Thresholds

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Historical Approach to Dose/Response

- Physicians recommended completed avoidance (ZERO threshold)
- Ingestion of small amounts (not well defined) could elicit allergic reactions
- DBPCFC was the gold standard for diagnosis but challenges often started at 400 – 500 mg
- 20%+ of patients reacted to first challenge dose – some severe rxns
Entrenched Zero Threshold Concept

- Physicians recommended complete avoidance
- Food-allergic consumers attempt to practice complete avoidance
- Labeling laws and regulations in many countries (e.g. FALCPA in USA) based on zero threshold (no protein) approach
- Food industry adopts zero threshold in many situations and advisory labeling abounds
Benefits of Zero Threshold Approach

- FDA and other public health authorities have easy decisions – presence or absence with no debates about amount
- Food-allergic consumers are protected
- Physicians can give same advice to all patients with diagnosis of food allergy – complete avoidance
- Food industry has limited flexibility with labeling so less likelihood of errors of enthusiasm
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 applies precautionary labeling (may contain) on widespread basis
- Zero keeps getting less
BIG Questions

- Do we now have enough information to move away from the zero threshold concept?
- If so, what will be the impacts/implications for all of those affected (consumers, physicians, public health authorities, food industry, test kit companies)
- What are the impediments to implementation of some finite threshold concept?
7 Key Questions

- How should we define “an allergic response that poses a risk to human health”?
- Which major food allergens are of greatest public health concern and what is the size of the at-risk population?
- How should clinical dose distribution data be used in establishing regulatory thresholds for the major food allergens?
7 Key Questions

- How should clinical dose distribution data be used in establishing regulatory thresholds for the major food allergens?
- What data and information exist on dietary exposure patterns for individuals on allergen avoidance diets?
- What data and information exist on current levels of exposure associated with consumption of undeclared major food allergens in packaged foods?
- What other information or data should we consider in establishing regulatory thresholds for major food allergens?
7 Key Questions

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- Which major food allergens are of greatest public health concern and what is the size of the at-risk population?
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Implications for the Grain Milling Industry

- Commodity grains standards have existed for decades
- Labeling of commodity grain contamination is not required under FALCPA (Congressional exemption)
- Soy in corn; soy in wheat; wheat in oats; etc.
- With zero threshold concept, pressure would exist to eliminate commodity contamination or label
- Consumer complaints do not exist but consumers and physicians are unaware of these residues
Regulatory Implications - Comingling

- Irish Food Safety Authority (IFSA) has detected undeclared soy in corn and wheat products in Irish market during 2011 and 2012
- IFSA has petitioned EFSA to require labeling of commodity contamination (decision expected 2014)
- Canadian Food Safety Authority detected soy in wheat in numerous products during 2012
- Health Canada advisory that soy in wheat is not hazardous based on known threshold information
- FDA Threshold Notice (Dec 2012)
Trace amounts (low mg) can elicit allergic reactions

A few clinics started doing very low dose DBPCFC and proved that safe doses exist for every subject and that severe reactions did not occur at very low doses (low mg)
Consumers and Thresholds
Current Situation

- Many food-allergic consumers believe that they are extremely sensitive
- Many consumers have experienced allergic reactions due to avoidance diet mistakes
- Some of those reactions have been quite severe
- Some consumers believe that they have suffered severe reactions due to low-dose exposures

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Public Health Authorities and Thresholds

Current Situation

- Widespread belief that low doses can provoke severe reactions
- Firm belief that zero threshold protects food-allergic consumers
- Fear of setting the wrong threshold outweighs empathy about quality of life situation for food-allergic consumers
- Use of uncertainty factors (100-fold or more)
Current Situation

- Public health authorities have not established regulatory thresholds for any of the allergenic foods except Japan (<10 ppm) and Switzerland (<1000 ppm)

- U.S. FALCPA – de facto zero threshold for source labeling of ingredients (similar laws in other countries)

- Industry acutely aware of allergens, no guidance on thresholds so rampant use of precautionary labeling
Current Situation

- Quality of life for food-allergic consumers suffers partially as a result of difficulties in adherence to avoidance diets
- Food-allergic consumers increasingly ignore products with precautionary labels
- Some physicians advise food-allergic patients to ignore precautionary labels
- Allergic reactions continue to occur but rarely with packaged foods
US FDA Allergen Thresholds

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

Current Focus

- 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!!
• 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 FARRP Approach

- Sought out published information on individual threshold doses from low-dose clinical challenges
- Sought out unpublished data from various allergy clinics in multiple countries
- Established partnership with our primary competitors, TNO in the Netherlands (Geert Houben and colleagues)
- Developed statistical approaches to model individual threshold data points to estimate population thresholds
- Developed interval censoring survival analysis technique to allow use of data from variable clinical challenge protocols
- Pioneered use of quantitative risk assessment using threshold data together with allergen exposure data.
Statistical Methodology

- Data modelled using interval-censoring survival analysis techniques.
- Data fitted to Log-Normal distribution (best fit); also tried Log-Logistic and Weibull (little difference)
- Population thresholds estimated
Interval-censoring survival analysis (2)

Subject 1: Left-censored
Subject 2: Interval-censored
Subject 3: Right Censored

0 10mg 50mg 150mg 500mg

No Reaction

Reaction Interval
Log-Normal Population Distribution (expressed as whole peanut)
Initial FARRP Effort

- Focused on peanut because likelihood of more clinical data on peanut due to prevalence and severity
- Found 185 peanut data points in published literature (from 12 studies)
- Mined 286 additional unpublished data points from a clinic in Nancy France; total of 450 patients in 2010
- Subsequently over 100 additional published data points
- Now have total of 750 data points for peanut allowing very confident prediction of population threshold
- Definitely sufficient to establish regulatory thresholds
- Also allows comparison of sub-populations e.g. severity
Table 4. ED_{10} doses for whole peanut as assessed by the log-normal probability distribution model for severity grade.

<table>
<thead>
<tr>
<th>Severity Grade</th>
<th>Total No. of Peanut Allergic Individuals</th>
<th>ED_{10}</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe^{1}</td>
<td>40</td>
<td>10.4</td>
<td>4.8, 22.6</td>
</tr>
<tr>
<td>Non-Severe^{2}</td>
<td>123</td>
<td>10.2</td>
<td>6.4, 16.1</td>
</tr>
<tr>
<td>No Prior History^{3}</td>
<td>123</td>
<td>27.0</td>
<td>17.4, 42.0</td>
</tr>
</tbody>
</table>

^{1}Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

^{2}Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%)

^{3}History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

All values reported in mg whole peanut
More Recent FARRP Approach

• In 2011, began to expand to information on other allergenic foods
• Partnered with TNO and combined data sets
• Collaborated with Australian Allergy Bureau to update VITAL program
• Voluntary Incidental Trace Allergen Labeling (VITAL)
• Originally developed in Australia in 2007 as a voluntary approach to limit use of advisory labeling
• Voluntary program; initiative from food industry; established Allergen Bureau
More Recent FARRP Approach

- Established Action Levels; if concentrations in foods exceeding established action levels then advisory labeling was recommended
- If level was below action level, then no advisory labeling needed
- Action Levels originally based on limited threshold information and use of arbitrary uncertainty factors
- Thus Action Levels were rather low and conservative
- FARRP convened expert panel to use clinical information to establish thresholds as basis for VITAL Reference Doses
Recent VITAL Action Level Revision

- Australian Allergen Bureau Management Committee and Food Allergy Research & Resource Program collaborated to assemble a Scientific Expert Panel to consider revision of Grid Action Levels (early 2011)

- 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)
Recent 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>
</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).
## VITAL Reference Doses

<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>Crustacea</td>
<td>1.0</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Moving Toward a Low Threshold Approach – A BIG STEP

- Fundamental paradigm shift
- Do we have enough data to make take action now? Very important question
- In my opinion, we do have enough data but there will be debate on this point
- Statistically, more data is always better so we should continue to collect data and use those data to improve the risk assessment and adjust Reference Doses where appropriate
- Public health authorities need to examine existing data and they have not yet done completely done that
Threshold Implications
Public Health Authorities

- FDA and others could focus on high risk situations where potential doses exceed the Reference Dose
- Allergen recalls would decrease to some extent
- Sound scientific basis would exist for ingredient source labeling exemptions saving considerable staff time in review of such petitions
- Sound scientific basis would exist for FSMA compliance with allergen control programs
- A sensible approach could be taken toward precautionary labeling
- A sensible approach could be taken toward “free” labeling
Threshold Impediments
Public Health Authorities – U.S.

- FDA must adopt the recommendation of its own Threshold Working Group – QRA is the best approach
- FDA needs to examine the existing data and consider various risk assessment models, other approaches; this will take some time
- FDA must then establish Reference Doses
- Will they want more data?
- Will they use the ED01?
- Will additional uncertainty factors be applied?
- Analytical uncertainties and consumption estimate assumptions
Threshold Progress

- Australian Allergy Bureau publicly released VITAL 2.0 in May 2012 using Reference Doses
- ILSI-Europe had adopted the same Reference Doses and will propose to EFSA
- FDA Threshold Notice
- Support for implementation of regulatory thresholds by consumer groups in Canada and several EU countries
- But lack of support for thresholds among consumer groups and some key physicians in U.S.
Probabilistic modeling; the idea

Data
- Surveys
- Analyses
- Clinical studies

Chance distributions
- Consumption
- Levels

Probabilistic model

Outcome

Allergen intake

Thresholds

Chance of allergic reaction
Conclusions

- FDA was correct: the quantitative risk assessment-based approach is the strongest.
- Industry, government and consumers need a science-based, transparent approach to establish action levels (thresholds).
- But consumers need to be educated about benefits of thresholds; consumer acceptance is critical.
- Ideally, government agencies act and provide guidance; international consensus would be nice.
- If government does not act, quantitative risk assessment still has benefits for industry.
- e.g. risk of soy in corn??