Approaches to risk assessment for food allergens

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Risk assessment for food allergens

- Why do we need risk assessment methods?
- Risk assessment methods
  - NOAEL/LOAEL
  - Benchmark
  - Probabilistic
- Examples
- Going from risk assessment to risk management
  - Is there an acceptable risk?
Why do we need risk assessment methods?

EFSA opinion

‘Based on the data provided by the applicant the Panel is unable to predict the likelihood of adverse reactions in cereal allergic individuals. Nevertheless, taking into account the levels of wheat proteins reported to cause allergic reactions in severe allergic individuals, the Panel considers that it is not very likely that this product will cause a severe allergic reaction in the majority of cereal allergic individuals.’

How to compare this to other risks?
How to translated this into risk management?
Approaches to risk assessment in food allergy: Report from a workshop “developing a framework for assessing the risk from allergenic foods”

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From hazard to risk – Assessing the risk


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Three approaches

• Traditional safety assessment, based on NOAEL or LOAEL and applying uncertainty factors

• Safety assessment based on a benchmark dose derived from dose-distribution modelling and calculation of a Margin of Exposure

• Probabilistic modelling
Safety assessment based on NOAEL

- Identify NOAEL from appropriate challenge studies – this will need to be the study showing lowest value (e.g. Wensing peanut study 30µg protein)
- Decide what uncertainty factors to apply e.g.
  - 2-10-fold for small size of test group
  - 2-10-fold for presumed exclusion of most sensitive
- Calculate safe dose
  - Using Wensing peanut study: 0.3µg protein
Safety assessment based on NOAEL

• Strengths
  – Easy to understand
  – Has been used for many years in toxicology
  – Inherently conservative

• Weaknesses
  – Uses a single data point from one study
  – Data quality
    • NOAEL strongly dependent on quality of study design
    • Little or no information on relationship to whole allergic population
  – No quantitative estimate of risk
  – Inherent conservatism may lead to impracticable and unusable results
Spice mix with undeclared wheat flour as carrier

• A sauce has 10 g spice mixture/kg as an ingredient
• The spice mixture contains (an unknown amount of) wheat flour as carrier
• The wheat flour does not appear on the list of ingredients

The question to the risk assessor is: Could the undeclared wheat flour be a risk to people with wheat allergy?
Spice mix with undeclared wheat flour as carrier - LOAEL/NOAEL

- Assumption: 50% of the spice mix is wheat flour
- Protein content of wheat flour: 10%
- Serving size of the sauce 150 g
- 75 mg wheat protein per serving
- LOAEL for wheat protein 2.6 mg (children, objective symptoms)
- 75 mg wheat protein is significantly higher than the LOAEL

Answer: Yes, the undeclared wheat flour can be a risk to people with wheat allergy (as well as those with coeliac disease).
Benchmark dose and Margin of Exposure

- Model dose distribution of challenge results
- Fit to an appropriate statistical model
- Calculate benchmark dose
  - Usually dose to which no more than 10% would react
  - In practice and more conservatively the BMDL$_{10}$ is used as basis for calculations
- Assess exposure to allergenic food
- Calculate Margin of Exposure
  \[ \text{MoE} = \frac{\text{BMDL}_{10}}{\text{Exposure}} \]
Benchmark dose and Margin of Exposure

• Strengths
  – Makes use of all data points in distribution
  – More robust – favours good study design
  – More consistent basis for decision-making
  – Easy to understand

• Weaknesses
  – Not a quantitative estimate of risk
  – How representative are the data used?
  – Exposure estimates need to be validated for relevant groups
  – Use of MoE as a basis for regulatory thresholds requires consideration of tolerability of risk
Spice mix with undeclared wheat flour as carrier – risk analysis using the BMD Approach

- 75 mg wheat protein per serving
- The Reference Dose for wheat is 1.0 mg wheat protein. (95% lower confidence interval of the dose giving reactions in 5% wheat allergic patients (BMDLow5))
- Margin of Exposure/Margin of Safety = 0.01
  - Reference Dose (BMDL5)/exposure = 1.0 mg/75 mg = 0.01
- MoE is <<1 indicating that there is a high risk of an allergic reaction.

Conclusion: The dose of 75 mg wheat protein per serving can be a risk to wheat allergic patients.
Probabilistic modelling

- Considers probabilities that lead to an allergic reaction
- Uses distributions for both thresholds and exposure
- Generates distribution for probability of reaction
Probabilistic modelling

• Strengths
  – Provides quantitative risk estimate, including uncertainty
  – Favours good study design and uses all available data
  – Very useful to investigate different allergen management options, set food safety objectives, etc

• Weaknesses
  – Highest data requirements of all 3 approaches
    • More reliant on data quality, both for threshold and intake data
  – Requirement for statistical/mathematical computing tools
  – Application requires understanding of statistical background to approach
Spice mix with undeclared wheat flour as carrier - Probabilistic Approach

- 500 mg wheat protein/kg in the sauce
- Consumption data based on tomato sauce intake in the 2003-2008 United States National Health and Nutrition Examination Survey
- Intake data were conservatively based on a per day basis
- Estimated 2.8% of the U.S. population consumes tomato sauce
- Challenge data from 40 wheat allergic persons, objective symptoms
Spice mix with undeclared wheat flour as carrier - Probabilistic Approach

• From the inputs we can estimate
  – Risk of an objective reaction in the wheat allergic population is 1.2 in 100
    • (assuming that persons with wheat allergy eat tomato sauce in the same amounts and frequency as non allergic)
  – Risk of an objective reaction in the wheat allergic user population is 41.4 in 100
Spice mix with undeclared wheat flour as carrier - Probabilistic Approach

Reference Dose (1.0 mg)
Lowest LOAEL (2.6 mg)
Spice mix with undeclared wheat flour as carrier

<table>
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<tr>
<th>Approach</th>
<th>Results</th>
<th>Conclusion</th>
<th>Suggested Action?</th>
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</thead>
<tbody>
<tr>
<td>NOAEL/LOAEL</td>
<td>75 mg wheat protein in 150 g of sauce</td>
<td>500 mg/kg wheat protein may trigger an allergic reaction in a significant part of the wheat allergic population.</td>
<td>Recall may be warranted, change product label to declare the presence of wheat</td>
</tr>
<tr>
<td>BMD</td>
<td>MoE$_{05}$ = 0.01</td>
<td>(see above)</td>
<td>(see above)</td>
</tr>
<tr>
<td>Probabilistic</td>
<td>Risk of a reaction in the wheat allergic population is 1.2% (allergic user risk of 41.4%)</td>
<td>(see above)</td>
<td>(see above)</td>
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Lemonade company learns of peanut proteins in a flavour carrier ingredient

- Analyses revealed 50 ppm of peanut proteins in the highest sample
- Other samples down to below the limit of quantitation
- A lemonade company uses the flavour carrier at 0.5% in their final product.
- 0.25 ppm peanut protein in lemonade

- Does 50 ppm peanut protein in a flavour carrier present a significant health risk to the peanut allergic population?
Peanut proteins in lemonade
NOAEL/LOAEL approach

- Assumption: The 0.25 ppm peanut protein is homogeneously distributed through the lemonade
- The average consumption of lemonade per eating occasion is 410 g
- 0.103 mg peanut protein per eating occasion
- LOAEL of 0.1 mg peanut protein (objective symptoms)

- Answer: The most sensitive portion of the peanut allergic community could be at risk when consuming this product
Peanut proteins in lemonade
BMD approach

- 0.103 mg peanut protein per eating occasion
- The Reference Dose (BMD\textsubscript{1}) for peanut is 0.2 mg based on challenge data from 750 persons
- Margin of Exposure (MoE) = 2.0 (0.2 mg/0.1 mg)
- MoE >1 the risk is lower than the risk posed by the Reference Dose
- MoE of 2 could still pose an unacceptable risk due to the uncertainty associated with the determination of the Reference Dose and the consumption estimates
Peanut proteins in lemonade
Probabilistic approach

• 0.25 ppm peanut protein in lemonade
• Consumption data for lemonade from the 2003-2008 United States National Health and Nutrition Examination Survey
• Intake data based on a per eating occasion
• Estimated 5.7% of the U.S. population consumes lemonade
• Challenge data from 750 peanut allergic patients
Peanut proteins in lemonade
Probabilistic approach

From the inputs we can estimate

• risk of an objective reaction is 1.8 in 10,000 in the peanut allergic population
  – (assuming that persons with peanut allergy drink lemonade in the same amounts and frequency as non allergic)

• risk of an objective reaction in the peanut allergic population using the product is 3.0 in 1,000

• >70% of the predicted reactors had thresholds below the most sensitive LOAEL
Peanut proteins in lemonade
Probabilistic approach

% of Predicted Reactions "User Population"

mg Peanut Protein

Lowest LOAEL (0.1 mg)
Reference Dose (0.2 mg)
# Peanut proteins in lemonade

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<tr>
<td>NOAEL/ LOAEL</td>
<td>0.1 mg peanut protein in 410 g of lemonade</td>
<td>Could pose a risk to the most sensitive peanut allergic individuals</td>
<td>Not conclusive, risk of a reaction present</td>
</tr>
<tr>
<td>BMD</td>
<td>MoE_{01} = 2.0</td>
<td>(see above)</td>
<td>(see above)</td>
</tr>
<tr>
<td>Probabilistic</td>
<td>Risk of a reaction in the peanut allergic population is 0.018% (allergic user risk of 0.3%)</td>
<td>Analysis shows nearly all predicted reactions are below the lowest reactive doses observed in clinical setting</td>
<td>No recall needed</td>
</tr>
</tbody>
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Workshop conclusions

• All three methods examined had positive attributes
  – Traditional safety assessment: simple, easy to understand
  – Benchmark dose: uses available data better, also easy to understand output
  – Probabilistic modelling: best use of data, provides quantitative estimate of risk

• All three approaches have a role
  – A rational approach would be to use a method commensurate with the complexity of the problem
  – Probabilistic approach preferred for population-based risk assessments
Can we define a tolerable level of risk in food allergy? Report from a EuroPrevall/UK Food Standards Agency workshop


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Workshop conclusions

• zero risk was not a practicable or realistic option

• it is essential to address the current lack of agreed action levels for cross-contamination of allergens if food allergy and food allergen management are to be improved

• it was difficult to define and quantify a tolerable level of risk, but a higher number of reactions could be tolerated for mild symptoms than for severe symptoms

• not doing anything was not a viable option
Suggested actions

Action 1
1 Review available food challenge data and derive provisional action levels. Develop different scenarios and implications for each level and ask stakeholders to comment
2 Propose a value for the tolerable level of risk (e.g. as a level of protection)

Action 2
Conduct a ‘one-dose’ clinical trial in multiple centres across the world using a standardized food challenge protocol with a low dose