Recent developments in risk assessment of food allergens

Geert Houben
TNO Principal Scientist & Science Leader Food Allergy & Immune Health
TNO, The Netherlands

In collaboration with:
Food allergy

A potentially lethal condition affecting around 3% of the western population

Effects:
- Lip swelling
- Oral Allergy Syndrome (OAS)
- Gastro-intestinal complaints
- Vomiting
- Skin effects
- Respiratory effects
- Cardio-vascular effects
- Anaphylactic shock
- Death

- Mortality
- Morbidity
- Social and emotional aspects/quality of life

Ability by allergic consumers to avoid allergenic foods is of life importance!

Over 20.000 ER visits per year in NLD?
Contains egg, soy and wheat. That’s fine!

Smoked Chicken filet (seasoned), Sliced for sandwiches. A quite common product in NL

May contain: Almonds, Cashews, Barley gluten, Oats, Hazelnuts, Kamut, Lactose, Lupin, Macadamias, Milk, Mustard, Parasnuts, Pecan, Peanuts, Pistachios, Rye, Sellery, Sesame, Spelt, Sulfites, Fish, Walnuts

Fresh and prepared with care!
Avoidance of allergenic foods is hardly or not possible!

Use of precautionary (“May contain”) warning:

- Products with a warning: 6.5 - 93 % contained allergen
- Products without a warning: 11 - 53 % contained allergen

There is a need for
- methods for quantifying the risks of allergens
- quantitative guidance for the use of precautionary warning

TNO allergen risk assessment and risk management program
ILSI Europe task force activities
TNO in food allergen risk assessment and risk management

Joint TNO-FARRP Threshold Database
Since 2011 continuously expanded and updated and registered in e-depot

TNO clinical thresholds datamining project in collaboration with FARRP and many clinical centres

---

All reactions (Weibull)

Objective reactions (Weibull)

Currently > 3000 datapoints
TNO in food allergen risk assessment and risk management

Joint TNO-FARRP Threshold Database
Since 2011 continuously expanded and updated and registered in e-depot

We have the most complete database worldwide on sensitivities of food allergic individuals (shared with FARRP)

We have developed food intake models specifically for the purpose of food allergy risk assessment

This allowed us to develop a quantitative risk assessment method
Probabilistic risk assessment developed by TNO:

- Thresholds: from threshold database (see previous slides)
- Consumption: from food intake models (see previous slides)
- Levels: from analysis of samples or estimates/calculations/modelling
Probabilistic risk assessment:
Computer program draws samples from distributions
Probabilistic risk assessment:
Computer program draws samples from distributions
Probabilistic risk assessment:
Computer program draws samples from distributions

Sample 3
0.3 mg  3.1 mg
No allergic reaction
Probabilistic risk assessment:

Computer program draws samples from distributions
Probabilistic risk assessment:

Computer program draws samples from distributions
10,000 samples
25 runs of 10,000 samples
Percentage of predicted responders & CI

Sample
Sample
Sample
Sample
Sample

Allergic reaction

Probabilistic model

Data
Surveys
Analyses
Clinical studies

Chance distributions
Consumption
Levels

Allergen intake
Thresholds
Concentrations of undeclared allergens in food products can reach levels that are relevant for public health.


Percentages of predicted responders in the milk-allergic population (users and non-users);
For users only: 8 (M) – 10 (F) x higher

Concentrations of undeclared allergens in food products can reach levels that are relevant for public health.
TNO in food allergen risk assessment and risk management

Joint TNO-FARRP Threshold Database
Since 2011 continuously expanded and updated and registered in e-depot

We have the most complete database worldwide on sensitivities of food allergic individuals (shared with FARRP)

We have developed food intake models specifically for the purpose of food allergy risk assessment

This allowed us to develop quantitative guidance for precautionary warning
The Australian New-Zealand Allergen Bureau
VITAL approach for deriving concentration action levels for precautionary warning

- a quantitative guidance -

VITAL Scientific Expert Panel

Expert Panel:
Steve Taylor, Joe Baumert, FARRP
Rene Crevel, Unilever
Geert Houben, TNO
Simon Brooke-Taylor, consultant
Katie Allen, Melbourne allergist

Goal:
establishment of reference doses for deriving concentration action levels for precautionary labelling
The Australian New-Zealand Allergen Bureau VITAL approach for deriving concentration action levels for precautionary warning

- a stepwise process -

Step 1

Accepted residual risk level
Max. …% risk

Step 2

Threshold distribution

Reference dose

Step 3

Food intake

Should I use a “may contain” warning or not?

Action level
VITAL approach for deriving concentration action levels

- In consultation with stakeholders
- Aimed at < 1% mild objective reactions
- Incidental effects will in general be mild and transitory, generally requiring no medical intervention


Step 1
- Accepted residual risk level
- Max. 1% risk

Step 2
- Reference doses for major allergens

Step 3
- e.g.: 0.2 mg for peanut protein

Threshold distribution modelling

Action level

Reference dose

Step 1
- Accepted risk

Step 2
- Reference dose

Step 3
- Food intake
Reference Doses (in mg protein)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>mg Protein Level</th>
<th>Quantitative Risk</th>
<th>Quality of database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>0.2</td>
<td>ED01</td>
<td>Excellent</td>
</tr>
<tr>
<td>Milk</td>
<td>0.1</td>
<td>ED01</td>
<td>Excellent</td>
</tr>
<tr>
<td>Egg</td>
<td>0.03</td>
<td>ED01 and ED05 95% lci*</td>
<td>Excellent</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>0.1</td>
<td>ED01 and ED05 95% lci</td>
<td>Good</td>
</tr>
<tr>
<td>Soy</td>
<td>1.0</td>
<td>ED05 95% lci</td>
<td>Sufficient</td>
</tr>
<tr>
<td>lupin</td>
<td>4.0</td>
<td>ED05 95% lci</td>
<td>Sufficient</td>
</tr>
<tr>
<td>sesame</td>
<td>0.2</td>
<td>ED05 95% lci</td>
<td>Marginally Sufficient</td>
</tr>
<tr>
<td>Shrimp</td>
<td>10</td>
<td>ED05 95% lci</td>
<td>Marginally Sufficient</td>
</tr>
<tr>
<td>Celery</td>
<td>n/a</td>
<td></td>
<td>Insufficient</td>
</tr>
<tr>
<td>Fish</td>
<td>n/a</td>
<td></td>
<td>Insufficient</td>
</tr>
<tr>
<td>Other tree nuts</td>
<td>n/a</td>
<td></td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

* Lower Confidence Interval

Based on threshold database update 2015/2016, additional reference doses will be elaborated and proposed in 2016/2017.
ILSI Europe Food Allergy Taskforce
Expert Group “Food Allergy: From Thresholds to Action Levels”

• Assessed and adopted the VITAL 2.0 approach

• Particularly considered:
  o The importance of selecting an appropriate intake figure!
    ➢ Guidance needed!
  o Do risks indeed remain at or below the accepted risk level taken as a starting point? (answer: yes)
  o Are there relevant differences among countries? (answer: no)
  o The risk of meals with 2 or more food products that all may be contaminated with the same allergen
    (outcome: in case of incidental trace scenario's (eg. 10% of products contaminated), risks will be << accepted risk taken as starting point)
International stakeholder meeting
“Food Allergy: From Thresholds to Action Levels”
Reading, UK, September 13-14, 2012

Organised by ILSI Europe in collaboration with:
- The Food Allergy Research & Resource Program (FARRP)
- Health Canada Food Directorate
- ILSI Japan
- ILSI North America
- The University of Nebraska (US)

Representatives from all continents
- Patient organisations, industry, government, clinicians, dieticians, science, …
- Report from the ILSI Europe Expert Group “Food Allergy: From Thresholds to Action Levels” presented and discussed
Stakeholders agreed that a consistent, transparent set of reference doses (as a basis for action levels) would be a desirable outcome.

Data from food challenge studies are the appropriate foundation from which these action levels can be derived.

Sufficient data exist to move forward.

The proposed reference doses constitute a reasonable first pass to minimise risk to the allergic consumer while maintaining food choices.

Appropriate training, education and communication needed.
The VITAL approach

› Has been discussed in various (inter)national stakeholder meetings

› Stakeholders agree on the approach and consider the proposed reference doses appropriate to minimise risks to the allergic consumer while maintaining food choices for allergic consumers and practicality for industry

› The approach and reference doses are increasingly being used by food companies and authorities globally

› TNO in collaboration with many parties is working on further international enrolment and supports authorities and companies in the implementation of the approach
Case study on the risks from residual peanut protein in highly refined vegetable oil

Marty Blom, Astrid Kruizinga, René Crevel and Geert Houben

- Refined vegetable oils (incl. peanut oil) are widely used in foods and their production.

- Refined vegetable oils include peanut oil, which is produced on the same equipment and therefore cross contact of refined vegetable oils with refined peanut oil can occur.

- Refined vegetable oil may contain small amounts of peanut proteins.

- Consequently, food products produced with refined (non-peanut) vegetable oils might contain very small residues of peanut protein.

What is the possible health impact for the peanut allergic population?
Risk assessment for residual peanut protein in highly refined vegetable oil

- Probabilistic Quantitative Risk Assessment developed by TNO

- Distribution of thresholds for 750 peanut allergic individuals as also used for reference dose elaboration for VITAL

- Concentration of peanut protein in refined peanut oils (0.69 ± 0.3 mg peanut protein/kg refined peanut oil, based on analysis of 22 samples)

- Carryover estimates during production of refined vegetable oils is 2% (average “A”) and 5% (worst case “B”)

- Selection of foods with a high fat content and/or high consumption

- Risk assessment for peanut-allergic users of the product of interest
Risk assessment for residual peanut protein in highly refined vegetable oil

- Various scenario’s:
  - **Scenario 1**: product made with a vegetable oil produced immediately after production of peanut oil
  - **Scenario 2**: product made with a vegetable oil mixture of which 1% of the oils has been produced immediately after production of peanut oil (peanut protein concentration is 100\(^{th}\) of that in scenario 1)
  - **Scenario 3**: separate batches of the product made with separate batches of vegetable oils of which 1% had been produced immediately after production of peanut oil (1% of the products will contain peanut protein residues at a concentration as in scenario 1)

- For each scenario 2 carryover percentages assessed: 2 (A) and 5% (B)
Risk assessment for residual peanut protein in highly refined vegetable oil

To give a perspective:

- Refined peanut oil max. 1 mg peanut protein/kg
- Refined vegetable oil (5%) max. 0.05 mg peanut protein/kg
- Food product (e.g. 50% fat) max. 0.025 mg peanut protein/kg
- Consumption (e.g. 250 g) max. 0.006 mg peanut protein

VITAL reference dose: 0.2 mg peanut protein
Result: risk for peanut-allergic users of the food products per eating occasion is low

- Risks of all scenario’s, including worst case < 0.3%
- All risks < VITAL accepted residual risk level
All predicted reactions occur at doses below those at which the most sensitive peanut-allergic individuals are reported to react.

- The risk assessment is rather conservative.
- Probabilistic modelling will *always* predict reactions.
The risk assessment is rather conservative. Probabilistic modelling will always predict reactions. Individual thresholds predicted to have a reaction in the simulation (mg protein)

All predicted reactions occur at doses below those at which the most sensitive peanut-allergic individuals are reported to react

Risk based approach requires agreement among stakeholders on how to deal with risks (risk perception and risk acceptance) and willingness to take another perspective
Thank you for your attention!

Dr. Geert F. Houben
Principal Scientist
TNO Earth, Life and Social Sciences
PO Box 360, NL 3700 AJ Zeist, The Netherlands
Tel: +31 88 866 17 10
E-mail: geert.houben@tno.nl

Acknowledgements:

- Center for Food Allergy TNO/UU/UMCU
- UMCU-AZU; UMCU-WKZ; UMCG; JBZ; FARRP
- Ministry of Health, Welfare and Sports of the Netherlands
- ILSI Europe Expert Groups, Allergen Bureau Australia, VITAL Scientific Expert Panel,
  Dutch “May Contain” Working Group, FoodDrinkEurope Ad Hoc Allergen Expert Group

In particular: