

# › **The Modelling Behind the Translation from Individual Thresholds to Population Threshold Dose Distributions**

Benjamin C. Remington, PhD

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# The Modelling Behind the Translation from Individual Thresholds to Population Threshold Dose Distributions

Joost Westerhout, PhD  
Benjamin C. Remington, PhD  
Marty Blom, PhD  
Marie Meima, MSc  
Astrid Kruizinga, MSc  
Prof. Geert Houben, PhD

Prof. Joe Baumert, PhD  
Prof. Steve Taylor, PhD  
Jamie Kabourek, MSc, RD

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UNIVERSITY OF  
**Nebraska**  
Lincoln

food allergy research  
& resource program  
**farrp**

# Bayesian Stacked Parametric Survival with Frailty Components and Interval Censored Failure Times

Matthew W. Wheeler<sup>1\*</sup> | Joost Westerhout<sup>2†</sup> | Joe L.  
Baumert<sup>3‡</sup> | Benjamin C. Remington<sup>2†</sup>

<sup>1</sup>Risk Evaluation Branch, National Institute for Occupational Safety and Health, Cincinnati, OH, Postal Code, Country

<sup>2</sup>TNO, Zeist, Netherlands

<sup>3</sup>University of Nebraska-Lincoln, Department of Food Science and Technology, FARRP, Lincoln, NE 68588-6207

To better understand exposure to food allergens, food challenge studies are designed to slowly increase the dose of an allergen delivered to allergic individuals until mild reaction occurs. These dose-to-failure studies are used to determine acceptable intake levels and are analyzed using parametric failure time models. Though these models can provide esti-

(Manuscript is currently being prepared for submission)

????



# Topics

- › Deriving individual threshold values
- › Deriving population-based eliciting dose (ED<sub>p</sub>) values
- › Model averaging to improve ED<sub>p</sub> estimates
- › Risk assessment implications

# Introduction

- › Data on individual no-observed adverse effect levels (NOAELs) and lowest-observed adverse effect levels (LOAELs) is available from low-dose oral clinical challenge studies
- › Individual thresholds from food allergic subjects can be grouped and analyzed to statistically determine the population threshold for a number of regulated food allergens
- › These data can be utilized in a number of food allergen risk assessment and risk management programs

# Deriving Individual threshold values

# Deriving Individual threshold values methodology

- › Based on objective DBPCFCs (Double-blind, placebo-controlled food challenges)
  - › Open challenge allowed if patient is under 3 years old
- › Description of NOAEL and/or LOAEL
- › Data on individual patients
- › Objective symptoms



# Deriving Individual threshold values methodology

## The derivation of individual threshold doses from clinical food challenge data for population risk assessment for food allergens

Joost Westerhout<sup>1</sup>, Joseph L. Baumert<sup>2</sup>, W. Marty Blom<sup>1</sup>, Katrina J. Allen<sup>3</sup>, Barbara Ballmer-Weber<sup>4,5,6</sup>, René W.R. Crevel<sup>7</sup>, Anthony E.J. Dubois<sup>8</sup>, Montserrat Fernández-Rivas<sup>9</sup>, Matthew J. Greenhawt<sup>10</sup>, Jonathan O'B Hourihane<sup>11</sup>, Jennifer J. Koplin<sup>3</sup>, Astrid G. Kruizinga<sup>1</sup>, Thuy-My Le<sup>12</sup>, Hugh A. Sampson<sup>13</sup>, Wayne G. Shreffler<sup>14</sup>, Paul J. Turner<sup>15,16</sup>, Steve L. Taylor<sup>2</sup>, Geert F. Houben<sup>1</sup>, Benjamin C. Remington<sup>1</sup>

(Manuscript is currently being revised for publication in The Journal of Allergy and Clinical Immunology)

# Deriving Individual threshold values methodology

- › In depth insight into the methodology applied by TNO and FARRP to derive individual NOAELs and LOAELs for objective symptoms from clinical food challenge data
- › Aim is to stimulate harmonization and transparency in quantitative food allergen risk assessment and risk management programs

## The derivation of individual threshold doses from clinical food challenge data for population risk assessment for food allergens

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# Deriving Individual threshold values methodology

- › Differentiates between:
  - 1) clear clinical challenge stopping criteria for confirmation of food allergy
  - 2) the NOAEL – LOAEL for allergen risk assessment and risk management

- › For example:

- › Dose 1:
- › Dose 2: single, mild objective symptom
- › Dose 3: single, mild objective symptom
- › Dose 4: single, mild objective symptom
- › Dose 5: multiple objective symptoms

**NOAEL for risk assessment**  
**LOAEL for risk assessment**

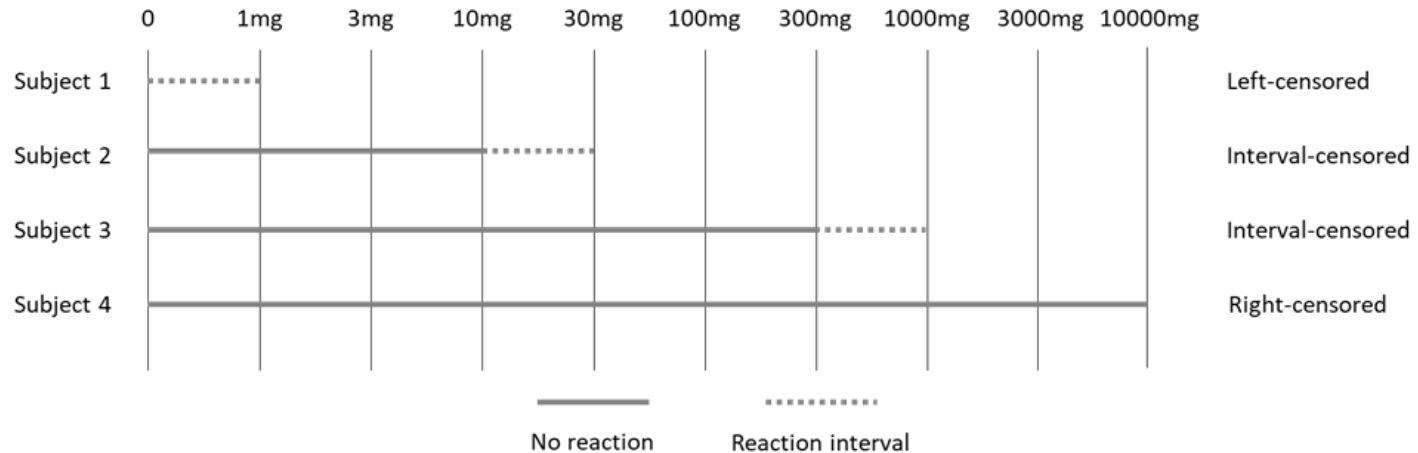
- › Dose 5: Clinical challenge stopping criteria
- › Dose 1 & Dose 2: NOAEL – LOAEL for RA & RM

The derivation of individual threshold doses from clinical food challenge data for population risk assessment for food allergens

Joost Westerhout<sup>1</sup>, Joseph L. Baumert<sup>2</sup>, W. Marty Blom<sup>1</sup>, Katrina J. Allen<sup>3</sup>, Barbara Ballmer-Weber<sup>4,5,6</sup>, René W.R. Crevel<sup>7</sup>, Anthony E.J. Dubois<sup>8</sup>, Montserrat Fernández-Rivas<sup>9</sup>, Matthew J. Greenhawt<sup>10</sup>, Jonathan O'B Hourihane<sup>11</sup>, Jennifer J. Koplin<sup>3</sup>, Astrid G. Kruizinga<sup>1</sup>, Thuy-My Le<sup>12</sup>, Hugh A. Sampson<sup>13</sup>, Wayne G. Shreffler<sup>14</sup>, Paul J. Turner<sup>15,16</sup>, Steve L. Taylor<sup>2</sup>, Geert F. Houben<sup>1</sup>, Benjamin C. Remington<sup>1</sup>

# Deriving Individual threshold values methodology

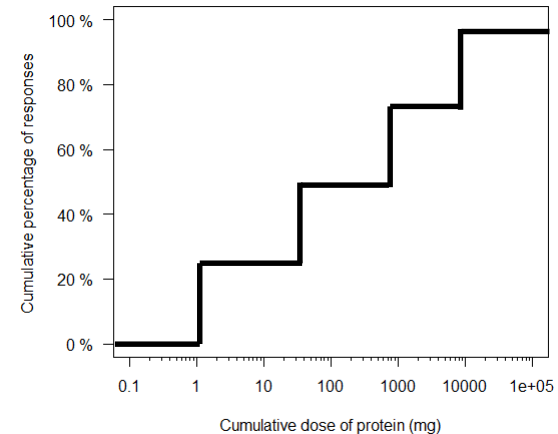
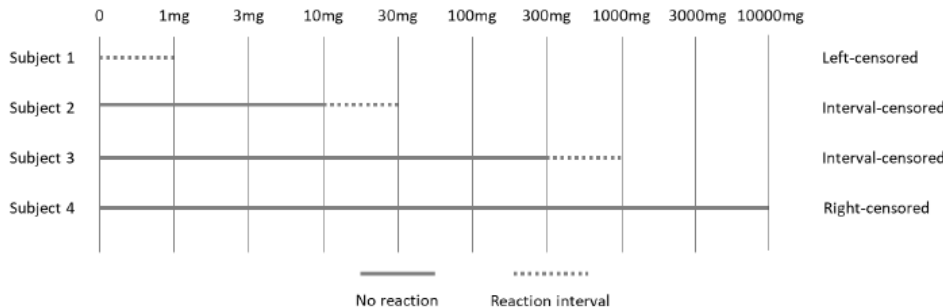
- › Individual NOAELs and LOAELs are then mapped according to the intervals in the dosing scheme of the food challenge



# Deriving population-based eliciting dose (ED<sub>p</sub>) values

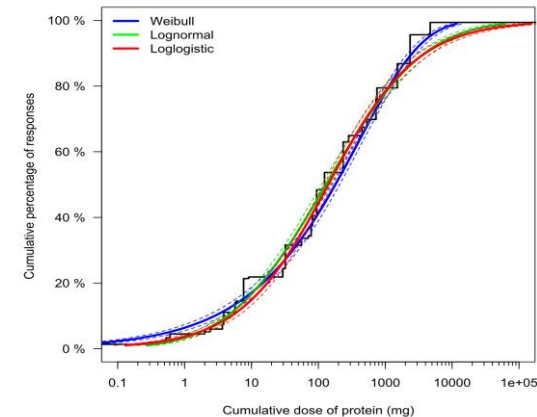
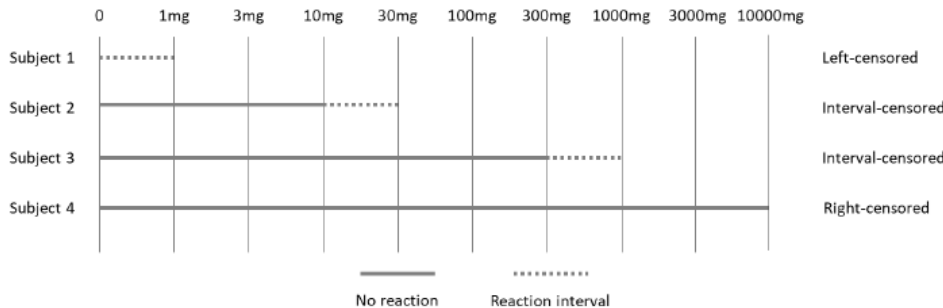
# Deriving population-based eliciting dose (ED<sub>p</sub>) values

- › Individual eliciting dose values utilized for a specific allergen to allow for derivation of population-based eliciting dose values (ED<sub>p</sub>)
- › This was previously done by interval-censoring survival analysis using by fitting three parametric models (Log-Normal, Log-Logistic, and Weibull) to the data



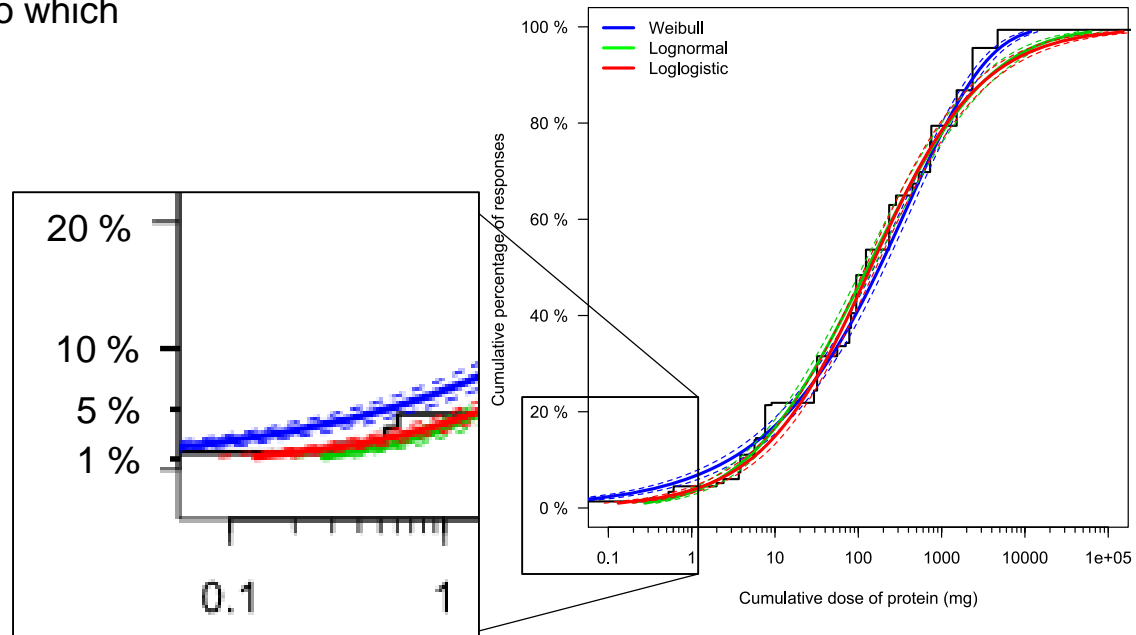
# Deriving population-based eliciting dose (EDp) values

- › Individual eliciting dose values utilized for a specific allergen to allow for derivation of population-based eliciting dose values (EDp)
- › This was previously done by interval-censoring survival analysis using by fitting three parametric models (Log-Normal, Log-Logistic, and Weibull) to the data



# Deriving population-based eliciting dose (ED<sub>p</sub>) values

- › All models seem to fit the data well, so which model is best?
- › The Weibull model fits the upper part of the data well, but seems to be over-conservative at the lower doses
- › The Lognormal and Loglogistic models show comparable fits
- › Selection of the most appropriate ED was previously based on expert judgement



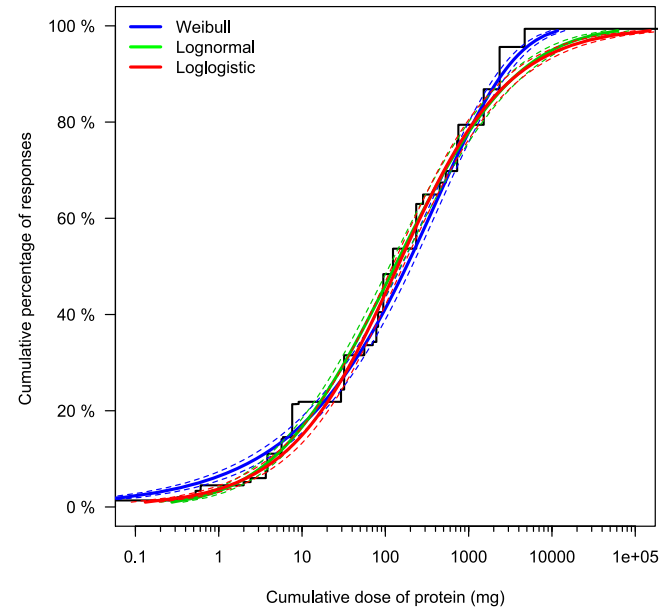


# How to simplify the EDp process?

# “Stacked” Model Averaging

# Why Stacked Model Averaging?

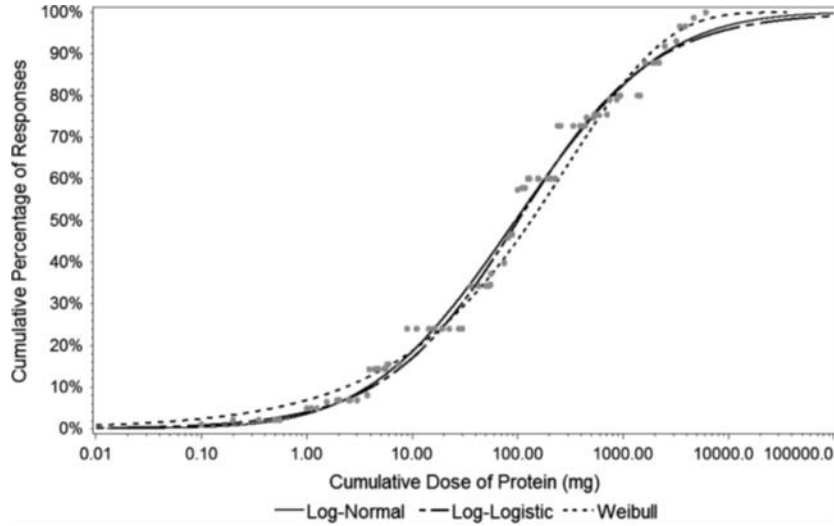
- › No biological reason to select between different models
- › Model averaging is a methodology for accommodating model uncertainty when estimating risk
- › Combines all knowledge regarding threshold dose distributions based on goodness-of-fit to create an “averaged” distribution



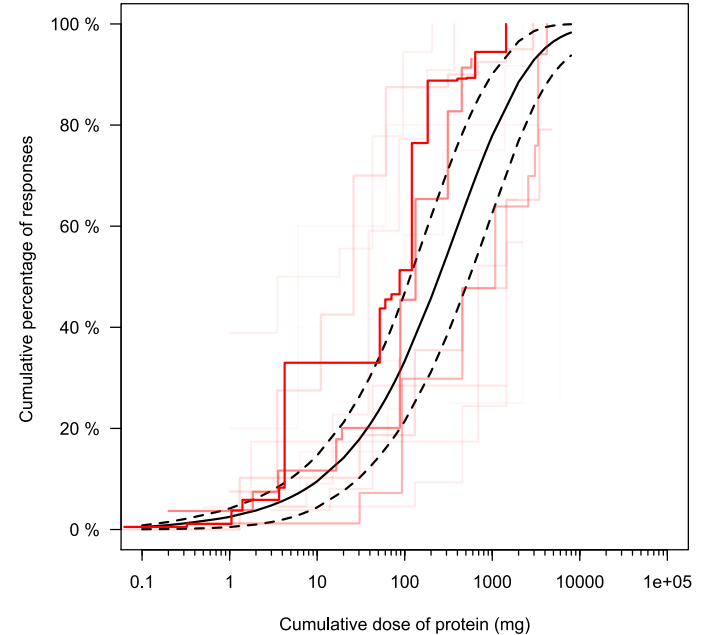
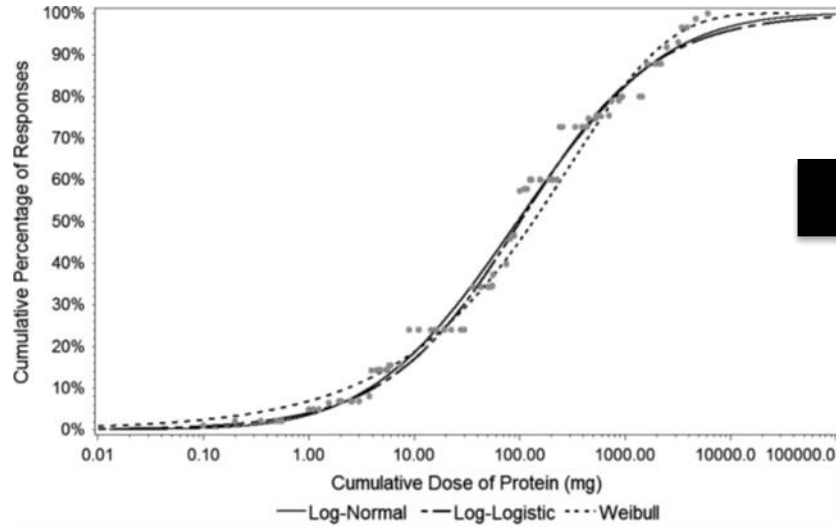
# Stacked Model Averaging

- › International collaboration with:
  - › Dr. Matthew Wheeler, US CDC - National Institute for Occupational Safety and Health (NIOSH)
- › Previously available survival models for interval-censored data were limited to single, simple “standard models” (i.e., Weibull, Loglogistic and Lognormal)
  - › Models also limited by the available software (e.g., Survreg in R)
- › Picking a single model is well known to underestimate the true uncertainty in the system of interest
- › New stacked model averaging program incorporates 5 different models
  - › Weibull, Log-Logistic, Log-Normal, Log-Double Exponential, General Pareto

# Old figure display has now been replaced by...

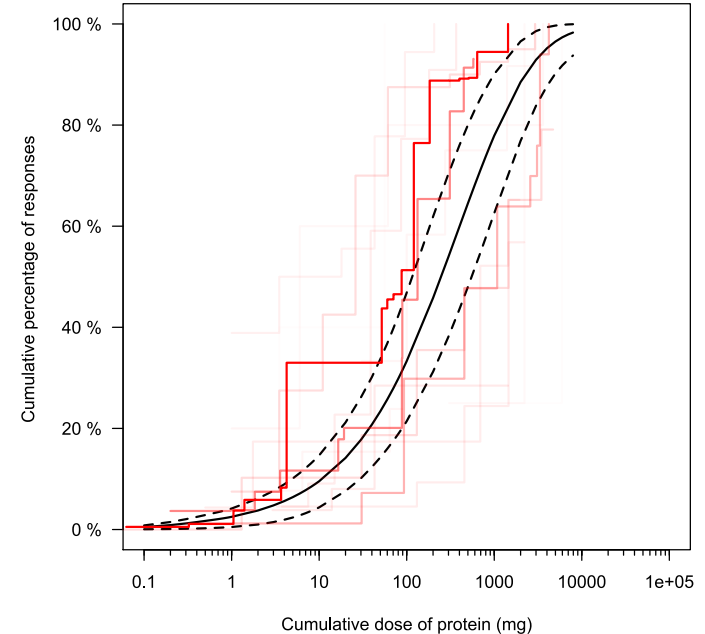


# Individual Kaplan-meier curves for each study



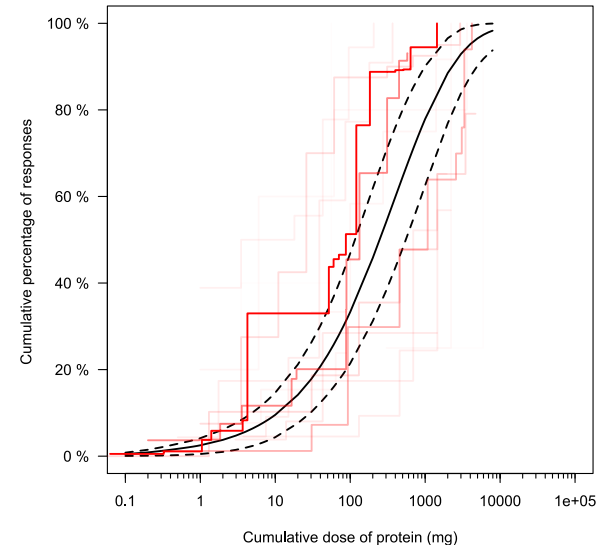
# Individual Kaplan-meier curves for each study

- › Each **stepwise** function is an individual peanut study as identified in the database
- › **Darker lines** indicate more individuals in the study
- › Kaplan-Meier curves are non-parametric survival distributions
- › Model averaged distribution is fitted to the data (black line with 95% CI's)



# Stacked 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
  - › However,  $n = 1$  case studies are no longer able to be included in the dataset for use
- › Combine all knowledge to create an “averaged” distribution





# Stacked Model Averaging

## ORIGINAL ARTICLE

Journal Section

## Bayesian Stacked Parametric Survival with Frailty Components and Interval Censored Failure Times

Matthew W. Wheeler<sup>1\*</sup> | Joost Westerhout<sup>2†</sup> | Joe L. Baumert<sup>3‡</sup> | Benjamin C. Remington<sup>2†</sup>

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(Manuscript is currently being prepared for submission)

- › The modelling method is completed
- › We are also creating an R package to model these data in general
- › Food Allergy is not the only place where these methods will be used
- › We believe this utility has many Risk Analysis contexts
- › 2 Publications from model averaging results will be coming soon
  - › First: presentation of new statistical methods, R package publicly available
  - › Second: applies MA methods to updated dataset and presents new MA results

# Stacked Model Averaging

## ORIGINAL ARTICLE

Journal Section

## Allergen specific dose distributions generated from food challenge data, accounting for different available models and study-to-study heterogeneity

Matthew W. Wheeler<sup>1\*</sup> | Joost Westerhout<sup>2†</sup> | Joe L. Baumert<sup>3‡</sup> | Benjamin C. Remington<sup>2†</sup>

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# Results if this method was available in 2011?

# Peanut

|      | Total number<br>of allergic<br>individuals | Left<br>Censored | Right<br>Censored |
|------|--|------------------|-------------------|
| 2011 | 750  | 30               | 132               |

| <u>Discrete</u><br>ED01<br>(mg protein) | <u>Cumulative</u><br>ED01<br>(mg protein) |
|---|---|
|   |   |

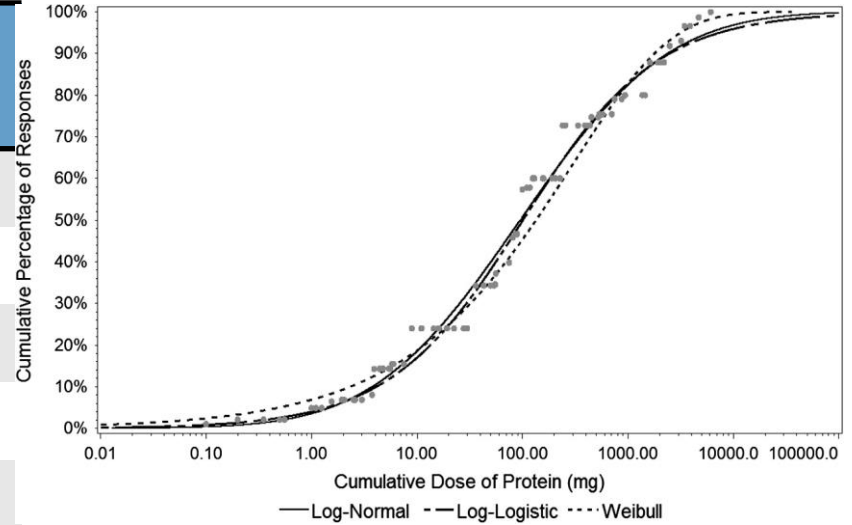
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# Peanut

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|---|---|
|   |   |
|   |   |
|   |   |
|   |   |



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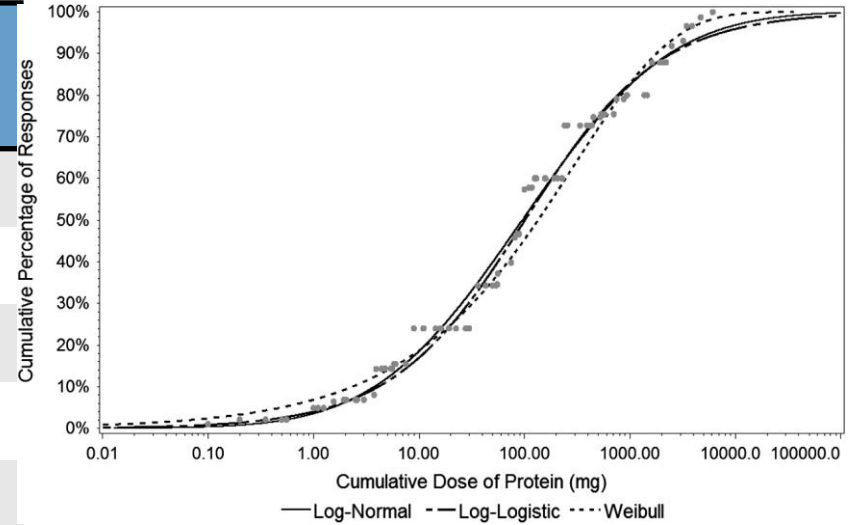
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|  |  |  |
|--|--|--|
|  |  |  |
|--|--|--|

|                   |     |      |
|-------------------|-----|------|
| 2011 Log-Logistic | 0.1 | 0.13 |
|-------------------|-----|------|

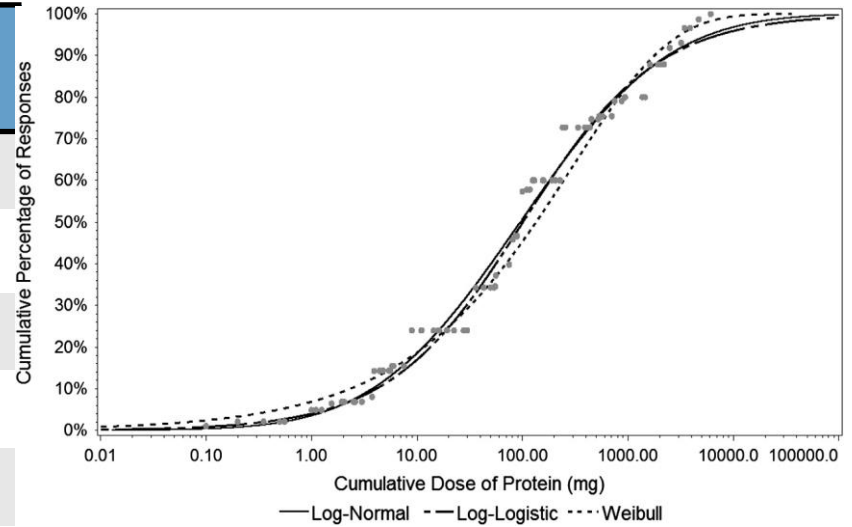
|                 |      |      |
|-----------------|------|------|
| 2011 Log-Normal | 0.22 | 0.28 |
|-----------------|------|------|

|              |  |  |
|--------------|--|--|
| 2011 Weibull |  |  |
|--------------|--|--|



|      | Total number of allergic individuals | Left Censored | Right Censored |
|------|--------------------------------------|---------------|----------------|
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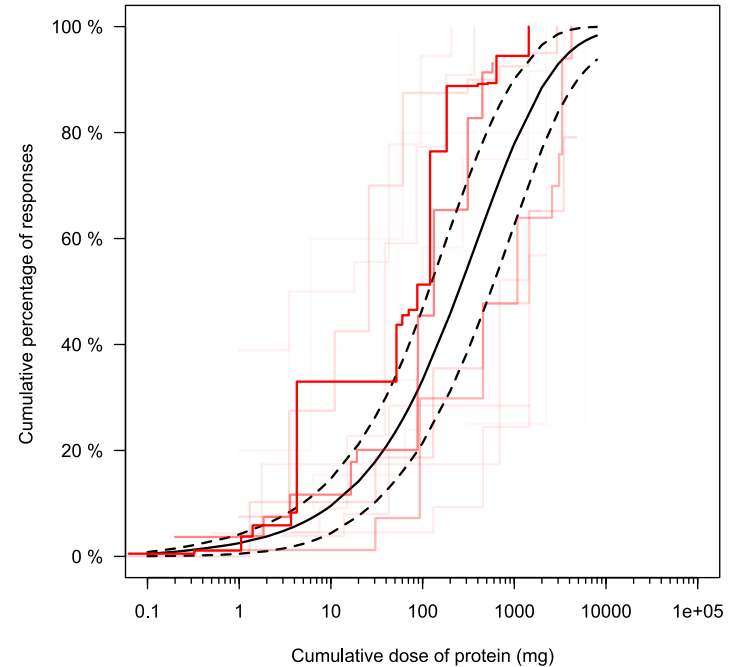
|                            | Discrete ED01 (mg protein) | Cumulative ED01 (mg protein) |
|----------------------------|----------------------------|------------------------------|
| <b>2011 Reference Dose</b> |                            | <b>0.2</b>                   |
| 2011 Log-Logistic          | 0.1                        | 0.13                         |
| 2011 Log-Normal            | 0.22                       | 0.28                         |
| 2011 Weibull               |                            |                              |



# Peanut

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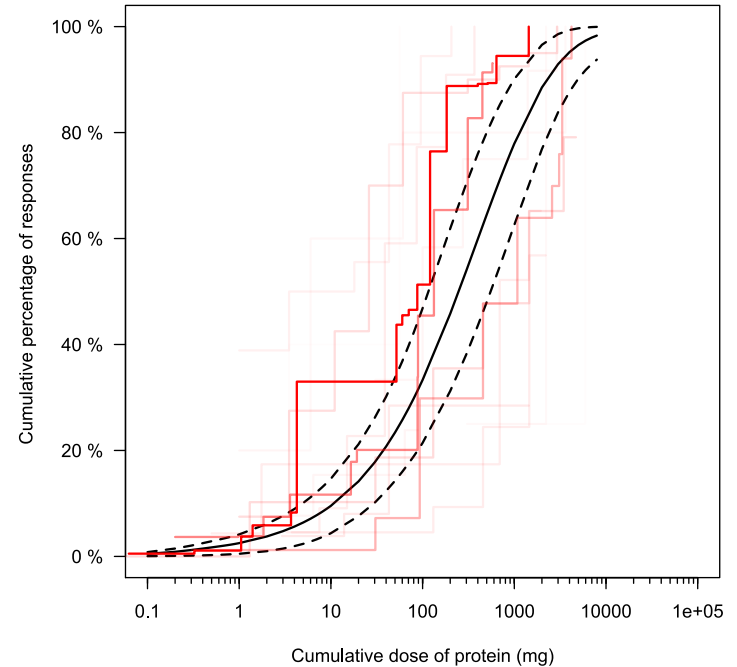




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|                              | Discrete ED01 (mg protein) | Cumulative ED01 (mg protein) |
|------------------------------|----------------------------|------------------------------|
| <b>2011 Reference Dose</b>   |                            | <b>0.2</b>                   |
| 2011 Model Averaging (round) |                            | 0.2                          |
| 2011 Log-Logistic            | 0.1                        | 0.13                         |
| 2011 Log-Normal              | 0.22                       | 0.28                         |
| 2011 Weibull                 |                            |                              |



# Allergen threshold database

# Allergen threshold database 2011 vs 2019

| Allergen           | 2011 total no. of allergic individuals | 2019 total no. of allergic individuals |
|--------------------|--|--|
| Egg                | 206                                    | 431                                    |
| Hazelnut           | 200                                    | 410                                    |
| Lupin              | 24                                     | 25                                     |
| Milk               | 344                                    | 440                                    |
| Mustard            | 33                                     | 33                                     |
| Peanut             | 744                                    | 1294                                   |
| Sesame             | 21                                     | 40                                     |
| Shrimp             | 48                                     | 75                                     |
| Soy (milk + flour) | 51                                     | 87                                     |
| Wheat              | 40                                     | 99                                     |

# Allergen threshold database 2011 vs 2019

| Allergen | 2011 total no. of allergic individuals | 2019 total no. of allergic individuals |
|----------|--|--|
| Cashew   | 31                                     | 245                                    |
| Celery   | 39                                     | 82                                     |
| Fish     | 19                                     | 82                                     |
| Walnut   | ~15                                    | 74                                     |

# Conclusions and Implications

# Conclusions

- › Individual data analysis and EDp calculations have been completed for 14 allergens
  - › ED<sub>01</sub> - ED<sub>05</sub> - ED<sub>10</sub> - etc
- › How can these updated EDp information best be utilized to inform allergen risk management programs?
  - › Covered more in following presentations

