Evolution of Risk Assessment of Food Allergens

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ILSI Seminar “Food Allergens – Science & Challenges for Southeast Asia”
7 April 2015

Allergens of concern

Cereals containing gluten
Milk
Egg
Peanuts
Fish
Crustacea
Molluscs (EU)
Soybeans

Sesame seeds
Tree Nuts (EU named nuts)
Added Sulphites ≥10 mg/kg
Celery (EU)
Lupins (EU)
Mustard (EU, Canada)

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.

Ingredients: Unbleached Wheaten Flour, Grains 15% (Kibbled Rye, Linseed, Malted Wheat Flakes, Kibbled Maize), 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 (E481).
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)

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**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"?

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**2005 Australia**

**AFGC Allergen Risk Assessment Project**

**Objective:** Development of a standardised allergen risk assessment tool which can be used to assist in determining appropriate voluntary allergen labelling statements

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**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® Operation

Reference Dose
mg allergen protein (from risk assessment)

Action Level Threshold
mg/kg

Reference Amount
gm of food (determined by manufacturer)

Action Level 2
precautionary label 'may be present'

Action Level 1
no label

Key Assumption: if allergen present allergic individual may be exposed

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® 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

Panel Members:
- Dr Steve Taylor (FARRP)
- Dr Joseph Baumert (FARRP)
- Dr Geert Houben (TNO)
- Dr Rene Crevel (Unilever)
- Dr Katie Allen (Royal Childrens 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**

**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

Dose Distribution Modelling

Interval-Censoring Survival Analysis

- 0 10mg 50mg 150mg 500mg
- Subject 1
- Subject 2
- Subject 3
- Left-censored
- Interval-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.
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

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
**Probability distribution models - individual peanut thresholds**

- Discrete dose
- Cumulative dose

Mean ± 95% confidence limit

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**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.

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**Data point summary by Allergen**

Allen et al 2013
### 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>original VITAL® value (0.1mg) applied</td>
</tr>
<tr>
<td>Fish</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

### 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

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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*
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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