U.S. FOOD & DRUG ADMINISTRATION

Assessing the Public Health Burden and Risks of Food Allergen Exposures

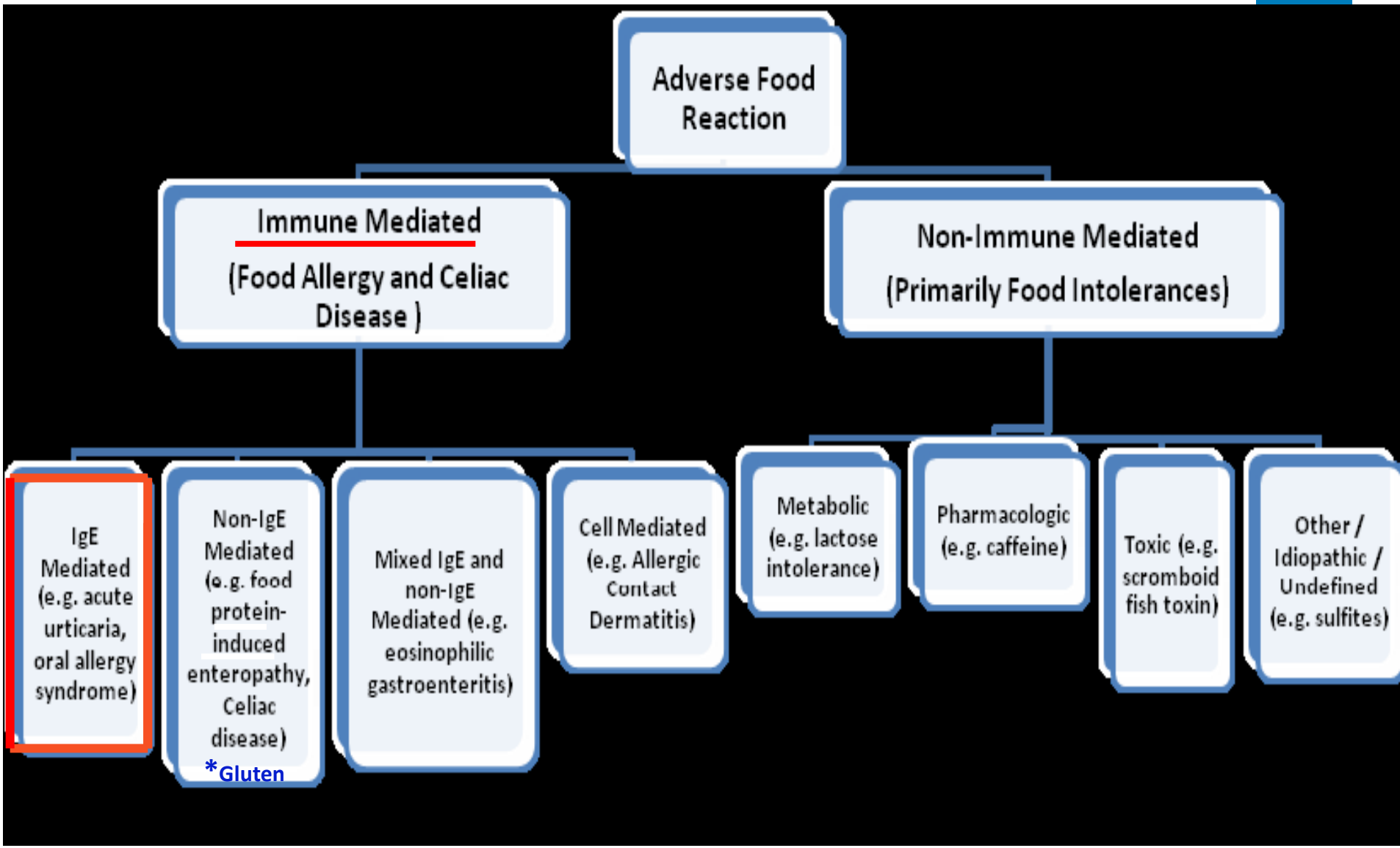
Stefano Luccioli, MD
Medical Officer, Office of Compliance
Center for Food Safety and Applied Nutrition (CFSAN)
U.S. Food and Drug Administration (FDA)

Goals

- Define and provide brief overview of food allergy –mechanism and health sequelae
- Address public health burden and risks posed by food allergens
- Discuss FDA activities/experience in managing/assessing food allergen hazards – labeling, enforcement and risk assessment
- Future activities

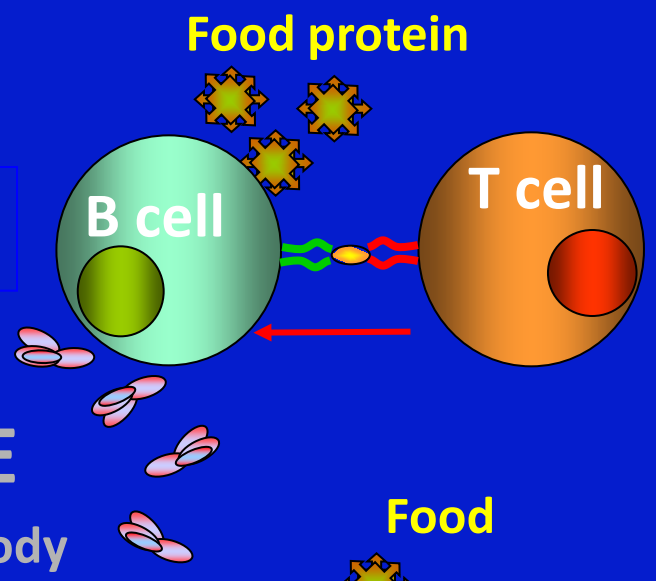
"Food allergy"

- "Adverse reaction to food that is IgE Ab-mediated"
  - "immediate gastrointestinal allergy/anaphylaxis"
- Involves foods/proteins commonly consumed in diet
  - US: peanut, soy, egg, milk, wheat, tree nuts, fish, shellfish
  - > 170 foods; Sesame, mustard, celery, lupin, buckwheat..
- Affects 3-4% of Americans, mostly children
- Genetic AND environmental
- No effective treatment – Labeling/ avoidance is key!
- Lifetime risk for many
- Avoidance is difficult→ decreased QOL

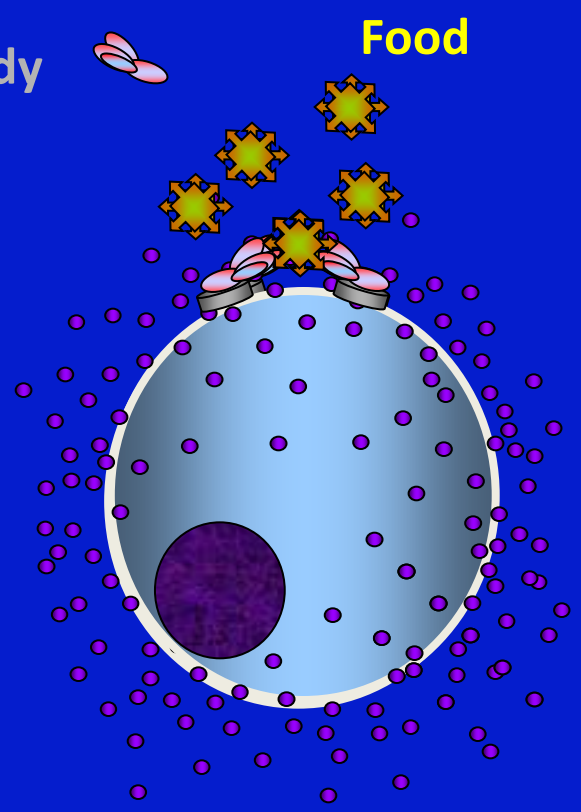


http://www3.niaid.nih.gov/topics/foodAllergy/clinical/PDF/guidelines.pdf

Sensitization



Elicitation/
Reactivity



Food allergy –symptoms/response

- Skin- itchiness, flushing, hives, swelling, eczema
- GI- nausea, vomiting, abdominal pain, diarrhea
- Respiratory- chest tightness, runny nose, wheezing, throat closing/swelling
- Vascular- dizziness, low blood pressure, heart irregularities, shock

↓

Anaphylaxis

ED=eliciting dose

ED ED ED ED ED ED ED

Subjective Objective Anaphylaxis Shock

Severity Continuum

Health sequelae

- Accidental reactions in community are common (despite avoidance)
- Most common cause of anaphylaxis seen in ERs
  - Teenagers/young adults at highest risk for fatal reactions
  - Tree nuts and peanuts most commonly involved
  - Difficult to predict who is at risk and at what dose
- May lead to asthma and other conditions/ malnutrition
- Psychosocial impact/ decreased quality of life (QOL)
  - Limited food choices, social stigma/ bullying, anxiety/ fear of death from accidental exposures

Assessing public health burden and other risks

Food allergens

- One food → multiple allergens
  - Food – peanut, soy, milk, etc.
  - Proteins in food (peanut) – Ara h 1, Ara h 2, Ara h 8, etc.; storage proteins vs enzymes, etc.

- Derived ingredients vary in hazard potential
  - milk whey (high protein); soy lecithin (low protein)

- Not all foods/ allergens are the same
  - Prevalence of Crustacean allergy >>> fish
  - Potency for severe reactions: Peanut >>> Soy
    - Different thresholds of reactivity observed

Food crossreactivities

Lupin- up to 30% crossreactivity to peanut; GF foods

Crossreactivity with molluscs < 20%

Lone star tick bite and delayed allergy to beef/ mammalian meat - Galactose-alpha-1,3-galactose (Alpha gal allergy)

Known allergy	Risk of infection (to at least one)	Percent risk
A legume: Peanut	Other legumes: Peas, Lentils*, Beans	5%
A tree nut: Walnut	Other tree nuts: Brazil, Cashew, Hazelnut	37%
A fish: Salmon	Other fish: Swordfish, Sole	50%
A shellfish: Shrimp	Other shellfish: Crab, Lobster	75%
A grain: Wheat	Other grains: Barley, Rye	20%
Cow's milk	Beef: Hamburger	10%
Cow's milk	Goats's milk: Goat	92%
Cow's milk	Mare's milk: Horse; camel	4%

Luccioli et al, in Bellanti Immunology IV book 2012

Biological Endpoint

- No validated animal models

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

- Double-blinded placebo-controlled food challenge (DBPCFC) in humans ⇒ eliciting dose (ED) and severity info
  - Timing/escalation of doses and type of food ingredient
  - Interpretation of "adverse effect" (subjective/objective)
  - Inclusion of most sensitive individuals?
  - Mimics real-life exposure?

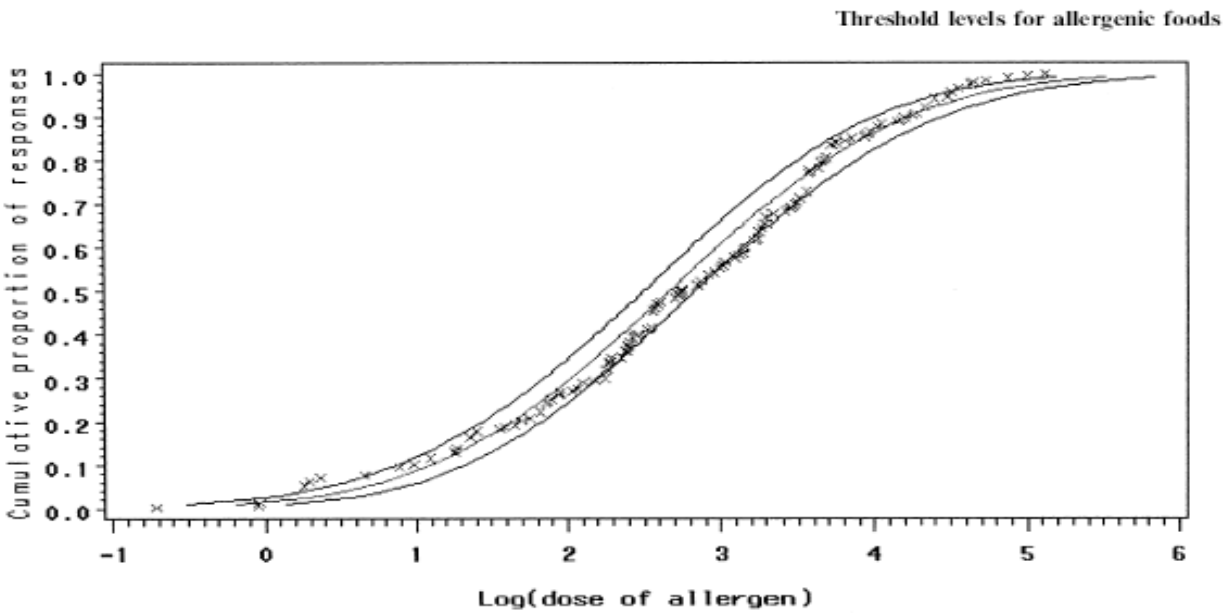
At Risk Population

Food	*Children	*Adults	^Objective	*Outgrown?
Milk	2.5%	0.3%	0.6-0.9%	80%
Egg	1.3%	0.2%	0.3-0.9%	60-80%
Peanut	0.8%	0.6%	0.4-0.8%	20%
Tree nut	0.2%	0.5%	0.4%	9%
Fish	0.1%	0.4%	0.2-0.3%	No ?
Shellfish	0.1%	2.0%	0.6%	No ?
Other	-	-	Soy – 0.03-0.7% Wheat- 0.2-1.2%	Wheat 30-65%
Total	6%	3.7%	3.0%	_

*Sampson, JACI, May 2004; ^NIH clinical guidelines, 2010

- FA: Self-reported (9- 13%) >> clinically diagnosed (3-4%); Infants >> adults
- Surveys: FA prevalence in US children doubled 1997-2007; peanut (US and UK)
- Self-report of FA in adults increased 2001-2010 (*Verrill,Bruns,Luccioli.All Asth Proc.2015;36:458-67*)

Population sensitivities

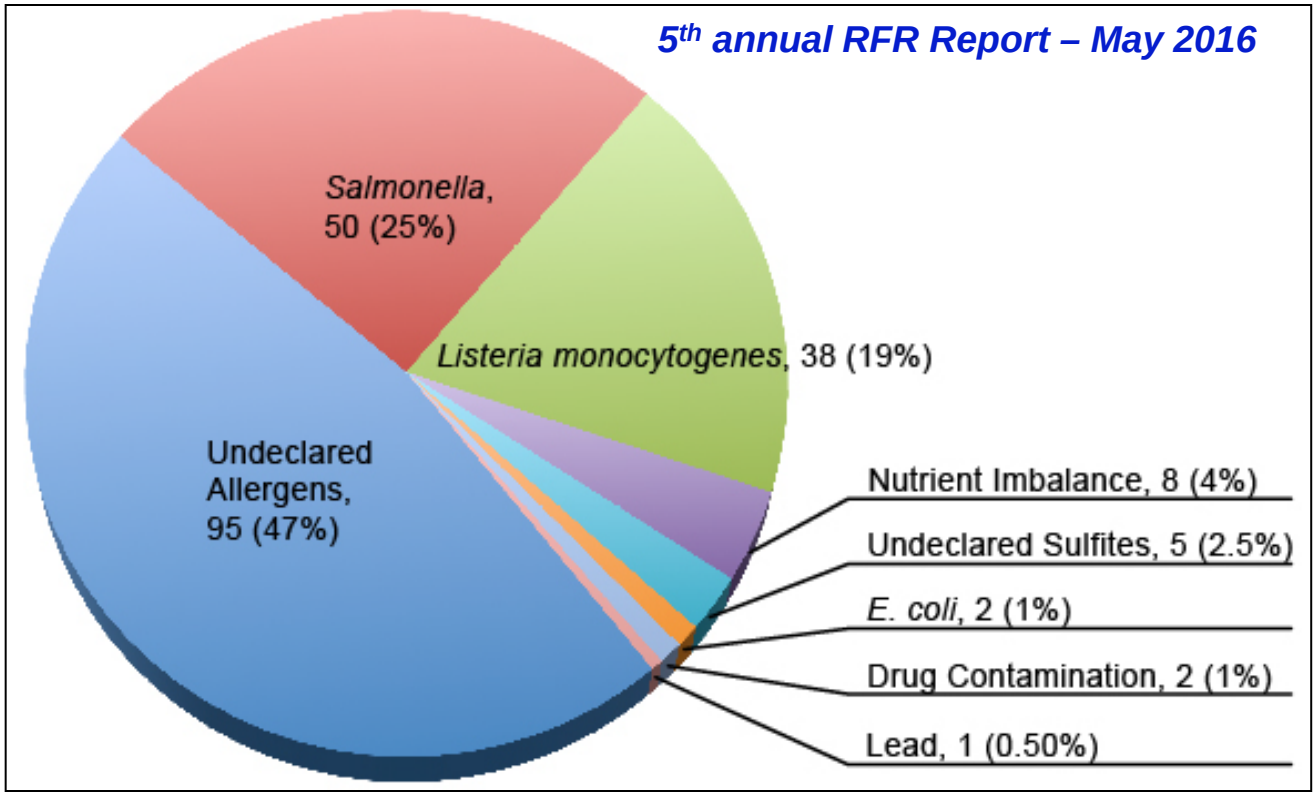


- **Million-fold distribution of eliciting (threshold) doses among individuals in allergic population (little information on severity)**
  - **Large inter-individual variability in dose responses**
    - **May be impacted by various extrinsic factors (exercise, alcohol, infection)**
  - **Individual sensitivities may vary over time**
  - **Most individuals do not know their threshold dose**

Other issues that impact health burden

- Avoidance is not easy
  - Allergens abundant in food supply
  - Proliferation of allergen label / advisory/ PAL statements
    - Limited food choices
    - Mistrust/disregard of labels → risky consumer behaviors
- Allergenic food hazards difficult to control
  - Multiple different foods/ingredients and equipment
  - Global food market – novel/ emerging allergens
  - Analytical detection methods are limited for most allergens
  - Mistakes can happen → recalls

Recalls



- **Undeclared allergens are #1 cause of food product recalls**
- **Milk is most common cause >> wheat > soy > tree nuts**
- **Main root cause is wrong package or label**
- **↑ in bakery, snacks and candy**
  - ***Recall data FY2007-2012**. Gendel and Zhu. Journal of Food Protection.2013; 76:1933–1938*

Other allergic reaction information – FDA

- Recalls (2005-2010)
  - 5-15% of allergen recalls associated with consumer reactions
  - Milk – cause of 59% of all consumer-related events
  - Chocolate products have high association of reactions
    - Malyukova, Gendel, Luccioli. JACI 129(2):S234, 2012.
    - https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm433555.htm (dark choc)

- CFSAN Adverse event reporting system (CAERS):2007-2011
  - About 3% of all CAERS events ascertained to be allergic events – 0.5% of total were consistent with anaphylaxis
  - Common food categories included bakery (16.3%), cereal/breakfast food (10.0%), and ice cream (6.7%)
    - Oladipo, Luccioli. JACI 133(2):S207, 2014

Regulatory activities- US experience

CFSAN activities involving food allergens

CFSAN mission: ensuring that the nation's food supply is safe, sanitary, wholesome, and honestly labeled

- **Implementation of food allergen labeling laws**
- **Enforcement**
  - **Inspections and compliance**
  - **Analytical methods to detect allergens in food**
- **Safety/risk assessments- novel foods, label exemptions/thresholds**
- **Postmarket surveillance – Medwatch (CAERS)**
- **Policy, guidance and consumer education**

Labeling of allergenic substances

Food Allergen Labeling & Consumer Protection Act of 2004 (FALCPA)

- "Major food allergens" include these food groups and food ingredients that contain their <u>protein</u>(s):

- Peanut

- Tree nuts (list species; incl. coconuts)

- Milk

- Wheat (any species in *Triticum* genus)

- Egg

- Fish (list species)

- Soybean

- Crustacean shellfish (list species)

- Defines "gluten-free" standard (2013)
- Other: Sulfites (>10ppm), yellow 5, yellow 6, carmine (cochineal)

FALCPA

- Involves packaged food and dietary supplements
  - Not drugs, cosmetics, retail/restaurants
  - Not non-major allergens used in ingredients with common or usual name ("tahini"-sesame) or as processing aid, color, flavors or spice

- Does not address unintentional introduction of allergens into products by way of "cross-contact"
  - Manufacturers may voluntarily place allergen advisory or precautionary allergen labeling (PAL) statements ('may contain', etc) to alert consumers
  - Regulatory concerns: truthful and not misleading? Not used in lieu of good manufacturing practices (GMPs)?
  - Industry concerns: Need for advisory statement?

FDA Food Safety Modernization Act (FSMA)

Final Rule for Preventive Controls for Human Food (2015)

- **Defines "cross contact"**

- **Facilities that use major food allergens must establish and implement a food safety system that includes an analysis of hazards and risk-based preventive controls**
  - **Prevent allergen cross contact**
  - **Ensure accurate labeling of finished foods**
  - **Training**

- **Guidance pending**

❖ **Does not require testing for validation; no thresholds**

Risk/safety evaluations

- Premarket allergenicity assessment of novel foods

- Labeling exemptions
  - Statutory exemption: highly refined oils from MFA
  - Ingredient <u>exemption standards</u>:

  ❑ "does not contain allergenic protein"

    - Ex: Ice structuring protein (ISP- fish)

  ❑ "does not cause an allergic response that poses risk to human health"

    - Ex: Solae-brand soy lecithin as release agent

  Draft Guidance to Industry –Food Allergen Labelling Exemption Petitions and Notifications (May, 2014)

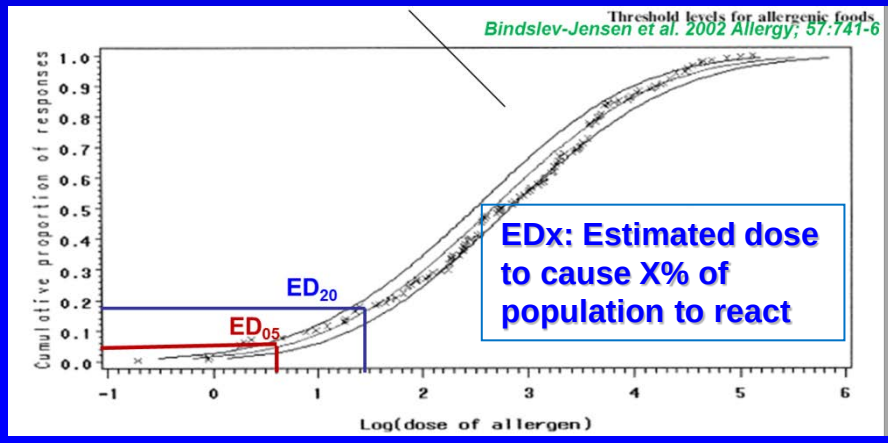
- Threshold? - No established threshold for any food allergen (case by case basis)

"Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food"

Journal of Food Protection, Vol. 71, No. 5, 2008, Pages 1043–1088

- **Analytical methods-based**
  - **Is it there or not? Ex: label sulfites >10 ppm**
- **Safety assessment-based**
  - **LOAEL/NOAEL + safety factors → ADI ("safe" dose)**
  - **Human challenge data available**
- **Risk assessment-based****
  - **Risk in relation to dose, exposure (and severity)**
  - **<u>Threshold dose</u>: interval between LOAEL and NOAEL**
  - **<u>Statistical modeling</u>: Plotting dose distributions to characterize hazard**

peanut, milk, egg, gluten, hazelnut, almond, walnut, soy



Future steps/ developments

- Address increased number of recalls for undeclared allergenic ingredients
- Implementation of FSMA
  - Increase compliance with allergen label controls in industry's food safety plans to reduce allergen recalls from preventable errors
  - Allergen guidance pending
- Data quality assessment of existing threshold data
  - Continue participation in global threshold discussions
  - Continue analytical test method development for all food allergens
- FDA Food Safety Survey 2016- questions on thresholds and advisory label avoidance
- National Academy of Sciences study on food allergies (Nov, 2016) –recommended need for risk-based labeling approach

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Thank you for your attention

Stefano.Luccioli@fda.hhs.gov

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