

Clinical thresholds and their application in risk assessment and risk management in food allergy

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TNO | Knowledge for business



Impact of food allergy

- Food allergic patients have poorer Health-Related Quality of Life than patients with diabetes mellitus !

Source: PhD Thesis, Flokstra-de Blok, RUG, The Netherlands, 2009

- Annual health loss in DALY's (Disability Adjusted Life Years) due to:
 - known microbiological hazards in food: 1000 – 4000
 - known chemical hazards in food: 1500 – 2000
 - allergenic proteins in food: 1000

Source: Ons eten gemeten, RIVM, The Netherlands, 2004

“May contain labelling”

To warn allergic consumers for possible contamination of a product with allergen and to protect companies from claims

Non use of “may contain-labelling”:

- reduces choice of allergic consumers to avoid risks
- poses risks to allergic consumers
- increases vulnerability of food production chain companies

Non-selective use of “may contain-labelling”:

- reduces food choice of allergic consumers unnecessarily
- reduces information value of “may contain-labelling”

Use “may contain” labelling (only) when needed:

- No “may contain” if risk (chance and severity) is acceptable, to optimize
 - food choice of consumers
 - information value of warning
- Use “may contain” labelling in case of relevant/unacceptable risk !

Risk-taking and coping strategies of adolescents and young adults with food allergy

Sampson *et al. J Allergy Clin Immunol*, 2006; 117: 1440-5

“A significant number of teens with food allergy admit to risk taking that varies by social circumstances and perceived risks”.

54%: **purposefully** ingesting potentially unsafe food

42%: **willing** to eat a food labeled “may contain”

29%: **willing** to eat a food labeled “may contain” while not carrying epinephrine

Role of food labels in accidental exposures in food-allergic individuals in Canada

Shashank S. Sheth, MD* *Ann Allergy Asthma Immunol.* 2010;104:60–65.

Results: Of 1,862 potential participants, 1,454 (78.1%) responded. Of the 47.8% (95% confidence interval [CI], 45.1%–50.5%) of respondents who experienced an accidental exposure, 47.0% (95% CI, 43.1%–50.9%) attributed the event to inappropriate labeling, 28.6% (95% CI, 25.1%–32.2%) to failure to read a food label, and 8.3% (95% CI, 6.3%–10.7%) to ignoring a precautionary statement. Food-allergic individuals who were allergic to peanut, tree nut, fish, or shellfish were less likely to experience an accidental exposure due to the allergen not being identified in plain language.

Table 2. Food-Allergic Individuals Experiencing an Accidental Exposure Who Attribute at Least 1 Exposure to a Food Labeling-Related Issue

Food labeling-related issue	Respondents, No. (%) [95% CI] (n = 651)
Food label was read but listed allergen was not noticed	86 (13.2) [10.7–16.1]
Allergen was not identified in plain language (eg, “casein” instead of “milk”)	87 (13.4) [10.8–16.2]
Allergen was listed but not clearly visible on the label or package (eg, the allergen information was not boldfaced or listed on the main food label with the other ingredients)	87 (13.4) [10.8–16.2]
Allergen was a hidden ingredient that was not listed/declared on the food label (eg, ingredients listed “natural flavoring” but did not indicate that “milk” was part of the “natural flavoring”)	106 (16.3) [13.5–19.3]
Error in translating ingredients from one language to another	24 (3.7) [2.4–5.4]
Unintentional cross-contamination during manufacturing or packaging at the distribution site and there was no precautionary statement	108 (16.6) [13.8–19.7]
Any of the above	306 (47.0) [43.1–50.9]

Abbreviation: CI, confidence interval.

Presence of non-ingredient allergens in food

Fact sheet, Dutch Food and Consumer Product Safety Authority, July 2007

Allergen not declared			
Allergen	N	Allergen not detectable	Allergen detectable
Peanut	44	30 (< 1mg/kg)	14 (32%) *
Casein	64	35 (<1.6 mg/kg)	29 (45%) *
"May contain" declaration			
Allergen	n	Allergen not detectable	Allergen detectable
Peanut	52	40 (< 1mg/kg)	12 (23%)*
Casein	25	2 (<1.6 mg/kg)	23 (92%)*

Allergen not declared but detectable *			
Level in mg/kg and number (n) of products			
	1-10: n = 10	10-20: n = 3	>20: n = 1
1.6-5: n = 16	5-10: n = 4	10-25.6: n = 5	>25.6: n = 4

* Cause: presumably cross contamination



Presence of non-ingredient allergens in food

Pele et al, Food Additives and Contaminants, 2007, 24 (12), 1334-1344

	label	(hazel)nut		peanut	
		n	% analysed positive	n	% analysed positive
Cookies	May contain	66	36	68	25
	Present in environment	43	23	69	25
	No reference	169	25	159	11
	Total	278	28	269	23
Chocolate	May contain	167	79	181	43
	Present in environment	15	60	15	7
	No reference	40	53	52	25
	Total	222	73	248	37

Chocolate sample	Casein content (mg/kg)
D1	2
C1	15
A2	85
G1	213
F1	222
B1	459
E1	775
A1 (complaint sample)	1500
B2	1568
A3	3015
H1	3
I1	88
I2	156
B3	53000
H2	63000
I3	73000

Presence of non-ingredient allergens in food

(market samples analysed following complaint; Spanjersberg et al. Food additives and Contaminants, 27, 2, 2010)

Plain chocolate;
no reference to milk

Plain chocolate;
"may contain milk"

Milk chocolate

Presence of non-ingredient allergens in food

- 100% avoidance and guarantee is not feasible
- How much is too much?
- Thresholds
 - Lowest dose that can induce an effect in
 - an individual patient
 - one or more individuals in a group of patients
 - one or more individuals in a whole population
 - Lowest concentration of an allergen in a food that can....(see above)
 - Lowest amount of food that can....(see above)

 - Lowest amount of allergen that can be detected or determined
 - Regulatory threshold
 - Maximum concentration accepted in view of tolerated residual risk(s)

 -

Thresholds

Lowest dose that can induce an effect
in an individual patient

Results peanut challenge*

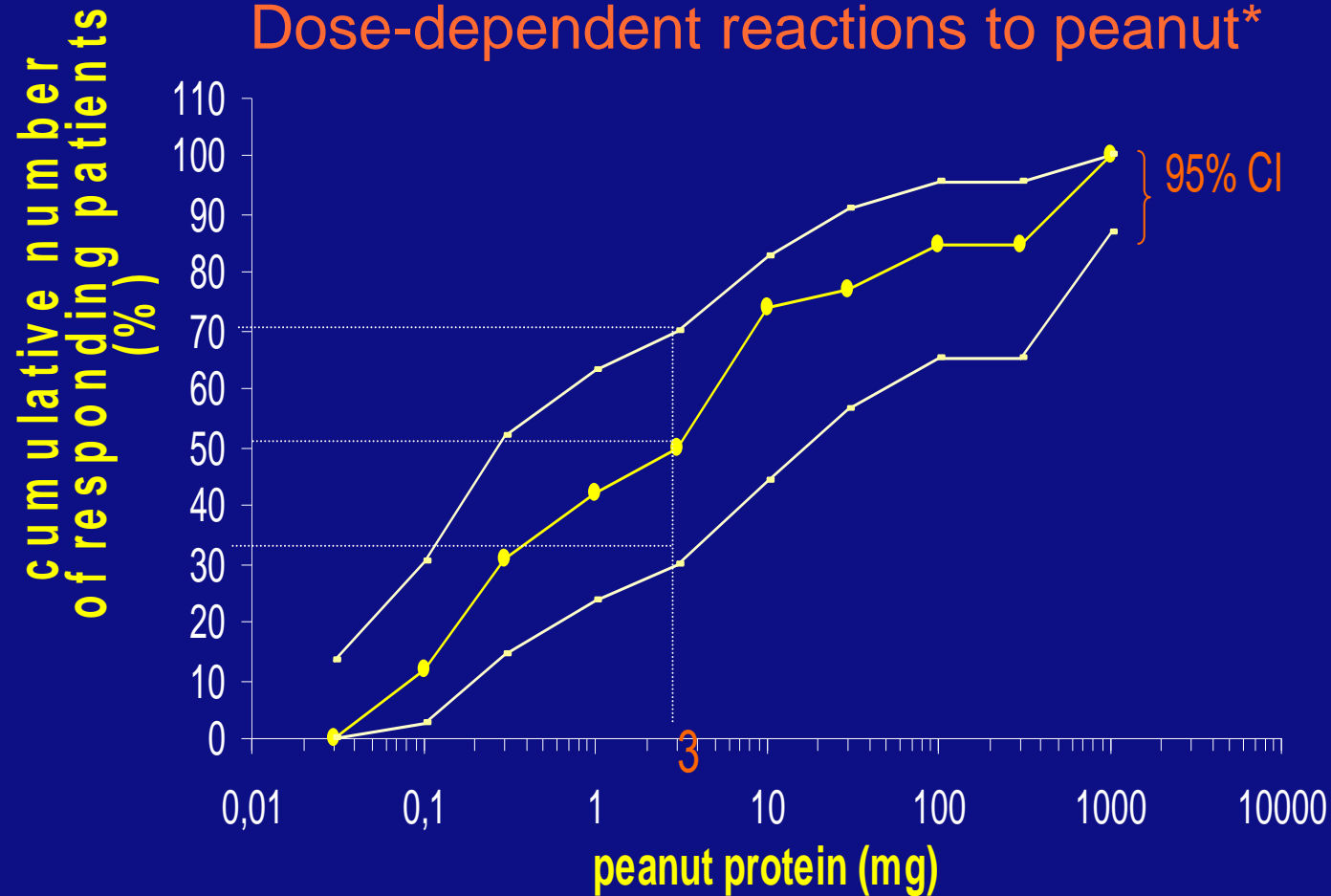
Meal	Dose (mg)	Reaction
1	0,03	-
2	0	-
3	0	-
4	0,1	oral symptoms
5	0,3	oral symptoms
6	0	-
7	0	-
8	1	oral symptoms
9	0	-
10	3	oral symptoms
11	0	-
12	10	oral symptoms + lip swelling

*Figure obtained from Dr. A.C. Knulst, UMC Utrecht

Thresholds

Lowest dose that can induce an effect
in one or more individuals in a group of patients

Dose-dependent reactions to peanut*



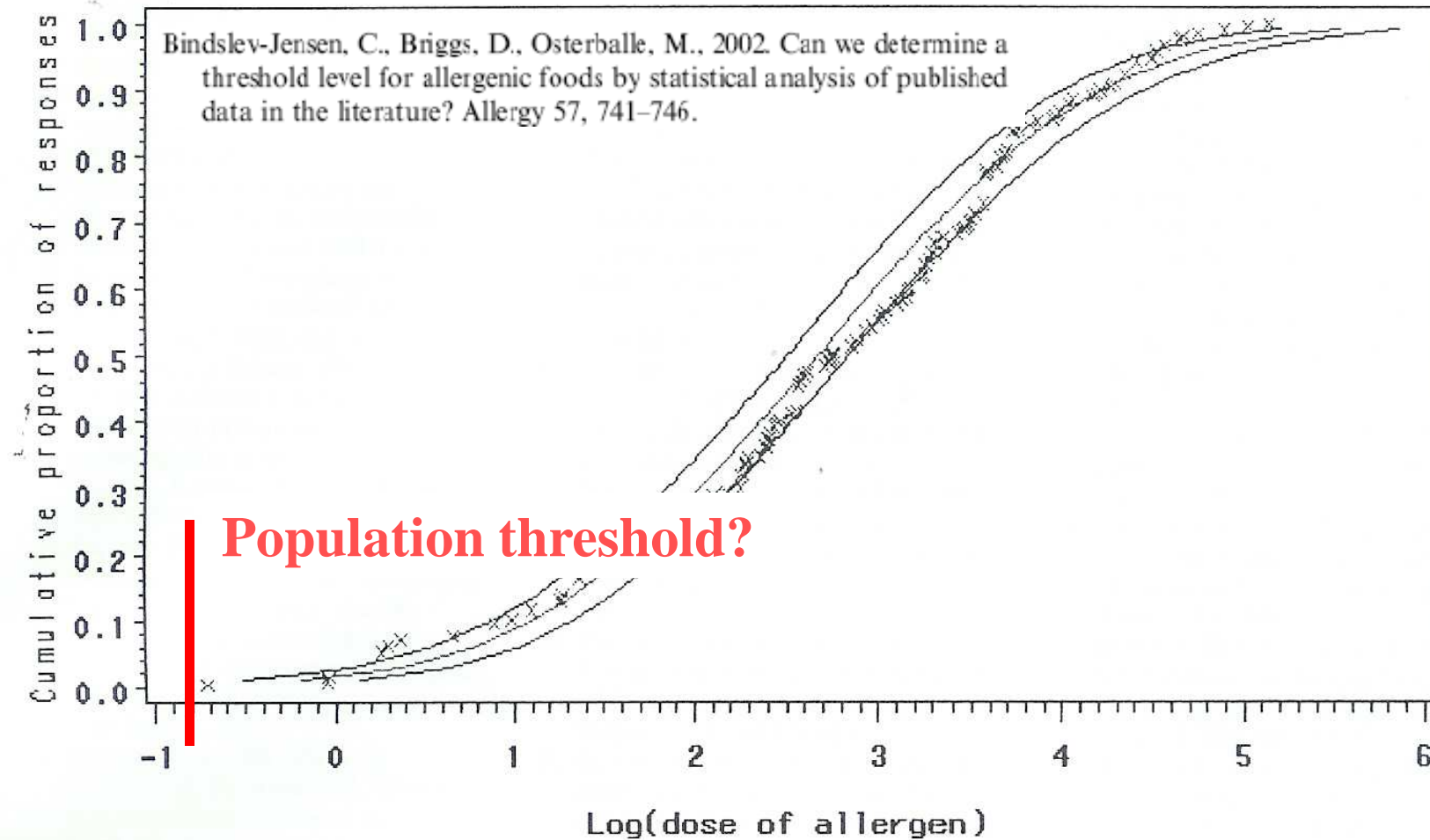
Wensing et al. JACI 2002;110:915

* Figure obtained from Dr. A.C. Knulst, UMC Utrecht



Establishment of population thresholds?

Based on protein Threshold levels for allergenic foods



Establishment of population thresholds

- Establishment of a population threshold remains uncertain due to methodological and statistical uncertainties.

Crevel et al., Fd Chem Toxicol 45 (2007) 691-701

- Even if it were possible to establish a population threshold, it would be of limited value for risk management in a public health context.
 - Population thresholds would result in such low action levels
 - that would be too difficult to comply with within normal food production operating procedures and constraints;
 - that would be too low to monitor or enforce.

Example for peanut protein

Wensing et al., JACI 2002;110:915:

- LOAEL: 0.1 mg; NOAEL: 0.03 mg
- Safety margin to account for possible more sensitive individuals
 - assume a safety margin of 10
- Safe dose: $\text{NOAEL/safety margin} = 0.03/10 = \underline{0.003 \text{ mg?}}$

Assume a food of which 100 g is consumed

- A safe dose of 0.003 mg would correspond with a safe concentration of 0.03 mg/kg food

Problems:

- Current analytical methods generally have a LOD in a range of 1-5 mg/kg
- > 30% of food products not carrying a warning for the possible presence of peanut proteins and produced within normal food production operating procedures and constraints contained peanut proteins > 1 mg/kg*

* : Source: Fact sheet, Dutch Food and Consumer Product Safety Authority, July 2007

We need other approaches of using threshold information

- We need to leave the idea of trying to find **THE** population threshold for allergic reactions; this will not be of help as it will be too low to be practical.
- We need to shift towards **a risk analytical approach** and think from a perspective of acceptable residual risks
 - establish accepted residual risk levels
 - elaborate concentration action limits for may contain labelling
- Needed: insight into the quantitative relationship between:
 - thresholds
 - concentrations of allergens in food
 - risks



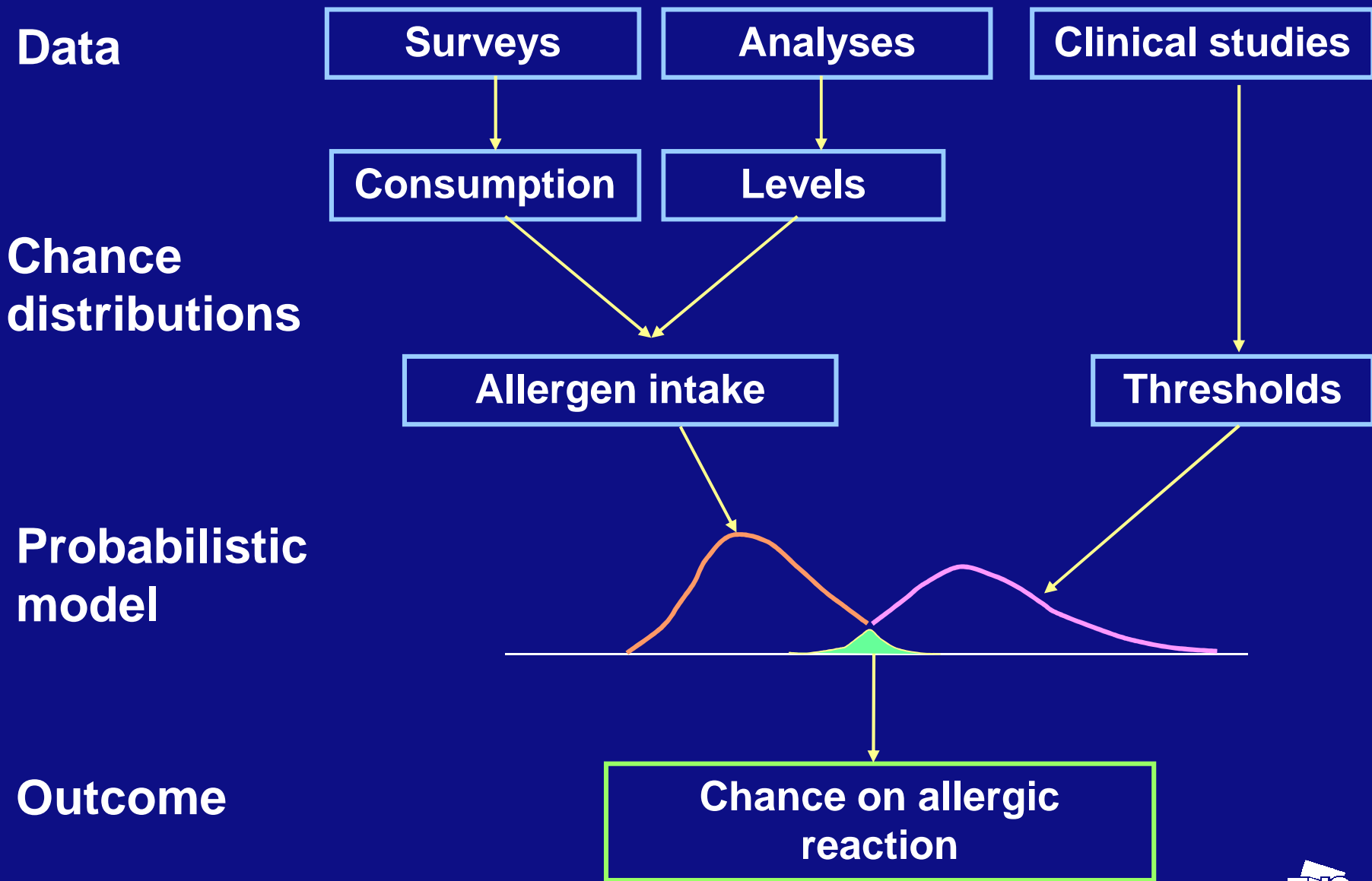
Risk assessment !

Probabilistic risk assessment developed by TNO

Some key publications:

- Spanjersberg et al.
Food and Chemical Toxicology, 2007, 45: 49-54.
- Kruizinga et al.
Food and Chemical Toxicology, 2008, 46, 1437-1443.
- Madsen et al.
Food and Chemical Toxicology, 2009, 47, 480–489.
- Spanjersberg et al.
Food additives and Contaminants, 2010, 27, No. 2, 169–174.

Probabilistic risk assessment; the idea



Threshold data distributions available (Feb 2010)

<u>Priority</u>	<u>Allergen</u>	<u>adults</u>	<u>children</u>	<u>infants & toddlers</u>
1	Milk			
1	Egg			
1	Peanut			
1	Soy			
1	Hazelnut			
1	Walnut	DBPC in 2010/2011		
1	Cashew	no & hardly patients available		
1	Other nuts	no & hardly patients available		
2	sesame seeds	no patients available	no patients available	
2	Lupine		no patients available	
3	Mustard	no extra activity; low priority since no patients available		
3	Celery		low priority and hardly patients available	
3	Wheat (IgE reaction)		low priority and hardly patients available	
3	fish	low priority and hardly patients available	no	
3	crustaceans, mollusc	no	no	

Threshold distribution available in tool

Data available, awaiting decision for incorporation in tool

Insufficient data available

Threshold distribution available, more data available for improved distribution

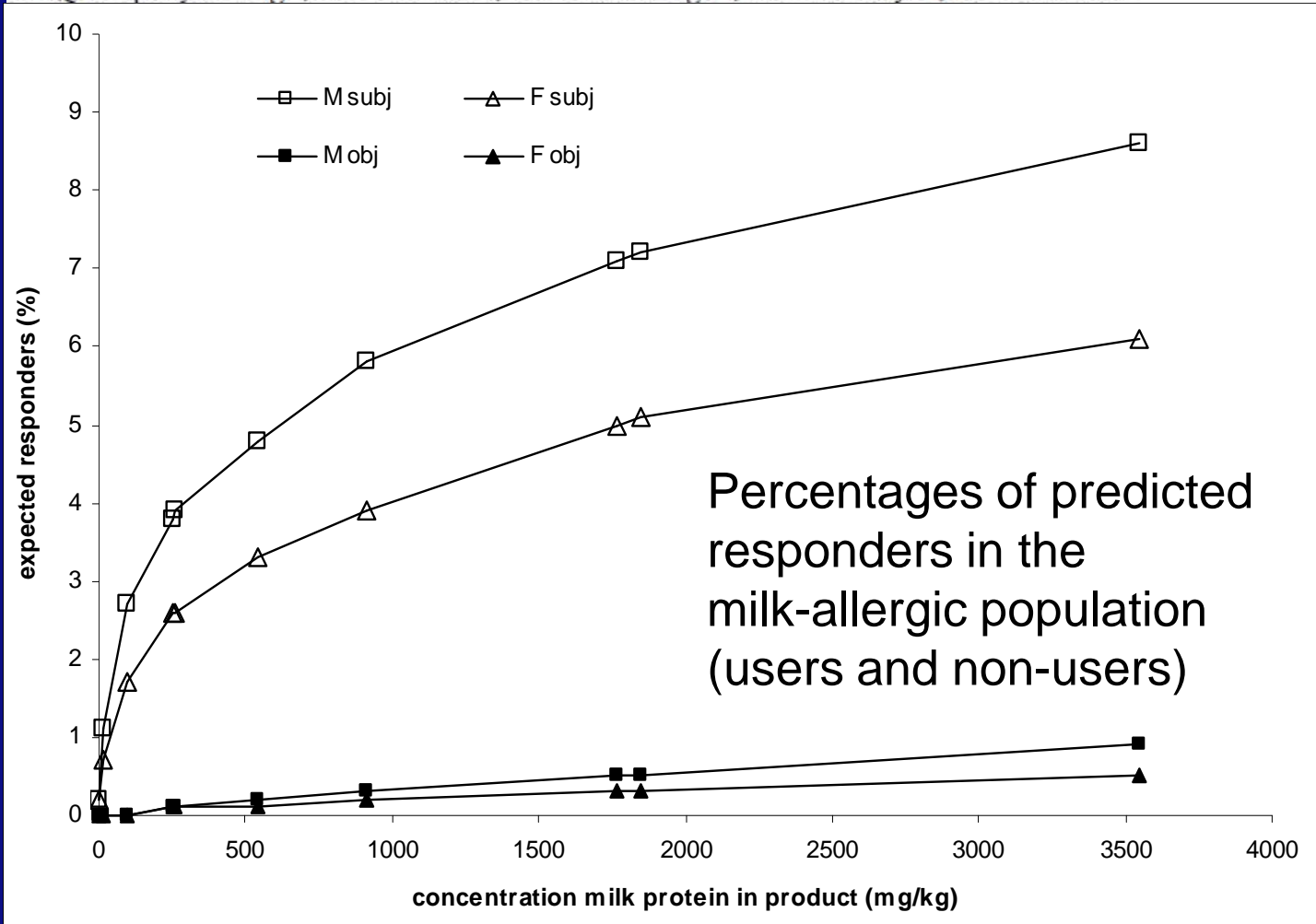
Some data available, not clear yet if sufficient



Risks of presence of non-ingredient allergens in food

Concentrations of undeclared allergens in food products can reach levels that are relevant for public health

M. Q. I. Spanjersberg^a; A. C. Knulst^b; A. G. Kruizinga^a; G. Van Duijn^c; G. F. Houben^a



Food Additives and Contaminants
Vol. 27, No. 2, February 2010, 169–174



There is a need for quantitative guidance!

Guidance's for “may contain labelling”
(existing or in preparation)

- FNLI (Federation of the Food Industry, the Netherlands)
- FEVIA (Federation of the Food Industry, Belgium)
- CIAA (Confederation of the Food and Drink Industries of the EU)
- FSA (Food Standards Agency, UK)
-

Existing guidance's or guidance's in preparation
generally only give qualitative guidance

Example: FSA guide

Sometimes traces of the foods that some people are allergic to can get into products by accident, during the manufacturing process or during transport or storage. This is called 'cross-contamination'.

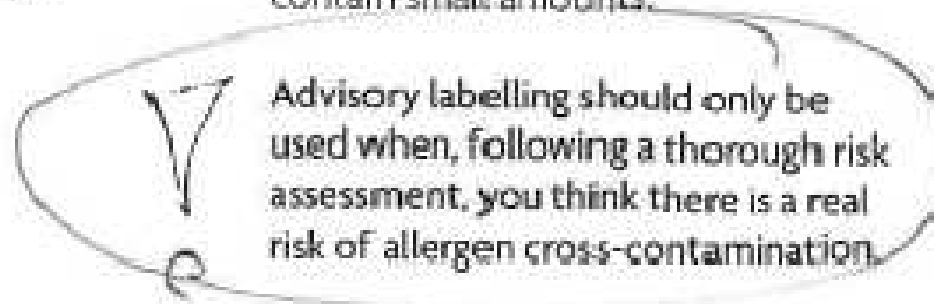
Ideally, you should prevent this from happening (see the section 'How can allergen cross-contamination be avoided?' on page 6). But in some circumstances this may not be possible, so some manufacturers choose to say on the label that a certain food could have got into the product by accident. This is called advisory labelling.

ADVISORY LABELLING

If you think there is a real possibility of a food product being affected by cross-contamination with an allergen, it is good practice to say so on the label using one of these phrases:

- 'may contain X'
- 'not suitable for someone with X allergy'

This means that even though the allergen has not been deliberately added to the product, you cannot be sure that it does not accidentally contain small amounts.



Australian VITAL-grid

a quantitative guidance

a solution for
may contain labelling?

Australian VITAL-grid

Voluntary Incidental Trace Allergen Labeling

Guidance by the Australian Food and Grocery Council Allergen Forum
and supported by the New Zealand Food & Grocery Council
June 2007

VITAL GRID as at 12 June 2007

	Allergen Milk*	Egg*	Soy^^	Fish*	Peanuts*	Sesame Seed*	Tree Nuts*	Crustacea*	Gluten#
No labelling	Action Level 1 (ppm)	<5	<2	<10	<20	<2	<2	<2	<20
Labelling	Action Level 2 (ppm)	5 - 50	2 - 20	10 - 100	20 - 200	2 - 20	2 - 20	2 - 20	20 - 100
Labelling	Action level 3 (ppm)	>50	>20	>100	>200	>20	>20	>20	>100

* mg/kg (ppm) of total protein

Gluten includes all gluten type proteins as defined in the Food Standards Code

^^The Action Level for soy is highly conservative

Values are in mg total protein per kg food

**(in case allergenic protein is measured,
conversion tot total protein needed,**

**Kim Leighton & Simon Brooke-Taylor,
Australian Food and Grocery Council,
March 2008)**

Residual risks in applying VITAL-grid: peanut proteins

Calculated % of allergic responses due to peanut protein at a level of 2 mg protein/kg product (= action level for peanut protein)*

Products	consumption male/female		Chance on allergic response in allergic population (users and non-users)			
	chance (%)	gram/moment	Males		Females	
			subjective	objective	subjective	objective
Bread	62.8/53.3 (H) users (100%)	112/74 (H)	14.0 22.4	2.9 4.6	9.8 18.3	2.1 3.9
Chips	29.0/28.9 (H)	52/36 (L)	4.6	1.0	4.1	0.9
Sprinkles	12.5/10.1 (H)	16/11 (L)	1.4	0.3	1.0	0.2
Potato products (frozen)	4.8/4.3 (L)	146/141 (H)	1.3	0.2	1.1	0.2
Small chocolates	2.8/6.3 (L)	18/21 (L)	0.3	0.1	0.7	0.2

* probabilistic risk assessment TNO



Residual risks in applying VITAL-grid: milk proteins

Calculated % of allergic responses due to milk protein at a level of 5 mg protein/kg product (= action level for milk protein)*

Products	consumption male/female		Chance on allergic response in allergic population (users and non-users)			
	chance (%)	gram/moment	Males		Females	
			subjective	objective	subjective	objective
Bread	62.8/53.3 (H)	112/74 (H)	8.1	0.08	5.9	0.05
Chips	29.0/28.9 (H)	52/36 (L)	2.4	0.02	1.8	0.02
Sprinkles	12.5/10.1 (H)	16/11 (L)	0.4	0.004	0.3	0.003
Potato products (frozen)	4.8/4.3 (L)	146/141 (H)	0.7	0.01	0.6	0.01
Small chocolates	2.8/6.3 (L)	18/21 (L)	0.1	0.0004	0.2	0.004

* probabilistic risk assessment TNO



Towards an EU/NL approach for “may contain labelling”?

Action levels in product category-allergen (category) matrix?

Internet portal

Select product

Select allergen

Action level

Background action level matrix

Product category	Allergen (category)				
	A	B	C	D	...
1	Action level	Action level	Action level	Action level	...
2	Action level	Action level	Action level	Action level	...
3	Action level	Action level	Action level	Action level	...
...

Towards an EU/NL approach for “may contain labelling”?

Action levels in product category-allergen (category) matrix?

filling of matrix based on accepted residual risk levels

Risk assessment →

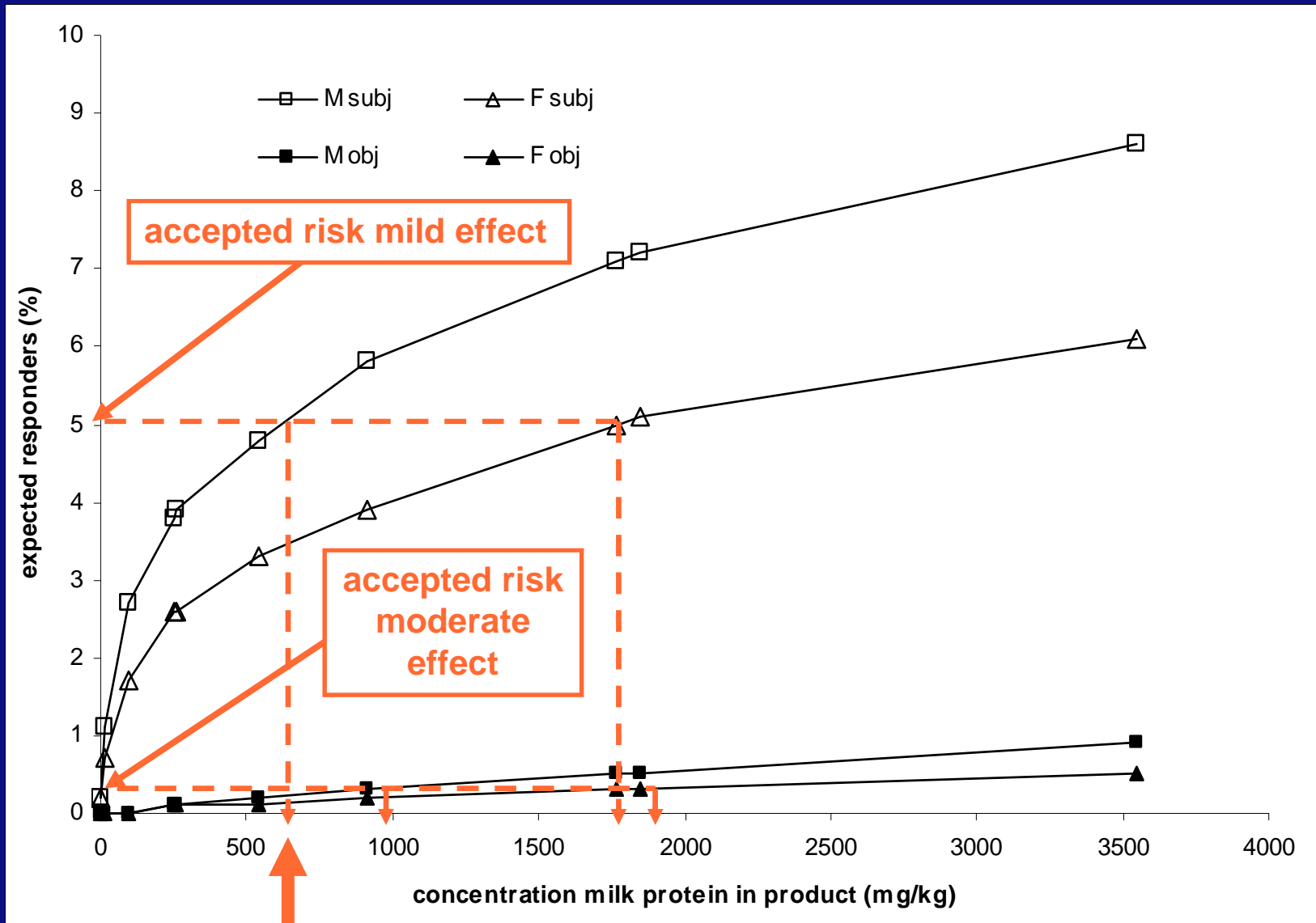


concentration action levels for may contain labelling

Accepted residual risk levels

A food product that does not carry a warning for the possible presence of an allergen may not cause

- in more than out of 10.000 persons
- in more than out of 10.000 persons
- in more than out of 10.000 persons



**concentration action level
for may contain labelling**

For more information:

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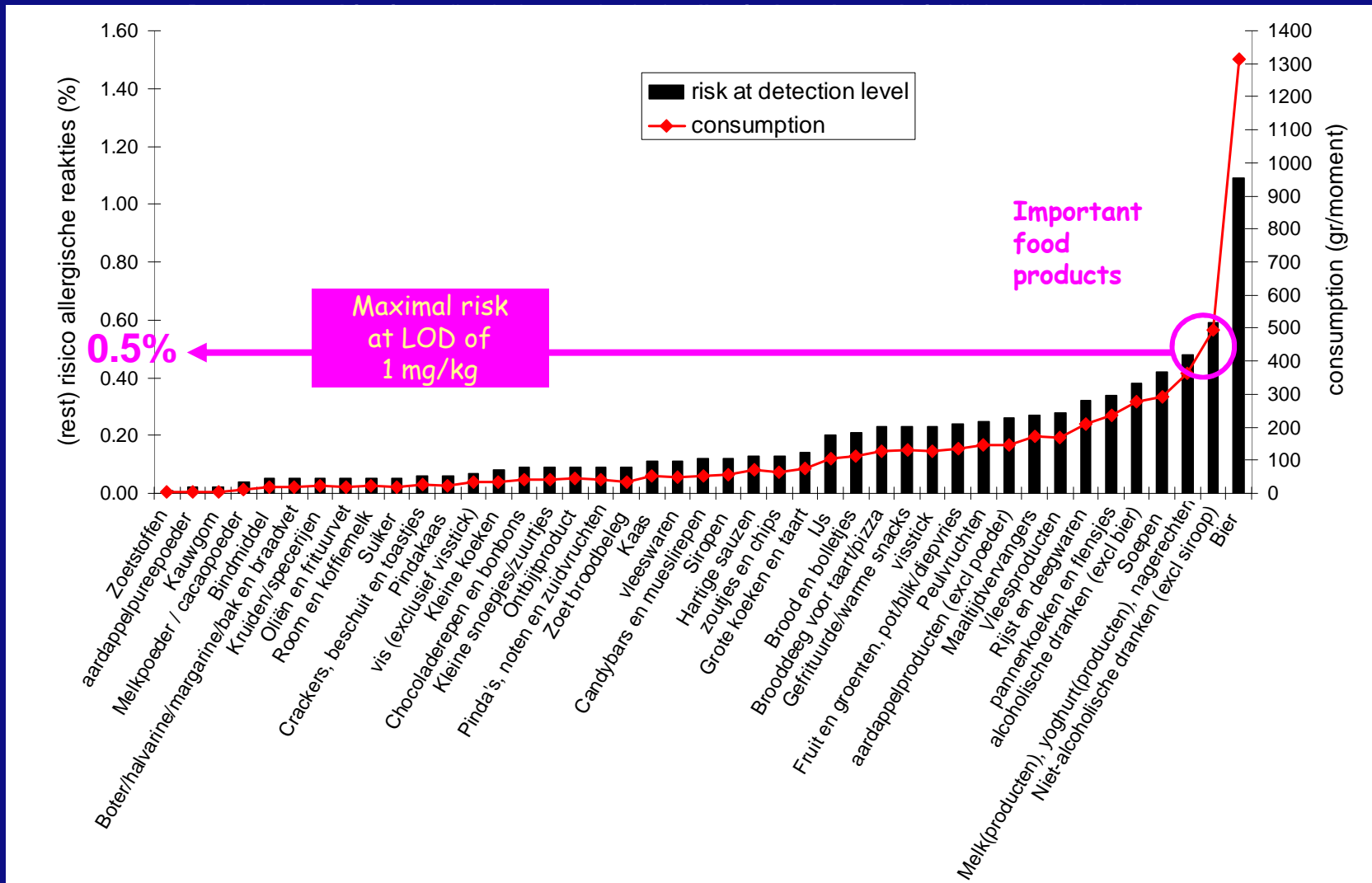
www.tno.nl/foodsafety or www.tno.nl/voedselveiligheid

Thank you for your attention!

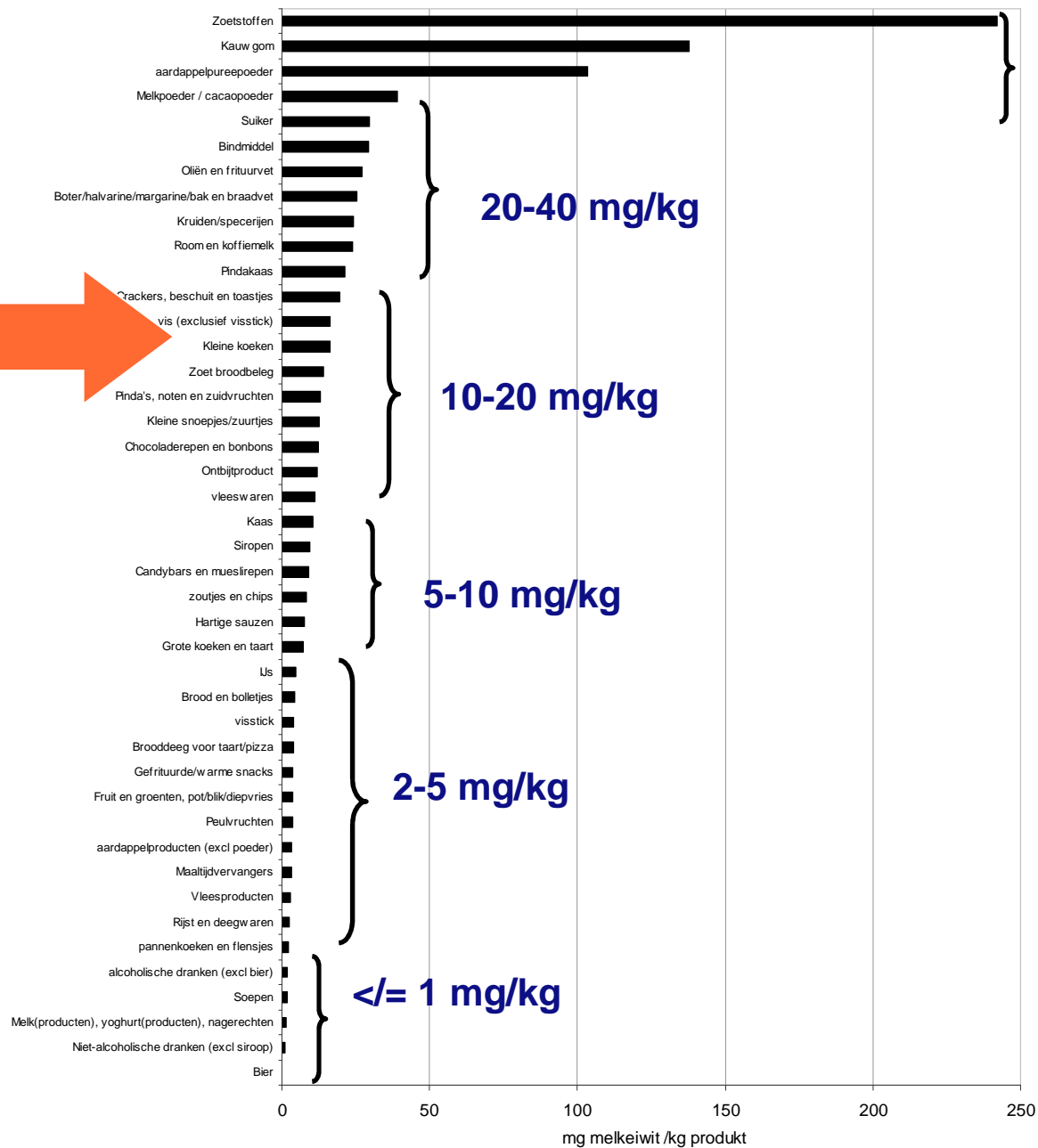


Risk of objective allergic reactions due to presence of milk proteins in various food product categories

Food product categories based on amounts of the food products consumed



With an accepted residual risk of 0.5%, the maximum concentrations of allergen may be



100-300 mg/kg

20-40 mg/kg

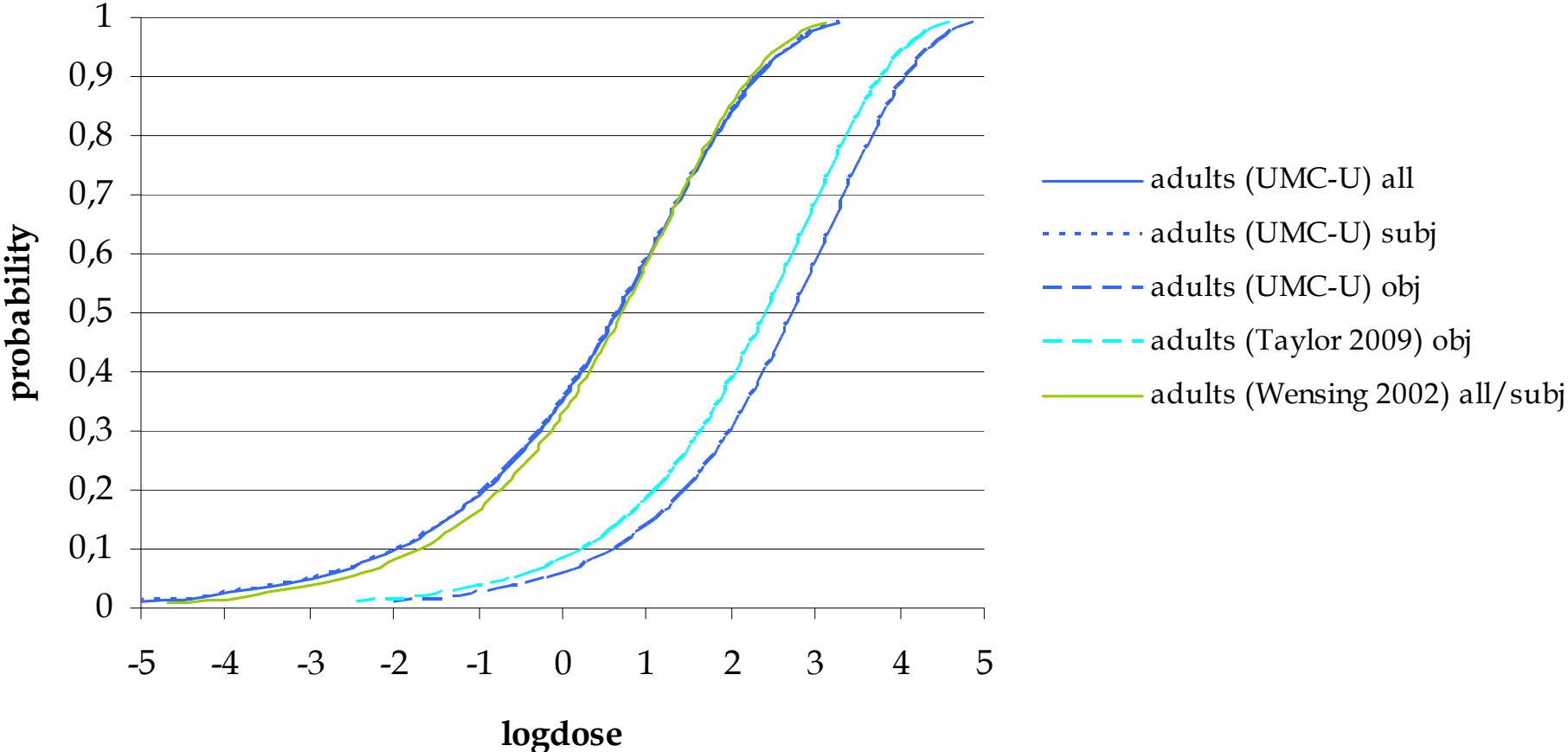
10-20 mg/kg

5-10 mg/kg

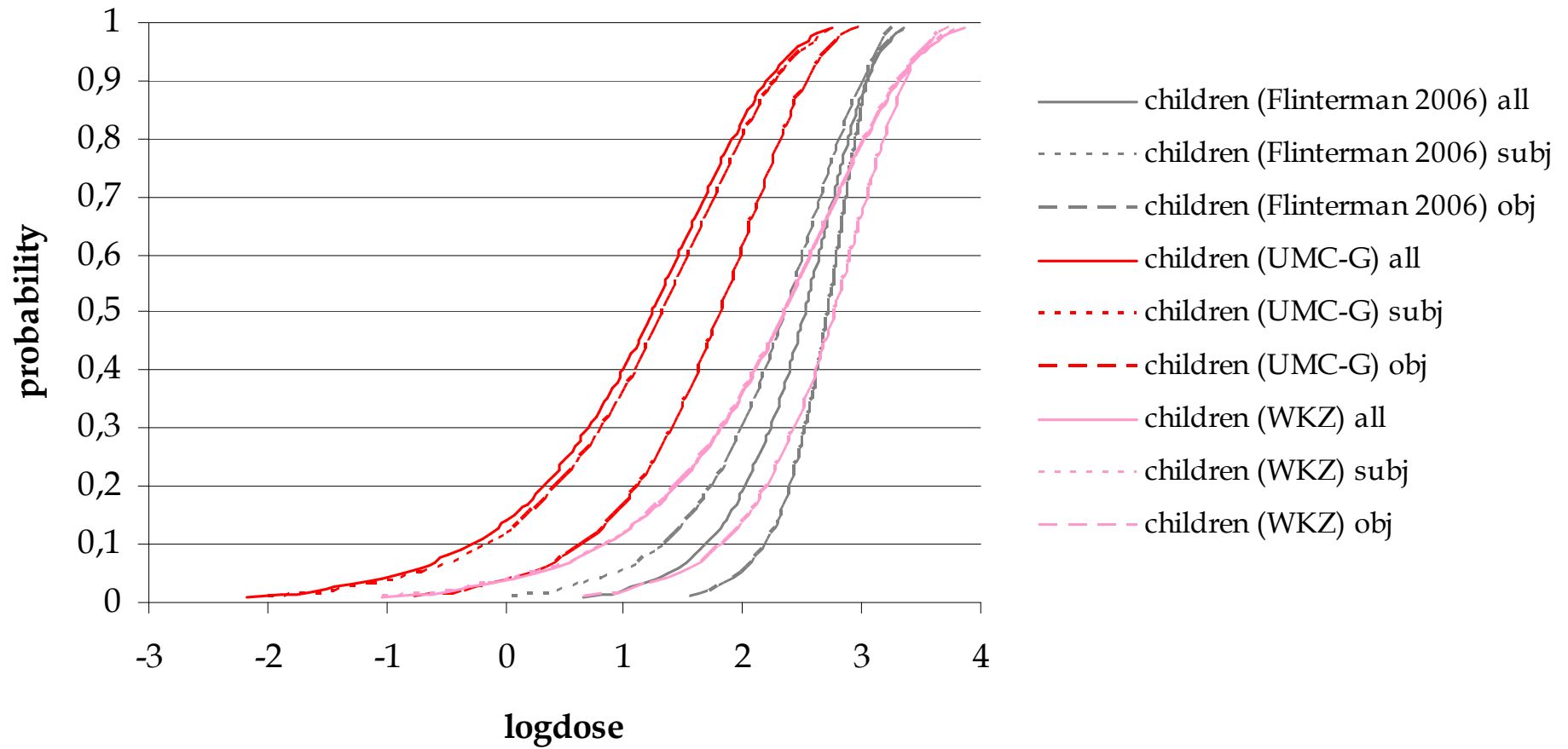
2-5 mg/kg

<= 1 mg/kg

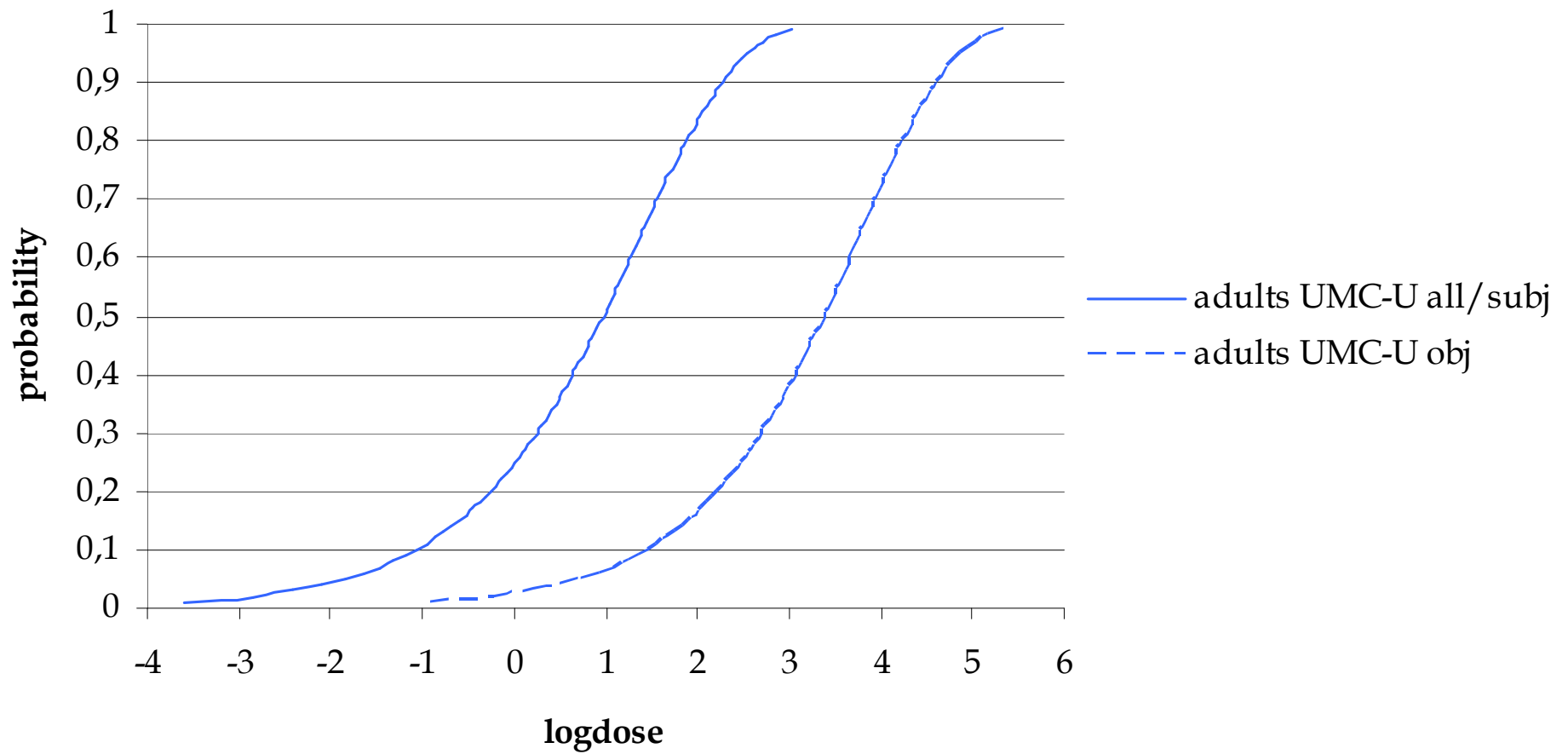
Peanut threshold distributions for adults



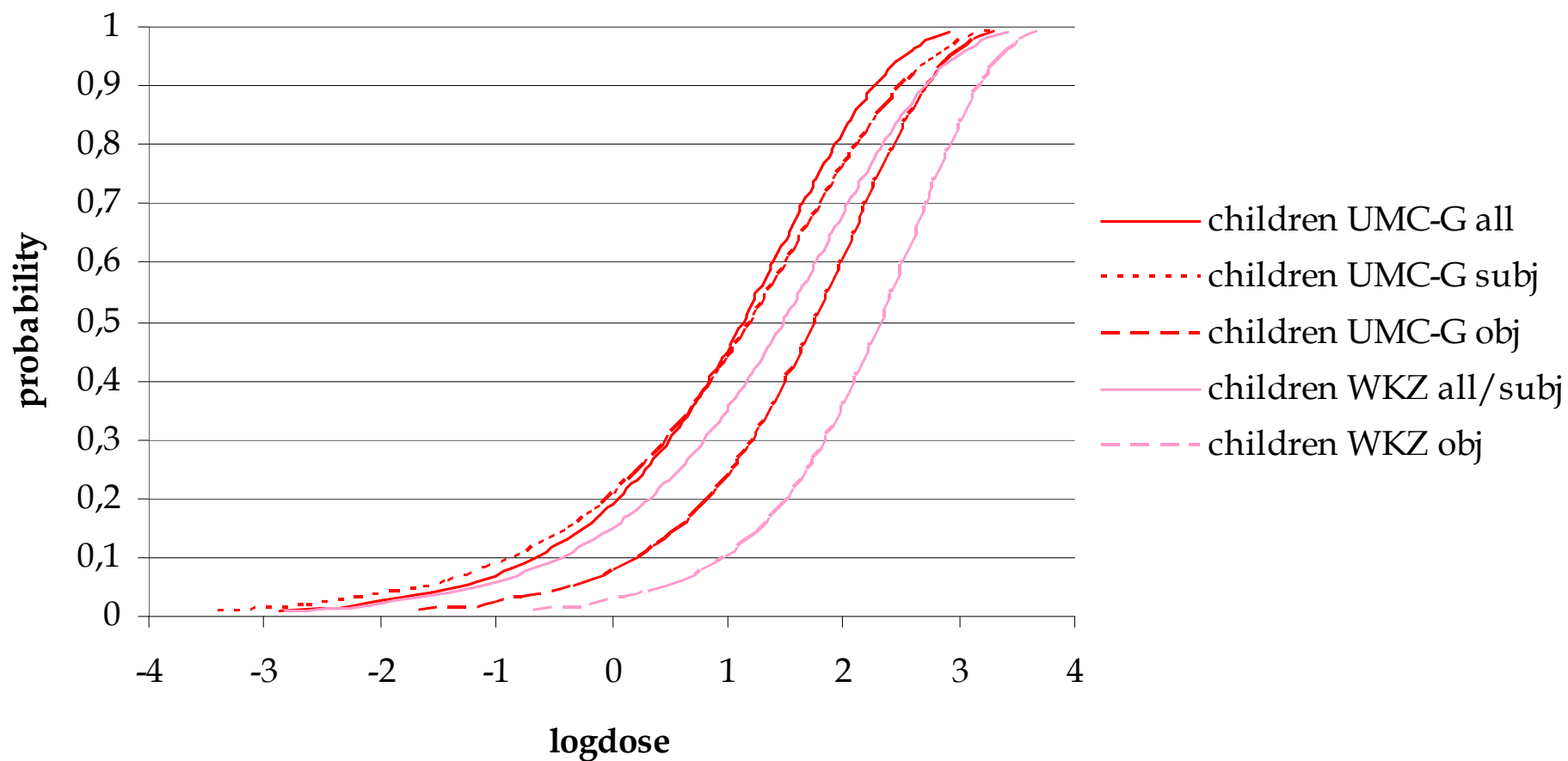
Peanut threshold distributions for children



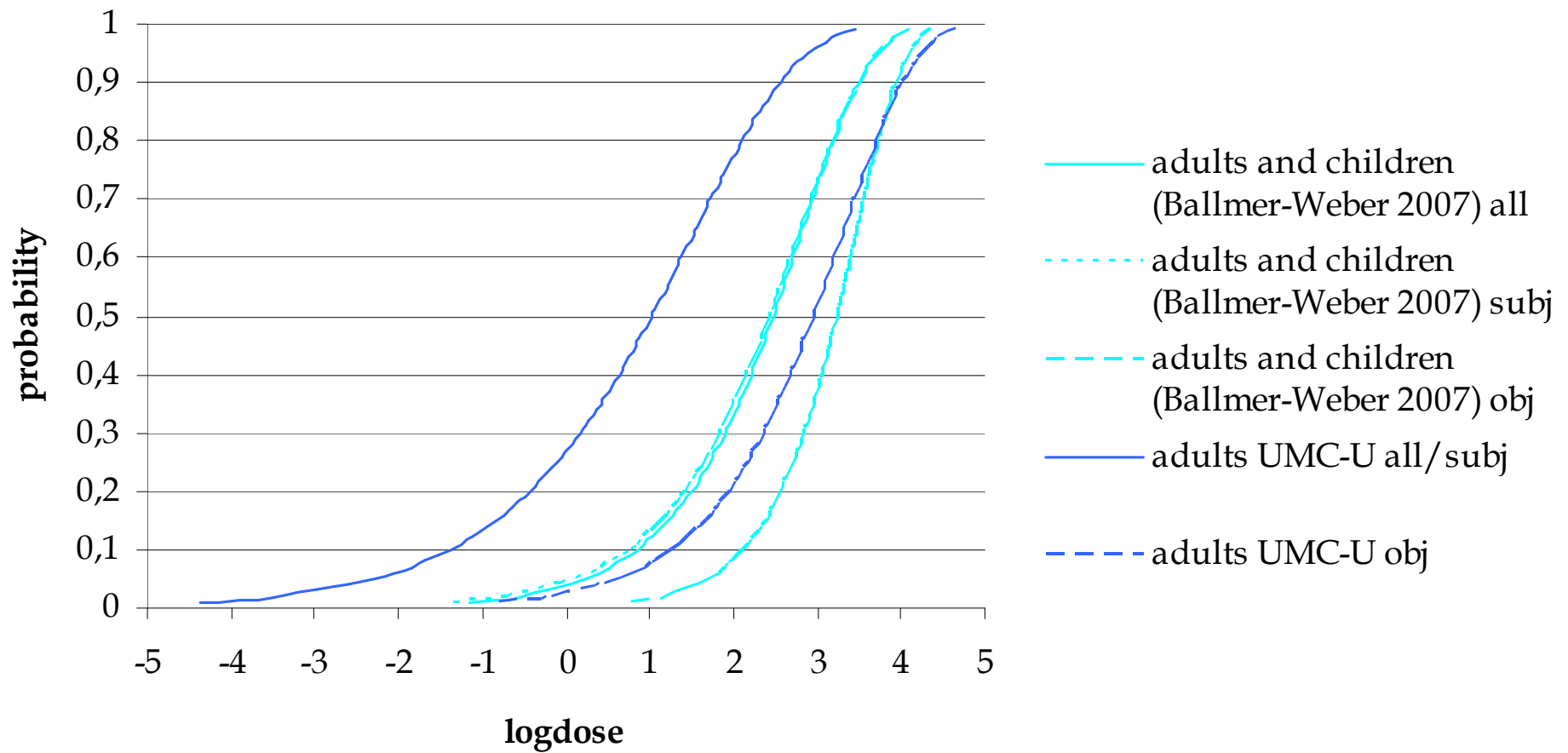
Hazelnut threshold distributions for adults



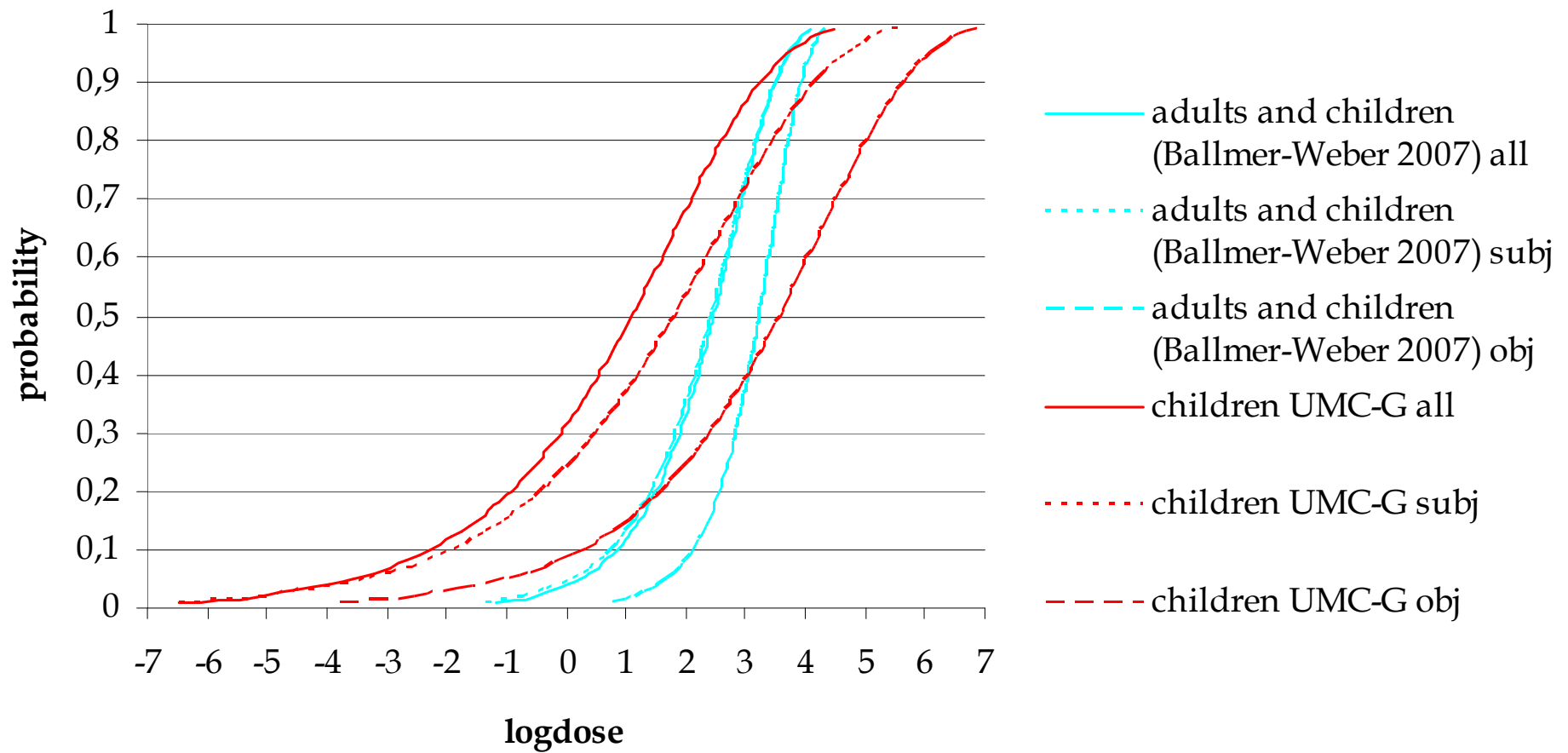
Hazelnut threshold distributions for children



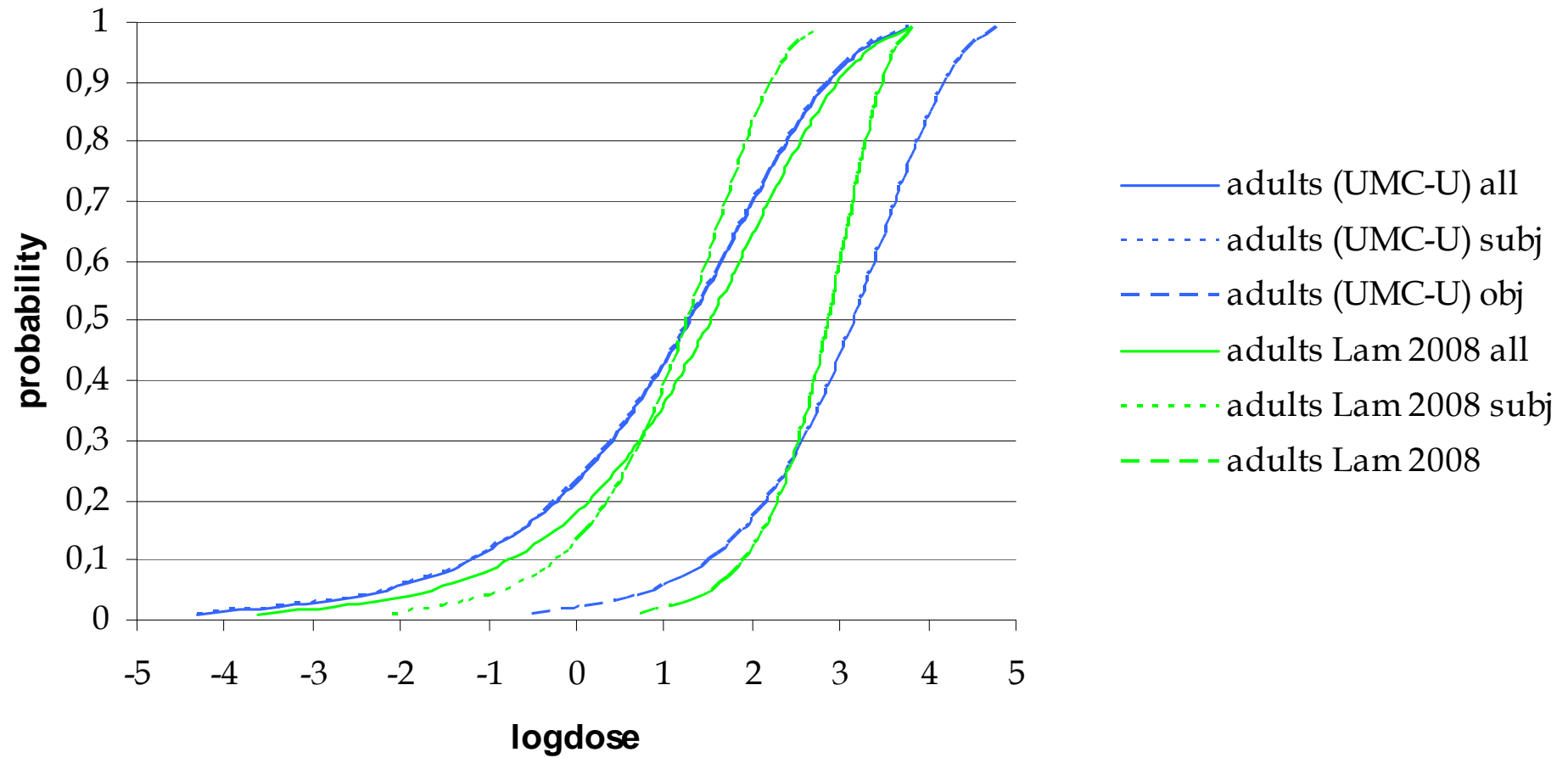
Soy threshold distributions for adults



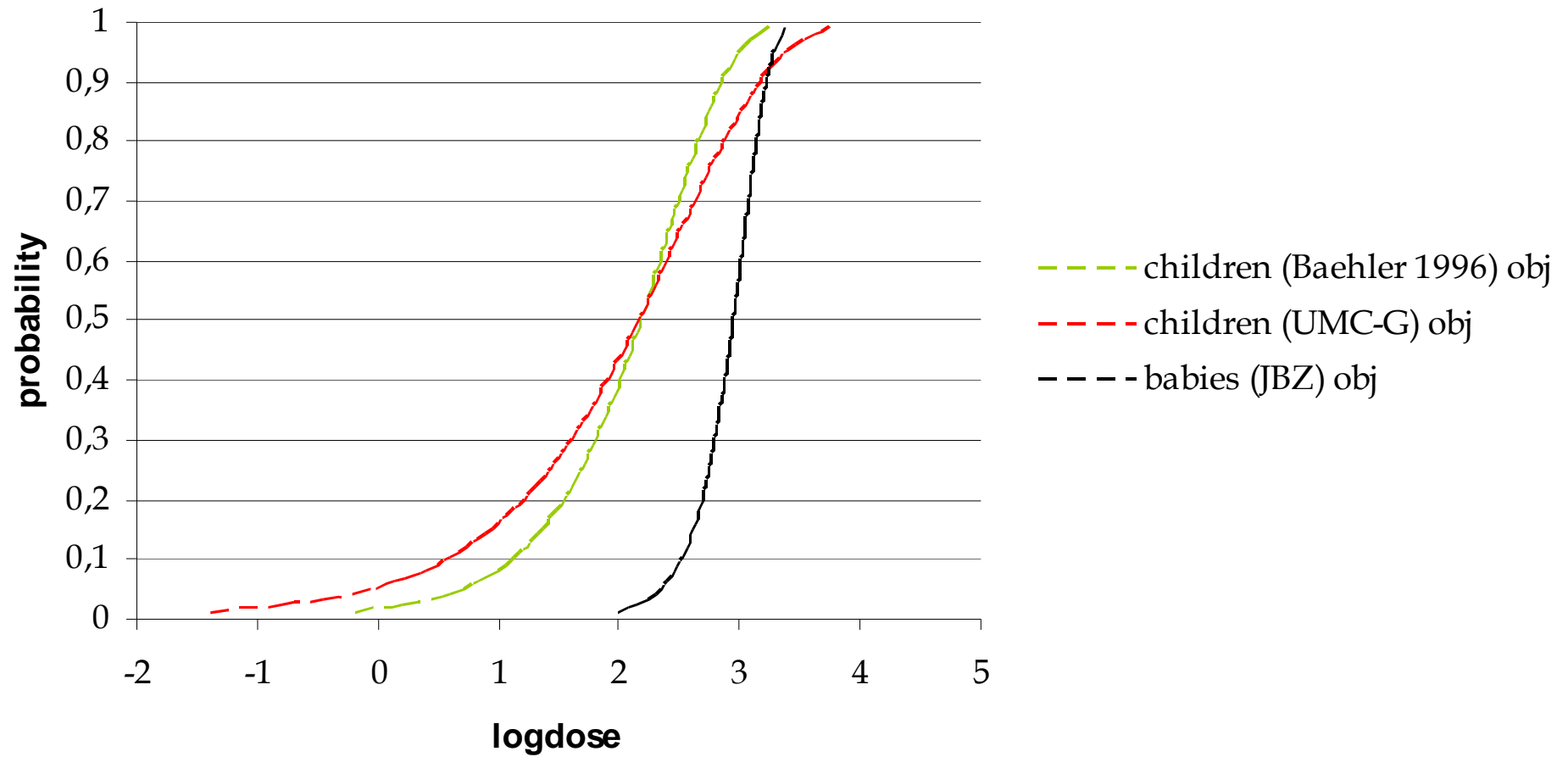
Soy threshold distributions for children



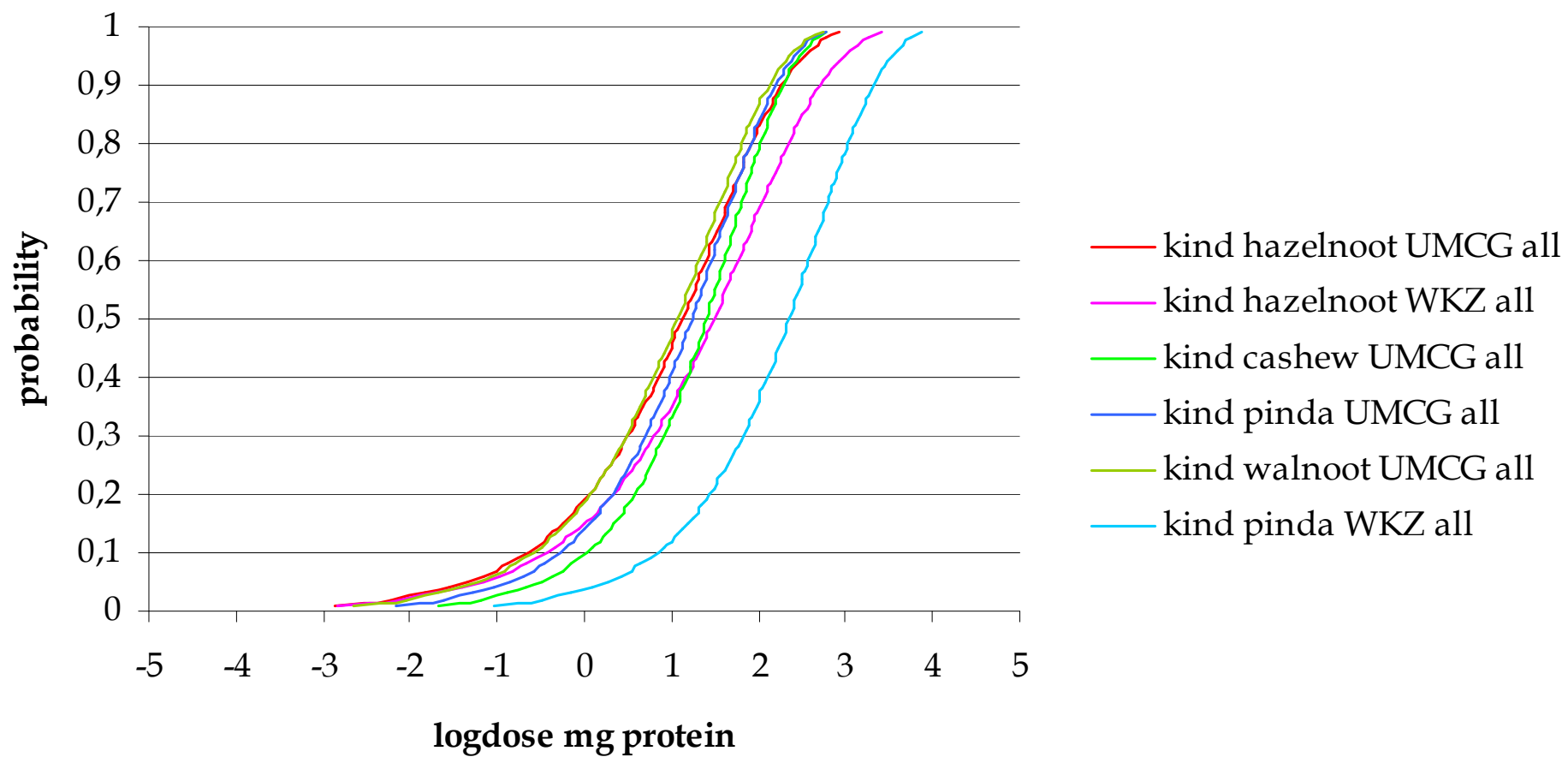
Milk threshold distributions for adults



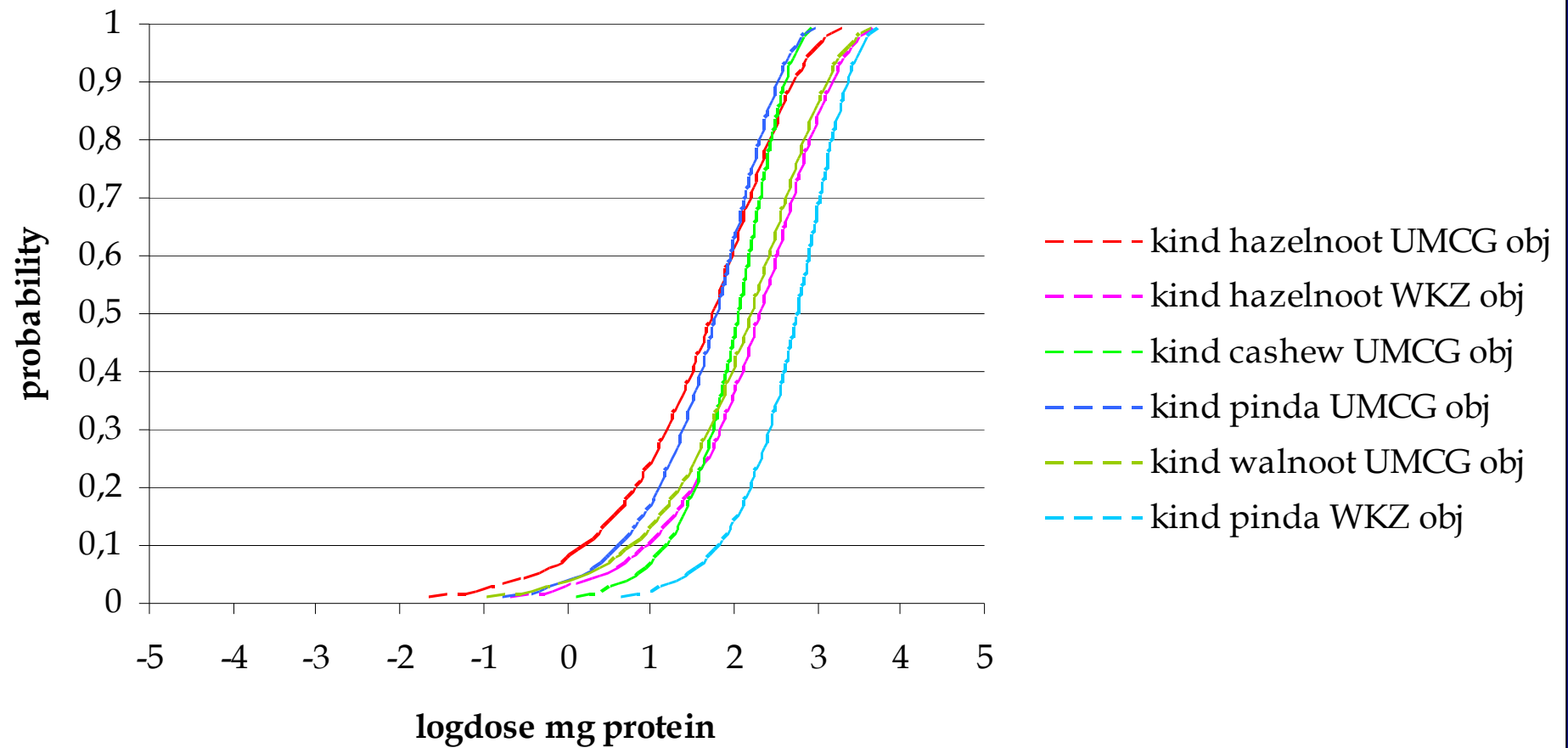
Milk threshold distributions for children (objective reactions)



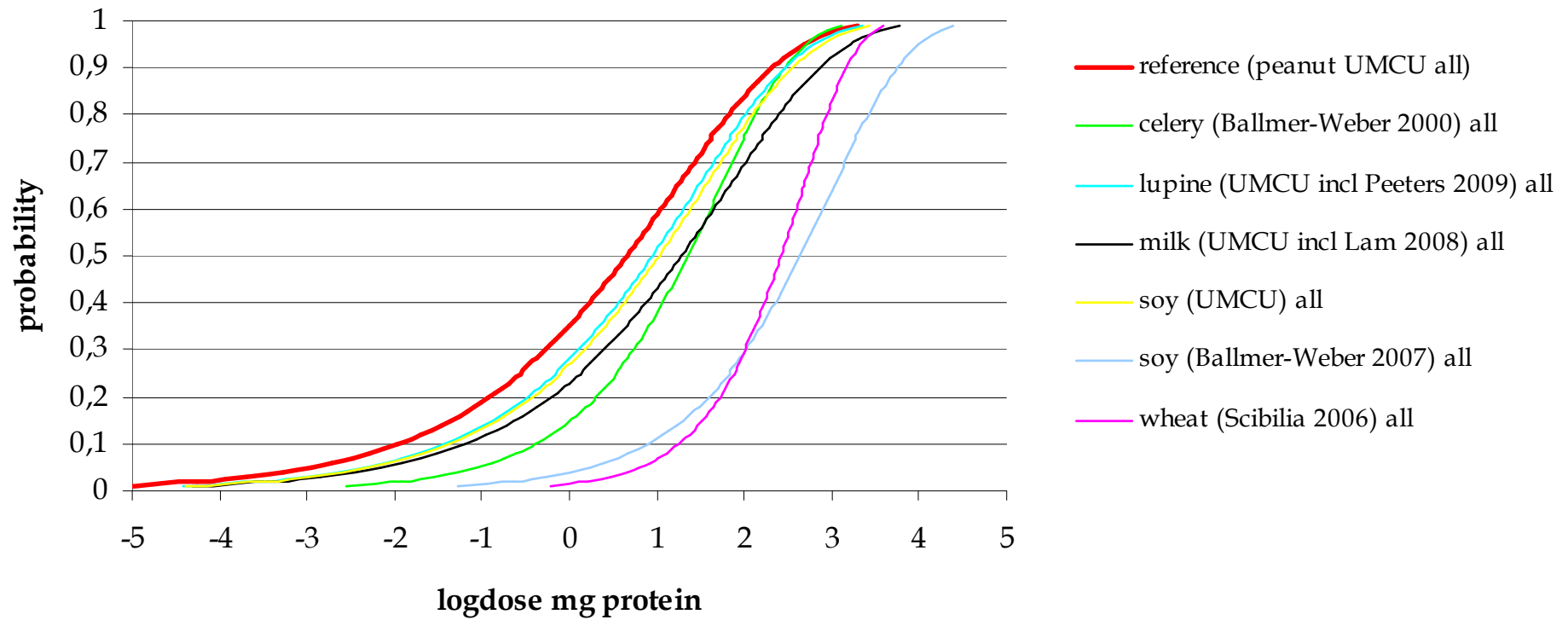
De noten en pinda: kinderen (alle reacties)



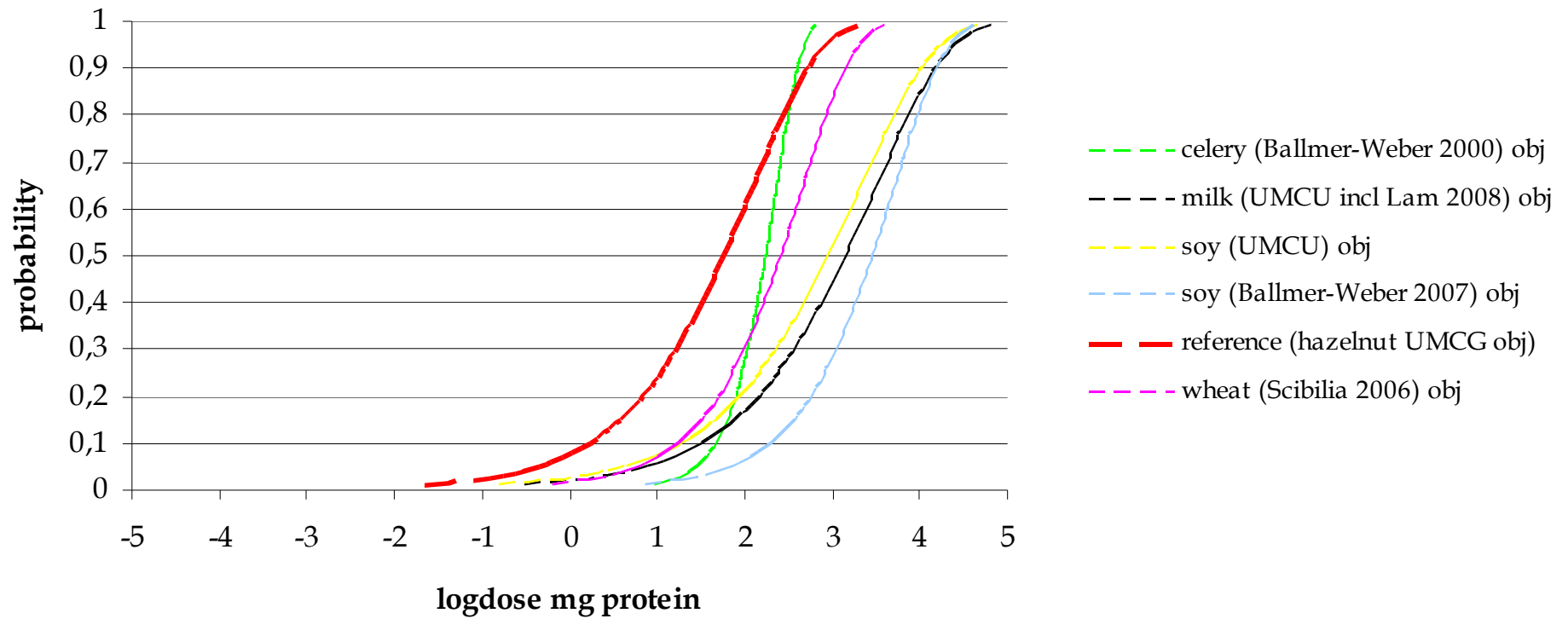
De noten en pinda: kinderen (objectieve reacties)



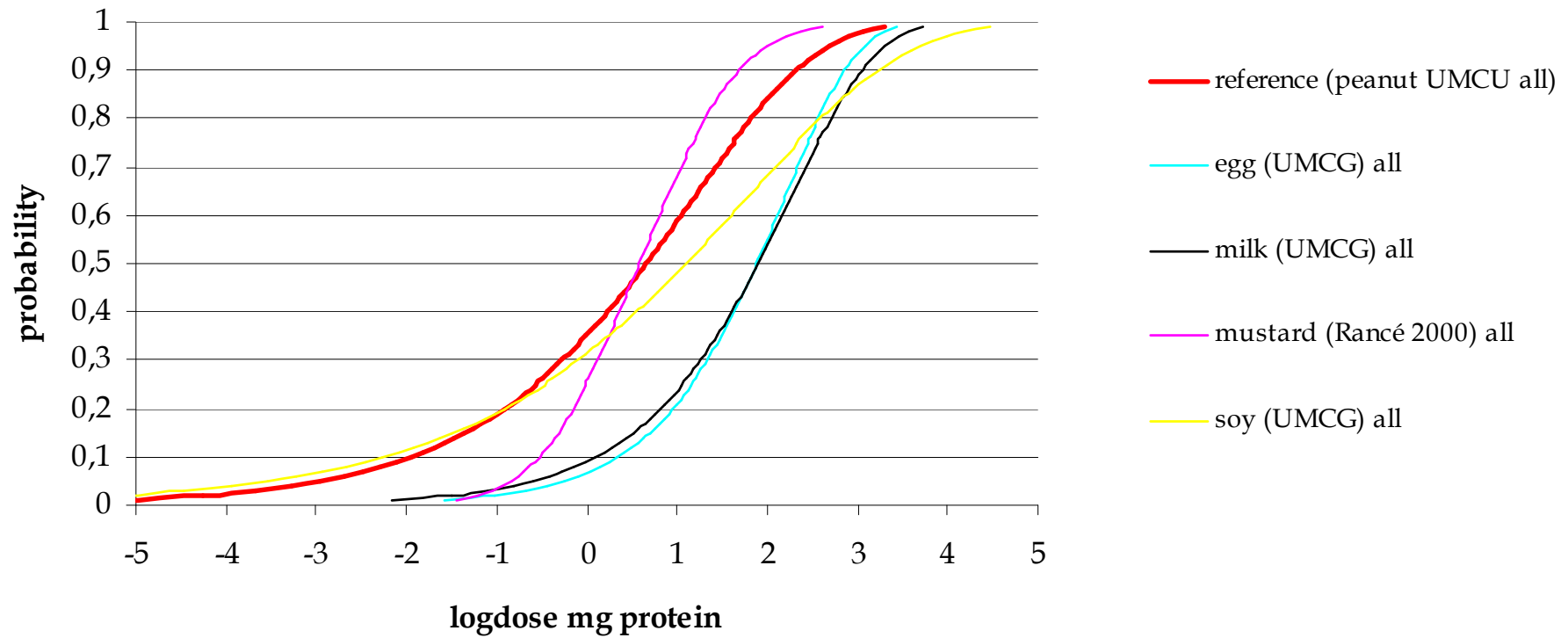
Comparison allergens to worst case distribution (adults, all reactions)



Comparison allergens to worst case distribution (adults, objective reactions)



Comparison allergens to worst case distribution (children, all reactions)



Comparison allergens to worst case distribution (children, objective reactions)

