Food Allergen Thresholds & Probabilistic Risk Assessment: Current State of the Science

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Current Situation

- Food allergies impact millions of consumers on a worldwide basis
- Symptoms of allergic reactions can be severe and even life-threatening for some affected persons
- 8 foods or food groups (Big 8) are responsible for 90% of allergic reactions
- Important allergenic foods beyond the Big 8 can exist in some countries/regions
Current Situation

- Only preventive approach is a specific avoidance diet for the affected individual
- Awareness of food allergies within the food industry has improved immensely in past 20 years but inconsistencies continue to exist especially on worldwide basis
- Most public health authorities rely upon labeling as the principal approach to food allergy prevention

Current Situation

- Public health authorities have not established regulatory thresholds for any of the allergenic foods
- Labeling laws/regulations in many countries impose a de facto zero threshold for source labeling of ingredients
- Industry acutely aware of allergens, no guidance on thresholds so rampant use of precautionary labeling (“may contain”)
Timeline of the Threshold Concept

- For many years, physicians realized that ingestion of small amounts (not well defined) could elicit allergic reactions
- Physicians recommended complete avoidance (ZERO threshold)
- Consumers were told by their physicians to completely avoid the offending food(s)
- Zero threshold became the concept
Disadvantages of Zero Threshold Approach

- Food-allergic consumers have diminished quality of life due to limited food choices
- FDA and other public health authorities spend time chasing zero
- Physicians deal with scared and frustrated patients – if you treat all of them the same, then they will all believe that they are the most sensitive
- Food industry focuses attention on zero and sometimes misses forest for trees
  - Zero keeps getting less with advancement of analytical methods

Moving Toward a Finite Threshold Concept

- Very low doses have been proven to be safe
- Quality of life of food-allergic consumers could improve with establishment of finite threshold approach
- Clinical data are emerging that could allow the establishment of consensus thresholds
- Consensus is emerging in U.S., EU, and Australia to support establishment of thresholds
- Discussion and education still needed
  - Includes food industry, regulators, allergic consumers, clinicians, dietitians
The Threshold Concept Timeline

- 1999-2004: FARRP sponsored 3 Threshold Roundtables that focused increased attention on desirability of thresholds, developed consensus clinical approach, and began to encourage physicians to collect and disseminate the data

- 1997: Jonathan Hourihane and colleagues published first threshold study on peanuts; 14 patients; most sensitive one had a mild objective reaction at 2 mg; 12/14 had no objective response at top dose of 50 mg peanut!!


US FDA Allergen Thresholds

- Threshold Working Group Report

- “Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food” (March, 2006)

FDA Threshold Working Group

- QRA based on knowledge of individual threshold doses within the overall population of individuals with a particular food allergy and then uses statistical dose distribution modeling.
- Very data intensive!!

FDA Conclusion

- 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?
The Threshold Concept Timeline

- 2006: FARRP switches our focus from conduct of small individual threshold studies to acquisition of clinical data to satisfy the probabilistic modeling approach
- 2007: Allergen Bureau of Australia releases the VITAL concept based upon reference doses for precautionary labeling decisions
- 2008: ILSI-Europe and EuroPrevall Workshop, Madrid also endorses probabilistic modelling as the optimal approach to estimation of thresholds
- Japan establishes 10 ppm as threshold level based upon analytical detection limits

The Threshold Concept Timeline

- 2010: FARRP publishes expanded dose distribution curve for peanut thresholds using data points gleaned from a single clinic in Nancy France (Taylor et al., Food Chem Tox 48:814-819, 2010) – 286 subjects or 450 total
- 2010: ILSI-Europe organizes Task Force on Thresholds to Action Levels
The Threshold Concept Timeline

- 2011: FARRP establishes partnership with Australian Allergy Bureau and TNO (Netherlands) to assemble existing threshold data on commonly allergenic foods and use those data to establish Reference Doses based upon quantitative risk assessment
- May 2012 – VITAL 2.0 released with Reference Doses
- Sept 2012 – ILSI-Europe conference on Thresholds to Action Levels recommends same Reference Doses
- Dec 2012 – FARRP initiates One-Shot Peanut Trial in Ireland, Australia and USA to validate the predicted ED05

Threshold Data Search: Methodological Approach

- Criteria for inclusion:
  - Published studies or unpublished clinical data
  - Allergic to specific food by history or other factors
  - DBPCFC
  - Description of NOAEL and/or LOAEL (if dosing regimen provided, then can determine NOAEL from LOAEL)
  - Data on individual patients
  - Objective symptoms @ doses
Allergen Threshold Studies

- The accuracy of threshold estimates depends upon the population sampled, the number of subjects, and the statistical approach used.

- From the NOAELs and LOAELs of selected patients, a dose-distribution model was constructed using interval-censoring survival analysis (Taylor et al., 2009).
  - Data fitted to Log-Normal distribution (best fit); also tried Log-Logistic and Weibull (little difference)
  - ED$_{10}$ and ED$_{05}$ estimated (even ED$_{01}$ if enough data)
Peanut Threshold Population Distribution (expressed as mg peanut protein)

Cumulative Percentage of Responses

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Cumulative Dose of Protein (mg)

1.00E-03 1.00E-02 1.00E-01 1.00E+00 1.00E+01 1.00E+02 1.00E+03 1.00E+04 1.00E+05 1.00E+06

Log-Normal Log-Logistic Weibull

Dose of Peanuts Causing Reactions in Highly Sensitized Patients

Taylor et al. Food Chem Tox., 2011
Pioneering VITAL Effort

- Australian Allergen Bureau Management Committee and Food Allergy Research & Resource Program collaborated to assemble a Scientific Expert Panel to consider revision of VITAL Action Levels
- Panelists: Steve Taylor, FARRP
  Joe Baumert, FARRP
  Rene Crevel, Unilever
  Geert Houben, TNO
  Simon Brooke-Taylor, consultant
  Katie Allen, Melbourne allergist
- Considerable assistance provided by: Ben Remington (FARRP), Astrid Kruizinga (TNO), Ellen Dutman (TNO), and Harrie Buist (TNO)

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
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>
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<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>
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<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>
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</tr>
<tr>
<td>Sesame</td>
<td>21</td>
<td>1</td>
<td>2</td>
<td>Children and Adults</td>
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<tr>
<td>Shrimp</td>
<td>48</td>
<td>26</td>
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<td>Adults</td>
</tr>
<tr>
<td>Celery</td>
<td>39</td>
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<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).

Conclusions

- Good dose distribution models were built for 11 allergens of public health importance
- Sufficient data exist to establish reference doses
  - Based upon the ED_{01} for peanut, milk egg and hazelnut
  - Based upon the 95% LCI of ED_{05} for the remaining 7 allergens
- Interpretation
  - Reference doses are conservative; no need for additional uncertainty factors
- Data gaps
- Reference doses provide a realistic basis for defining action levels which can be used operationally
Reference Doses (*VITAL)

<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>Other Tree Nuts*</td>
<td>0.1</td>
</tr>
<tr>
<td>Sesame*</td>
<td>0.2</td>
</tr>
<tr>
<td>Crustacean shellfish*</td>
<td>10.0</td>
</tr>
<tr>
<td>Fish*</td>
<td>0.1</td>
</tr>
<tr>
<td>Mustard</td>
<td>0.05</td>
</tr>
</tbody>
</table>

VITAL vs. Risk to Allergic Consumers

- No additional uncertainty factors needed
- Because of use of ED$_{01}$ or lower 95% confidence interval of ED$_{05}$
- Risk of mild, transitory objective reactions typically requiring no pharmacological intervention with possibly a few noteworthy exceptions
- Allergic populations studied appear to be representative or skewed toward more highly sensitive (referral clinics, immunotherapy studies)
Recent VITAL Grid Revision
Original Questions

- Can we combine pediatric and adult data points?
- Can we combine data from different clinics?
- Cumulative vs. discrete doses?
- Does the choice of statistical model make a difference?
- Do sufficient data exist to use the ED_{01} in every case?
  Alternate – lower 95% confidence interval of ED_{05}

Clinical Questions

- Are the patients representative of the affected population?
- Do they include a sufficient number of the most highly sensitive/severely affected individuals?
- Do differences exist between patients with and without histories of severe reactions?
- Do differences exist between adults and children?
- Do geographic differences occur?
- Do differences occur between different clinic populations?
- How do you adjust for differences in clinical protocols?
- Does the form of the allergenic food make a difference?
Clinical Questions

- The 2013 clinical manuscript is intended to answer many of these questions
- Previously showed in 2010 publication that no difference existed in Nancy France peanut-allergic population between individuals with histories of severe reactions and those without such histories
- Previously showed that Interval Sensing Survival Analysis could be used effectively to adjust for differences in dosing patterns in different clinical studies

Future Studies

- Fill the existing voids (almond, walnut, etc.)
- Publish the unpublished data
- Attempt to find additional useful data on foods where low numbers of data points exist
- The one-shot experiment (discrete dose with ED_{05} in three different countries (Ireland, USA, Australia)
- Incorporate any new data on thresholds
Using Probabilistic Modeling to Determine Quantitative Risk Assessments to Protect Allergic Consumers:

QRA Inputs Available

Primary Inputs

- Prevalence of Food Allergy
- Food Allergen Threshold
- Consumption of Specific Product
- Concentration (ppm) of Allergen in Product
**QRA Diagram**

- NHANES Survey
- Product analyses
- Clinical studies

- Consumption Quantity (g)
- Levels (ppm)
- Allergen intake (mg)
- Thresholds (mg)

- No Allergic Reaction
- Allergic Reaction

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