From Population Thresholds to Reference Doses

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3rd Food Allergen Management Symposium
Melbourne, VIC, Australia
May 14, 2019

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Chair, VITAL Scientific Expert Panel
Allergen Bureau of Australia & New Zealand

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Comparative Quality for Food Safety Risk Management Data

- Dose-response data from small groups (50) of experimental animals; usually confined to rats or mice
- Man is not a big white rat!
- Genetically similar animals living in consistent environment
- Limited, if any, information on human health hazard except for occasional case reports involving unusual exposure circumstances
- Apply fixed uncertainty factor (10 X 10 = 100) to NOAEL or LOAEL to account for species differences and individual variation

Comparative Quality
Existing Threshold Data for Allergenic Foods

- Human data on individual NOAELs and LOAELs 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

VITAL Scientific Expert Panel

- Formed in 2011 to assist Allergen Bureau by recommending Reference Doses
- A team of international experts on allergen risk assessment:

  Steve Taylor, Chair, FARRP – Univ. of Nebraska
  Joe Baumert, FARRP – Univ. of Nebraska
  Geert Houben, TNO, the Netherlands
  Rene Crevel, ReneCrevelConsulting, U.K.
  Simon Brooke-Taylor, consultant, Australia
  Katie Allen, Royal Children's Hospital, Australia
  Ben Remington, TNO, the Netherlands

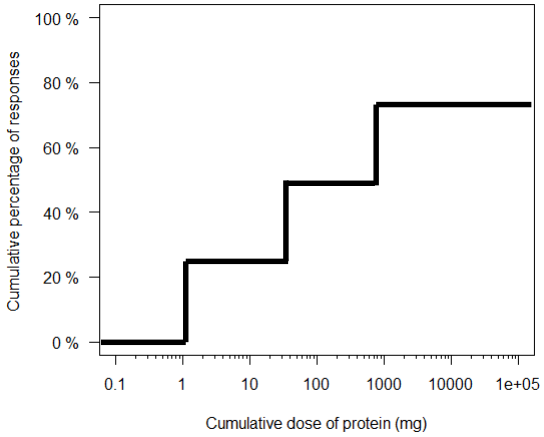
VITAL Scientific Expert Panel

- FARRP and TNO collaborated to screen publications and clinical records for data on individual thresholds of patients with allergies to any food
- Curated the dataset by standardizing screening methods and normalizing doses to total protein from food
- Applied statistical parametric models to the data to obtain population dose-distribution models
- Estimated ED01, ED05, etc. from the models

Deriving Population-Based Eliciting Dose (ED) Values

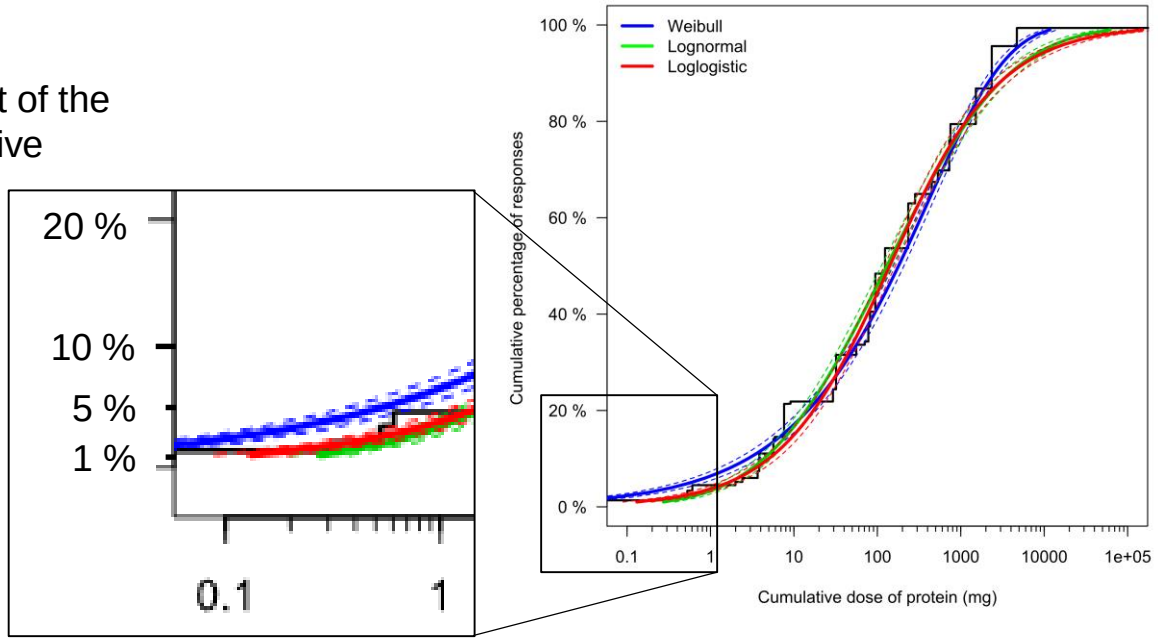
DERIVING POPULATION-BASED ELICITING DOSE (ED) VALUES

- Using individual eliciting dose values for a specific allergen allows derivation of population-based eliciting dose values (EDs)
- This was usually done by interval-censoring survival analysis using three probability distribution models (Log-Normal, Log-Logistic, and Weibull)



DERIVING POPULATION-BASED ED 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 over-conservative at the lower doses
- The Lognormal and Loglogistic models show comparable fits
- Selection of the most appropriate model is based on expert judgement



Deriving Reference Doses from Population-Based Eliciting Dose (ED) Values

Allergen Bureau of Australia & New Zealand

- Setting Reference Doses from VSEP recommendations is a risk management decision
- That decision appropriately belongs to Allergen Bureau in the case of VITAL Reference Doses
- Initially in 2012, used ED01 estimates for peanut, hazelnut, egg, and milk and LCI of ED05 for other foods
- All tree nuts were set equal to hazelnut in terms of Reference Dose

VITAL® Reference Doses 2011-12

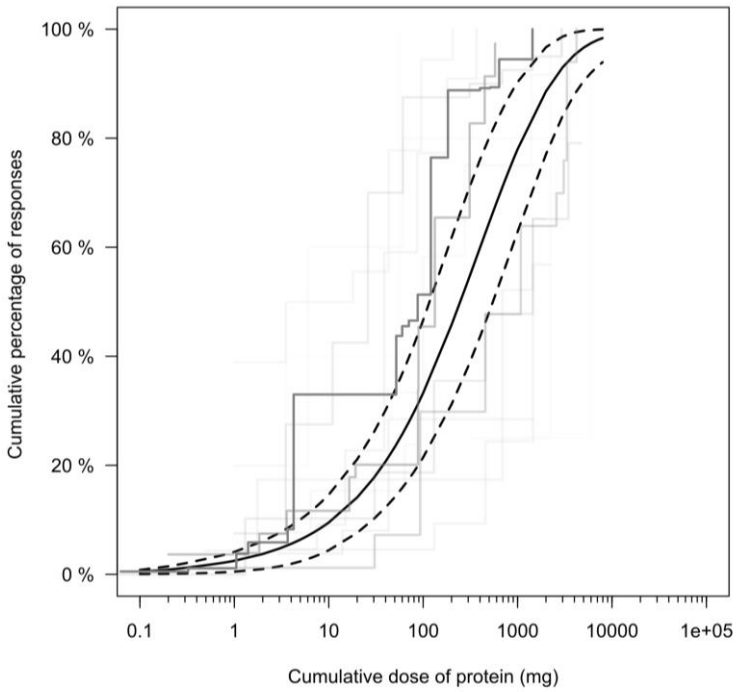
Allergen	mg Protein Level
Peanut*	0.2
Milk*	0.1
Egg*	0.03
Hazelnut*	0.1
Soy*	1.0
Wheat*	1.0
Other Tree Nuts*	0.1
Sesame*	0.2
Crustacean shellfish*	10.0
Fish*	0.1
Mustard	0.05

Deriving Population-Based Eliciting Dose (ED) Values

PEANUT

	Total number of allergic individuals	Left Censored	Right Censored
2014	750	30	132
2018	1294	49	275

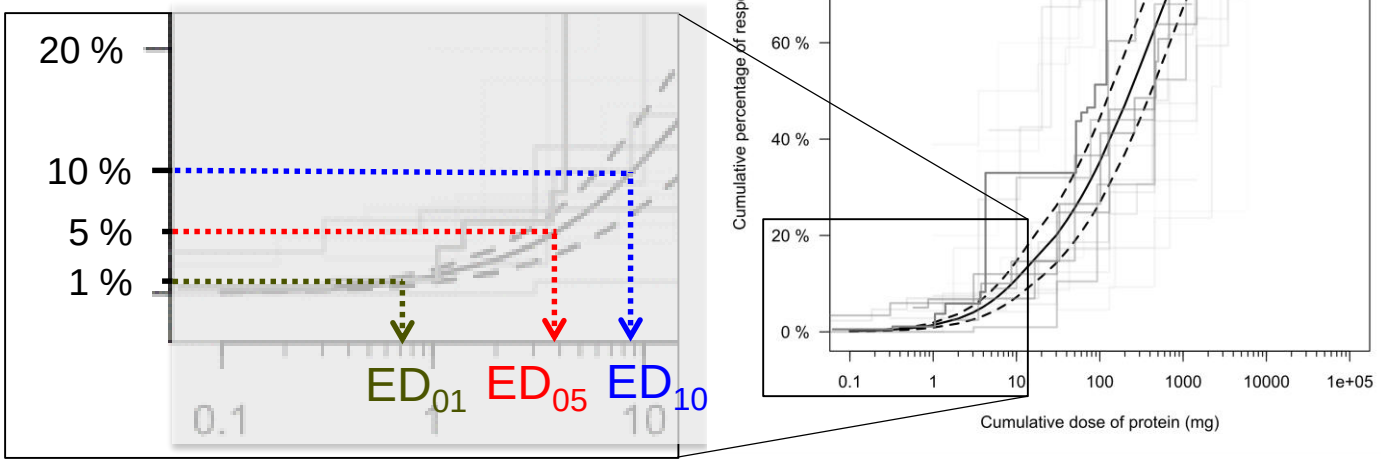
	Discrete ED01 (mg protein)	Cumulative ED01 (mg protein)	Discrete Lower 95% CI of ED05 (mg protein)	Cumulative Lower 95% CI of ED05 (mg protein)	Cumulative ED05 (mg protein)
2018 Model Averaging	0.15	0.71	1.2	2.8	3.9
2014 Reference Dose		**0.2**			
2014 Model Averaging		0.24		1.4	3.3
2014 Log-Logistic	0.1	0.13	0.75	0.99	1.4
2014 Log-Normal	0.22	0.28	0.88	1.1	1.5
2014 Weibull					



Deriving Reference Doses from Population-Based Eliciting Dose (ED) Values

STACKED MODEL AVERAGING

- What level of risk is acceptable?
- What is the appropriate population-based ED value?
- Analysis done for both discrete and cumulative dosing schemes



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

Validation of Statistical Models (PATS)

- Validate the Log-normal ED05 dose
  - 8 of 378 (2.1%) reacted; confidence interval (3.1 – 7.8%)
  - Thus, the log-normal distribution is too conservative
- Why?
  - The peanut-allergic individuals used in the original dose-response studies were not representative of the overall population
  - Possibly because immunotherapy patients may be more sensitive than average
  - The criteria used for a positive response were more restrictive in the PATS than in other studies
- General conclusion is that PATS did validate the ED05 for peanut

Other PATS Conclusions

- Reactions occurring at ED05 for peanut were mild and transitory
- Severe reactions did not occur at the ED05 for peanut
- Use of the more conservative Weibull model is not justified (for peanut)
- The ED01 (the VITAL 2.0 Reference Dose) is even safer

Risk Management Decisions

- Allergen Bureau – VITAL 2.0 (and soon VITAL 3.0)
  - Based upon ED01 or LCI of ED05
- Belgium – Relied on VITAL and PATS
  - Based upon LCI of ED05 with most sensitive model
- Germany – Used VITAL Reference Doses but set 100 g serving size and converted from protein to whole food
- Japan – adopted 10 ppm limit based on analytical capability

Risk Management Decisions

- Consensus is desperately needed to avoid global trading chaos and allergic consumer uncertainty
- Codex Committee on Food Labelling could be the ideal originator of consensus approach

Conclusions

- Sufficient human data exist to establish Reference Doses
- Use low ED values instead to uncertainty factors
- Validate with additional single-dose trials
- Continue to build threshold database
- Reference Doses are only a part of risk management but an essential starting point
- Use Reference Doses not only for PAL but also for ingredient source labeling decisions and food industry allergen preventive control limits

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