Evolution of Risk Assessment of Food Allergens

Simon Brooke-Taylor PhD
ILSI Seminar "Food Allergens – Science & Challenges for Southeast Asia"
7 April 2015
## Allergens of concern

<table>
<thead>
<tr>
<th>Cereals containing gluten</th>
<th>Sesame seeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>Tree Nuts (EU named nuts)</td>
</tr>
<tr>
<td>Egg</td>
<td>Added Sulphites ≥10 mg/kg</td>
</tr>
<tr>
<td>Peanuts</td>
<td>Celery (EU)</td>
</tr>
<tr>
<td>Fish</td>
<td>Lupins (EU)</td>
</tr>
<tr>
<td>Crustacea</td>
<td>Mustard (EU, Canada)</td>
</tr>
<tr>
<td>Molluscs (EU)</td>
<td></td>
</tr>
<tr>
<td>Soybeans</td>
<td></td>
</tr>
</tbody>
</table>

**Mandatory labelling if intentionally added**

- Codex, ASEAN, ANZ, EU, USA, Canada etc
Mandatory Allergen Labelling

Ingredients: Organic Full Cream Milk, Organic Milk Powder, Cultures (including Acidophilus Bifidobacterium).
CONTAINS MILK.
Keep Refrigerated. Store below 4°C
Made in Australia.
Mandatory Allergen Labelling

BREAD MIX INGREDIENTS: Unbleached Wheaten Flour, Grains 15% (Kibbled Rye, Linseed, Malted Wheat Flakes, Kibbled Maize), Wheat Bran, Gluten, Dark Malt (Barley), Non-iodised Salt, Soy Flour, Malt Extract (Barley), Emulsifier (E481), Ascorbic Acid (Vitamin C), Mineral Salt (E516), Enzyme, Vitamin (Thiamine, Folic Acid).

YEAST SACHET INGREDIENTS: Dry Yeast incorporating Emulsifier (E491)

CONTAINS: Gluten containing Cereals and Soy
All ingredients are from non-animal sources and are GMO Free.
Mandatory Labelling Exemptions

Case by case,

eg

- isinglass (ANZ, EU)
- coconut (ANZ)
- alcohols from:
  - cereals (ANZ, EU)
  - whey & tree nuts (EU)
- glucose syrups and maltodextrin (EU)
- lactitol (EU)
- refined soybean oils, tocopherols, phytosterols and stanols (EU)
May Contain ..... what does it mean?

- Cross-contact allergens
  - i.e. not added intentionally
- Contact with ingredients
  - e.g. during harvest, transport, storage
- Contact during processing
  - e.g. use of shared equipment, atmospheric transfer, operator transfer
- Consumer understanding
  - Is the allergen really present?
  - "Does may contain" also mean "May not contain"?
Objective: Development of a standardised allergen risk assessment tool which can be used to assist in determining appropriate voluntary allergen labelling statements.
VITAL®

Voluntary Incidental Trace Allergen Labelling System

A standardised allergen risk assessment tool for food producers
Elements of VITAL®

Incorporate in HACCP Food Safety Programme

1. Ingredient and Processing Impact Assessment
2. Compare with VITAL® Grid
   – integrated in VITAL® calculator
3. Identify Action Levels & recommended labelling
   – "may be present:"
4. Record Assumptions, Validate, Monitor
VITAL®
Ingredient and Processing Impact Assessment

• Identify
  • relevant allergens (*intended country of sale*)
  • added allergens

• Identify and quantify cross contact allergens
  • due to ingredients
  • due to processing

• Calculate total cross contact allergen in final product
VITAL® Operation

**Reference Dose**
mg allergen protein
(from risk assessment)

**Reference Amount**
gm of food
(determined by manufacturer)

**Action Level 2**
precautionary label
'may be present"

**Action Level Threshold**
mg/kg

**Action Level 1**
no label

Key Assumption: if allergen present allergic individual may be exposed
VITAL® V1 - Scientific Approach

• Key data source FDA Threshold Working Group Report (2006)
  • LOAELs from FDA TWG tables
  • Applied uncertainty factors (UF) to set reference doses
• Expressed action levels in concentration (ppm) not amount of protein (mg);
  • 5 g serving size (teaspoon/mouthful)
• Most VITAL® min levels 2 ppm (exceptions fish, milk, soy, gluten)
  • very conservative
VITAL® Scientific Expert Panel (VSEP) 2011

- Role: Advise Allergen Bureau on VITAL® review
  - Collaboration between:
    - The Allergen Bureau;
    - FARRP (Food Allergy Research and Resource Program (University of Nebraska) and;
    - TNO (The Netherlands Organisation for Applied Scientific Research)
  - Access to new data sources
  - Expertise in Allergen Risk Assessment
VITAL® Scientific Expert Panel (VSEP)

Panel Members:
- Dr Steve Taylor (FARRP)
- Dr Joseph Baumert (FARRP),
  - supported by Mr Benjamin Remington (FARRP),
- Dr Geert Houben (TNO)
- Dr Rene Crevel (Unilever)
- Dr Katie Allen (Royal Children's Hospital, University of Melbourne),
- Dr Simon Brooke Taylor (Food Safety/Risk Analysis Consultant, AB)
VSEP principles for Allergen Risk Assessment

- Scientifically & clinically sound, defensible and transparent
- Reference Dose
  - express as mg of total protein
- Action Level determined using the reference amount (or serving size)
- Exquisitely allergic consumers not protected
  - Assume not eat processed foods without contact with manufacturer
VSEP principles (cont)

• Level of Acceptable Risk
  • protection for vast majority of allergic individuals - 95-99%

• Reference doses set with highest degree of safety
  • increasing availability of clinical data = increasing confidence in models
  • drive research to fill the data gaps

• Potentially opens choice to more ‘safe’ foods

• Reference Doses subject to ongoing review
**VSEP: Quantitative allergen risk assessment**

- **Threshold predictive for the whole population**
  - Representative population weighted to include both individuals who react to very low amounts & those who require large amounts to provoke response

- **Statistically based risk assessment - population thresholds**
  - Requires individual threshold doses from a sufficiently large number of allergic individuals

- **Analysis of the clinical literature**
  - Determine if sufficient quantity and quality of published and unpublished data accessible
The VSEP Methodology
Allergen Cross Contact - Population at Risk

from Crevel et al 2008
Threshold Definitions

- **Individual Threshold**
  - LOAEL or NOAEL for an individual patient

- **Population Threshold**
  - LOAEL or NOAEL for a group of food-allergic individuals
    - all allergic individuals
    - allergic individuals in a defined group/sub-group or from a particular clinic
Data Harvesting & Screening

• Review Clinical Challenge Data
  • Screen for individual NOAEL and or LOAELs
    • Published literature
    • Raw data from FARRP and TNO publications
    • Unpublished clinical data European clinics and FARRP studies
  • DBPCFC with low starting doses
    • NOAELS and LOAELS for individual patients.
      • If LOAELS only then NOAELS determined statistically
• Objective responses
• Data points standardised as mg total protein
The Tools Applied

• Interval Censoring Survival Analysis (ICSA)
  • Appropriate when exact provoking dose is unknown, but fall into a known interval (between NOAEL & LOAEL)

• Statistical modelling
  • 3 probability models:
    • log-normal, log-logistic, and Weibull
  • look for the model that provides data best fit
  • goodness of fit in low dose part of the dose range is important

• Determine eliciting dose from dose distribution
  • ED01, ED05, ED10 and 95% confidence intervals
Interval-Censoring Survival Analysis

Subject 1 is left-censored, Subject 2 is interval-censored, and Subject 3 is 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.
Dose Distribution Modelling

Proportion of Reactions (clinical studies)

Dose (mg protein)

ED5, ED10, ED50

log normal, log logistic, or Weibull
Dose Distribution Modelling

![Graph showing dose distribution modelling](image)

Fig. 2. Representation of challenge data from Wensing et al. (2002), illustrating different statistical fits.

from Crevel et al Food Chem Toxicol 2007
VSEP - Questions that were addressed

- Can we
  - combine paediatric and adult data points?
  - combine data from different clinics?
  - use cumulative and/or 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 Harvesting

- Published studies (15) and unpublished clinical data (3)
- Subjects all Peanut-allergic by history or other factors
  - (eg skin prick tests)
- DBPCFC
- Individual data points expressed as peanut (mg) or peanut protein (mg)
- Objective symptoms

- 750 individual data points
  - 132 right censored
  - 30 left censored
## 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>
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</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Atkins et al.</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<td>(J Allergy Clin Immunol, 1985, 75:356-363)</td>
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<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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<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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<tr>
<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>
<td></td>
<td>Oppenheimer et al.</td>
<td>4</td>
<td>0</td>
<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>
<td>Adults</td>
<td>(J Allergy Clin Immunol, 1997, 99:744-751)</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></td>
<td>Anagnostou et al.</td>
<td>18</td>
<td>0</td>
<td>7</td>
<td>Adults and Children</td>
<td>(Clin Exp Allergy, 2009, 39:1937-1958)</td>
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<tr>
<td></td>
<td>Nicolaou et al.</td>
<td>10</td>
<td>0</td>
<td>2</td>
<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>Walenstein et al.</td>
<td>8</td>
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<td>0</td>
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<td>(Pediatr Allergy Immunol, 2010, 21:603-611)</td>
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<td>Patriarca et al.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Adults</td>
<td>(Digestive Diseases and Sciences, 2006, 51:471-473)</td>
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<td></td>
<td><strong>WKZ</strong></td>
<td>85</td>
<td>5</td>
<td>1</td>
<td>Children</td>
<td>(Unpublished Clinical Data)</td>
</tr>
<tr>
<td></td>
<td><strong>UMCU</strong>*</td>
<td>42</td>
<td>17</td>
<td>0</td>
<td>Adults</td>
<td>(Unpublished Clinical Data)</td>
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<tr>
<td></td>
<td><strong>UMCG</strong>**</td>
<td>135</td>
<td>50</td>
<td>5</td>
<td>Children</td>
<td>(Unpublished Clinical Data)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>750</td>
<td>132</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 Gronigen  

Probability distribution models - individual peanut thresholds

- Discrete dose
- Cumulative dose

Mean ± 95% confidence limit

Information has been reproduced from the presentation 'Thresholds & Risk Assessment' (Dr Steve Taylor et al) and remains the property of FARRP
VSEP Peanut Eliciting Dose – ED01

VSEP recommendation: ED1 based on log normal and log logistic distributions for discrete and cumulative doses for both adults and children = 0.2mg peanut protein.

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Data / pooled children</td>
<td>585 (79, 36)</td>
<td>Ilog</td>
<td>0.14</td>
<td>0.085</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lnor</td>
<td>0.27</td>
<td>0.18</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weib</td>
<td>0.017</td>
<td>0.008</td>
<td>0.034</td>
</tr>
<tr>
<td>data / pooled adults</td>
<td>99 (44, 1)</td>
<td>Ilog</td>
<td>0.21</td>
<td>0.045</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lnor</td>
<td>0.57</td>
<td>0.17</td>
<td>1.9</td>
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<tr>
<td></td>
<td></td>
<td>weib</td>
<td>0.069</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>data / pooled children &amp; adults</td>
<td>750 (132, 41)</td>
<td>Ilog</td>
<td>0.1</td>
<td>0.062</td>
<td>0.16</td>
</tr>
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<td></td>
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<td>lnor</td>
<td>0.22</td>
<td>0.15</td>
<td>0.32</td>
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<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>
<td>Ilog</td>
<td>0.18</td>
<td>0.11</td>
<td>0.3</td>
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<td></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>
<td></td>
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<td>weib</td>
<td>0.021</td>
<td>0.01</td>
<td>0.042</td>
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<tr>
<td>data / pooled adults</td>
<td>99 (44, 1)</td>
<td>Ilog</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>
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<td>weib</td>
<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>Ilog</td>
<td>0.13</td>
<td>0.08</td>
<td>0.2</td>
</tr>
<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>
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</table>
## Data point summary by 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>
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<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>
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<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>
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<tr>
<td>Shrimp</td>
<td>48</td>
<td>26</td>
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<td>Adults</td>
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<tr>
<td>Celery</td>
<td>39</td>
<td>4</td>
<td>15</td>
<td>Children and Adults</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).
## VSEP Recommended Reference Doses

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Protein Level (mg)</th>
<th>VITAL® implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Hazelnut</td>
<td>0.1</td>
<td>Used as generic tree nut value</td>
</tr>
<tr>
<td>Soy</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>1.0</td>
<td>Coeliac &amp; wheat allergic - max 20ppm</td>
</tr>
<tr>
<td>Cashew</td>
<td>2.0</td>
<td>not used - see hazelnut</td>
</tr>
<tr>
<td>Mustard</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Lupin</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Sesame</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Shrimp</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Celery</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>NA</td>
<td>original VITAL® value (0.1mg) applied</td>
</tr>
</tbody>
</table>
Probability distribution curves (Weibull) for peanut, hazelnut, cashew nut, cow’s milk and hen’s egg (discrete doses) pediatric population.

from Blom et al 2013
Overview

- **VSEP approach:**
  - all available published data plus some unpublished data
- **Implemented in VITAL®2 (2012):**
  - ppm based on typical amount consumed
- **Protects 95-99% of allergic consumers:**
  - 99% when sufficient data available
    - ED01 or lower 95% confidence interval of ED05
  - Risk of mild, transitory objective reactions
    - typically requiring no pharmacological intervention
  - Exquisitely sensitive allergic consumers not fully protected
    - (advise contact with manufacturer before consuming packaged foods)
  - No additional uncertainty factors needed
- **Allergic populations in trials appear representative or skewed toward more highly sensitive (referral clinics, immunotherapy studies)**
Other Approaches

- Probabilistic Modelling
  - TNO
    1. Threshold from Dose-Distribution Model
    2. Distribution of allergen in product in question
      - Probably levels, frequency etc.
    3. Population consumption data
      - Amount and Frequency of consumption

- Foods typically consumed in small amounts (e.g. condiments) = potentially lower doses of the allergenic food
- Foods (e.g. entrees) consumed in much larger amounts, = potentially higher doses of the allergenic food
Probabilistic Modelling - Risk Assessment

Fig. 1. Schematic presentation of the probabilistic approach in food allergen risk assessment.

Spanjersberg et al 2007
Future challenges

- Standardised food challenge protocols (DBPCFC)
  - dose ranges
  - food/challenge form
  - subject selection/exclusion criteria
  - EuroPrevall

- Relating population & individual thresholds

- Communication:
  - Informing consumers and clinicians about use of risk assessment in allergen labelling decisions

- Acceptable levels of risk (ED01 - 99%?)
- Global acceptance/implementation
Thank you

Acknowledgements:
Allergen Bureau
- Robin Sherlock
- Fiona Fleming
- Kirsten Grinter

VITAL® Co-ordinator
- Georgina Christensen
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simon@brooketaylor.com.au