Thresholds- Definitions, Data Collection, Limitations and Harmonization

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Why are we interested in Thresholds?

- Very small amounts of specific allergens can provoke reactions in some individuals, but
  - we don't know in how many
  - we don't know how small the amounts are
  - we don't know how severity of reaction relates to an individual's sensitivity
  - allergic people are known to react differently on different occasions

So it is difficult to assess how much needs to be done to achieve the desired level of safety with respect to allergens.

Source: R. Crevel, IUFoST - Chicago, July 2003

Historical Approach to Dose/Response

- Physicians recommended completed avoidance (ZERO threshold)
- Ingestion of small amounts (not well defined) could elicit allergic reactions
- DBPCFC was the gold standard for diagnosis but challenges often started at 400 – 500 mg
- 20%+ of patients reacted to first challenge dose – some severe rxns

Historical Approach to Dose/Response

- Peanut-allergic consumers have practiced complete avoidance (zero threshold)
- Peanut-allergic consumers still experienced occasional allergic reactions (hidden ingredients, cross contact, FOOD SERVICE)
- Unexpected allergic reactions to peanuts were occasional severe leading to widespread belief that low doses elicited severe reactions

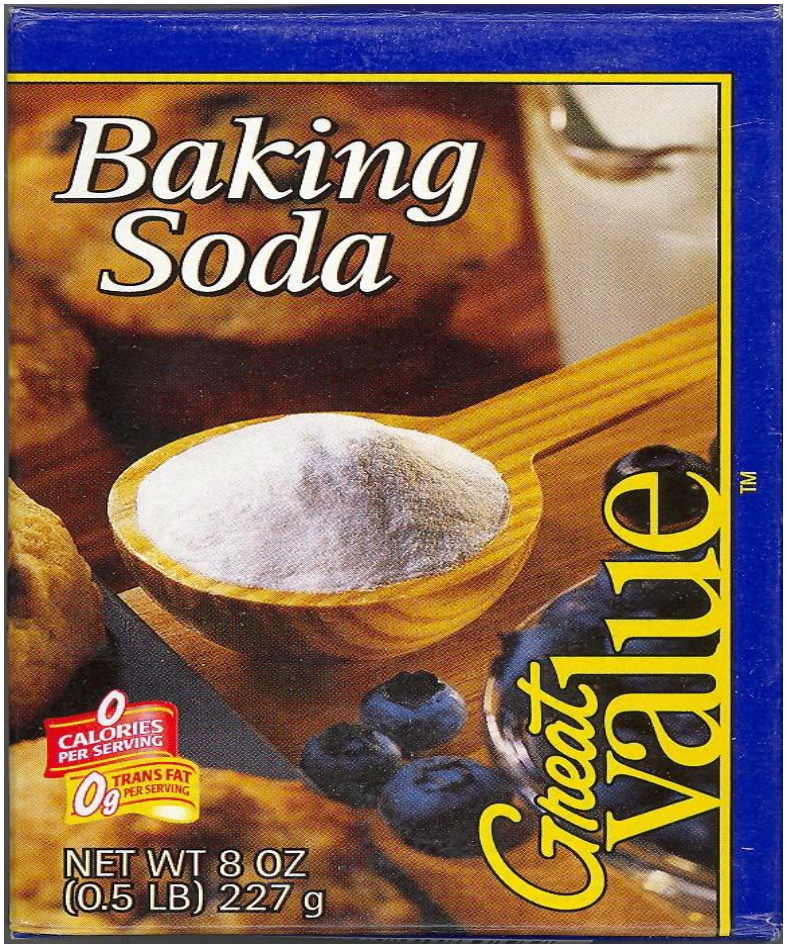
Status of Dose/Response Knowledge circa 2005

- Trace amounts (low mg) can elicit allergic reactions
- Severity of response is related directly to dose (even that might not be universally held opinion)
- Individuals vary in degree of sensitivity
- How much is too much?
- A few clinics started doing very low dose DBPCFC and proved that safe doses exist for every subject and that severe reactions did not occur at very low doses (low mg)

Our 1st indication of safe doses

Current Situation

- Public health authorities have not established regulatory thresholds for allergenic foods
- U.S. FALCPA – de facto zero threshold for source labeling of ingredients
- Many regulatory authorities establish zero threshold for undeclared allergen
- Industry acutely aware of allergens, no guidance on thresholds so rampant use of precautionary labeling



Baking Soda

Nutrition Facts

Serving Size 1/8 tsp (0.6g)
Servings Per Container about 378

Amount Per Serving

Calories 0 Calories from Fat 0

	% Daily Value*
Total Fat 0g	**0%**
Saturated Fat 0g	**0%**
Trans Fat 0g	
Polyunsaturated Fat 0g	
Monounsaturated Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Potassium 0mg	**0%**
Total Carbohydrate 0g	**0%**
Dietary Fiber 0g	**0%**
Sugars 0g	
Protein 0g	

Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 0%

% Daily Value*
Folic Acid 0%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

INGREDIENTS: SODIUM BICARBONATE.

ALLERGY WARNING: MANUFACTURED IN A FACILITY THAT PROCESSES MILK, EGGS, WALNUTS, PEANUTS, WHEAT, SOYBEANS.

MARKETED BY:
Wal-Mart Stores, Inc.
Bentonville, AR 72716
©2000

Current Situation

- Quality of life for food-allergic consumers suffers partially as a result of difficulties in adherence to avoidance diets
- Food-allergic consumers increasingly ignore products with precautionary labels
- Some physicians advise food-allergic patients to avoid precautionary labels
- Allergic reactions continue to occur but rarely with packaged foods

US FDA Allergen Thresholds

- Threshold Working Group Report
- "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food" (March, 2006)

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

Terminology

- NOAEL – the No Observed Adverse Effect Level
- NOAEL – the maximum tolerated dose that produces no symptoms as determined by oral clinical challenge trials in food-allergic subjects

- LOAEL – the Lowest Observed Adverse Effect Level
- LOAEL - the minimal eliciting dose as determined by oral clinical challenge trials in food-allergic subjects

Terminology

- Individual Threshold – LOAEL or NOAEL for an individual patient
- Population Threshold – LOAEL or NOAEL for a group of food-allergic individuals e.g.
  - all peanut-allergic individuals
  - peanut-allergic individuals in a particular clinic or group/sub-group

Terminology

- In reality, an individual's personal threshold lies somewhere between their NOAEL and LOAEL

- Interval Sensoring Survival Analysis
  - assigns equal probability that the true threshold dose could fall anywhere on the continuum from NOAEL to LOAEL

Terminology – What Consitutes a Reaction?

- A response that poses a risk to human health
  - Regulatory view under U.S. FALCPA
- The first response of any type inclulding mild, subjective (cannot be confirmed by physician or other observer), transitory responses
- The first objective response that can be visually observed by a physician or other observer (also usually mild and transitory if oral challenges started at sufficiently low dose
- An objective response that meets some defined criterion e.g. 3 or more hives lasting 5 minutes or more, a single episode of vomiting, erythema, etc.

Data Collection – The FARRP/TNO Dataset What Consitutes a Reaction?

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FARRP/TNO Threshold Database Methodological Approach

- Criteria for inclusion:
  - Published study or clinic files
  - Food-allergic by history or other factors
  - DBPCFC (open challenges for infants)
  - Description of NOAEL and/or LOAEL (if dosing regimen provided, then can determine NOAEL from LOAEL)
  - Data on individual patients
  - Objective symptoms @ doses

FARRP/TNO Threshold Dataset Mining Existing Clinical Literature

- Individual NOAELs identified in some cases; discerned from LOAELs in other cases
- Individual LOAELs were available in many cases
- Data not available on all of the subjects from some studies because of method of reporting
- With interval-censoring survival analysis, both NOAEL and LOAEL are used to derive a “true” threshold value

LITERATURE REVIEW TOOL

LITERATURE REVIEW TOOL

- TNO uses a literature review tool (developed in house) to keep track of published research and considerations whether or not the published research contains data of interest
- The literature review tool contains all (potentially) relevant publications from 2011 onwards

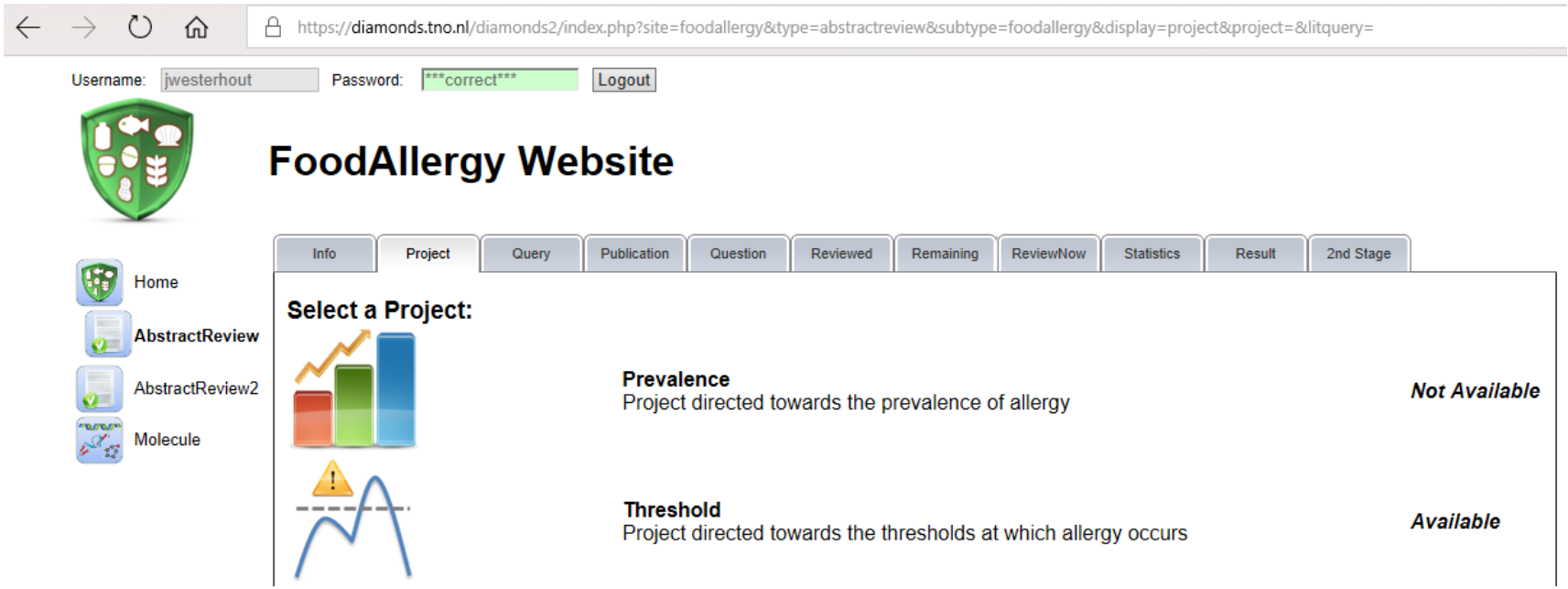
- ((allergy AND (food OR nutrition) AND (DBPCFC OR challenge OR provocation OR threshold OR eliciting)))

PubMed Scopus®

- Additional custom searches done by FARRP, which can be imported in the tool

BibTeX Google Scholar WEB OF SCIENCE™ MEDLINE U.S. National Library of Medicine

LITERATURE REVIEW TOOL



LITERATURE REVIEW TOOL
STEP 1: ABSTRACT SCREENING

Wainstein BK,Saad RA
Asia Pacific allergy.(2015)

Repeat oral food challenges in peanut and tree nut allergic children with a history of mild/moderate reactions.

BACKGROUND
In peanut and tree nut allergic children a history of anaphylaxis is associated with subsequent severe reactions.

OBJECTIVE
We aimed to prospectively rechallenge peanut and tree nut allergic children with a history of mild/moderate reactions to assess their allergy over time.

METHODS
In this cohort study peanut and tree nut allergic children with a history of mild/moderate reactions during a controlled oral challenge were invited to have a follow-up oral challenge to the same food at least 1 year later.

	Yes	No	If...
Keep for review?	◉	○	If Yes

- ☐ DBPCFC
- ☐ PCFC
- ☐ Open
- ☑ Unclear
- ☑ Diagnostic
- ☐ Threshold
- ☐ Immunotherapy
- ☐ Unknown

Submit answers

LITERATURE REVIEW TOOL
STEP 2: READING FULL ARTICLE

Wainstein BK,Saad RA
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Does the publication contain quantitative data? yes ○ no ◉

If...

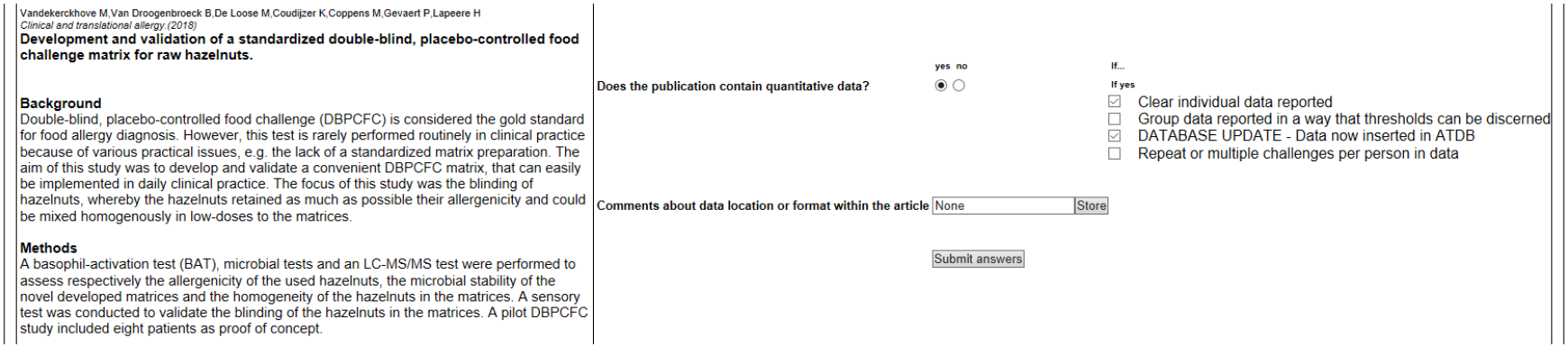
If no

- ☑ Additional information needed from authors
- ☐ Dosing Scheme Missing
- ☐ Threshold values missing
- ☐ Individual Protein
- ☐ Research not fit for our purpose
- ☐ Already in our database
- ☐ ALERT - Contact the authors for collaboration

Comments about data location or format within the article 1. This a test comment Store

Submit answers

LITERATURE REVIEW TOOL
STEP 2: READING FULL ARTICLE



Vandekerckhove M,Van Droogenbroeck B,De Loose M,Coudijzer K,Coppens M,Gevaert P,Lapeere H
Clinical and translational allergy (2018)

Development and validation of a standardized double-blind, placebo-controlled food challenge matrix for raw hazelnuts.

Background
Double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard for food allergy diagnosis. However, this test is rarely performed routinely in clinical practice because of various practical issues, e.g. the lack of a standardized matrix preparation. The aim of this study was to develop and validate a convenient DBPCFC matrix, that can easily be implemented in daily clinical practice. The focus of this study was the blinding of hazelnuts, whereby the hazelnuts retained as much as possible their allergenicity and could be mixed homogenously in low-doses to the matrices.

Methods
A basophil-activation test (BAT), microbial tests and an LC-MS/MS test were performed to assess respectively the allergenicity of the used hazelnuts, the microbial stability of the novel developed matrices and the homogeneity of the hazelnuts in the matrices. A sensory test was conducted to validate the blinding of the hazelnuts in the matrices. A pilot DBPCFC study included eight patients as proof of concept.

yes no — If...

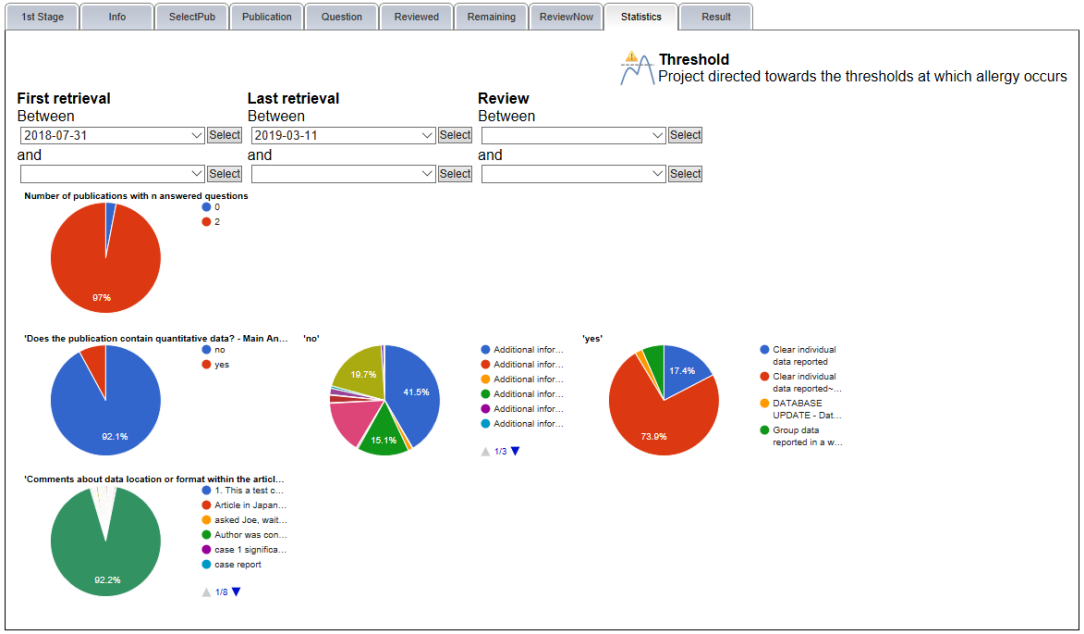
Does the publication contain quantitative data? (●) yes ( ) no — If yes

- [x] Clear individual data reported
- [ ] Group data reported in a way that thresholds can be discerned
- [x] DATABASE UPDATE - Data now inserted in ATDB
- [ ] Repeat or multiple challenges per person in data

Comments about data location or format within the article None [Store]

[Submit answers]

LITERATURE REVIEW TOOL STATISTICS

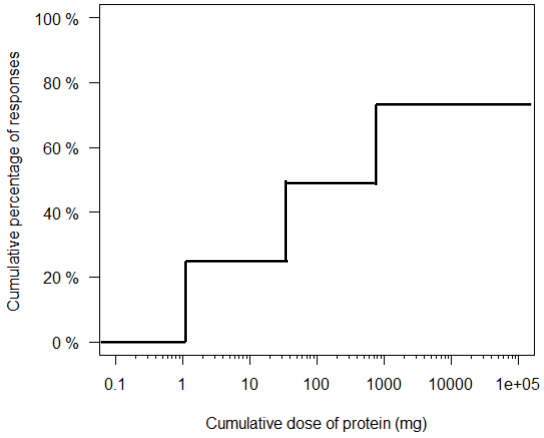


LITERATURE REVIEW TOOL FROM 2011 TO NOW

- > 2500 Titles and Abstracts reviewed
- > 570 Kept for full PDF review
- > 50 Identified as containing quantitative data in a usable format

Normalizing and Modelling Dose Distributions

- Normalize doses on basis of total protein from the food
- Use individual NOAELs and LOAELs
- Done by interval-censoring survival analysis using three probability distribution models (Log-Normal, Log-Logistic, and Weibull); now model averaging



Peanut Threshold Population Distribution (expressed as mg peanut protein)

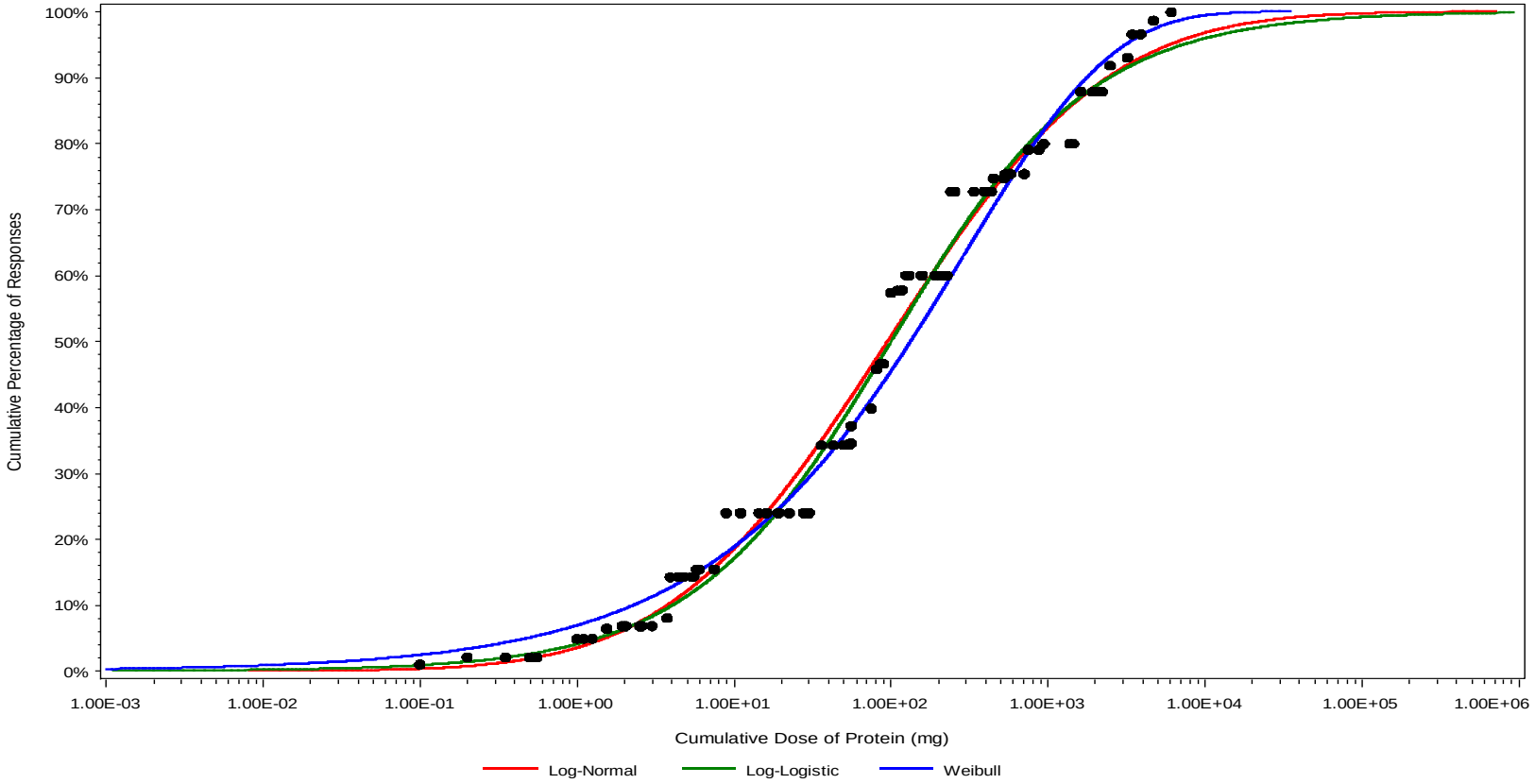


Table 2. ED_{10} and ED_{05} Doses for Whole Peanut as Assessed by the Log-Normal Probability Distribution Models

Source	Total No. of Peanut Allergic Individuals	ED_{10}	95% CI	ED_{05}	95% CI
Nancy Data	286	14.4	10.7, 19.6	7.3	5.2, 10.4
Published Papers[1]	164	14.1	6.6, 29.9	4.2	1.7, 10.1
Combined	450	12.3	9.0, 16.8	5.2	3.6, 7.4

[1]Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals. Twenty-one individuals from 3 papers (A, B, and D; See Taylor et al., 2009) were excluded from analysis to avoid potential duplication of individuals as these studies included individuals from the Nancy clinic.

All values reported in mg of whole peanut

VITAL® Reference Doses 2011-12

Allergen	mg Protein Level
Peanut*	0.2
Milk*	0.1
Egg*	0.03
Hazelnut*	0.1
Soy*	1.0
Wheat*	1.0
Other Tree Nuts*	0.1
Sesame*	0.2
Crustacean shellfish*	10.0
Fish*	0.1
Mustard	0.05

Existing Threshold Data for Allergenic Foods

- Human data on individual minimal eliciting doses on dozens to hundreds of individuals
- Data from the actual sensitive sub-population: food-allergic human subjects
- Data from controlled clinical oral challenges conducted by experienced medical professionals
- Known, small challenge doses

The BIG Question

- Are these data sufficient to establish population threshold doses that could be used by public health authorities to protect food-allergic consumers?
- If not, what data gaps exist and how do we go about filling those data gaps?

Questions on the Existing Dataset

- Do we have sufficient data on all commonly allergenic foods?
- Are the patients representative of the affected population?
- Do they include a sufficient number of the most highly sensitive/severely affected individuals?
- Do differences exist between patients with and without histories of severe reactions?
- Do differences exist between adults and children?
- Do geographic differences occur?
- Do differences occur between different clinic populations?
- How do you adjust for differences in clinical protocols?
- Does the form of the allergenic food make a difference?

Questions on the Existing Dataset

- Do we have sufficient data on all commonly allergenic foods? Except a few tree nuts
- Are the patients representative of the affected population? Yes
- Do they include a sufficient number of the most highly sensitive/severely affected individuals? Yes
- Do differences exist between patients with and without histories of severe reactions? No
- Do differences exist between adults and children? No
- Do geographic differences occur? No
- Do differences occur between different clinic populations? ??
- How do you adjust for differences in clinical protocols? OK
- Does the form of the allergenic food make a difference? No??

Table 4. ED_{10} doses for whole peanut as assessed by the log-normal probability distribution model for severity grade.

Severity Grade	Total No. of Peanut Allergic Individuals	ED_{10}	95% CI
Severe[1]	40	10.4	4.8, 22.6
Non-Severe[2]	123	10.2	6.4, 16.1
No Prior History[3]	123	27.0	17.4, 42.0

[1]Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

[2] Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%)

[3]History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

All values reported in mg whole peanut

Questions on the Existing Dataset

- Uncertainty Factors
  - exercise
  - alcohol
  - medications
  - illnesses and general clinical health
  - stress
  - menstruation
- These factors exist for most chemical hazards in foods
- Risk management

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