Food Allergens: Best Practices for Identifying & Controlling Allergens in the Production Facility – Joe Baumert

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Food Allergy

- Continues to be a major public health issue in the U.S. and around the world
  - 4% of the overall U.S. population (15 million Americans)
  - Economic cost of food allergy in children ~$25 billion/yr

- 18% increase in children under 18 years of age in the U.S. from 1997-2007
  - Peanut ~1.1% in US (~3 million Americans)
    - US (children) allergy 0.4% to 1.4% (1997-2008)
    - UK peanut sensitization 1.3% to 3.2% (1989-1995)

Perceived Prevalence of Food Allergy

- The perceived prevalence in the U.S.
  - 1 in 5 Americans believe they have food allergies
  - Many consumers do not differentiate between IgE-mediated allergy and other food sensitivities

- Many consumers have not sought professional diagnosis
  - Are unnecessarily avoiding foods that are otherwise safe and wholesome
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Classification of Food Sensitivities:

- **Food Intolerance**
  - Immune system is not involved
  - Individual can tolerate a limited amount of the food
  - Ex. Lactose Intolerance

- **Food Allergy**
  - Involve immunological mechanisms
  - Total avoidance of the offending food is necessary
  - Ex. IgE-mediated food allergy; Celiac disease

Food Sensitivities

- Defined as abnormal physiological responses to particular foods

  - Primary Food Sensitivity
  - Secondary Food Sensitivity
  - Food Intolerances
  - Food Allergies
  - Immunological
  - Non-immunological
    - Anaphylactic reactions, e.g., IgE-mediated
    - Mast cell-mediated reactions, e.g., histamine release
    - Idiosyncratic reactions, e.g., sulfite-induced asthma

IgE-Mediated Food Allergy

- Defined as an abnormal or heightened response of the immune system to specific food components (proteins)
- Inflammatory response results from cross-linking 2 immunoglobulin E (IgE) antibodies
  - Immediate reactions – can typically within minutes to 2 hours after ingestion of the food
- IgE developed in human body to defend against parasitic infection
  - Theory: decreased infection may result in immune system looking for other foreign proteins?
**Food Allergens**

- Humans consume 1000s of plant and animal proteins in the diet on a daily basis.
- Only a small number of proteins from plant and animal origin cause and IgE-mediated immune response in only a small number of humans.
- What factors are involved in the development of IgE-mediated food allergen?
- Why are some proteins allergenic while others are not?

**Similar Characteristics Among Food Allergens?**

- Naturally-occurring proteins
- Heat-resistant
- Resistant to proteolysis
- Resistant to extremes in pH
- Usually major proteins of the food
- Foods can have 1 or many allergens in them

**Potential Risk Factors that May Contribute to Development of Food Allergies**
Mechanism of IgE-Mediated Food Allergy: Sensitization Phase

- Antigen (allergen) exposure
- Plasma cells produce IgE antibodies against the allergen
- IgE antibodies attach to mast cells and basophils
- Mast cell with food IgE antibodies
- Granules containing histamine, tryptase

Mechanism of IgE-Mediated Food Allergy: Elicitation Phase

- More of same allergen invades body
- Allergen combines with IgE attached to mast cells and basophils, which triggers degranulation and release of histamine and other chemical mediators
- Mast cell granules release contents after antigen binds with IgE antibodies
- Histamine, tryptase and other mediators

http://farrp.unl.edu/resources/qi-fas/food-allergy-sensitivities
Symptoms of IgE-Mediated Reactions

Skin:
- Urticaria (hives)
- Eczema (rash)
- Angioedema (swelling)
- Puritus (itching)

GI Tract:
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea

Respiratory:
- Asthma
- Rhinitis (runny nose)
- Laryngeal edema (swelling of the throat)

Cardiovascular:
- Hypotension (low blood pressure)

Multiple Organ Systems:
- Anaphylactic shock

Food Allergy

- Food allergy is the most common cause of anaphylaxis in U.S. emergency rooms (~30%)
  - Yearly estimates
    - 50,000 anaphylactic reactions
    - 2,000 hospitalizations
    - 100 – 150 deaths
    - (commonly quoted but likely an overestimation)
- Currently, no active treatment for food allergy other than strict avoidance of the offending food

Fatalities by Age

- Teens are the highest risk group for fatal allergic reactions
Prevalence of Food Allergy

- The perceived prevalence in the U.S.
  - 1 in 5 Americans believe they have food allergies
- IgE-mediated food allergies are estimated to affect:
  - 6-8% of infants and children
  - 3.5-4.0% of adults in the U.S.
- Food allergies extend beyond the allergic individual
  - Families avoid the allergenic foods
  - Caregivers, daycares, schools, etc. may limit allergenic foods in facilities

Most Prevalent Food Allergens

- There are 160+ other foods that can cause allergic reactions
- The most prevalent food allergens are:
  - Peanuts
  - Tree nuts
  - Milk
  - Egg
  - Soy
  - Fish
  - Shellfish
  - Wheat

- 90% of allergies are caused by these top eight foods
- 10% of allergies are caused by hundreds of others
Prevalence of Specific Food Allergens

<table>
<thead>
<tr>
<th>Food</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Egg</td>
<td>1.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Peanut</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tree Nuts</td>
<td>0.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Crustaceans</td>
<td>0.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>0.1%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>


Federal Food Allergen Labeling Regulations

- Law amended the Federal Food, Drug, and Cosmetic Act
  - Requires food manufactures to label food products that contain a major food allergen by common name in the ingredient statement or use a “contains” statement
  - Examples:
    - Ingredients: Lecithin (soy), whey (milk)
    - Contains: Soy, Milk

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Allergen Declaration within the Ingredient Label

Allergen Declaration Using a “Contains” Statement

FALCPA
Definition of Source

- Species of fish (e.g. cod, salmon, perch)
- Species of crustacea (e.g. shrimp, crab, lobster)
- Type of tree nuts (e.g. walnut, almond, hazelnut)
U.S. List of Most Common Causes of IgE-Mediated Food Allergy

- Cows’ milk
- Egg
- Crustacean shellfish
- Fish
- Peanut
- Soybean
- Tree nuts
- Wheat

*Other countries require labeling of ‘cereals containing gluten (wheat, rye, barley, oats, spelt)’ rather than specifically calling out wheat

Tree Nuts Included as Major Allergens in FALCPA (based on 2006 FDA guidance)

- Almond
- Brazil nut
- Cashew
- Hazelnut
- Macadamia nut
- Pecan
- Pine nut
- Pistachio
- Walnut
- Beech nut
- Butternut
- Chestnut
- Chinquapin
- Coconut
- Ginko nut
- Hickory nut
- Lichee nut
- Pili nut
- Sheanut

Additional Commonly Allergenic Foods in Other Countries

<table>
<thead>
<tr>
<th>Food</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sesame seed</td>
<td>Canada, EU, Australia/New Zealand, Japan</td>
</tr>
<tr>
<td>Mustard</td>
<td>EU, Canada</td>
</tr>
<tr>
<td>Celery</td>
<td>EU</td>
</tr>
<tr>
<td>Buckwheat</td>
<td>Japan, Korea</td>
</tr>
<tr>
<td>Molluscan shellfish</td>
<td>Canada, EU</td>
</tr>
<tr>
<td>Lupine</td>
<td>EU</td>
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2012-2013 FDA Reportable Food Registry

- First time food allergens ranked #1 in RFR entries
- Bakery (cookies & cakes) and chocolate/confections accounted for 32/88 entries (36%)

2009-2013 FDA RFR

U.S. FDA Food Allergen Recall Incidents 1988-2014

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Current Regulations: USDA FSIS

- USDA FSIS also requires labeling of priority allergens
  - Wheat, Crustacean Shellfish, Eggs, Fish, Peanut, Milk, Tree Nuts and Soy
- Labeling policy outlined in FSIS Notice 29-13
  - April 30, 2013
- No established threshold for food allergens
- FSIS – Compliance Guidelines: Allergens and Ingredients of Public Health Concern: Identification, Prevention and Control, and Declaration through Labeling
  - Docket No. FSIS-2013-0029
  - Comment period until June 20, 2014

FSIS/ USDA Food Allergen Recalls
Calendar Years 1999-2014
**Treatment for True Food Allergies**

**Specific Avoidance Diets**
(currently no treatment or cure for food allergies)

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**Exquisite Sensitivity of Some Food-Allergic Individuals**

- Trace amounts of the offending food will trigger reactions
  
  How much is too much?
  
  or
  
  How clean is clean enough?
  
  low mg amounts or ppm concentrations

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**Dose of Peanuts Causing Reactions in Highly Sensitized Subjects**

<table>
<thead>
<tr>
<th>0.2mg</th>
<th>0.4mg</th>
<th>1.0mg</th>
<th>5.0mg</th>
<th>25mg</th>
<th>100mg</th>
<th>400mg</th>
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Lowest Eliciting Dose

State of the Science of Food Allergen Thresholds and Risk Assessment

Current Situation

- Public health authorities have not established regulatory action levels for any of the allergenic foods – With the exception of Japan (10 µg/g protein limit for labeling)
- Labeling laws/regulations in many countries impose a de facto zero threshold for source labeling of ingredients
- Food industry is acutely aware of allergens - no guidance on action levels/threshold so use of precautionary labeling ("may contain") is common

Consumer Adherence to Precautionary Labeling

Disadvantages of Zero Threshold Approach

- Food-allergic consumers have diminished quality of life due to limited food choices
- Healthcare professionals need to advise scared and frustrated patients
  - Very difficult since precautionary labeling is not consistently used
  - Advice varies from one healthcare professional to the next
- Public health authorities spend time chasing zero
- Food industry focuses attention on trying to achieve zero
  - Zero keeps getting less with advancement of analytical methods
  - Does ‘chasing zero’ really increase the safety of the food for allergic consumers?

Moving Toward a Finite Threshold Concept

- Very low doses have been proven to be safe
- Quality of life of food-allergic consumers could improve with establishment of finite threshold approach
- Clinical data are emerging that could allow the establishment of consensus thresholds/action levels
- Consensus is emerging in U.S., EU, and Australia to support establishment of thresholds/action levels
- Discussion and education still needed
  - Includes food industry, regulators, allergic consumers, healthcare professionals

Determination of Individual Threshold Doses

- Determination of individual threshold doses for food-allergic patients is not currently common practice
- Data from low-dose DBPCFC trials have become increasingly available in recent years
  - Published and unpublished threshold data from diagnostic series, threshold studies and immunotherapy trials available
- Statistical dose-distribution modelling of individual NOAELs & LOAELs can be used to establish population thresholds for individual food allergens
Are We Ready to Move Forward with Reference Doses or Regulatory Action Levels?

- Currently no regulatory establishment of action levels or reference doses (except Japan)
- Could food industry move forward with a systematic approach to assess the need for precautionary labeling?
  - A harmonized system that guides the appropriate use of precautionary labeling would benefit allergic consumers
  - Requires risk communication among multi-stakeholder groups to establish a common understanding of an accepted level of risk

Implementation of Reference Doses: The VITAL® Approach as an Example

Voluntary Incidental Trace Allergen Labeling (VITAL) program
Allergen Bureau of Australia & New Zealand

VITAL® - A Risk Assessment Tool

- Used to assess the impact of allergen cross contact
- Uses an action level grid to determine if the presence of residual protein from allergenic substances through cross contact requires precautionary labelling
- Stipulates a consistent precautionary allergen labelling statement – “may be present”
- Aims to avoid indiscriminate use of precautionary labelling and preserve a valuable risk management tool.
The VITAL® Process
A systematic approach to processes and allergenic contributors
Part of a HACCP based food safety program

Considerations:
- Ingredient and processing impact
- Consider the form of allergenic material
- Determine the amount of cross contact allergen in the finished product (in terms of protein content)
- Consider the VITAL® grid and determine the appropriate allergen labelling statement
- Review significant contributors and reduce cross contact
- Ongoing Monitoring

Where Allergen Risks Occur
- Research and Development
- Engineering and System Design
- Raw Materials/Suppliers/Co-Packers/Purchasing
- Operations/Manufacturing
- Packaging and Labeling
- Sanitation
- Human Error/Training

Strategies to Effectively Manage Food Allergens in Food Processing Facilities
Allergen Management is a Key Food Safety Step

- Form an allergen control team
- Conduct a systematic risk assessment
- Develop an allergen process flow diagram (allergen map)
- Develop an allergen control plan specific to each processing facility
- Review the ACP on some regular basis and especially for new products, introduction of new processing capabilities, new ingredients

Allergen Control Team

- Manufacturing
- Quality
- Labeling/Regulatory Compliance
- Product Development
- Engineering/Equipment Selection & Design
- Sanitation
- Packaging
- Purchasing
- Management, Consumer Affairs, Marketing, Human Resources

Product Development Strategies

- Develop an approach to review potential new products at the concept stage to identify potential allergenic components
- Use the allergenic components if they are truly necessary
  - Only use allergic ingredients if they make a discernable difference to taste or functionality
- Create a process to assure that the processing facility is notified before start-up
Supplier Qualification

- Documented allergen control plan
- Letters guaranteeing the absence of undeclared allergens; do they check their suppliers?
- Require notification of changes that affect allergen status of ingredients sold to your company
- Don’t believe them – Audit
- Validated sanitation procedure
- Ingredient shipments in clearly marked, sealed containers

Receiving

- Review and inspect incoming shipments of raw materials for allergen information
- Develop a company-wide system for tagging all raw materials for easy identification in your facilities (Ex. color coding, symbols/icons, etc.)
- Assure that each incoming container is appropriately tagged
- Have a plan to handle any damaged containers to avoid allergen cross-contact and use it

Storage – Raw Material

- Segregate allergenic raw materials/products separately to avoid cross contact if possible
- Designate areas of storage to one particular allergen type – all milk, all soy, etc.
- Avoid storing allergenic ingredients above non-allergens or different allergens.
- Develop, use and document plan for control of any spills of allergenic ingredients
Operations Strategies

- Schedule long runs of allergenic products wherever possible (minimize changeovers)
- Schedule manufacturing of allergenic products just prior to end of shifts with major clean-up
- Introduce allergenic components into the products as late in the process as possible
- Review labels and package material carefully – triple check
- Develop an exact-into-exact rework policy or forbid the use of rework

Cleaning and Sanitation

- Knowledge of system and product
- Sanitation design of equipment
  – access and ability to thoroughly clean; no static or hidden areas
- Personnel that are trained, dedicated, alert, and thorough

Cleaning and Sanitation

- Allergen content/potency of ingredient
- Uniform formulation vs. particulate
- Allergen composition – stickiness
  – Peanut Pieces?
  – Peanut Flour?
  – Peanut Butter?
- Consider:
  Difficulty to clean and potential risk factors.
  How much equipment will be exposed?
Prevent Re-Contamination

- Protect clean equipment and areas
- Follow procedures, in sequence
- Control people and activities
- Remove allergen ingredients
- Label and seal clean systems
- Communicate during and after cleaning
- Re-inspect prior to start-up
- Flush and examine first product

Validation of Allergen Control Programs

Using ELISAs for Sanitation Validation/Assessment

- Visually clean is the standard in the food industry
  - Best approach when particulates are involved
- Visual inspection can be quite effective
  - Analytical validation and verification of allergen removal is needed
  - Swabbing equipment surfaces (contact surfaces and hard to reach areas) or testing CIP final rinse water (when possible) is commonly done for allergen assessment
ELISA and ELISA-Based Technologies

- Include ELISA kits, lateral flow tests, swabs
- Have become the standard method for allergen validation
- Specific and sensitive
- Rapid analytical assessment
  - 10 min-1 hr analytical process
- Suitable for food-processing settings

Source: microscopesblog.com

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Lateral Flow ELISAs

- Lateral flow device (strip test/ dipstick)
  - Qualitative ELISAs
  - Used primarily for sanitation assessment, but can be used for food product testing**
    **Affects of matrix on sensitivity?
  - 10 minute assay time
  - 5 ppm limit of detection depending on food matrix

Neogen RAPID 3-D™ and Reveal Lateral Flow Tests

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Detection of Allergenic Food Residues

- But be careful!!
- All allergen detection methods are not created equal!!
- The right choice for one application may be wrong for another!
- Results can differ qualitatively and quantitatively

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Key ELISA Decisions

- What do you want to measure?
  - Select appropriate detection system according to major components in the product
    - Example: Milk
      - Total Milk
      - β-lactoglobulin
      - Casein
  - What protein source is used as the standard in the method?
  - What units are the results reported in?
    - Example: ppm casein or ppm NFDM

Which ELISA Is More Sensitive?

- An ELISA with a sensitivity limit of 2.5 ppm NFDM?
- An ELISA with a sensitivity limit of 1.0 ppm BLG?

Which ELISA Is More Sensitive?

- BLG is approx. 10% of total milk protein
- So, 1 ppm BLG is equivalent to 10 ppm milk protein
- But milk protein is about 35% of NFDM
- So, 1 ppm BLG is equivalent to 28.6 ppm NFDM
Change Management

- When **anything** changes, then you must re-evaluate the entire allergen control plan
  - Re-Validate by doing a new Quantitative Risk Analysis
  - Does the existing Allergen Control Plan still work with the new conditions?

Thank You for Your Attention

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