Food allergens: Challenges for risk assessment

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Goals

• Introduce “food allergy”

• Describe challenges for risk assessment
  ➢ Food allergen
  ➢ Food allergic reaction - mechanisms and key scientific issues
  ➢ Threshold/ Biological end point
    ▪ Food challenge/ Eliciting doses
    ▪ Severity

• Conclusions
“Food allergy”

- Serious public health problem:
  - 30000 ER visits/ 2500 hospitalizations/ 150 deaths/yr

- Increased prevalence over past 20 years
  - 4% of total US population: Infants > adults

- Over 150 foods implicated; wide distribution of major allergenic foods:
  - US: peanut, tree nut, soy, egg, milk, wheat, fish, shellfish
  - Europe: ... sesame, mustard, celery
  - Japan: ... buckwheat

- No effective treatment – Avoidance / product labeling is key!

- Lifetime risk + consumer fears ⇒ psychosocial impact
Food allergy

Adverse reactions to food

- Immunological (Hypersensitivities)
  - IgE Mediated
    - Food Allergy
  - Non-IgE Mediated
    - Celiac Disease
- Non-Immunological (Intolerances)
  - Toxicological Example: Scombroid Poisoning
  - Metabolic Example: Lactose Intolerance
- Microbial
  - Infections Example: Salmonellosis
  - Toxins Example: Staphylococcal enterotoxins

http://www.cfsan.fda.gov/~dms/alrgn2.html#ii
Food allergen

- Food - peanut, soy, milk, etc.
- Protein in food - Ara h1, Ara h2, Ara h3, etc. (peanut)

- One food ⇒ multiple allergens
- Not all foods/ allergens the same

- Widely distributed in food supply
Food allergic reaction

- Unique toxicological response:
  - Immunological
  - Two phase (sensitization and elicitation)
  - Amplifier mechanism
- One exposure
- Minute amounts can trigger (*thresholds*)
- Potentially fatal
ALLERGY

Sensitization

IgE
Antibody

Elicitation/ Reactivity

Food protein

Food

B cell

T lymphocyte

Mast cell/ Basophil

Anaphylaxis

Skin- itchiness, flushing, hives, swelling, eczema

GI- nausea, vomiting, abdominal pain, diarrhea

Respiratory- tightness, runny nose, wheezing, throat closing/swelling

Vascular- dizziness, low blood pressure, heart irregularities, shock

Subjective
Sensitization

- Few individuals affected - genetic AND environmental factors
  - Exposure, cultural, processing

- Diagnose by food-specific IgE levels

- Risk assessment: Novel food proteins
  "Allergenicity safety assessment of foods derived from recombinant DNA plants - Codex Alimentarius, 2003"
Elicitation/ Reactivity

- Dose-dependent release of mediators, cytokines (Amplification mechanism)
  - Rapidly progresses in severity

- Varies according to allergen type/bioavailability/meal
  - GI absorption, alcohol use
  - Food matrix, exercise

- Specific IgE levels - poor predictors

- Genetics/host sensitivity to mediators

- Risk assessment: Allergen “Thresholds”
  - Safe exposure dose
  - Biological end points?

Mast cell/ Basophil

Food protein

• IgE independent ~20%

IgE Antibody

Food/Protein
Biological end point

- No validated animal models

- No good serum marker for predicting reactivity and/or severity

- Food challenge ⇒ eliciting dose
  - Double-blinded placebo-controlled (DBPC) food challenge in humans
  - Real-life exposure

- Reaction severity considerations
Food Challenge – typical protocol

- **NOAEL** and **LOAEL**

X  2X  4X  8X  16X  32X  64X  108X

- Starting dose (X) varies (usually mg doses)
- Time interval varies (15-60 min)
- Usually 2 to 10-fold (X) dose increments over 2-6 hrs

- **Dose escalation** of divided doses in food vehicle (w/ placebos) to final target dose*

- Stop after **objective** sign; some also record **subjective** symptoms

- Report eliciting dose - discrete (4X) and/or cumulative (7X) - interpreted as **Lowest Observed Adverse Effect Level (LOAEL)**; prior dose is No Observed....(NOAEL)
Food Challenge – data gaps

- Purpose mainly for diagnosis not for minimal eliciting dose determinations
  - Many first dose responders – NOAEL rare; ? true LOAEL

- Lack of standardization of allergen doses/ use of different food matrices for challenge

- Selection bias – patients with most severe reactions (anaphylaxis) often excluded.
  - Is the most sensitive population tested?
  - Children vs adults
  - Adolescents and individuals w/ asthma – fatal reactors
Reaction severity end point

- Allergic dose-response severity is on a continuum

**Subjective**  **Objective**  **Anaphylaxis**  **Death**

- Anaphylaxis poorly defined - many end points possible
  - Early subjective/ objective complaints may be mild/ short-lived or signal something worse

- Symptoms may not be reproducible on subsequent rechallenge

- Potentiating/ mitigating factors for severity
  - Anxiety/stress; medications; asthma

- Do challenges mimic real-life severity exposures?
Conclusion: Food allergen = unique risk

- Allergens are normal constituents in food
- Potentially fatal
- No hazard to a large majority of population ⇒ ? label
- One food ⇒ Multiple allergens
- Complex and unique immune response - two phases (sensitization and elicitation/reactivity)
- Lack of good biological marker(s) for predicting reactivity and/or severity - many end points possible
- Dose-response relationship not well defined
  - Human food challenge data limited
  - Varies among different allergens and meals
  - Wide individual variability in response
Comparison to traditional food safety assessment approaches

**Animal feeding models**
- Genetic Homogeneity
- One ingredient in food
- Defined endpoints for severity
- NOAEL defined
- Reproducible
- Dose response

**Allergen food challenges**
- Genetic Heterogeneity
- Multiple allergens in food
- Multiple endpoints; severity not well defined
- LOAEL mainly; rare NOAEL
- May not be reproducible
- Dose distribution