Limitations and possibilities of animal models for human allergenic risk evaluation

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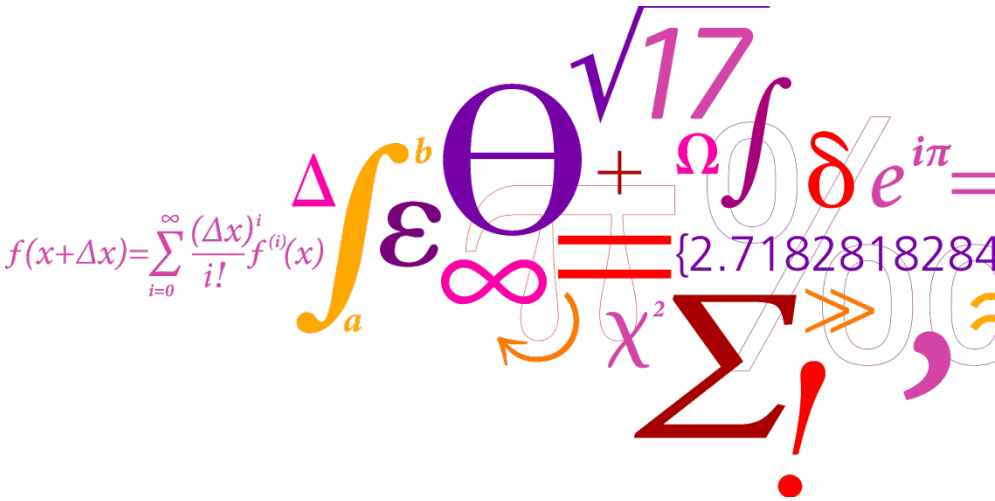


DTU Food
National Food Institute

State of the art

- An animal model for food allergy should mimic human disease giving rise to relevant symptoms upon challenge

- Is this possible in relation to risk evaluation?

What we don't know about sensitisation to food allergens in humans

- Route – oral, dermal, respiratory
- Dose response relations
- Frequency of exposure
- Role of digestion
- Role of infection
- Bystander effect of other allergens
- Tolerance induction
- Tolerance to cross-reacting allergens

Design a test system with few animals that predict sensitisation

What are the consequences if predicitive tests need to mimic human disease?

- Elicitation of symptoms require high IgE responses

- High IgE responses require
  - The use of adjuvant
  - And/or a route that is not oral
    - Bypasses the digestive system
    - Can only test extracts or pure proteins
    - Relevance of dose?

- Interpretation of results difficult in relation to risk assessment

Predictive tests for chemical contact sensitisation

The only allergy tests where there are international guidelines

History

Guinea pig maximisation test mimic human disease

Sensitisation - FCA

Elicitation – Finn chambers

Mechanisms of skin sensitisation

Dose-response relation

Concentration/cm2

Potency

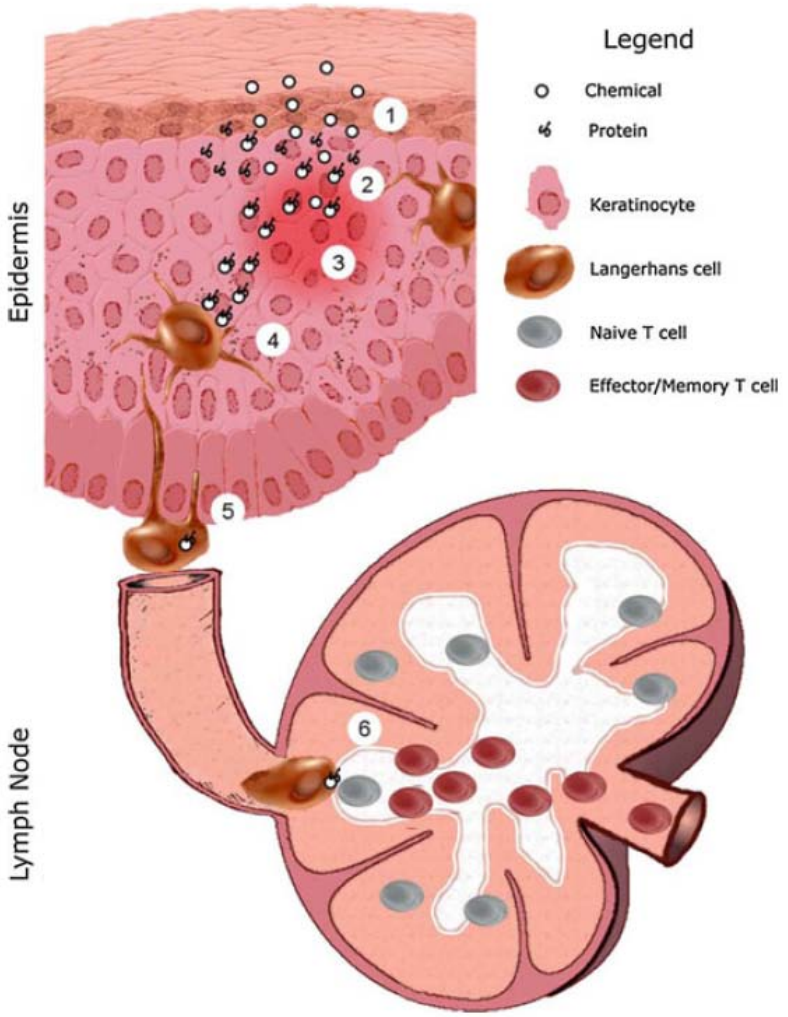
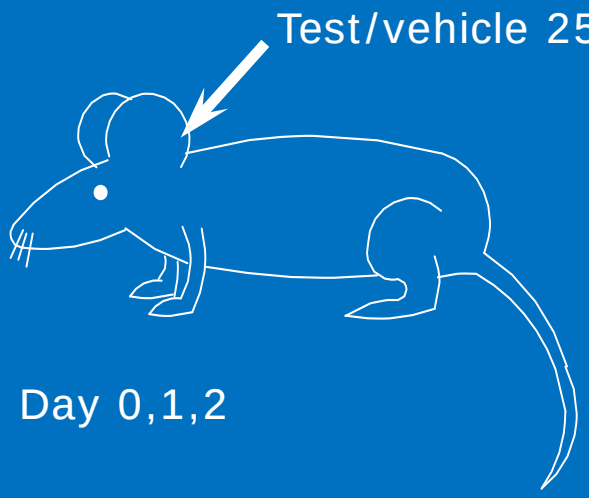


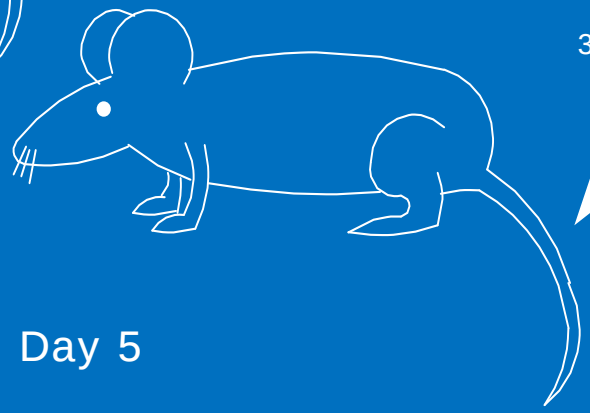
Fig. 8 Main steps in the mechanism of skin sensitisation induction. The numbers correspond to the steps described in the text. (*1*) Skin bioavailability, (*2*) haptenation, (*3*) epidermal inflammation, (*4*) DC activation, (*5*) DC migration, (6) T-cell proliferation. This figure contains elements of an image in the public domain from the National Cancer Institute

Adler et al. 2011

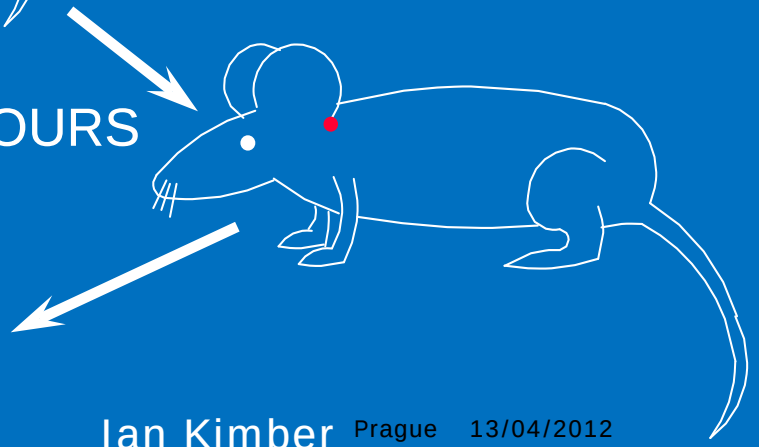
LOCAL LYMPH NODE ASSAY



Day 0,1,2



Day 5

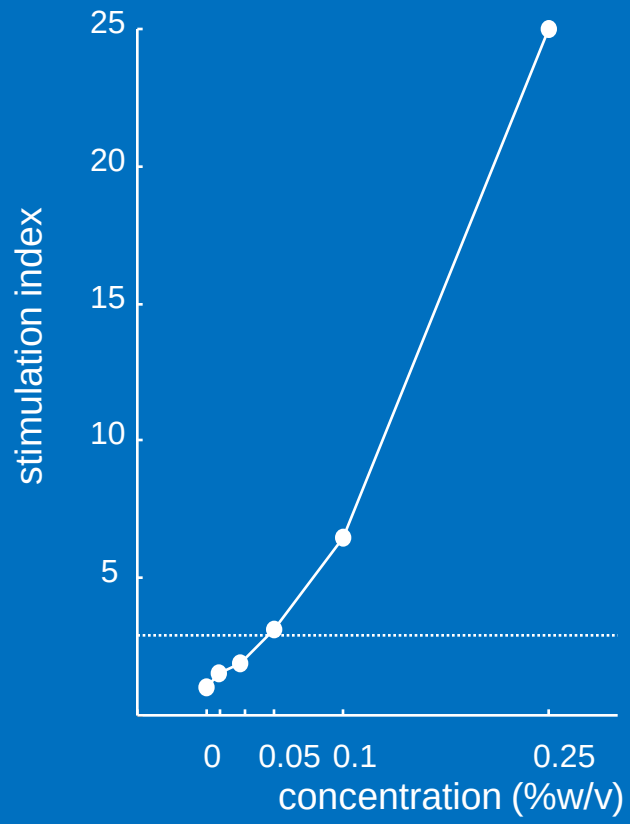


Measures **sensitisation,** only

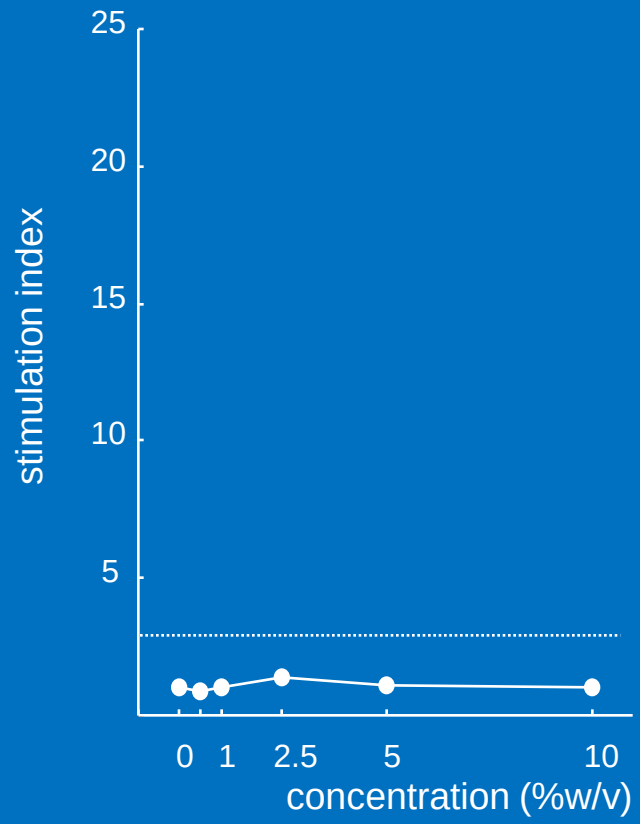
Make cell suspension – measure ^{3}H Thymidine

LOCAL LYMPH NODE ASSAYS

DNCB



PABA



Predictive tests for food allergens measuring sensitisation only?

Sensitisation

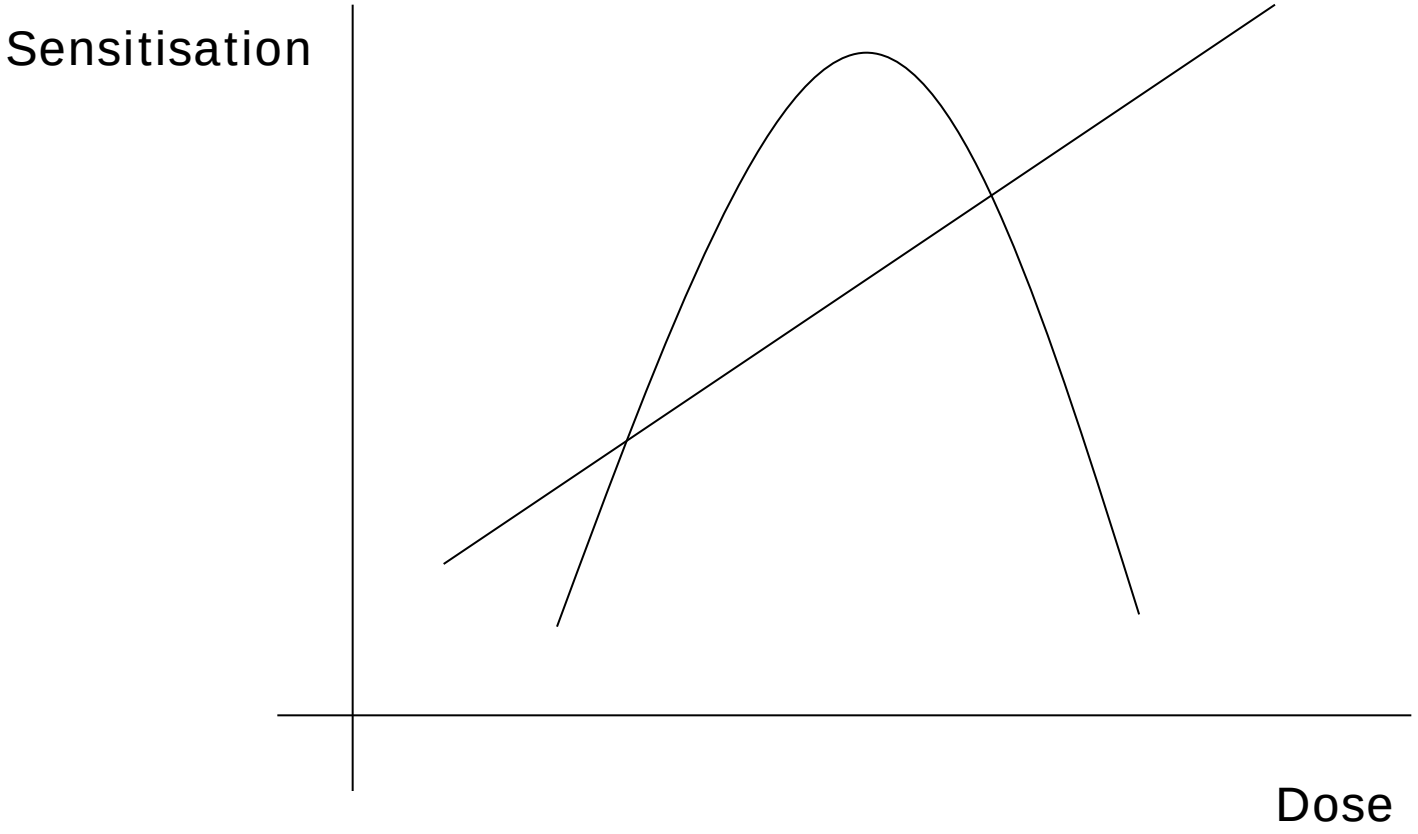
- Specific serum IgE
  - Functionality of IgE (RBL assay, PCA)

Oral route

- 'Natural foods'
- No adjuvant
- Animals on a diet free from allergen or cross-reacting allergens

Dose-response relations

Evaluation of risk is dependent on knowledge of dose / response relations



Food allergens are major constituents of their 'parent' food

- Implication for sensitisation?
  - In chemical contact allergy the dose that sensitises is larger than the dose that may elicit reaction
- Implication for risk assessment?
- Exceptions?
  - LTP's
  - Wheat alpha-amylase inhibitor
    - Extremely resistant to proteolysis

Conclusion I

- It is currently not possible to include dose/response relations in the interpretation of sensitisation studies

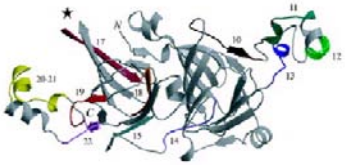
- Consequences
  - Hazard identification – possible sensitiser (oral)
  - Risk characterisation - ?

Animal models measuring sensitisation
Examples of use

- Digestibility and sensitisation
- Matrix effects
- Properties of related allergens
- Tolerance
- Processing
- Epitope mapping

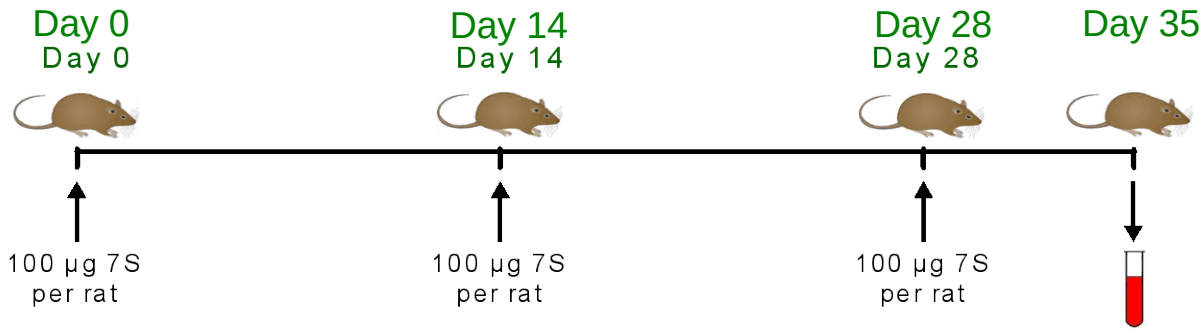
Sensitisation – what is important? Protein? Matrix? Processing?

Peanut	Hazelnut	Soy	Pea
			
43% fat 29-42 mg/g	54% fat 7-16 mg/g	18% fat 96-114 mg/g	1% fat 3-36 mg/g
Ara h 1	Cor a 11	Gly m 5	Pis s 1

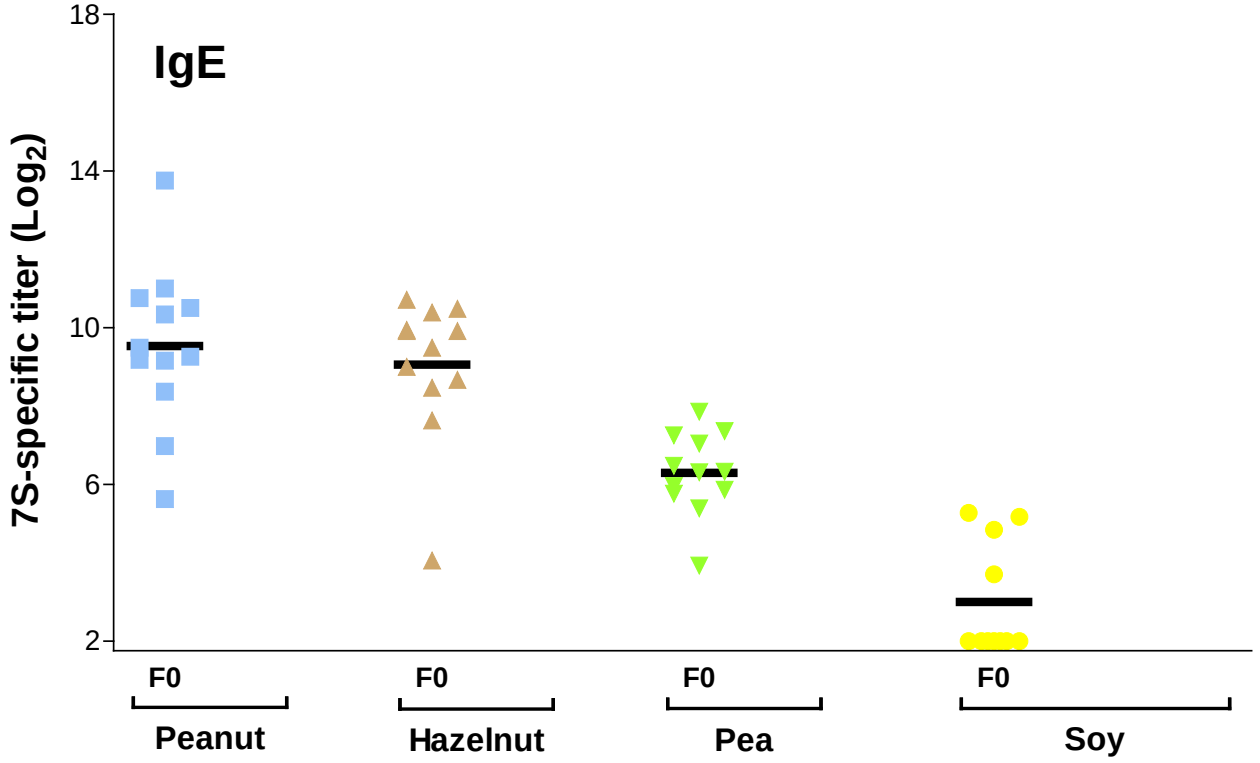


7 S globulins

All 4 7S are labile to digestion


Day 0
Day 0
Day 14
Day 14
Day 28
Day 28
Day 35
100 µg 7S
per rat
100 µg 7S
per rat
100 µg 7S
per rat

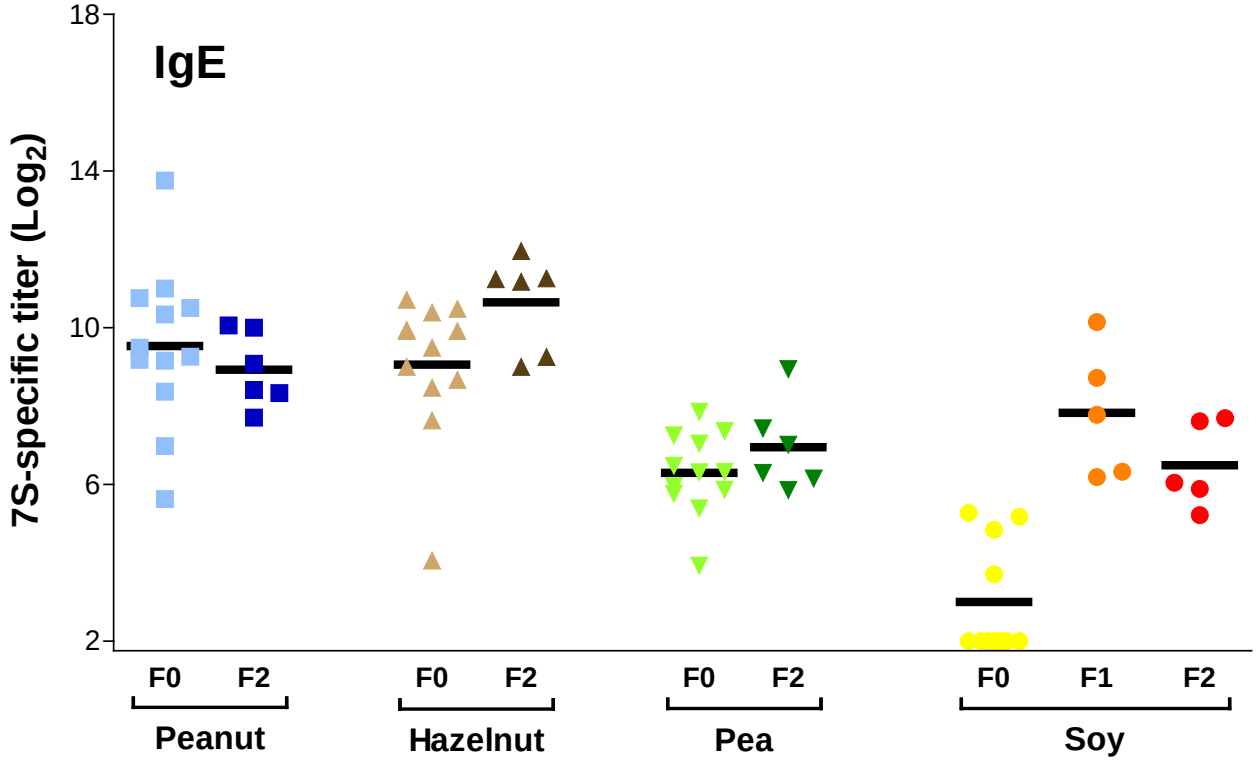
Sensitisation studies with purified 7S globulins



F0 = Soy free diet contaminated with soy

1-25 µg soy / g diet

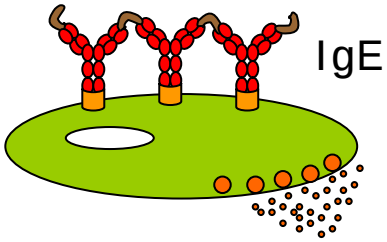
Sensitisation studies with purified 7S globulins

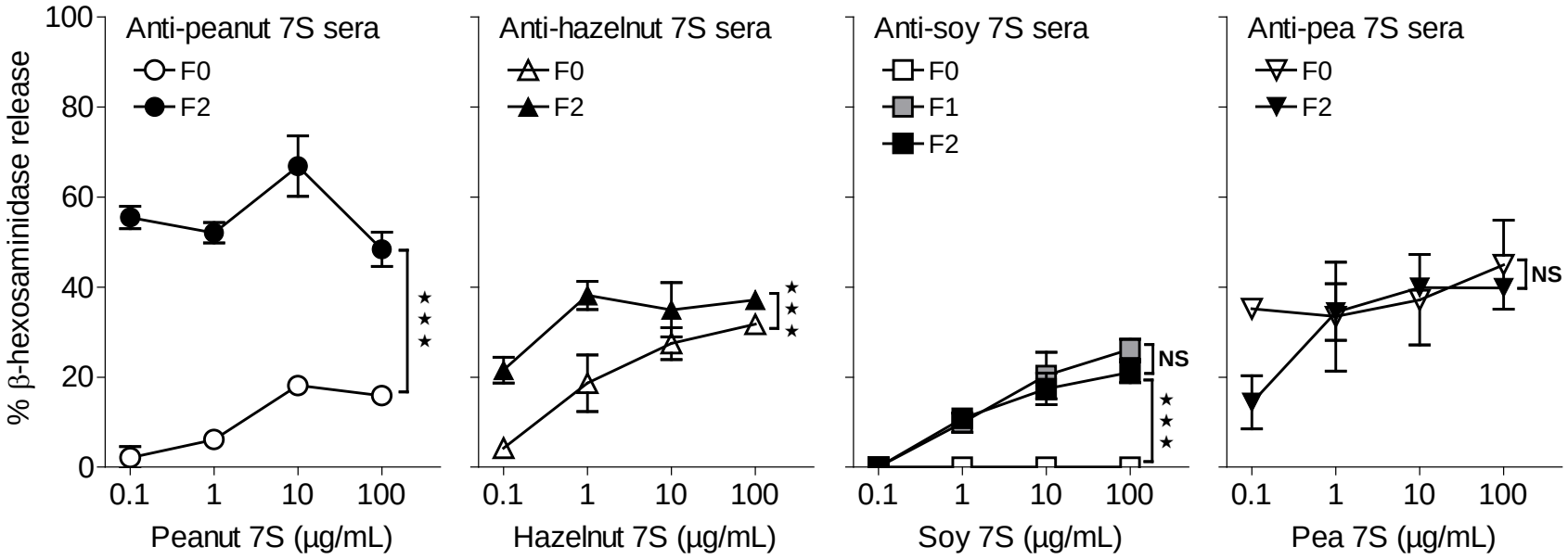


F0 = Soy free diet contaminated with soy

F1+F2 = Soy free diet WITHOUT soy contamination

Rat Basophilic Leukaemia cell assay





Kroghsbo et al. 2011

Conclusion II

- I.p. studies may be used to make comparisons, but care should be taken what to compare (no digestion involved)

- Oral studies without adjuvant can be used to study
  - Whole foods (extracts may be misleading)
  - Processing
  - Matrix effects
  - Limitations because of relatively low IgE response

- Tolerance may heavily influence the quality of the response

- Lack of knowledge on dose-response relations limit results to predict hazard

- This makes it impossible to estimate risk

Thank you (-;

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