 1 million peanut-allergic individuals (0.00028%)</td>
<td>1.3 reactions per 10 million peanut-allergic individuals (0.000013%)</td>
<td>1.0 reaction per 1 billion individuals (0.0000001%)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.046</td>
<td></td>
<td>1.6 reactions per 100,000 peanut-allergic individuals (0.0016%)</td>
<td>7.6 reactions per 10 million peanut-allergic individuals (0.000076%)</td>
<td>6.1 reactions per 1 billion individuals (0.00000061%)</td>
</tr>
</tbody>
</table>
# Concentration of Peanut in Chili

<table>
<thead>
<tr>
<th>Seasoning Product</th>
<th>ppm Peanut in Cumin</th>
<th>% Cumin in Chili Powder</th>
<th>% Cumin in Prepared Chili (includes added cumin as an ingredient + cumin in the chili powder)</th>
<th>ppm Peanut in the Prepared Chili Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chili Powder + Cumin</td>
<td>10</td>
<td>6</td>
<td>0.082</td>
<td>0.0082</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>6</td>
<td>0.082</td>
<td>0.021</td>
</tr>
</tbody>
</table>
Consumption of Chili Using the NHANES Dietary Survey

<table>
<thead>
<tr>
<th>Prepared Food Product Category</th>
<th># of Individuals Who Reported Consuming the Product</th>
<th>Estimated % of U.S. Population that Consume the Product</th>
<th>Daily Consumption Estimates (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chili</td>
<td>790</td>
<td>2.39</td>
<td>Average: 316, 90th Percentile: 572, 95th Percentile: 841, 99th Percentile: 1508</td>
</tr>
</tbody>
</table>
## Quantitative Risk Assessment Results - Chili

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chili Seasoning</td>
<td>10</td>
<td>0.0082</td>
<td>Chili</td>
<td>1.2 reactions per 1 million peanut-allergic individuals (0.00012%)</td>
<td>2.9 reactions per 100 million peanut-allergic individuals (0.0000029%)</td>
<td>2.3 reactions per 10 billion individuals (0.000000023%)</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.021</td>
<td></td>
<td>1.1 reactions per 100,000 peanut-allergic individuals (0.0011%)</td>
<td>2.5 reactions per 10 million peanut-allergic individuals (0.000025%)</td>
<td>2.0 reactions per 1 billion individuals (0.0000002%)</td>
</tr>
</tbody>
</table>
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.

- Regulatory authorities have NOT established regulatory thresholds/action levels for food allergens:
  - Products may be subject to recall despite the low levels in both the cumin and finished products.