ED₀₁ vs. ED₀₅ Explained

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5th Food Allergen Management Symposium May 31, 2023





Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens

- Part 1: Review and validation of Codex priority allergen list through risk assessment
- Part 2: Review and establish threshold levels in foods of the priority allergens
- Part 3: Review and establish precautionary labelling in foods of the priority allergens
- Part 4: Review and establish exemptions for the food allergens



<u>More info on Part 1</u> (full report), virtual meeting, 30 November – 11 December 2020, 28 January 2021, 8 February 2021 <u>More info on Part 2</u> (summary and conclusions), virtual meeting, 15 March – 2 April 2021 <u>More info on Part 3</u> (summary and conclusions) <u>More info on Part 4</u> – Recently completed (November 2022)







RISK ASSESSMENT OF FOOD ALLERGENS PART 1: REVIEW AND VALIDATION OF CODEX ALIMENTARIUS PRIORITY ALLERGEN LIST THROUGH RISK ASSESSMENT

Criteria for Assessing Priority Allergen Status





https://www.fao.org/documents/card/en/c/cb9070en

Summary: <u>https://www.who.int/news-room/events/detail/2020/11/30/default-calendar/ad-hoc-joint-fao-who-expert-</u>consultation-on-risk-assessment-of-food-allergens-part1



Potency





Potency: Data Sources

- The Expert Committee noted that the data reported in the publications of Remington, et al., (2020) and Houben, et al., (2020) were the most comprehensive and best described source available, both in terms of content and curation, with supportive peer-reviewed publications.
- Dose-distribution analysis methodology was similarly well-described within this dataset.
- The Committee reviewed the data sources for each priority allergen, taking into consideration both included publications and those which had been collated but excluded, and the extent and type of bias in the data.





Potency: Objective Symptoms

TABLE 8 MOST COMMON SIGNS AND SYMPTOMS OF ALLERGIC REACTIONS TO FOOD, AS REPORTED IN PUBLICATIONS AND UNPUBLISHED CLINICAL DATA

SUBJECTIVE SYMPTOMS	OBJECTIVE SYMPTOMS
Oral cavity	
Pruritus (itching) and paresthesia (tingling sensation) of the oral cavity, pharynx and/or lips (so called oral allergy symptoms [OAS])	 > Lip swelling > Redness/swelling of the oral mucosa > Blisters of the oral mucosa
Skin	
> Pruritus (itching)	> Urticaria > Angioedema > Flush > Erythema (Redness)
Eyes and Nose	
> Pruritus (itching)	 Red eye/conjunctival hyperemia Tearing Sneezing Rhinorrhea
Gastrointestinal	
 > Dysphagia > Abdominal/gastric pain* > Cramps > Nausea > Bloating 	> Diarrhea > Vomiting**
Neurological	
 Headache Dizziness Anxiety Tension/agitation 	> Seizures

SUBJECTIVE SYMPTOMS	OBJECTIVE SYMPTOMS
Respiratory	
 > Laryngeal/throat tightness > Thoracic/chest tightness > Dyspnea/shortness of breath 	 > Laryngeal edema > Dysphonia > Wheezing > Reduced peak expiratory flow/drop in FEV1 > Silence (in lung auscultation) > Breathless to speak > Rapid breath > Chest retractions > Cough
Cardiovascular	
> Faintness > Tiredness	 Change in heart rate/tachycardia Hypotension/drop of blood pressure Change in consciousness
Other	
> Uterine cramps/contractions	

*Abdominal pain and gastric pain are considered objective symptoms provided they are observed in children less than three years old.

**Vomiting is not considered an objective symptom in children less than one year of age unless the clinician stops the challenge because of vomiting. If vomiting occurs at the final dose of the challenge, it is not considered an objective symptom in children less than one year old, unless additional objective symptoms are present.

Source: Adapted from Westerhout et al., 2019





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Potency: Classification Output

FIGURE 4. EDP CURVES FROM THE MODEL AVERAGED POPULATION THRESHOLD DOSE DISTRIBUTIONS FOR 14 PRIORITY ALLERGENIC FOODS, BASED ON DISCRETE (UPPER GRAPHS) AND CUMULATIVE (LOWER GRAPHS) DOSE DATASETS. DOSES ARE EXPRESSED IN MG TOTAL PROTEIN FROM THE ALLERGENIC FOOD



Medium Egg Peanut Medium Medium HazeInuts Cashew nuts Medium Low (shrimp); N/A for others in group Crustacean Medium Wheat - IgE Fish Medium Medium Walnuts Medium Sesame Pistachio N/A (cross with cashew) N/A (cross with walnut) Pecan nuts High Mustard Medium/Low Soybean Medium Lupin N/A Brazil nut N/A Almond N/A Other cereals N/A Kiwi N/A Pine nuts N/A Molluscan shellfish N/A Coconut N/A Chestnuts Celery Medium N/A Macadamia

N/A

Medium

POTENCY



Virtual meeting, 30 November – 11 December 2020, 28 January 2021, 8 February 2021, More info on Part 1 (full report)



TABLE 9 THE OUTCOME FROM THE SUBGROUP OF THE EXPERT COMMITTEE FOR POTENCY

ALLERGEN

Milk

Buckwheat

Severity





Severity: Classification Criteria

- The working group considered the outputs from the systematic review undertaken and then categorized allergens into the following groups
- Group A
 - Allergens which cause at least 5–10 percent of anaphylaxis reactions in three or more Codex regions
- Group B
 - Allergens which are considered to cause at least 5–10 percent of anaphylaxis reactions in only one or two Codex regions
- Group C
 - (i) Allergens which cause a lower proportion of anaphylaxis reactions in all regions OR
 - (ii) Allergens which cause at least 5–10 percent of anaphylaxis reactions in only one CODEX region, but a lower proportion of anaphylaxis reactions elsewhere







Definitions of Anaphylaxis Vary

Cardona et al. World Allergy Organization Journal (2020) 13:100472 http://doi.org/10.1016/j.waojou.2020.100472



POSITION PAPER

World allergy organization anaphylaxis guidance 2020

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(Not anaphylaxis)		ANAPHYLAXIS							
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5					
Symptom(s)/sign(s) from 1 organ system present	Symptom(s)/ sign(s) from ≥2 organ	Lower airway	Lower airway	Lower or upper airway					
Cutaneous		Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment	Severe bronchospasm eg, not responding or worsening in spite of treatment	Respiratory failure and/or					
Urticaria and/or erythema-warmth and/ or pruritus, other than localized at the injection site		And/or	And/or	Cardiovascular					
And/or		Gastrointestinal	Upper airway	Collapse/ hypotension					
Tingling, or itching of the lips ^a or Angioedema (not laryngeal)*		Abdominal cramps* and/or vomiting/ diarrhea	Laryngeal edema with stridor	And/or					
Or Upper respiratory		Other	Any symptom(s)/ sign(s) from grades 1 or 3 would be included	Loss of consciousness (vasovagal excluded)					
Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)		Uterine cramps		Any symptom(s)/ sign(s) from grades 1, 3, or 4 would be included					
And/or		Any symptom(s)/ sign(s) from grade 1 would be included							
Throat-clearing (itchy throat) ^a									
And/or									
Cough not related to bronchospasm									
Or Conjunctival									
Erythema, pruritus, or tearing									
Or Other									
Nausea									
Metallic taste									



FIGURE 2. HIERARCHY OF RISKS FACED BY PEOPLE SUSCEPTIBLE TO IgE-MEDIATED FOOD ALLERGY



Source: Reproduced with permission from Dubois *et al.*, 2018. **Dubois**, **A.E.J.**, **Turner**, **P.J.**, **Hourihane**, **J.**, **Ballmer-Weber**, **B.**, **Beyer**, **K.**, **Chan**, **C.-H.**, **Gowland**, **M.H.** *et al.* 2018. How does dose impact on the severity of food-induced allergic reactions, and can this improve risk assessment for allergenic foods?: Report from an ILSI Europe Food Allergy Task Force Expert Group and Workshop. *Allergy*, 73(7): 1383–1392. https://doi.org/10.1111/all.13405



Virtual meeting, 15 March – 2 April 2021, More info on Part 2 (full report)

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Severity: Heat Map

Severity: Classification Criteria

- Initial assignment was based on Table 10, but then included a consideration of the quality of other evidence relating to food allergy severity endpoints and a consensus decision was reached. An assessment of the evidence justifying the above categorization was also made for each allergen:
- Level 1
 - High level of confidence by the working group in the estimate of the proportion of anaphylaxis reactions due to a given food allergen (and thus further data is unlikely to substantially change confidence in this estimate).
- Level 2
 - Lower confidence that the available data indicates that a given allergen causes at least 5–10 percent of anaphylaxis reactions, and thus other evidence relating to fatal food anaphylaxis, allergen cross-reactivity and/or expert judgement required."

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	PEANUT	TREE NUTS	SESAME	WHEAT	HEN'S EGG	COW'S MILK	CELERY	CRUSTACEA	MOLLUSCA	FISH	SOYBEAN	LUPINE	OTHER LEGUMES	FRUIT	BUCKWHEAT
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AFRICA															
Логоссо	×.	~	 Image: A start of the start of	1	1	 Image: A start of the start of	~	 Image: A set of the set of the	 Image: A start of the start of	 Image: A set of the set of the	~	~			
South Africa	1	1		~	1	1		~	~	×	~				
ISIA															
China	~	×		1	~	~		×		×	~				
China, Hong Kong Special Administrative Region	×	×		×	×	~		1		× .	~				
apan	~	(🗸)		1	1	1		×		(🗸)	(🗸)			(~)	~
Republic of Korea	×	$\langle \checkmark \rangle$						1	(🗸)		>				1
Pakistan															
Philippines	1	~		1	~	×				× .	>				
Singapore	×	×		×	 Image: A second s	~				×	~				
Sri Lanka															
hailand	~	~		×	~	~		×		× .	~				
UROPE															
EU Member States	1	1	~		1	1	1		×		×	~			
srael															
Russian Federation															
Switzerland	1		~	~	×	~	1	~	~	~	1	~			
ūrkey	1		~	~	1		~	~	~	~	~	~			
Inited Kingdom of Great Britain and Northern Ireland	1		×	~	× .	1	~	× .	× .	× .	>	~			
ATIN AMERICA/CARIBBEAN (LAC)															
Argentina	×	×		×							×				
Brazil	× .	× .		~							~				
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ran (Islamic Republic of)															
Qatar	×		8	>		8		× .		1	>	>			
Saudi Arabia	1		1	>	× .	× .		× .		× .	>	>			
unisia															
IORTH AMERICA/SW PACIFIC (NASWP)															
Australia	1		×	×	×.	1		1	\checkmark	1	×	×			
Canada	1		× .	×	×	×.		×	~	×	×				
New Zealand	1		×	×	×.	1		×.	×	×.	×	1			
Inited States of America	× .		(🗸)	× .	× .	× .				1	× .				

イ' indicates local legislation requiring disclosure for that allergen; (イ) indicates more limited or voluntary disclosure recommended. Heat map olours indicate relative (rather than absolute) prevalence of that allergen (group) as a common cause of food anaphylaxis in that region/country/area.



RISK ASSESSMENT OF FOOD ALLERGENS PART 2: REVIEW AND ESTABLISH THRESHOLD LEVELS IN FOODS FOR THE PRIORITY ALLERGENS

Full report of the Ad hoc Joint FAO/WHO Expert **Consultation on Risk Assessment of Food Allergens.**

Part 2: Review and establish threshold levels in foods of the priority allergens









Full report of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens.

Part 2: Review and establish threshold levels in foods of the priority allergens

 Safety objective "to minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses (MEDs) and supported by data regarding severity of symptoms in the likely range of envisioned Reference Doses (RfD)".





Food and Agriculture Organization of the United Nations World Health

Severity Assessment

- Assessment of severity is a critical component of hazard characterization, but the relationship of severity to exposure is complex and depends on many factors other than the amount of allergen (Dubois *et al.*, 2018).
 - Data are currently insufficient and inadequate to describe it mathematically, but clinical and epidemiological observations can provide relevant supporting data in relation to the amounts of allergen protein involved.
 - The expert committee agreed that considerations for reproducibility of thresholds (day-to-day variations in individual thresholds), cofactors, matrix effects, and data confounders should also be considered. Additionally, data on anaphylaxis in controlled challenge studies could be used.
- Based on an understanding that anaphylactic reactions according to accepted definitions (Cardona *et al.*, 2020; WAO) span a wide spectrum of severity/risk to
 Iife and include mild/non-severe reactions.



Supporting information for hazard characterization: Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens

 Using data from food challenges to inform management of food-allergic consumers: a systematic review with individual participant data meta-analysis

Ananhylaxis at < 5mg eliciting dose

Taylor et al (2010)	1	22	+			4.55	[0.12; 22.84]
Blom et al (2013)	0	8				0.00	[0.00; 36.94]
Van Erp et al (2013)	2	8			•	25.00	[3.19; 65.09]
STOP-II (2014)	0	12	*			0.00	[0.00; 26.46]
EuroPrevall (2015)	0	3				0.00	[0.00; 70.76]
Klemens et al (2015)	1	6				16.67	[0.42; 64.12]
Kukkonen et al (2015)	1	9				11.11	10.28; 48.251
FAHF-2 (2015)	3	13				23.08	[5.04; 53.81]
VIPES (2017)	3	20				15.00	[3.21; 37.89]
TAKE-AWAY (2017)	1	19				5.26	[0.13; 26.03]
Purington et al (2018)	0	57	-			0.00	[0.00; 8.27]
PALISADE (2018)	0	66	-			0.00	10.00; 5.441
PEPITES (2019)	4	23				17.39	[4.95; 38.78]
TRACE (2019)	1	4	-			25.00	[0.63; 80.59]
BOPI (2019)	0	4		· · ·		0.00	10.00: 60.241
POISED (2019)	0	12		2		0.00	[0.00; 26.46]
ARTEMIS (2020)	1	38				2.63	[0.07: 13.81]
UMC-Groningen (2020)	a	12		-		0.00	10.00: 26.461
						4.47	[1.92: 10.07]
Heterogeneity: 12 = 57%, 72 = 1.3277, p = 0.97		336	-				
Heterogeneity: $l^2 = 57\%, \tau^2 = 1.3277, p = 0.97$	Pe	336 ircenta	0 10 20 pe of participents experience	30 40 ng anaphylaxis a	"] 50 t≤ 5mg elic	ating dose	
Heterogeneily: $l^2 = 57\%$, $\tau^2 = 1.3277$, $p = 0.97$	Pe	336 ircenta	0 10 20 pe of participants experience Anaphylaxis at < 1r	30 40 ng anaphylaxis a mg eliciting	⊐ 50 t≤5mg elk dose	ating dose	
Heterogeneily: $l^2 = 57\%, \tau^2 = 1.3277, p = 0.97$ Study	Pr	336 ercenta	0 10 20 pr of participants experience Anaphylaxis at < 1r	30 40 1g anaphytaxis a ng eliciting	⊐ 50 t≤5mg elic dose	ting does	95% CI
Heterogeneity: $l^2 = 57\%, \tau^2 = 1.3277, p = 0.97$ Study	Pe n 0	336 roenta N 6	0 10 20 a of participants experience Anaphylaxis at < 1r	30 40 ng anaphytaos a ng eliciting	⊓ 50 ts5mg eik dose	ting dose % patients 0.00	95% Ci [0.00; 45.83]
Heterogeneity: $l^2 = 57\%, r^2 = 1.3277, \rho = 0.97$ Study Taylor et al (2010) Van Ee ort al (2013)	Pe n 0	336 ercenta N 6 1	0 10 20 er of participants experience Anaphylaxis at ≤ 1r	30 40 ng anaphylaos a ng eliciting	⊓ 50 ts5mg elk dose	ting dose % patients 0.00 0.00	95% Cl [0.00; 45.83] [0.00; 97.50]
Heterogeneity: $l^2 = 57\%$, $z^2 = 1.3277$, $\rho = 0.97$ Study Taylor et al (2010) Van Exp et al (2010) Van Exp (2015)	Pr n 0 0 0	336 roenta N 6 1 3	o 10 20 pa of participants expenses	30 40 ng anaphylaxis a ng eliciting	⊐ 50 t⊴ 5mg elk dose	ting does % patients 0.00 0.00 0.00	95% Cl [0.00; 45.83] [0.00; 97.50] [0.00; 70.76]
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Heterogeneity: <i>I²</i> = 57%, <i>z²</i> = 1.3277, <i>p</i> = 0.97 Study Taylor et al (2010) Van Epe et al (2010) Kenmens et al (2015) Kenmens et al (2015) Kenmens et al (2015) FAUFES (2017) FAUFES (2017	n 0 0 0 0 1 0 0 3 1 1 0	336 N 6 1 3 7 2 26 6 3 19 8	Anaphylaxis at < 1r	ng eliciting	⊐ 50 ts5mg wik dose	Constraints Constraints 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 50.00 33.33 5.28 0.00 0.00	95% CI [0.00; 45.63] [0.00; 77.60] [0.00; 77.60] [0.00; 97.60] [0.00; 44.90] [0.00; 44.90] [0.00; 44.90] [0.00; 44.90] [0.84; 90.57] [0.132.205] [0.132.205] [0.00; 56.44]
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Heterogeneity: $l^2 = 57\%$, $z^2 = 1.3277$, $\rho = 0.97$ Study Taylor et al (2010) War Eo et al (2013) EuroPreval (2015) FAV#2 (2015) VFES (2017) PARISDE (2015) PARISDE (2015) PARI	Pa 0 0 0 0 1 0 0 0 3 1 1 0	336 rroantia N 6 1 3 1 3 7 2 26 6 3 19 8 85	Anaphylaxis at <1r	1 1 30 40 g sneptytees a ng eliciting - - - 40 50 6	⊐ 50 tis 5mg wk dose	String does % patients 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 33.33 5.26 0.00 4.18	95%, CI [0.00, 45, 80] [0.00, 77.00] [0.00, 77.00] [0.00, 40, 90, 277.00] [0.00, 44, 90, 277.00] [10.00, 44, 90, 277.00] [11.67, 86, 190] [10.00, 34, 8047] [10.00, 34, 8047]

Patel et al., 2021. https://doi.org/10.1016/j.jaci.2021.01.025



Source: Reproduced with permission from Turner et al., 2022a.

Note: EDo1, the eliciting dose predicted to provoke reactions in 1% of the allergic population; ED05, the eliciting dose predicted to provoke reactions in 5% of the allergic population. **Turner**, **P.J.**, **Patel**, **N.**, **Ballmer-Weber**, **B.K.**, **Baumert**, **J.L.**, **Blom**, **W.M.**, **Brooke-Taylor**, **S.**, **Brough**, **H.** *et al.* 2022a. Peanut can be used as a reference allergen for hazard characterization in food allergen risk management: a rapid evidence assessment and meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice*, 10(1): 59–70. https:// doi.org/10.1016/j.jaip.2021.08.008

Turner et al., 2021. https://doi.org/10.1016/j.jaip.2021.08.008





PROPORTION OF PEANUT-ALLERGIC INDIVIDUALS EXPECTED TO HAVE SUBJECTIVE OR

OBJECTIVE SYMPTOMS FOLLOWING EXPOSURE TO AN EDOS OR EDO1 AMOUNT OF PEANUT.

Source: Adapted with permission from Turner et al., 2022a.

Note: OAS = oral allergy symptoms.

Note: EDo:, the eliciting dose predicted to provoke reactions in 1% of the allergic population; EDO5, the eliciting dose predicted to provoke reactions in 5% of the allergic population. Turner, P.J., Patel, N., Ballmer-Weber, B.K., Baumert, J.L., Blom, W.M., Brooke-Taylor, S., Brough, H. et al. 2022a. Peanut can be used as a reference allergen for hazard characterization in food allergen risk management: a rapid evidence assessment and meta-analysis. The Journal of Allergy and Clinical Immunology: In Practice, 10(1): 59–70. https://doi.org/10.1016/j.jaip.2021.08.008 FIGURE 5. PROPORTION OF PEANUT-ALLERGIC INDIVIDUALS WHO WOULD BE EXPECTED TO HAVE Objective symptoms (including anaphylaxis) following exposure to ≤5 mg or ≤1 mg amount of peanut, and an indication of reproducibility, i.e. proportion of individuals who do not experience objective symptoms on one occasion who might react on a second subsequent exposure



Source: Adapted with permission from Patel *et al.*, 2021a. Patel, N., Adelman, D.C., Anagnostou, K., Baumert, J.L., Blom, W.M., Campbell, D.E., Chinthrajah, R.S. *et al.* 2021a. Using data from food challenges to inform management of consumers with food allergy: a systematic review with individual participant data meta-analysis. *Journal of Allergy and Clinical Immunology*, 147(6): 2249–2262.e7. https://doi. org/10.1016/j.jaci.2021.01.025



FIGURE 4.

TABLE 10 SUMMARY TABLE FOR THE RATE OF ANAPHYLAXIS TO ED05 LEVELS OF EXPOSURE IN ALLERGIC INDIVIDUALS. IT SHOULD BE NOTED THAT THE UPPER LIMIT OF THE 95 PERCENT CI FOR THE CUMULATIVE ED05 FOR SESAME SEED IS NOW ESTIMATED TO BE LESS THAN 58 MG SESAME SEED PROTEIN. AS SUCH, THE RESULTS FOR SESAME SEED IN THIS TABLE ARE CONSIDERED CONSERVATIVE

ALLERCEN	EVIDENCE BASE (number of FC	UPPER LIMIT OF The 95% CI	EXPECTI OF SYMPTOM OF ALLERGEI ≤ UPPER 9 THE CU	ED RATE S TO A LEVEL N EXPOSURE 5% CI FOR IM ED05	EXPECTED RATE OF ANAPHYLAXIS TO AN ALLERGEN EXPOSURE ≤ UPPER 95% CI FOR THE CUM ED₀5, AS A PROPORTION OF			
ALLERGEN	included in dataset)	FOR CUM ED05 (mg protein)	Any symptoms	Objective symptoms	Individuals reacting to EDos exposure with objective symptoms	All individuals allergic to this food		
PEANUT	3 151 DBPCFC	7.1 mg	35–45%	8%	4.5% (95%CI: 1.9% to 10%)	2.3 per 1 000 (95%Cl: 1.0 to 5.1 per 1000)		
CASHEW	323 DBPCFC 421 Open FC	9.4 mg	32%	12%	4.9% (95%Cl: 2.2% to 10.5%)	2.5 per 1 000 (95%Cl: 1.1 to 5.3 per 1000)		
HAZELNUT	391 DBPCFC 43 Open FC	15.7 mg	~75%	9%	2.5% (95%Cl: 0.3% to 15.8%)	1.2 per 1 000 (95%Cl: 0.2 to 7.9 per 1000)		
WALNUT	194 DBPCFC 156 Open FC	13.0 mg	~60%	14%	5.3% (95%Cl: 2.0% to 13%)	2.7 per 1 000 (95%Cl: 1.0 to 6.7 per 1000)		
SESAME	59 DBPCFC 214 Open FC	58 mg	Not reported	20%	3.0% (95%Cl: 0.8% to 11%)	1.5 per 1 000 (95%Cl: 0.4 to 5.7 per 1000)		
COW'S MILK	728 DBPCFC 317 other FC	6.6 mg	20%	9%	4.9% (95%Cl: 2.1% to 11%)	2.5 per 1 000 (95%Cl: 1.1 to 5.5 per 1000)		
EGG	637 DBPCFC 543 other FC	5.3 mg	14%	9%	1.5% (95%Cl: 0.02% to 55%)	0.8 per 1 000 (95%Cl: 0 to 27 per 1000)		
WHEAT	123 DBPCFC 23 Open FC	25 mg	Not reported	11%	2.2% (95%Cl: 0.02% to 75%)	1.1 per 1 000 (95%Cl: 0 to 38 per 1000)		
FISH	59 DBPCFC	102 mg	58%	25%				
SHRIMP	12 DBPCFC 46 Open FC	1 850 mg	57%	19%	Insufficient data	for meta-analysis		
SOYA	89 DBPCFC 51 Open FC	76 mg	Not reported	Not reported	0% (95%Cl: 0% to 16.8%)	0 per 1 000 (95%CI: 0 to 8.4 per 1000)		

Source: Reproduced with permission from Turner *et al.* (2022a). Turner, P.J., Patel, N., Ballmer-Weber, B.K., Baumert, J.L., Blom, W.M., Brooke- Taylor, S., Brough, H. *et al.* 2022a. Peanut can be used as a reference allergen for hazard characterization in food allergen risk management: a rapid evidence assessment and meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice*, 10(1): 59–70. https://doi.org/10.1016/j.jajp.2021.08.008









18

Full report of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens.

Part 2: Review and establish threshold levels in foods of the priority allergens

- The latter indicated that all symptoms up to ED05 fell into a mild or moderate category,
- Analysis of clinical data indicated that up to 5% of reactions at both ED01 and ED05 could be classed as anaphylaxis, although none were severe, based on the World Allergy Organization definition.
- Furthermore, the Committee noted the extreme rarity of fatal food anaphylaxis (1 per 100,000 person-years in the allergic population) and observed that no fatal reactions had been observed following exposure to doses at or below those considered for RfD (i.e. the ED01 and the ED05).





SCIENTIFIC RATIONALE FOR RfD

- The RfD meet the criterion of "exposure without appreciable health risk"
 - This was defined as a probability of objective symptoms of <5 percent in the population of individuals with a relevant IgE-mediated food allergy when ingesting a dose not exceeding the RfD;
 - In those who do develop objective symptoms to a dose not exceeding the RfD, a probability of non-severe anaphylaxis (according to the World Allergy Organization definition) of <5 percent;
 - a risk of severe anaphylaxis (according to the World Allergy Organization definition) of <1:100
 000 person years in the population of individuals with a relevant IgE-mediated food allergy; and
 - a risk of fatal reaction of <1 per million in the population of individuals with a relevant IgEmediated food allergy when ingesting a dose not exceeding the RfD.
 - Note: No severe or fatal anaphylaxis events have been reported following exposure to a dose not exceeding the RfD.
- When non-severe anaphylaxis was observed in clinical studies, at least 80 percent resolve without any treatment, and >98 percent of the remainder respond to first line treatment (epinephrine/adrenaline).





TABLE 17 CONSENSUS REFERENCE DOSE (RfD) RECOMMENDATIONS FOR CODEX PRIORITY ALLERGENS

	RFD RECOMMENDATION (mg total protein from the allergen c source)
WALNUT (AND PECAN*)	1.0
CASHEW (AND PISTACHIO*)	1.0
ALMOND**	1.0
MILK	2.0
PEANUT	2.0
EGG	2.0
SESAME	2.0
HAZELNUT	3.0
WHEAT	5.0
FISH	5.0
CRUSTACEA	200









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Translating Reference Doses into Action Levels



Method performance criteria indicate that the limits of quantification (LoQ) of any method utilized for a specific food should be approximately 3-fold lower than the action level for that food in order to account for real-world performance variability and to assure that the analytical result is truly at or below the action level.





TABLE 13 LIMITS OF QUANTIFICATION (LoQ) REQUIRED FOR ANALYTICAL METHODS TO MEET CALCULATED ALS (TABLES 11 AND 12), TAKING INTO ACCOUNT METHOD PERFORMANCE

RfD in mg	CRUSTACEA	FISH	WHEAT	HAZELNUT	SESAME	MILK	EGG	PEANUT	CASHEW	WALNUT
RFA in g	200	5	5	3	2	2	2	2	1	1
10	<mark>6 666</mark>	166	166	100	66	66	66	66	33	33
20	3 333	83	83	50	33	33	33	33	16	16
30	2 166	50	50	33	21	21	21	21	10	10
40	1 666	33	33	25	16	16	16	16	8.3	8.3
50	1 333	33	33	20	13	13	13	13	6.6	6.6
60	1 000	26	26	16	10	10	10	10	5	5
70	833	23	23	13	8.3	8.3	8.3	8.3	3.3	3.3
80	833	20	20	11	8.3	8.3	8.3	8.3	3.3	3.3
90	666	18	18	10	6.6	6.6	6.6	6.6	3.3	3.3
100	666	16	16	10	6.6	6.6	6.6	6.6	3.3	3.3

ppm action levels based on RfD of the ED05

RfD in mg	Crustacea	Fish	Wheat	Hazelnut	Sesame	Milk	Egg	Peanut	Cashew	Walnut
RFA in grams	25	1.3	0.7	0.1	0.2	0.2	0.2	0.2	0.05	0.03
10	833	43	23	3	7	7	7	7	2	1.0
20	417	22	12	2	3	3	3	3	0.8	0.5
30	278	14	8	1.1	2	2	2	2	0.6	0.3
40	208	11	6	0.8	2	2	2	2	0.4	0.3
50	167	9	5	0.7	1.3	1.3	1.3	1.3	0.3	0.2
60	139	7	4	0.6	1.1	1.1	1.1	1.1	0.3	0.2
70	119	6	3	0.5	1.0	1.0	1.0	1.0	0.2	0.1
90	93	5	3	0.4	0.7	0.7	0.7	0.7	0.2	0.1
100	83	4	2	0.3	0.7	0.7	0.7	0.7	0.2	0.1

ppm action levels based on RfD of the ED01

*NOTE: concentrations denoted in units of ppm (mg/kg) of total protein from the allergenic source



Thank You For Your Attention

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