The VITAL Scientific Expert Panel Review (VSEP)

An Allergen Bureau Presentation based on the work of the VITAL Scientific Expert Panel

April 2012
VITAL – The Scientific Journey

- VSEP January 2011 - Collaboration
- Reviewing the Science – Methodology & Working Example
- VSEP Panel Recommendations
- VITAL & Risk
- Questions Remaining
- The VITAL Scientific Future
VSEP – The 2011 Scientific Review Timeline

- **January** – VSEP first meeting

- **February** - FARRP supported another face to face meeting of some of the key Panel members in The Netherlands at TNO

- **February until end May** - Extensive review and collation of data by TNO and FARRP, many teleconference meetings

- **June (end)** - Preliminary recommendation’s reported

- **August** - Extensive agreement achieved on 11 allergenic foods; Insufficient data for 2 foods

- **September (end)** - Report finalised

- **October (end)** - Public communication - Media Release
VSEP January 2011 Collaboration

• The first VITAL Scientific Expert Panel (VSEP) meeting was held in Sydney on January 19-20, 2011

• Significant collaboration was required to ensure the event could proceed:
  • The Allergen Bureau;
  • FARRP (Food Allergy Research and Resource Program (University of Nebraska) and;
  • TNO (The Netherlands Organisation for Applied Scientific Research)

• Meeting focus & objective was to review and discuss Action Levels in the VITAL Grid
  • Underpinning science
VITAL Scientific Expert Panel (VSEP)

- Scientific Expert Panel

Panel Members are:

- Dr Steve Taylor (FARRP)
- Dr Joseph Baumert (FARRP), supported by Mr Benjamin Remington (FARRP),
- Dr Geert Houben (Program Manager Food Safety, TNO. NL)
- Dr Rene Crevel (Allergy & Immunology, Unilever)
- Dr Katie Allen (Paediatric Gastroenterologist/Allergist, Royal Childrens Hospital, University of Melbourne), supported by Ms Jennifer Koplin
- Dr Simon Brooke Taylor (Food Safety & Risk Analysis Consultant, Allergen Bureau)

- The VSEP received significant support from Astrid Kruizinga (TNO), Ellen Dutman (TNO) & Harrie Buist (TNO)
VITAL Scientific Review – January Mtg

• The Panel established principles used in selecting reference doses;
  • scientifically & clinically sound, defensible and transparent

• Determined that the original Action Levels in VITAL were:
  • appropriate based on available science at that time

• Relevance of Portion/Serving Size/Reference Amount
  • allergen protein expressed as mg of protein with concentration determined by using the reference amount or serving size

• Exquisitely allergic consumers will not be accounted for in VITAL, we continue to assume they do not eat processed foods
VITAL Scientific Review – January Mtg

• Level of Acceptable Risk
  • protection for vast majority of allergic individuals

• Reference doses set with highest degree of safety
  • Increasing availability of clinical data enables the model to be applied with increasing confidence
  • Acknowledges & drives research to fill the data gaps

• Potentially opens up choice to a larger number of ‘safe’ foods
  • Consistent approach across industry
  • Precautionary labels applied when appropriate and in a consistent manner

• Plan is for reference doses to be subject to ongoing review
Original VITAL Scientific Approach

- Key information taken from the FDA Threshold Working Group Report of 2006

- Used LOAELs from FDA table

- Applied an uncertainty factor (UF) to action levels set

- Expressed action levels in concentration (ppm) rather than amount of protein (mg); based on 5 g serving size (teaspoon/mouthful)

- Most VITAL min levels set at >2 ppm (exceptions fish, milk, soy, gluten)
The VSEP Overarching Scientific Approach

Quantitative Risk Assessment

- The threshold needs to be *predictive* for the *entire population*
  - Representative population weighted to include individuals who react to very low amts & their counterparts who require large amts

- Statistically based risk assessment provides the ideal approach to the establishment of a population thresholds for allergenic foods
  - This type of risk assessment requires *individual threshold doses* from a sufficiently *large* number of allergic individuals

- Analysis of the clinical literature was conducted to determine if the *quantity* and *quality* of published and unpublished data was sufficient,
  - to apply RA modelling & prediction of population based thresholds
The VSEP Methodology (ILSI – FARRP)
Data Collection & Screening

- Reviewing data
  - Screening for NOAEL and or LOAEL on individual allergic subjects
  - Raw data on individual thresholds, taken from FARRP and TNO publications
  - Unpublished clinical data were also used from Dutch clinics and FARRP studies

- Publications looked for DBPCFC starting at low doses that potentially allowed identification of NOAELS and LOAELS for individual patients

- NOAELS & LOAELS were expressed in terms of doses of either whole food or food protein eliciting subjective or objective symptoms
  - Focus was objective symptoms as basis for the LOAEL
  - Objective symptoms, discernable to clinical observer, vomiting, Urticaria
The Tools Applied

• Applied Interval Censoring Survival Analysis (ICSA) approach
  • Considered appropriate when the exact dose that provoked a reaction is not known, but known to fall into a particular interval (NOAEL & LOAEL)
  • Determined NOAELs and LOAELs to estimate thresholds

• Used statistical dose-distribution modelling and applied 3 different probability models: log-normal, log-logistic, and Weibull to all data sets
  • Looking for the model that provides data best fit
  • Given that the principle application lay in low dose estimations, goodness of fit in that part of the dose range is important

• From dose distribution models the eliciting dose is decided (dose predicted to provide reactions in 1, 5 and 10% of the allergic population respectively)
  • ED01, ED05, ED10, ED50, and 95% confidence intervals
Questions that had to be addressed

- Can we combine paediatric and adult data points?
- Can we combine data from different clinics?
- Cumulative vs. discrete doses?
- Does the choice of statistical model make a difference? Application of different models for different allergens
- Does sufficient data exist to use the ED01 in every case?
  - Alternate – lower 95% confidence interval of ED05
Working Example

Peanut
Peanut Data

- Published studies or unpublished clinical data
- Peanut-allergic by history or other factors (skin prick tests)
- DBPCFC
- Individual NOAELs and LOAELs were expressed in terms of whole peanut (mg) or peanut protein (mg)
- Objective symptoms at doses
# Collecting & Reviewing the Data

## Peanut Threshold Data Gleaned From Publications and Unpublished Clinical Records

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Study</th>
<th>Total No. with Objective Symptoms</th>
<th>Right Censored</th>
<th>Left Censored</th>
<th>Population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Atkins et al.</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>Adults</td>
<td>(J Allergy Clin Immunol, 1985, 75:356-363)</td>
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<tr>
<td></td>
<td>Hourihane et al.</td>
<td>13</td>
<td>11</td>
<td>0</td>
<td>Adults and Children</td>
<td>(J Allergy Clin Immunol, 1997, 100:596-600)</td>
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<tr>
<td></td>
<td>Wensing et al.</td>
<td>26</td>
<td>20</td>
<td>0</td>
<td>Adults and Children</td>
<td>(J Allergy Clin Immunol, 2002, 110:915-920)</td>
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<td></td>
<td>Lewis et al.</td>
<td>40</td>
<td>0</td>
<td>3</td>
<td>Adults and Children</td>
<td>(Clin Exp Allergy, 2005, 35:767-773)</td>
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<tr>
<td></td>
<td>Flinterman et al.</td>
<td>22</td>
<td>11</td>
<td>0</td>
<td>Children</td>
<td>(J Allergy Clin Immunol, 2006, 117:448-454)</td>
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<tr>
<td></td>
<td>Leung et al.</td>
<td>23</td>
<td>8</td>
<td>1</td>
<td>Adults and Children</td>
<td>(NEJM, 2003, 348:986-993)</td>
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<tr>
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<td>Oppenheimer et al.</td>
<td>4</td>
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<td>0</td>
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<td>(J Allergy Clin Immunol, 1992, 90:256-262)</td>
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<td></td>
<td>Nelson et al.</td>
<td>12</td>
<td>0</td>
<td>1</td>
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<td>(J Allergy Clin Immunol, 1997, 90:744-751)</td>
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<tr>
<td></td>
<td>Nancy *</td>
<td>283</td>
<td>10</td>
<td>7</td>
<td>Adults and Children</td>
<td>(Food and Chem Tox, 2010, 48:814-819)</td>
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<td>Anagnostou et al.</td>
<td>18</td>
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<td>Adults and Children</td>
<td>(Clin Exp Allergy, 2009, 38:1937-1958)</td>
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<td>Nicolaou et al.</td>
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<td>Children</td>
<td>(J Allergy Clin Immunol, 2010, 125:191-197)</td>
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<td>Blumchen et al.</td>
<td>22</td>
<td>0</td>
<td>2</td>
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<td>(J Allergy Clin Immunol, 2010, 126:83-91)</td>
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<td>Wainstein et al.</td>
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<td>0</td>
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<td>Patriarca et al.</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>(Digestive Diseases and Sciences, 2006, 51:471-473)</td>
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<td>WKZ **</td>
<td>85</td>
<td>5</td>
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<td>Children</td>
<td>(Unpublished Clinical Data)</td>
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<td></td>
<td>UMCU ***</td>
<td>42</td>
<td>17</td>
<td>0</td>
<td>Adults</td>
<td>(Unpublished Clinical Data)</td>
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<td>UMCG****</td>
<td>135</td>
<td>50</td>
<td>5</td>
<td>Children</td>
<td>(Unpublished Clinical Data)</td>
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</tbody>
</table>

**Total 750**

* Published only in summarized form

**WKZ – Wilhelmina Kinderziekenhuis (children's hospital of the UMCU, The Netherlands)

***UMCU – University Medical Center Utrecht - Includes Peeters et al. (Clin Exp Allergy, 2007, 37:108-115)

****UMCG – University Medical Center Groningen

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The Tools Applied

Interval-Censoring Survival Analysis

Interval-censored

Left-censored

Right Censored

No Reaction

Reaction Interval

Information has been reproduced from the presentation 'Thresholds & Risk Assessment' (Dr Steve Taylor et al) and remains the property of FARRP
The Tools Applied

Adults and Children curve

LogNormal

LogLogistic

Weibull
### The Tools Applied

#### Eliciting Dose – ED1

<table>
<thead>
<tr>
<th>Individual data</th>
<th>Total Number of Data Points (RT, LT)</th>
<th>Model</th>
<th>ED1</th>
<th>LCI</th>
<th>UCI</th>
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</thead>
<tbody>
<tr>
<td>Data / pooled children</td>
<td>585 (79, 36)</td>
<td>llog</td>
<td>0.14</td>
<td>0.085</td>
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<td></td>
<td></td>
<td>lnor</td>
<td>0.27</td>
<td>0.18</td>
<td>0.4</td>
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<tr>
<td></td>
<td></td>
<td>weib</td>
<td>0.017</td>
<td>0.008</td>
<td>0.034</td>
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<td>data / pooled adults</td>
<td>99 (44, 1)</td>
<td>llog</td>
<td>0.21</td>
<td>0.045</td>
<td>1</td>
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<tr>
<td></td>
<td></td>
<td>lnor</td>
<td>0.57</td>
<td>0.17</td>
<td>1.9</td>
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<td></td>
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<td>weib</td>
<td>0.069</td>
<td>0.01</td>
<td>0.5</td>
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<tr>
<td>data / pooled children &amp; adults</td>
<td>750 (132, 41)</td>
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<td>0.1</td>
<td>0.062</td>
<td>0.16</td>
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<tr>
<td></td>
<td></td>
<td>lnor</td>
<td>0.22</td>
<td>0.15</td>
<td>0.32</td>
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<tr>
<td></td>
<td></td>
<td>weib</td>
<td>0.013</td>
<td>0.007</td>
<td>0.024</td>
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</table>

<table>
<thead>
<tr>
<th>Cumulative data</th>
<th>Total Number of Data Points (RT, LT)</th>
<th>Model</th>
<th>ED1</th>
<th>LCI</th>
<th>UCI</th>
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</thead>
<tbody>
<tr>
<td>Data / pooled children</td>
<td>585 (79, 25)</td>
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<td>0.11</td>
<td>0.3</td>
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<td>lnor</td>
<td>0.34</td>
<td>0.23</td>
<td>0.51</td>
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<tr>
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<td>weib</td>
<td>0.021</td>
<td>0.01</td>
<td>0.042</td>
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<td>data / pooled adults</td>
<td>99 (44, 1)</td>
<td>llog</td>
<td>0.26</td>
<td>0.05</td>
<td>1.3</td>
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<tr>
<td></td>
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<td>lnor</td>
<td>0.72</td>
<td>0.21</td>
<td>2.5</td>
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<tr>
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<td>0.076</td>
<td>0.01</td>
<td>0.59</td>
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<tr>
<td>data / pooled children &amp; adults</td>
<td>750 (132, 30)</td>
<td>llog</td>
<td>0.13</td>
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<tr>
<td></td>
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<td>lnor</td>
<td>0.28</td>
<td>0.19</td>
<td>0.4</td>
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<tr>
<td></td>
<td></td>
<td>weib</td>
<td>0.015</td>
<td>0.01</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Information has been reproduced from the presentation 'Thresholds & Risk Assessment' (Dr Steve Taylor et al) and remains the property of FARRP
### Threshold data points for each Allergen

<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).

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## VSEP Recommendations – Reference Doses

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Protein Level (mg)</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 *(VITAL – Level used as generic tree nut value)</td>
</tr>
<tr>
<td>Soy</td>
<td>1.0 *(VITAL – Soy protein isolates not soy milk)</td>
</tr>
<tr>
<td>Wheat</td>
<td>1.0 *(VITAL – GCC (Coeliac &amp; wheat allergic population))</td>
</tr>
<tr>
<td>Cashew</td>
<td>2.0 *(VITAL - Hazelnut as generic tree nuts value)</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>NA</td>
</tr>
<tr>
<td>Fish</td>
<td>NA *(VITAL – original VITAL value applied)</td>
</tr>
</tbody>
</table>
VITAL & Risk

- VITAL approach used all of the existing published data plus some unpublished data. **Unpublished data needs to be published**

- VITAL grid levels will protect 95-99% of allergic consumers (99% is desirable when sufficient data exists to allow statistically sound estimates at this level)

- Exquisitely sensitive allergic consumers may not be fully protected by the VITAL grid levels (assume do not consume packaged foods)

- No additional uncertainty factors needed because of use of ED01 or lower 95% confidence interval of ED05
VITAL & Risk (cont)

- Risk of mild, transitory objective reactions typically requiring no pharmacological intervention

- Allergic populations studied appear to be representative or skewed toward more highly sensitive (referral clinics, immunotherapy studies)
Remaining Questions

- Challenge data are not available for some commonly allergenic foods (e.g. almond, walnut) – how to establish action levels?
- Insufficient data for celery and fish, how to drive the research gaps?
- Challenge data exists for modest numbers of patients for other commonly allergenic foods (e.g. sesame seed, lupin, shrimp, mustard)
  - How to drive the research gaps?
- Species of fish and crustacea? Very limited data and the big unknown!
Continuing the VITAL Scientific Journey

• The Allergen Bureau plan is to maintain the VSEP ongoing and continue to invest in the VITAL future

• New science and data needs to continue to be considered

• The Allergen Bureau objective is to support initiatives, projects and collaborations where possible to drive the research gaps

• Currently reviewing the possibility of collaboration with the EU

• The Allergen Bureau continue to stay closely linked in to the ILSI Thresholds to Action Levels Group
VSEP - What does Success look like?

- Reference doses determined for each of the top food allergens, Research gaps continue to be addressed

- Standardised methodology or approach to determine appropriate reference dose information, consistent application

- The relevance and importance of Reference Amounts or Serving Size in determining Action Levels, clarity around actual consumption data

- Food industry adoption and implementation of the reference dose, reference amount, action level precautionary labelling risk assessment

- Consistent application globally to drive safe food choices, protection for the allergic consumer means protection for our industry

- International recognition by the scientific community
Dream becoming a Reality

Global Harmonised Action Levels
Within Our Reach
Imagine That!
Thank you

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David Henning – Campbell Arnotts

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