



Application of Risk Assessment Methods to Food Allergens

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International Life Sciences Institute

Research Foundation/Risk Science Institute



Overview

- **ILSI RF Project – Risk Assessment for Food Allergen Thresholds**
- **ILSI Europe & TNO Work**



Risk Assessment for Food Allergen Thresholds

- **Question: Can currently available data and risk assessment methods be applied to establishing thresholds for food allergens?**
- **Approach**
 - **Steering Committee to define scope and provide direction**
 - **Working group to gather/analyze data**



Steering Committee

Robert Buchanan, PhD

Wesley Burks, MD

René Crevel, PhD

Anne Muñoz-Furlong

Ian Munro, PhD

Craig Llewellyn, PhD

Martinus Løvik, MD, PhD

Steve Taylor, PhD

FDA/CFSAN

Duke University

Unilever, UK

FAAN

Cantox, CANADA

Wrigley Co.

**Norwegian Inst.
of Public Health**

U. Nebraska



Scope

- **Route of exposure: ingestion**
- **IgE-mediated allergic reactions**
- **Focus on elicitation (not sensitization) for modeling dose-response**
- **Develop approach and illustrate with peanut (most data)**



Initial Objectives

- Mine the published literature for data to establish dose-response curve
- Characterize population intake distributions of inadvertent allergenic contaminants
- Investigate use of information on allergic response mechanism to estimate theoretical lower limit on minimal eliciting dose (MED)

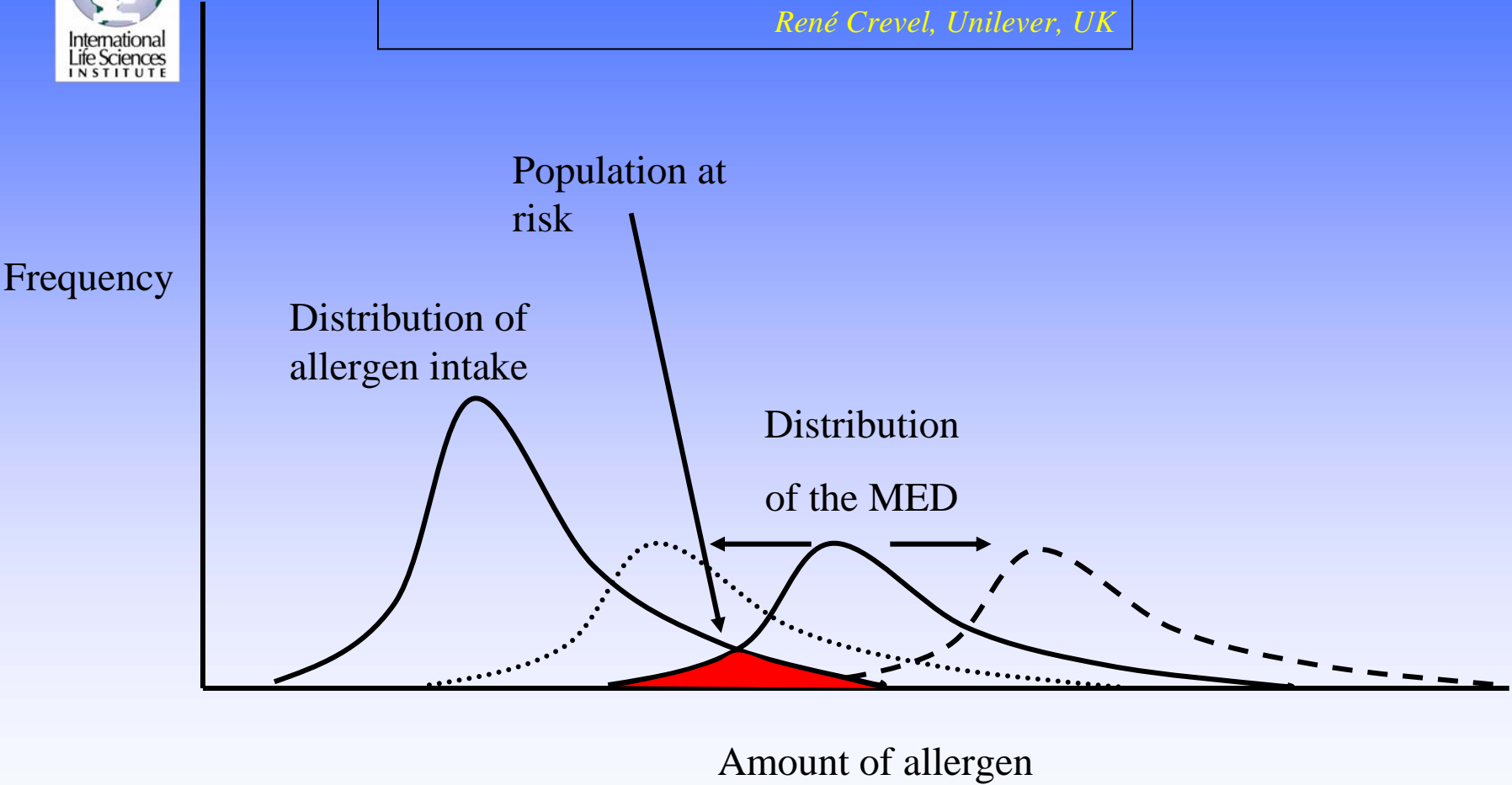


Mining the Clinical Data

- **Goal**: To describe the population distribution of MEDs for peanut to determine if a threshold can be established
- **Toxicologist's question**: What is the shape of the dose-response curve at low doses?
- **Risk manager's question**: Is there an intake level below which the risk of an allergic response is $<$ [some number]?



Illustration of the basic concept
René Crevel, Unilever, UK





Mining the Clinical Data

- **Most reliable data is from double-blind, placebo-controlled food challenges.**
- **Published literature is limited in:**
 - **Number of subjects**
 - **Individual vs. group data**
 - **Variable form of dose**
 - **Response criteria (objective/subjective)**
 - **Diagnostic vs. challenge studies**
 - **Other limitations in reporting**

Microsoft Excel - peanutmatrix

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	A	B	C	D	E	F	G	H	I
1									
2									
3	Study/ Reference	Patient Reference	Age	Gender	Objective Adjusted mg Protein ²		Objective Response as Reported		Test Material ¹
4					NOAEL (mg)	LOAEL (mg)	NOAEL (mg)	LOAEL (mg)	
60	Hourihane JACI 1997; 100:598-600	7	17y	??	88.93mg	None	355.72mg	None	peanut flour-50%protein
61									
62	Hourihane JACI 1997; 100:598-600	8	26y	??	88.93mg	None	355.72mg	None	peanut flour-50%protein
63									
64	Hourihane JACI 1997; 100:598-600	9	24y	??	3.93mg	8.93mg	15.72mg	35.72mg	peanut flour-50%protein
65									
66	Hourihane JACI 1997; 100:598-600	10	20y	??	1.93mg	3.93mg	7.72mg	15.72mg	peanut flour-50%protein
67									
68	Hourihane JACI 1997; 100:598-600	11	26y	??	88.93mg	None	355.72mg	None	peanut flour-50%protein
69									
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78									
79									

Peanut - Individual Peanut - Group Foot Notes & Column Descriptors

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Summary of Published

	Study/ Reference	Patient Reference	Objective Signs or Symptoms for MED (LOAEL)	Severity of Symptoms*	Subjective Adjusted mg Protein ²		Subjective Response as Reported		Significance
					NOAEL (mg)	LOAEL (mg)	NOAEL (mg)	LOAEL (mg)	
60	Hourihane JACI 1997; 100:596-600	7	none	NR			155.72mg	355.72mg	OA
61									
62	Hourihane JACI 1997; 100:596-600	8	none	NR			155.72mg	355.72mg	OA
63									
64	Hourihane JACI 1997; 100:596-600	9	vomiting, wheezing, urticaria, lip swelling	moderate			0.08mg	0.18mg	OA
65									
66	Hourihane JACI 1997; 100:596-600	10	lip swelling, OAS	moderate			0.08mg	0.18mg	OA
67									
68	Hourihane JACI 1997; 100:596-600	11	none	NR			355.72mg	None	NR
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	A	B	P	Q	R	S	T
1	d Data from Peanut Allergy Challenge Studies						
2							
3	Study/ Reference	Patient Reference	Subjective Signs or Symptoms for MED (LOAEL)	Severity of Symptoms*	Delivery		
Matrix					DBPCFC	Placebo	
60	Hourihane JACI 1997; 100:596-600	7	OAS	Mild	Rice pudding	DBPCFC	Rice pudding
61							
62	Hourihane JACI 1997; 100:596-600	8	OAS	Mild	Rice pudding	DBPCFC	Rice pudding
63							
64	Hourihane JACI 1997; 100:596-600	9	OAS	Mild	Rice pudding	DBPCFC	Rice pudding
65							
66	Hourihane JACI 1997; 100:596-600	10	OAS	Mild	Rice pudding	DBPCFC	Rice pudding
67							
68	Hourihane JACI 1997; 100:596-600	11	NR	NR	Rice pudding	DBPCFC	Rice pudding
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Peanut - Individual | Peanut - Group | Foot Notes & Column Descriptors

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	A	B	U	V	W	X
1						
2						
3	Study/ Reference	Patient Reference	Dose		Type of Study	Population Studied
4			Dose Time Interval	Dose Escalation Sequence		
60	Hourihane JACI 1997; 100:596-600	7	10-15min	0.01,0.02,0.05,0.1,0.25,0.5,1,2,5,10,20,50mg	Threshold	Peanut allergy
61						
62	Hourihane JACI 1997; 100:596-600	8	10-15min	0.01,0.02,0.05,0.1,0.25,0.5,1,2,5,10,20,50mg	Threshold	Peanut allergy
63						
64	Hourihane JACI 1997; 100:596-600	9	10-15min	0.01,0.02,0.05,0.1,0.25,0.5,1,2,5,10,20,50mg	Threshold	Peanut allergy
65						
66	Hourihane JACI 1997; 100:596-600	10	10-15min	0.01,0.02,0.05,0.1,0.25,0.5,1,2,5,10,20,50mg	Threshold	Peanut allergy
67						
68	Hourihane JACI 1997; 100:596-600	11	10-15min	0.01,0.02,0.05,0.1,0.25,0.5,1,2,5,10,20,50mg	Threshold	Peanut allergy
69						
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	A	B	Y	Z	AA
1					
2					
3	Study/ Reference	Patient Reference	Other Allergies	Treatment Given Following Adverse Reaction	Potential Confounding Factors
4					
60	Hourihane JACI 1997; 100:596-600	7 ??		None	??
61					
62	Hourihane JACI 1997; 100:596-600	8 ??		None	??
63					
64	Hourihane JACI 1997; 100:596-600	9 ??		None	??
65					
66	Hourihane JACI 1997; 100:596-600	10 ??		None	??
67					
68	Hourihane JACI 1997; 100:596-600	11 ??		None	??
69					
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Dealing with allergens in food; a risk analysis based approach

Dr. Geert F. Houben, TNO Quality of Life
On behalf of the Expert Group on
Determination of Eliciting Dose, ILSI
Europe Food Allergy Task Force

TNO | Knowledge for business



Expert Group on Determination of Eliciting Dose, Food Allergy Task Force, ILSI Europe:

Dr. David Briggs, Unilever, UK

Dr. René Crevel, Unilever, UK

Dr. Lutz Edler, German Cancer Research Centre, FRG

Dr. Thomas Hatzold, Kraft Foods, FRG

Dr. Claudia Hischenhuber, Nestlé, CH

Dr. Geert F. Houben, TNO Quality of Life, NL

Dr. Jonathan Hourihane, University College Cork, IR

Dr. André Knulst, University Medical Centre Utrecht, NL

Ms. Fiona Samuels, ILSI Europe, B

Dr. Josef Schlatter, Swiss Federal Office of Public Health, CH

Case study

Contamination of chocolate spread with hazelnut proteins

- Survey *
 - presence of hazelnut protein in chocolate spreads
 - according to formulation description & labeling: not expected to contain hazelnut or hazelnut proteins

- Hazelnut protein concentrations:
 - Brand 1: 0.752 +/- 0.059 mg/g
 - Brand 2: 0.115 +/- 0.015 mg/g
 - Brand 3: 0.011 +/- 0.002 mg/g

- Do these contamination levels pose a relevant risk for consumers?

* Koppelman SJ et. al., Journal of Immunological Methods 1999; 229: 107-120

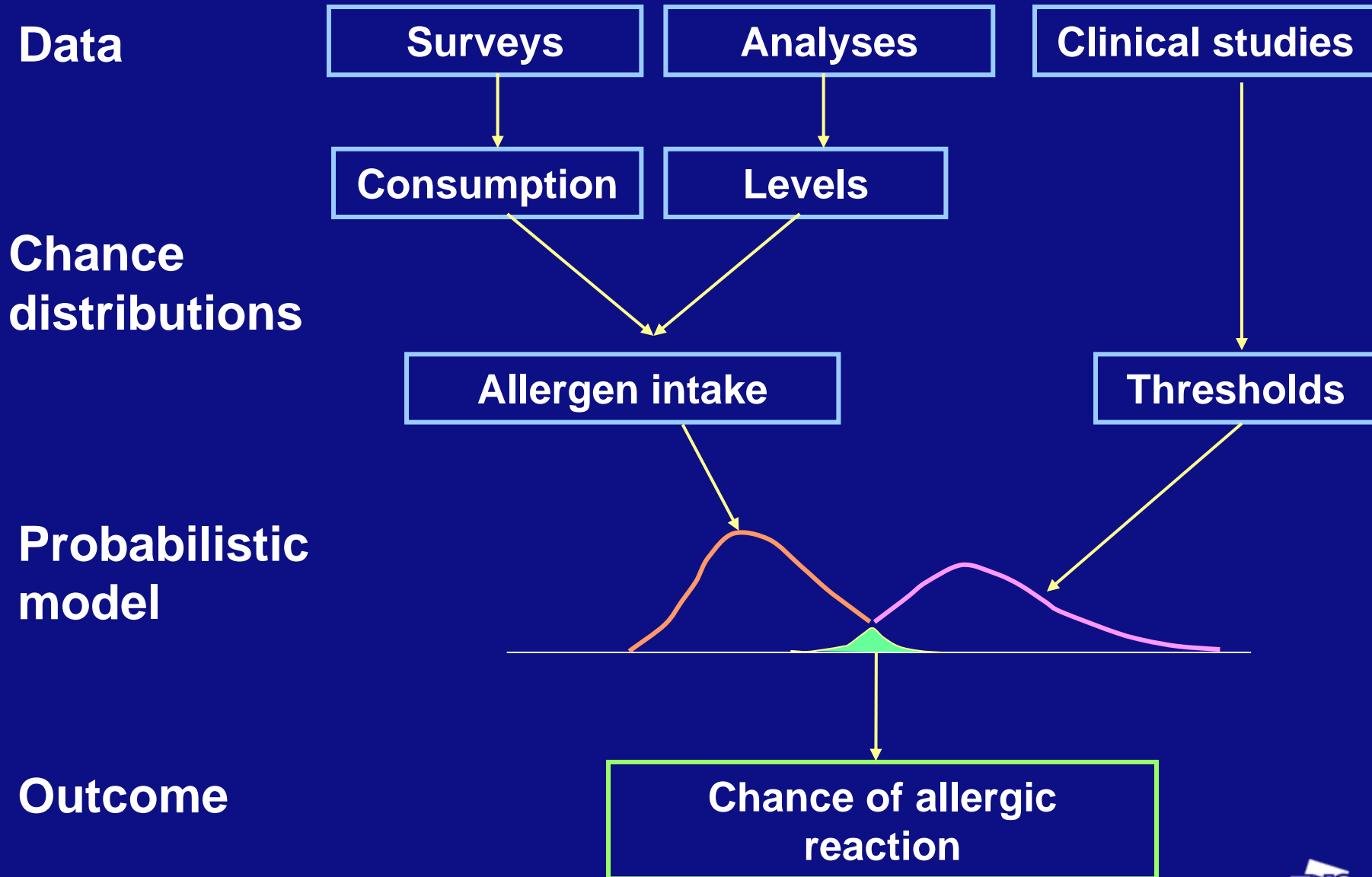
Risk assessment

Concentration	Consumption *	Intake	Threshold **	Risk?
mean brand 1 (0.75 mg/g)	mean (19 g)	14 mg	<1 mg	yes
mean brand 2 (0.12 mg/g)		2.2 mg		yes
mean brand 3 (0.01 mg/g)		0.2 mg		not known
worst-case brand 3 (0.02 mg/g)	maximum (60 g)	1.0 mg		yes

* Dutch 3rd national food consumption survey (Hulshof KFAM et al., Eur J Clin Nutr 2003; 57: 128-137)

** Wensing M et al., Clin Exp Allergy 2002; 32(12): 1757-1762

Probabilistic modeling; the idea



Risk assessment methodology developed by TNO - probabilistic assessment chocolate spread case -

- Results for the 3 concentration figures together:
 - highest mean risk: $< 0.05 \% (< 500 \times 10^{-6})$
 - P95 risk: $< 0.082 \% (\text{breakfast}) (< 820 \times 10^{-6})$
 $< 0.049 \% (\text{lunch}) (< 500 \times 10^{-6})$
- Results for concentration figure of brand 3:
 - highest mean risk : $< 0.004 \% (< 40 \times 10^{-6})$
 - P95 risk: $< 0.02 \% (\text{breakfast}) (< 200 \times 10^{-6})$
 $< 0.005 \% (\text{lunch}) (< 50 \times 10^{-6})$
- Each figure based on
 - worst case model
 - total food allergy prevalence
 - all reaction types



Next Steps

- **Seek partners & funding for two ILSI Research Foundation projects:**
 - **Risk Assessment for Food Allergen Thresholds**
 - **Global Threshold Project**
 - **Fundamental biology of thresholds (dose-response relationships at low doses) for chemicals, microbial pathogens, allergens, and nutrients**



Thank you!

Steve and Julie