SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

The Big 8: Advances in Food Allergy Risk Assessment and Management

October 11, 2018

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

How Much is Too Much? Threshold Dose for Allergenic Foods

Joe Baumert, Ph.D.
Associate Professor, Co-Director
Department of Food Science & Technology
Food Allergy Research & Resource Program (FARRP)
University of Nebraska-Lincoln
jbaumert2@unl.edu

Conflict of Interest Statement

- The University of Nebraska - Food Allergy Research & Resource Program (FARRP) receives funding from the food industry to support research and outreach programs focused on advancement of scientific knowledge and awareness of food allergies
- Royalties from Neogen Corporation for licensing of antisera for ELISA development
- Consultant for DBV Technologies
- Member of the VITAL Scientific Expert Panel and ILSI-EU Thresholds to Action Levels Expert Group

Early Questions About Food Allergen Thresholds & Risk Assessment

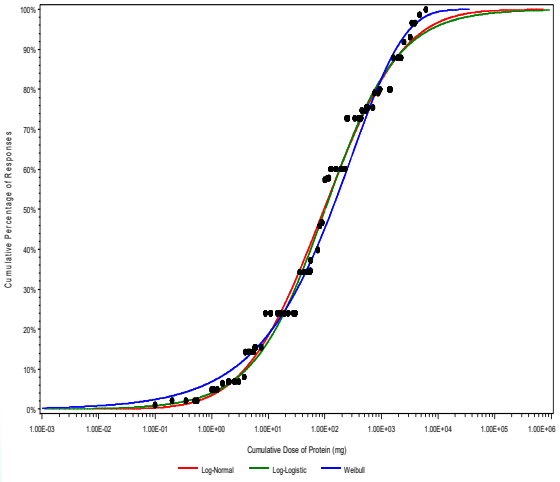
- In 1990s and early 2000s little data on the clinical dose-response to food allergens had been assembled
  - Do allergens obey classical toxicological approaches?
  - Do all allergic reactions occur at very small exposure doses?

Development of Risk Assessment Approaches for Food Allergens

- 2007 workshop on risk assessment approaches – EuroPrevall, ILSI-EU and UK FSA
  1. Safety Assessment Approach
  2. Benchmark Dose (BMD) and Margin of Exposure (MoE) Approach
  3. Probabilistic Approach
- Workshop concluded that the BMD/MoE and probabilistic approaches had the most merit (Madsen et al., 2009)
  - Rely upon low-dose extrapolation from dose-distributions of clinical thresholds rather than a single point estimate
- 2006 FDA Threshold Working Group also indicated that quantitative risk assessment approaches provided the best approach for food allergy risk assessment (Threshold Working Group, 2008)

Food Allergen Thresholds

- Clinical data exist on individual threshold doses of various allergenic foods from oral challenges conducted for diagnosis, threshold trials, and immunotherapy trials – published and unpublished
- Individual threshold data can be used to statistically model the population threshold distribution for allergenic sources

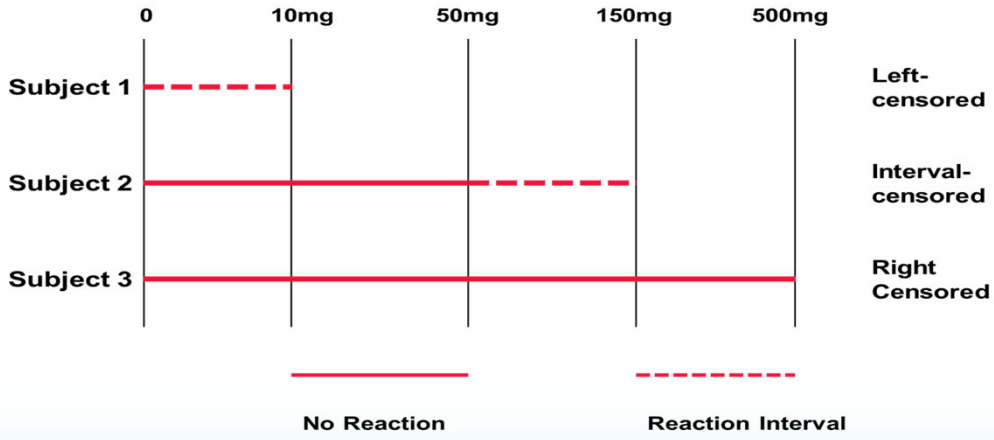


Taylor et al., 2009, 2010, 2014

Inclusion Criteria Used for Assessment of Clinical Threshold Data

- Published studies or unpublished clinical data
  - Diagnostic series, threshold studies, immunotherapy (baseline data)
  - Unpublished data from clinics in the Netherlands, Germany and from threshold studies sponsored by FARRP
- Allergic to the specific food by history of reaction and other factors (SPT+, sIgE)
- DBPCFC
  - Open or SBPCFC considered for infants and young children
- Description of NOAEL and/or LOAEL for individual patients
- Objective symptoms at doses or history and subjective symptoms at last dose of challenge

Interval-Censoring Survival Analysis



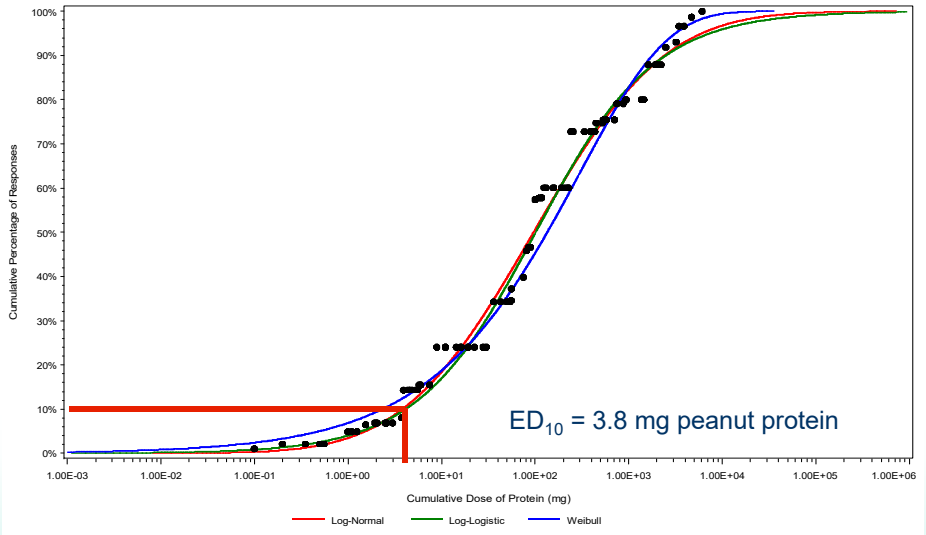
SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Statistical Dose-Distribution Modeling

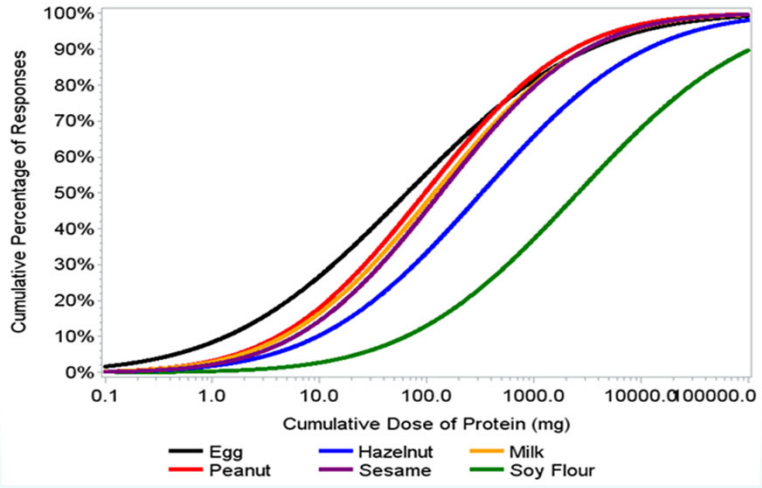
- Individual threshold data fitted to parametric models using the SAS LIFEREG procedure
  - Data fitted to Log-Normal, Log-Logistic and Weibull distributions
  - No biological rationale to prefer 1 model over another
  - All 3 models were evaluated for goodness of fit to the actual clinical data when considering appropriate eliciting dose values (ED_p)
- Data was modeled on the basis of both discrete and cumulative dosing
  - Data also evaluated for children and adults separately where sufficient data existed

Taylor et al., 2009, 2010, 2014

Dose Distribution for Various Food Allergens: Not All Food Allergens are Created Equal



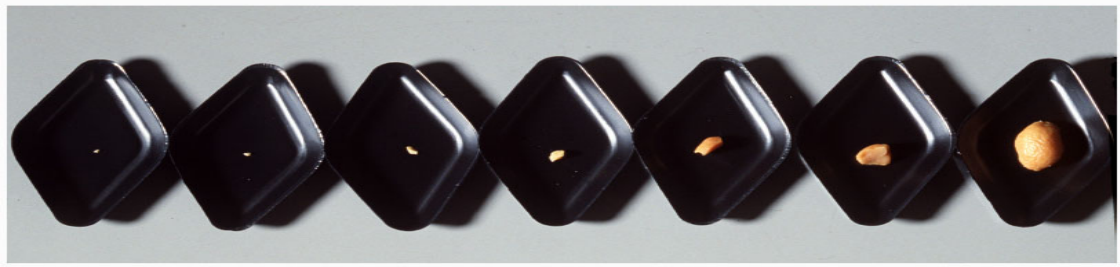
Dose Distribution for Various Food Allergens: Not All Food Allergens are Created Equal



FARRP-TNO Food Allergen Threshold Database

Allergenic Source	Included in 2012 VITAL Analysis	New Published or Clinic Threshold Data	Total
Peanut	744	563	1196
Milk	351	91	451
Egg	206	227	382
Hazelnut	202	209	411
Soy Flour	51	3	54
Soy Milk	29	4	33
Wheat	40	59	97
Cashew	31	213	245
Mustard	33	0	33
Lupine	24	1	25
Sesame	21	19	40
Shrimp	48	27	75
Celeriac*	39	43	82
Fish*	19	63	48
Buckwheat**		26	26
Walnut**		74	74
Total	**1838**	**1622**	**3460**

Allergic Patients Present with Different Levels of Sensitivity



Ballmer-Weber and Hourihane; image used with permission

- Low doses can elicit allergic reactions……BUT, do we have data to support the long-standing notion that very low doses cause severe or fatal reactions???

Validating Population Dose-Distribution Models: Peanut Allergy Threshold Study (PATS)

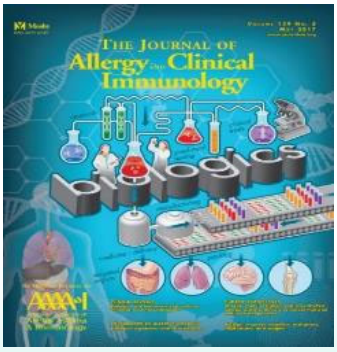
Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy

Jonathan O'B. Hourihane, MD, DM, Katrina J. Allen, MD, PhD, Wayne G. Shreffler, MD, PhD, Gillian Dunngalvin, PhD, Julie A. Nordlee, MS, Giovanni A. Zurzolo, PhD, Audrey Dunngalvin, PhD, Lyle C. Gurrin, PhD, Joseph L. Baumert, PhD, Steve L. Taylor, PhD

Altmetric 13

DOI: http://dx.doi.org/10.1016/j.jaci.2017.01.030 | CrossMark

J Allegy Clin Immunol. 2017; 139(5): 1583-1590.



- Objectives:
  - To validate the predicted ED_{05} (Log-Normal)
  - To assess severity of reactions at the ED_{05} dose (1.5 mg peanut protein
- Recruited 378 unselected consecutive patients in 3 centers (Cork, Boston, Melbourne)

Sample Size Estimation

- Hypothesis: the population distribution for peanut is correct and we predict that 5% of peanut allergic individuals challenged will react with objective reactions

Projected 95% confidence intervals for the prevalence of clinical reactivity in peanut allergic children and adults receiving the ED_{05} dose (6mg of whole peanut = 1.5mg of peanut protein) for sample sizes ranging from 70 to 200.

Sample size (#of peanut allergic individuals)	Value of target prevalence (5% for the ED_{05})	Projected 95% confidence interval
70	5%	0.9% - 12%
100	5%	1.6% - 11%
150	5%	2.3% - 10%
200	5%	2.4% - 9%
375	5%	3.1% - 7.8%

Calculation of 95% confidence intervals of the study population assumes there is an underlying binomial distribution (Clopper-Pearson analysis)

Zurzolo et al., 2013; Hourihane et al., 2017

Peanut Allergen Threshold Study (PATS): Criteria for Positive OFC

- Clinical staff were asked to record *any* physical or behavioural changes observed or self-reported changes during the OFC
- Predetermined objective criteria were used to assess the response to OFC because the ED_{05} was predicted on the basis of challenge-associated objective responses only:
  - 3 or more concurrent noncontact urticaria persisting for at least 5 minutes; or
  - perioral or periorbital angioedema; or
  - rhinoconjunctivitis including sneezing; or
  - diarrhoea; or
  - vomiting (excluding gag reflex); or
  - anaphylaxis (with evidence of circulatory or respiratory compromise, e.g. persistent cough, wheeze, change in voice, stridor, difficulty breathing, and collapse)

Zurzolo et al., 2013; Hourihane et al., 2017

Peanut Allergen Threshold Study (PATS): Results

- 8 subjects met pre-fixed criteria
- All reactions mild
- Only 4 received any medications (antihistamines)
- None needed adrenaline /epinephrine

Hourihane et al., 2017

Details Of 8 Subjects Who Met The Predetermined Objective Reactivity Criteria/Case Definition

Participant Number	Location	Age (yrs)	Sex	Diagnostic method	Peanut Wheal (mm)	Peanut SpIgE kUA/L	SpIgE rArah1	SpIgE Arah2	Outcome
35	Ireland	11	Female	History of typical exposure & reaction & positive SPT/ spIgE	15	69.10	11.20	59.20	Rhinoconjunctivitis
40	Australia	15	Male	History of typical exposure & reaction & positive SPT/ spIgE	13	2.06	0.53	1.74	Urticaria
43	Australia	9	Male	History of typical exposure & reaction & positive SPT/ spIgE	18	N/A	N/A	N/A	Vomiting
95	Australia	2	Female	Peanut never ingested but positive SPT/spIgE> 95% PPVs	13	N/A	N/A	N/A	Vomiting
31	U.S.	9	Male	Peanut never ingested but positive SPT/spIgE> 95% PPVs	11	0.36	0.10	0.14	Urticaria
97	U.S.	2	Male	History of typical exposure & reaction & positive SPT/ spIgE	N/A	100.00	14.80	100.00	Urticaria
109	U.S.	1	Male	History of typical exposure &reaction & positive SPT/ spIgE	N/A	57.70	0.10	49.60	Urticaria
124	U.S.	4	Male	History of typical exposure & reaction and positive SPT/ spIgE	N/A	46.70	14.70	16.20	Rhinorrhoea

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Single Dose Challenge
A New Risk Assessment Paradigm

- 2.1% met the predetermined objective criteria vs. 5% predicted
  - Potential selection bias toward more highly sensitive subjects used to model the dose-distribution curves since the data was recorded at tertiary allergy clinics??
  - Objective criteria in these studies used to establish the LOAEL not has stringent as the criteria used in PATS (i.e. single sneeze, cough, or hive considered objective)??
- Log-normal distribution seems to be reasonable and appropriately conservative for use in the estimation of EDs for peanut
  - The even more conservative Weibull distribution should not be used
- Safe; all reactions mild in peanut single dose challenge
  - Interpretable in same way as routine OFC
  - Easy to prepare and perform single dose OFC
  - Most useful for very anxious patients and parents

Hourihane et al., 2017

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

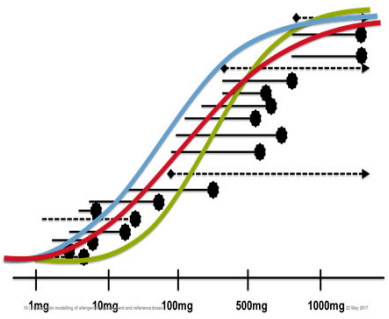
Advances in Statistical Methods for Analysis of Threshold Data

Statistical Introduction

- In 2010/2011, a statistical method combining interval-censoring survival analysis & the benchmark dose approach was used to determine reference doses for food allergen risk management purposes
- Expert judgement was used to determine the Reference Dose based on results from the Log-normal, Log-logistic and/or Weibull distributions
- Questions arose from stakeholders regarding the choice of models used for analysis, as well as the final Reference Dose chosen

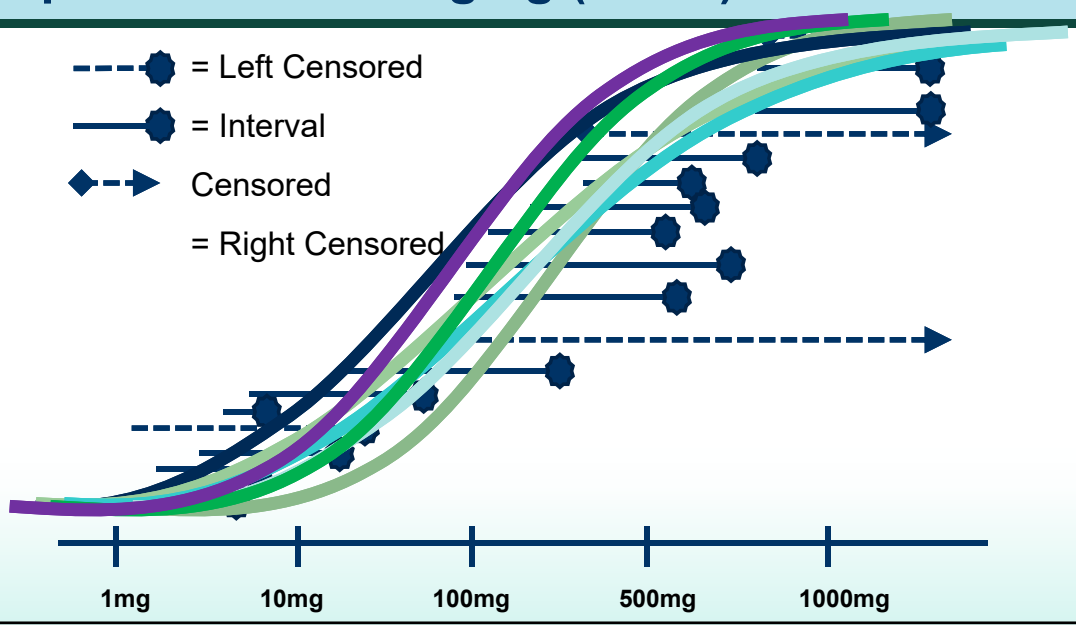
Applying Model Averaging

- No biological reason to select between different statistical options
- Model averaging is a method of accommodating model uncertainty when estimating risk
- Combines all knowledge regarding threshold dose distributions based on goodness-of-fit to create an “averaged” distribution

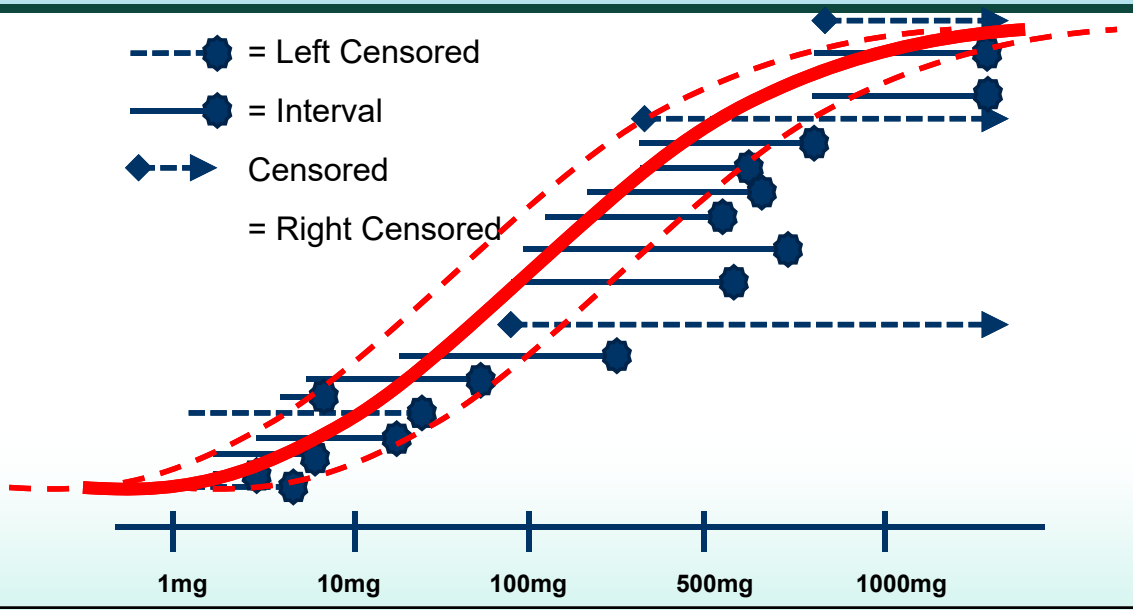


SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Example: Model Averaging (1 of 2)



Example: Model Averaging (2 of 2)



Applying Model Averaging

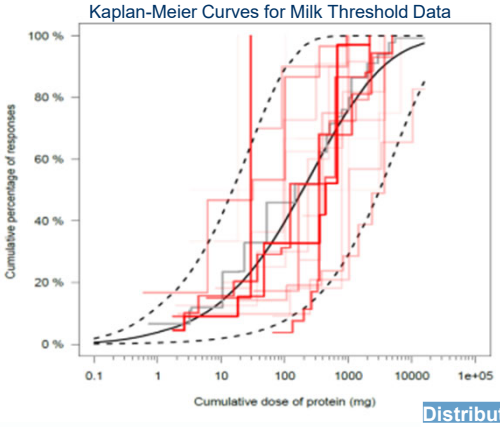
- TNO and FARRP are working with recognized model averaging experts to develop new methods for interval-censored data
- International collaboration with:
  - Dr. Matthew Wheeler, US CDC - National Institute for Occupational Safety and Health (NIOSH)
  - Dr. Kan Shao, Indiana University – School of Public Health

Bayesian Model Averaging

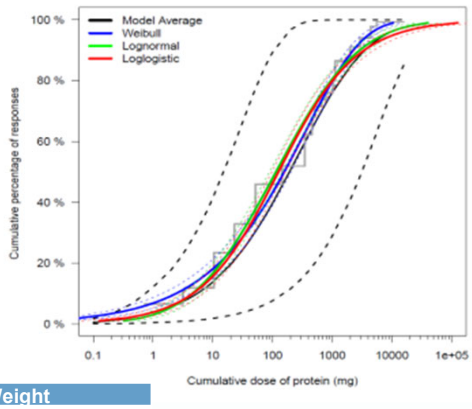
- Account for uncertainty in the survival curve by using a weighted average of the individual distributions based on “Goodness of Fit”
- Account for Study-to-Study heterogeneity
  - i.e. different locations, different protocols, different clinicians or nurses, etc
- Combine all knowledge to create an “averaged” distribution

Milk Threshold Analysis (example)

Kaplan-Meier Curves for Milk Threshold Data



Model Averaging vs. Survival Analysis of Milk Population Threshold Distributions



Distribution	Weight
Log-Logistic	0.000
Log-Gaussian	0.000
Weibull	0.999
Log-Double Exponential	0.001
Log-Gumbel	0.000

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Current Applications of Food Allergen Thresholds and Risk Assessment

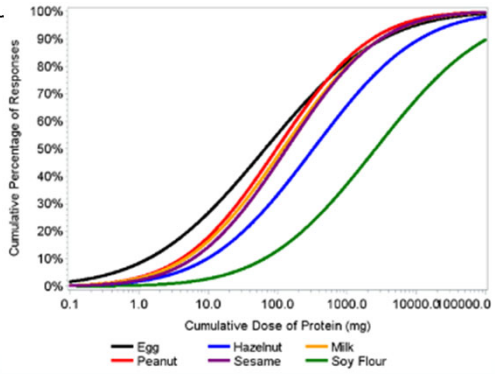
VITAL program

- In 2007, the Allergen Bureau of Australia & New Zealand released their VITAL (Voluntary Incidental Trace Allergen Labelling) program
  - Its goal was to limit the use of precautionary “may contain” labelling related to the unintended presence of allergens
- In 2010/2011, the VITAL program was revised and utilized the TNO-FARRP food allergen threshold database to create scientifically driven Actions Levels
  - VITAL 2.0 ® revision utilized interval-censoring survival analysis & benchmark dose approach to determine reference doses for food allergen risk management purposes

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

VITAL® Reference Doses

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



- Based upon the ED_{01} for peanut, milk egg and hazelnut
- Based upon the 95% LCI of ED_{05} for the remaining 5 allergens
- Other tree nuts based upon the hazelnut reference dose

Current Applications of Food Allergen Thresholds and Risk Assessment

- Endorsed by ILSI-Europe in 2014 and iFAAM in 2017
- Unofficially used by public health agencies in several countries for evaluation of unintended allergen presence
  - Dutch, Belgian and German authorities have proposed to use the allergen threshold dose distributions but are each considering *different* reference doses
- Japan and Switzerland are the only countries that have adopted a threshold/regulatory action level for food allergens
  - Japan: 10 µg/g protein limit for labeling
  - Switzerland: 1000 µg/g food limit

Conclusions

- Clinical threshold data from the sensitive segment of the human population are now available to model population threshold dose distributions
  - Single dose studies have been used to validate the statistical population estimates as well as provide information on the severity of reactions at very low doses
- Current labeling/regulations in many countries impose a zero threshold, but we can never assure zero (residue or risk)
  - Sufficient data now exists to derive reference doses/action levels which can be used as a benchmark for regulators and the food industry
    - With little or no guidance on thresholds/action levels, extensive use of precautionary/advisory labeling ("may contain") will continue

References

- Hourihane, J. O'B., Allen, K. J., Shreffler, W. G., DunnGalvin, G., Nordlee, J. A., Zurzolo, G. A., DunnGalvin, A., Gurrin, L. C., Baumert, J. L., and Taylor, S. L. (2017). Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in peanut allergic children. *Journal of Allergy and Clinical Immunology*. 139:1583-1590.
- Taylor, S.L., Baumert, J.L., Kruizinga, A.G., Remington, B.C., Crevel, R.W.R., Brooke-Taylor, S., Allen, K.J., The Allergen Bureau of Australia & New Zealand, Houben, G. (2014). Establishment of reference doses for residues of allergenic foods: report of the VITAL Expert Panel. *Food & Chemical Toxicology*. 63:9-17.
- Zurzolo, G.A., Allen, K.J., Taylor, S.L., Shreffler, W.G., Baumert, J.L., Tang, M.L., Gurrin, L.C., Mathai, M.L., Nordlee, J.A., DunnGalvin, A., Hourihane, J.O'B. (2013). Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol. *Allergy, Asthma & Clinical Immunology*. 9: 35-41.
- Taylor S.L., Moneret-Vautrin D.A., Crevel R.W.R., Sheffield D., Morisset M., Dumont P., Remington B.C., Baumert J.L. (2010). Threshold Dose for Peanut: Risk Characterization Based upon Diagnostic Oral Challenge of a Series of 286 Peanut-allergic Individuals. *Food & Chemical Toxicology*. 48:814-819.
- Madsen, C.B., Hattersley, S., Buck, J., Gendel, S.M., Houben, G.F., Hourihane, J.O., Mackie, A., Mills, E.N., Norhede, P., Taylor, S.L., Crevel, R.W., (2009). Approaches to risk assessment in food allergy: report from a workshop ''developing a framework for assessing the risk from allergenic foods''. Food Chem. Toxicol. 47, 480–489.
- Taylor, S.L., Crevel, R.W.R., Sheffield, D., Kabourek, J., Baumert, J.L. (2009). Threshold Dose for Peanut: Risk Characterization Based Upon Published Results from Challenges of Peanut-Allergic Individuals. *Food & Chemical Toxicology*. 47:1198-1204.
- THRESHOLD WORKING GROUP. (*2008*). Approaches To Establish Thresholds for Major Food Allergens and for Gluten in Food. Journal of Food Protection: May 2008, Vol. 71, No. 5, pp. 1043-1088.

Acknowledgements

- Steve Taylor
- Jamie Kabourek
- Dave Marx
- Rene Crevel
- Matthew Wheeler
- Kan Shao
- Ben Remington
- Geert Houben
- Marty Blom
- Astrid Kruizinga
- Carina de Jong-Rubingh
- Harrie Buist
- Joost Westerhout