INCREASING CLINICAL PEANUT THRESHOLDS THROUGH IMMUNOTHERAPY:
Quantitative Assessment of the Safety Benefits

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Background and Aim

- Several immunotherapy products are in development for the treatment of peanut allergy, with the goal of reducing the risk of a reaction following an accidental exposure.

- In clinical trials, after a defined period of treatment with immunotherapy, the degree of desensitization is evaluated by the change in Eliciting Dose by a double-blind placebo-controlled food challenge.*

- Successful therapy aims to increase peanut allergic individual’s threshold dose, but little is known about the risk reduction associated with a patient’s increase of threshold.

- The aim of our research is to use the Quantitative Risk Assessment (QRA) model developed by FARRP**, to assess the clinical benefit of increasing the threshold by immunotherapy.

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*FDA Jan 21 2016 Allergenic Products Advisory Committee Meeting Presentations - CBER

Cross-Contact in Foods is an Everyday Threat for the Peanut-Allergic Patient

Hostess recalls snack cakes, doughnuts over peanut residue

Learning from FDA Food Allergen Recalls and Reportable Foods

<table>
<thead>
<tr>
<th>Food Class</th>
<th>Number of Recalls</th>
<th>% Class 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakery</td>
<td>153</td>
<td>62</td>
</tr>
<tr>
<td>Snack</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Candy</td>
<td>45</td>
<td>63</td>
</tr>
<tr>
<td>Dairy</td>
<td>39</td>
<td>58</td>
</tr>
<tr>
<td>Dressing</td>
<td>38</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 1: Foods Most Often Involved in Allergen Recalls

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of Recalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrong package or label</td>
<td>82</td>
</tr>
<tr>
<td>Terminology</td>
<td>59</td>
</tr>
<tr>
<td>Failure to carry forward information from an ingredient to final label</td>
<td>41</td>
</tr>
<tr>
<td>Cross-contact</td>
<td>28</td>
</tr>
<tr>
<td>Ingredient mislabeled from supplier</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 3: Causes of Food Allergen Recalls

FARRP Tracking of FDA Food Allergen – Peanut Recalls
Calendar Years 2006-2017
Peanut Allergic Patients Present with Different Levels of Sensitivity

*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*
Consumers Eat Varying Quantities of Food Per Eating Occasion
Quantitative 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
Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy

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http://dx.doi.org/10.1016/j.jaip.2017.05.006
What is the Risk Reduction Associated with an Increase of Eliciting Dose?

**SERVING SIZE**

- Grams of food

**INPUT 1:** Consumption data

**CONTAMINATION LEVEL**

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

**INPUT 2:** Contamination levels

**PATIENT THRESHOLD**

- Milligrams peanut protein

**INPUT 3:** Threshold data
The QRA Model is Applied to Predict the Frequency of Reactions in Peanut-allergic Patients

**INPUT 1:** Consumption data

**INPUT 2:** Contamination levels

**INPUT 3:** Threshold data

5 million iterations of the risk assessment conducted for each individual threshold (1, 3, 10, 30, 100, 300, 1000 mg peanut protein)

**DATA SOURCE**

- NHANES Survey

**INPUT VARIABLE DISTRIBUTIONS (BAYESIAN INFERENCE)**

- Consumption Probability Distribution
- Amount Consumed Distribution (g)

**2ND ORDER MONTE CARLO SIMULATIONS**

**INPUT VARIABLE DISTRIBUTIONS (BAYESIAN INFERENCE)**

- Presence of Allergen Distribution
- Concentration of Allergen Distribution (mg/kg)

**DATA SOURCE**

- Product Analysis

**OUTPUT VARIABLE DISTRIBUTIONS**

- Exposure Dose Distribution (mg peanut protein)
### Input 1: Consumption Data of Key Product Categories

Four commonly consumed packaged product categories at risk for containing traces of peanut protein*

<table>
<thead>
<tr>
<th>Food Category</th>
<th># Individuals Who Reported Consuming the Food (% of total population surveyed)</th>
<th>Average</th>
<th>90th Percentile</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cookies</td>
<td>11,297 (34.2%)</td>
<td>32</td>
<td>78</td>
<td>105</td>
<td>178</td>
<td>634</td>
</tr>
<tr>
<td>Ice Cream</td>
<td>7877 (23.9%)</td>
<td>125</td>
<td>240</td>
<td>291</td>
<td>441</td>
<td>1227</td>
</tr>
<tr>
<td>Doughnuts/Snack Cakes</td>
<td>2128 (6.44%)</td>
<td>73</td>
<td>128</td>
<td>155</td>
<td>225</td>
<td>768</td>
</tr>
<tr>
<td>Snack Chip Mixes</td>
<td>7802 (23.6%)</td>
<td>37</td>
<td>64</td>
<td>96</td>
<td>172</td>
<td>380</td>
</tr>
</tbody>
</table>


** NHANES: 2003-2010 US National Health and Nutrition Examination Surveys. 30,000+ individuals, various product categories
Input 1: Consumption Data (Distribution Analysis)
## Input 2: Contamination Levels
Concentration (ppm or mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Concentration</th>
<th>Consumed Amount</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peanut Residue</strong></td>
<td>ppm (or mg/kg)</td>
<td>X kg (or gram/1000)</td>
<td>= mg Peanut Residue</td>
</tr>
<tr>
<td></td>
<td>↓ X 0.25*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peanut Protein</strong></td>
<td>ppm (or mg/kg)</td>
<td>X kg (or gram/1000)</td>
<td>= mg Peanut Protein</td>
</tr>
</tbody>
</table>

*Peanut kernel contains 25% peanut protein on avera

1000 ppm peanut (mg/kg) ✗ 100 grams of cookies = 100 mg DOSE of peanut (1/10th of a peanut kernel)
Peanut residue can occasionally be present in pre-packaged food products bearing precautionary allergen labels* (i.e. May Contain Peanut and other terms)

Concentrations of peanut residue in pre-packaged food products have varied
- Many products do not have detectable peanut residue
- Of those that were positive, the concentrations ranged from 1-1000 ppm (mg/kg) peanut protein generally
- Median of 10-30 ppm peanut protein

Conservative approach for risk assessment:
- Use range from 1 to 1000 ppm peanut protein (assume all products contain detectable peanut residue)
- Random selection with equal chance for low and high end of the range

Robertson, 2013 Food Addit Contam Part A;30(9):1467-72
Input 3: Range of Patient Baseline Threshold (Based on PRACTALL Guidelines)

Input for QRA model reflects patient sensitivity at baseline.

QRA Approach

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

Iteration #1:
- Amount: 40 g
- Concentration: 3 ppm
- Dose: 0.12 mg
- Threshold: 10 mg

Iteration #2:
- Amount: 110 g
- Concentration: 30 ppm
- Dose: 3.3 mg
- Threshold: 10 mg

Iteration #3:
- Amount: 260 g
- Concentration: 300 ppm
- Dose: 78 mg
- Threshold: 10 mg

Iteration #4:
- Amount: 50 g
- Concentration: 10 ppm
- Dose: 0.5 mg
- Threshold: 10 mg

Iteration #5,000,000:
- Amount: 6 g
- Concentration: 1000 ppm
- Dose: 6 mg
- Threshold: 10 mg
Predicted Probability of a Reaction Associated with the Four Selected Product Categories Containing Peanut Protein Residue

- **Cookies**
  - 1mg: 3mg
  - 10mg: 10mg
  - 30mg: 30mg
  - 100mg: 100mg
  - 300mg: 300mg
  - 1000mg: 1000mg

- **Ice Cream**
  - 1mg: 1mg
  - 3mg: 3mg
  - 10mg: 10mg
  - 30mg: 30mg
  - 100mg: 100mg
  - 300mg: 300mg
  - 1000mg: 1000mg

- **Doughnut/snack cake**
  - 1mg: 1mg
  - 3mg: 3mg
  - 10mg: 10mg
  - 30mg: 30mg
  - 100mg: 100mg
  - 300mg: 300mg
  - 1000mg: 1000mg

- **Snack chip mix**
  - 1mg: 1mg
  - 3mg: 3mg
  - 10mg: 10mg
  - 30mg: 30mg
  - 100mg: 100mg
  - 300mg: 300mg
  - 1000mg: 1000mg
Predicted Probability of an Allergic Reaction Occurring Due to Peanut Protein Contamination In Ice Cream

PEANUT-ALLERGIC INDIVIDUAL’S THRESHOLD VALUE

<table>
<thead>
<tr>
<th>Threshold</th>
<th>1 mg</th>
<th>3 mg</th>
<th>10 mg</th>
<th>30 mg</th>
<th>100 mg</th>
<th>300 mg</th>
<th>1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
<td>60.7%</td>
<td>46.9%</td>
<td>32.3%</td>
<td>19.0%</td>
<td>5.8%</td>
<td>0.295%</td>
<td>0.0040%</td>
</tr>
</tbody>
</table>

99.1% Risk Reduction*

*Risk reduction from 32.3% to 0.295%

32.3/0.295 = 109-fold, or \((32.3 - 0.295) / 32.3 \cdot 100\% = 99.1\%\)
Relative Risk Reduction: Ice Cream

~99% risk reduction is achieved when:
- reaching an Eliciting Dose of 300 mg from ≤ 10 mg
- reaching an Eliciting Dose of 1000 mg from ≤ 300 mg
Relative Risk Reduction Associated with Reaching Post-Therapy Threshold

% Reduction in Risk of an Allergic Reaction due to Cross-Contamination in Packaged Goods

<table>
<thead>
<tr>
<th>Baseline Threshold</th>
<th>Post-therapy Threshold: 300 mg</th>
<th>Post-therapy Threshold: 1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cookies</td>
<td>Ice Cream</td>
</tr>
<tr>
<td>1</td>
<td>99.9%</td>
<td>99.5%</td>
</tr>
<tr>
<td>3</td>
<td>99.9%</td>
<td>99.4%</td>
</tr>
<tr>
<td>10</td>
<td>99.9%</td>
<td>99.1%</td>
</tr>
<tr>
<td>30</td>
<td>99.8%</td>
<td>98.5%</td>
</tr>
<tr>
<td>100</td>
<td>97.0%</td>
<td>94.9%</td>
</tr>
<tr>
<td>300</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

FAARP: Food Allergy Research & Resource Program, University of Nebraska.
Conclusions

Quantitative Risk Analysis (QRA) provides a quantitative and transparent approach to assess the benefit of increasing a peanut-allergic individual’s threshold during immunotherapy.

**Significant risk reductions (99%) are reached**
- When ED is 300 mg if initial dose is 10 mg or lower
- When ED is 1000 mg if initial dose is 300 mg or lower
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