Uncertainty factors and thresholds

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Outline

- Uncertainty
- Review factors affecting thresholds (MEDs) and dose distributions of MEDs
- Consider how these factors influence thresholds and uncertainty and the possible/likely direction of that influence
- Consider how to assess and manage any incremental risk introduced by those factors, if necessary

Uncertainty

- *All types of limitations in the knowledge available to assessors at the time an assessment is conducted and within the time and resources available for the assessment.*
  (EFSA draft guidance on uncertainty)
- *Distinguished from **variability**, which refers to heterogeneity in the real world*

Factors affecting allergic reactivity and population distribution of minimum eliciting doses

- Host-associated factors
- Population-associated factors
- Food-associated factors

Derived from considerable clinical experience with challenges, but limited published qualitative or quantitative data available

Crevel RW, Baumert JL, Baka A, Houben GF, Knulst AC, Kruizinga AG, Luccioli S, Taylor SL and Madsen CB, 2014. Food and Chemical Toxicology, 67, 262-276.

Host-associated factors

- Genetics
- Biological cycles and life stages
- Homeostatic/physiological state
  - Infection
  - Active allergic disease
  - Physical activity
  - Stress
  - Use of pharmacologically active agents
    - Therapeutic drugs
    - Recreational drugs, including alcohol

Host-associated factors: evidence base

- Exercise-induced anaphylaxis well-documented for many years - thresholds usually very high (gram amounts or more)
- Peanut OIT: first experimental confirmation of effects of stress and physical exercise on threshold:
  - Pilot study: 2 out of 4 subjects reacted to previously tolerated dose when they were tired or had performed vigorous exercise *(Clark et al, Allergy 2009, **64**, 2018)*
  - Main study: 12/22 required a transient dose reduction for the same reasons and/or infection *(Anagnostou et al, Clin Exp Allergy 2011, 64, **41**, 1273)*
- "TRACE" study looking at exercise and stress, sponsored by the UK Food Standards Agency – paper currently under review

Host-associated factors: summary

Factor	Controlled for in studies?	Direction of influence on MED
Genetics, etc	No	Variable
Biological cycles/life stages, etc	No	Variable
Homeostatic/physiological state		
Infection	Yes	↓
Active allergic disease	Yes	↓
Physical activity	Yes	↓
Stress	Yes (as possible)	↓
Pharmacologically active agents		
Therapeutic drugs	Where relevant	↓ /variable
Recreational, etc drugs, including alcohol	Yes	↓ /variable

Population-associated factors

- Demographics – age profile, composition
- Selection and inclusion/exclusion criteria for studies
- Willingness to participate
- Type/purpose of study/protocol
  - Diagnostic
  - Threshold
  - Immunotherapy

Thresholds and history of severe reactions

Table 4. ED_{10} doses for peanut protein according to history of severity (Based on the log-normal probability distribution model).

Severity Grade (by history)	Total No. of Peanut Allergic Individuals	ED_{10} (mg protein)	95% CI (mg protein)
Severe[1]	40	2.6	1.2, 5.7
Non-Severe[2]	123	2.6	1.6, 4.0
No Prior History[3]	123	6.8	4.4, 10.5

[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 peanut protein

Conclusion: no evidence of relationship between prior severity and population sensitivity

Taylor SL, Moneret-Vautrin DA, Crevel RWR, Sheffield D, Morisset M, Dumont P, Remington BC, Baumert JL (2010). Food Chem Toxicol. 48, 814-819.

Thresholds and type of study

ED_{10} and ED_{05} Doses for Peanut Protein as Assessed by the Log-Normal Probability Distribution Models

Source	Total No. of Peanut Allergic Individuals	ED_{10} (mg protein)	95% CI (mg protein)	ED_{05} (mg protein)	95% CI (mg protein)
FARRP 450 Dataset	450	3.1	2.3, 4.2	1.3	0.9, 1.9
Immunotherapy Studies	64	0.7	0.2, 2.1	0.3	0.1, 0.9
Combined	750*	3.8	3.0, 5.0	1.5	1.1, 2.1

All values reported in mg of peanut protein; *436 patients from other clinical sources (most diagnostic challenge)

Conclusion: Immunotherapy studies appear biased toward more sensitive subjects

Taylor SL ILSI-Europe Workshop. Food Allergy: From Thresholds to Action Levels. Reading U.K.; Sept. 13-14, 2012

Population-associated factors: summary

Factor	Controlled for in studies?	Direction of influence on ED values
Demographics, composition, etc	No	Variable, unknown
Selection and inclusion/exclusion criteria	No	None apparent
Willingness to participate	Not usually	Variable
Type/purpose of study		
Diagnostic	Yes	Variable
Threshold	Yes	None (generally), but protocol effects
Immunotherapy	Yes	↓

Thresholds and food-associated factors

- Agronomic characteristics/variability
  - Peanut cultivars (Koppelman et al, Food Chem Tox 2016 91:82-90)
- Processing
  - Lower MEDs associated with raw compared to cooked egg
  - Lower MEDs associated with whole egg than egg white (dilution of more allergenic fraction)
  - Lower MEDs to milk associated with milk in baked products
- Matrix for delivery of allergenic food
  - Fat content and allergen bioavailability (Grimshaw et al, Clin Exp Allergy 2003, 33, 1581-5.)

Food-associated factors: summary

Factor	Controlled for in studies?	Direction of influence on ED values
Agronomic characteristics/variability	No	Variable, unknown
Processing	Sometimes	↓ ↑ None
Matrix for delivery of allergenic food challenge	Yes	↓ (compared to complex food matrices)

Thresholds, reference doses and uncertainties

- Sources of uncertainty can be classed into 3 categories in relation to derivation of MEDs or characterisation of dose distributions (establishment of population EDs):
  - **Not controlled** for (e.g. population demographics, food agronomics)
    factored in through modelling uncertainties
  - **Potentially controllable** but not controlled (e.g. baseline data from immunotherapy trials, minimally processed allergen)
    also factored in through modelling uncertainties; reduce population EDs
  - **Controlled** through exclusion to help interpretation and data harmonisation (extrinsic factors such as active allergy, exercise, stress, concurrent infection)
    potentially reduce actual protection afforded by any given reference dose

Managing incremental risk from extrinsic factors

- ***Do nothing?*** Combination of circumstances doesn't occur sufficiently often to warrant specific management
- ***Provide targeted, practical and evidence-based advice for individuals to manage their condition?*** Affected individuals need to know their condition and advice needs to be clearly communicated
- ***Apply assessment/safety factor to ED_p to derive reference dose?*** Need to consider wider implications/unintended consequences (e.g. increased PAL, verification, enforcement)
  - *However recent data from the TRACE study on the effects of stress and exercise on peanut thresholds suggest the VITAL 2.0 reference dose remains adequately protective in the presence of those factors.*

Risk management example in deriving a reference dose: US FDA gluten-free rulemaking

- Potential unintended consequences well-illustrated in the consideration by the US FDA of a regulatory threshold for gluten
  - Hazard assessment estimated tolerable daily intakes of 0.4 mg gluten/day for adverse morphological effects and 0.015 mg gluten/day for adverse clinical effects to protect the most sensitive (0.01ppm – 0.6ppm in food)
  - However “At the current time, FDA is not aware of any analytical methods that have been validated to reliably and consistently detect gluten below 20ppm”.
  - “We believe that we should set a gluten threshold level for “gluten free” labeling that best assists most individuals with celiac disease in adhering life-long to a “gluten-free” diet without causing adverse health consequences”.
  - “moving to a definition of “gluten-free” that adopts a criterion that is much lower than < 20 ppm gluten could have an adverse impact on the health of Americans with celiac disease”.

Food Labeling; Gluten-Free Labeling of Foods http://federalregister.gov/a/2013-18813

Concluding remarks

- Diverse factors contribute to the uncertainties in derived reference doses, associated with the individual participants, the population from which they are drawn, the type of study and the food and its presentation.
- Some of these factors contribute uncertainty which is accounted for in the overall model uncertainty, but some extrinsic factors are deliberately controlled and excluded from studies, with a possibility of biasing any derived reference dose.
- Managing the risk from those extrinsic factors requires balanced consideration of the public health risk and possible unintended consequences of mitigation strategies

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Thank You

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