Netherlands Food and Consumer
Product Safety Authority
Ministry of Economic Affairs

> PO Box 43006, 3540 AA Utrecht, The Netherlands

To the Minister of Health, Welfare and Sport
To the Minister for Agriculture
To the Inspector-General of the Netherlands Food and Consumer Product Safety Authority

Advisory report from the director of the Office for Risk Assessment and Research

Office for Risk Assessment and Research
Catharijnesingel 59
3511 GG Utrecht
PO Box 43006
3540 AA Utrecht
The Netherlands
www.nvwa.nl

Contact
T +31 (0)88 223 33 33
risicobeoordeling@vwa.nl

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Advice on preliminary reference doses for food allergens

Background

In 2007, the Health Council of the Netherlands (Gezondheidsraad) issued an advisory report on food allergies to the Minister of Health, Welfare and Sport (VWS). The Health Council considered food allergies a major problem for a limited group of people. A potentially life-threatening form of food allergy affects an estimated 4,000-6,000 Dutch people, including 1,000-1,500 children (Gezondheidsraad 2007). The Health Council concluded that avoiding the consumption of allergens is crucial and that correct product information is needed (Gezondheidsraad 2007).

With the exception of Switzerland and Japan, no population threshold values have been set for allergenic foods. However, there is legislation on the mandatory labelling of fourteen allergenic substances or foods that cause allergies or intolerances (Regulation (EU) No 1169/2011). In some cases, the presence of an allergen is not specified on the label. This may be because of an omission of an ingredient on the list or an unintentional blending of allergens during, for example, the production process. Until now, the Netherlands Food and Consumer Product Safety Authority's (NVWA) enforcement policy for the unintended contamination of allergens was based on zero risk: if unlabelled allergenic substances are present in a food, it is regarded as unsafe for allergic consumers.

In Australia and New Zealand, the Allergen Bureau, a collaborative initiative of industrial members, has developed a labelling system: the Voluntary Incidental Trace Allergen Labelling (VITAL) system. The Allergen Bureau has established a VITAL Scientific Expert Panel (VSEP) for scientific substantiation. Data are gathered in a database by researchers of the Netherlands Organisation for Applied Scientific Research (TNO) and the Food Allergy Research & Resource Program (FARRP) of the University of Nebraska. The system supports the food industry by establishing a policy for labelling foods to (precautionary) warn for the presence of allergens.

Research questions

As a result of the above situation, the Office for Risk Assessment and Research (BuRO) examined the following questions.

1. Is applying a zero-risk principle to allergens in food justified or can this be relaxed?
2. Can the VITAL system be applied for enforcing of foods that contain allergens or traces of allergen?

Research project
BuRO did not have access to the research data from which the VITAL reference doses are derived. The VSEP did not provide any additional statistical calculations, such as confidence intervals or goodness-of-fit analyses of the models used. BuRO therefore had to rely on published data in the literature.

Research results
- There are various analysis techniques for allergens. The results of the various analysis kits are not comparable because, with the exception of peanut, no reference material is available.
- People who are allergic to a certain food may have an allergic reaction to very small quantities of an allergen; 2-3% of infants, 1-3% of older children and 1-2% of adults have an IgE-mediated food allergy. Of all food allergies, peanut is the most frequent cause of serious allergic reactions.
- There are no guidelines for establishing the risks of foods with traces of unlabelled allergens.
- There is a chance of excessive use of precautionary allergen labelling ('may contain labelling').
- The VITAL system assumes that a food is safe for the allergic consumer if it is below a specific reference dose of an allergen. Reference doses are determined on the basis of thresholds. A 1% residual risk is applied in most cases. This means that 1% of the allergic population may have an allergic reaction (the eliciting dose, ED_{01}). Because of the low concentrations of the allergen, these reactions will probably be mild. The thresholds are scientifically derived from data on the NOAELs and LOAELs of clinical provocations of allergic people. Values for ED_{01} have been determined for peanut, milk, egg and hazelnut. Due to the limited amount of data, the lower limit of the 95% confidence interval of the ED_{05} has been determined for soybean, wheat, cashew, mustard, lupin, sesame seed and shrimp.
- Application of the VITAL system, i.e. the ED_{01} and ED_{05} values, means that 2-3% of the allergic population could possibly run the chance of a mild reaction.
- The European Food Safety Authority (EFSA) has published an opinion that describes minimal (observed) eliciting doses (M(O)ED). EFSA has not derived reference doses.

Conclusions
- Foods can contain traces of allergens.
- The current 'may contain labelling' leads to an inconsistent means of labelling of (traces of) allergens.
- A small residual risk for very sensitive allergic persons is unavoidable, but these people can protect themselves by injecting epinephrine.
- The approach used to derive VITAL reference doses for use by the industry for the voluntary labelling of unintended allergens in foods, is valid in itself. Although the VITAL database seems suitable to be used, inaccessibility to it means that this cannot be fully assessed at the moment.
- Reference doses were not determined from the threshold values in accordance to EFSA guidelines (EFSA 2009) and did not result in the most conservative values.
- There is no European reference laboratory for food allergens. The establishment of such a laboratory is important with a view to harmonising and standardising allergen detection methods and developing reference material.

Based on these conclusions, the answer to the research questions is as follows.

Re 1. The zero-risk principle with regard to the contamination of food with allergens can be released. The risks of allergens in food can be quantitatively estimated. Accordingly, the policy that food with an

unlabelled allergen in all cases is an unsafe food for allergic consumers can be relaxed.

Re 2. The VITAL database is unique. BuRO was not granted access to the VITAL database and did not receive any information about the analyses or methods used within the VITAL system to determine reference doses. The VITAL Scientific Expert Panel's description of how the reference doses were derived contains some ambiguities.

Advice

To the Minister of VWS

I advise you to:
- revise the zero-risk principle in the current legislation on food that may contain (traces of) allergens;
- take the initiative to achieve equal standards within Europe;
- adapt national legislation if there will be no European regulation in this area;
- take the initiative to provide a database to derive reference doses for allergens. This will also ensure that the emergence of new allergens can be identified in time;
- take the initiative to establish a European reference laboratory for food allergens.

To the Inspector-General of the NVWA

I advise you to:
- use temporary, lower, more conservative reference doses due to the lack of information on how reference doses are derived within the VITAL system. These preliminary reference doses are based on the information of the ED_{01} and ED_{05} values of allergens, as published by VITAL (Remington 2013). These values do not take into account the confidence limit of the value for the ED_{01}, which is recommended by EFSA. However, the ED_{01} is a reasonably strict criterion. If this ED_{01} is not available, the lower limit of the 95% confidence interval of the ED_{05} is an acceptable value;

	Preliminary reference dose, per mg of protein, per meal
Peanut	0.015
Milk	0.016
Egg	0.0043
Hazelnut	0.011
Soy flour	0.078
Wheat	0.14
Cashew	1.4
Mustard	0.022
Lupin	0.83
Sesame seed	0.10
Shrimp	3.7

Notes:
- Reference doses cannot be given for fish and celery.
- The reference doses are often under the detection limit of the methods of analysis.

- evaluate the use of the preliminary reference doses after one year on the basis of a list of all cases reported to the NVWA. Based in this evaluation or the availability of new data, the reference doses can be adapted, if necessary.

Finally, I will send the English translation of this advice to the European Food Safety Authority (EFSA). I will ask EFSA to issue an opinion on reference doses for allergens in foods.

Office for Risk Assessment and Research

Date
2 June 2016

Our reference
NVWA/BuRO/2016/150

Yours sincerely,

Prof. Antoon Opperhuizen, PhD
Director of the Office for Risk Assessment and Research

SUBSTANTIATION

Allergy

A food allergy is a reaction of the human immune system to a food that generally involves immunoglobulin E (IgE). In some people, the immune system is stimulated to produce specific IgE antibodies against proteins (allergens) in food. This type of antibodies can bind to specific mast cell receptors, which are mainly present on mucosal surfaces. After allergen-specific IgE is formed in the sensitisation phase and following renewed contact between the allergen with mast cell-bound allergen-specific IgE, degeneration of these sensitised mast cells may occur, during which substances (including histamine) are released that can induce clinical symptoms. The presence of allergen-specific IgE is thus a strong indicator for allergic hypersensitivity. Allergen-specific IgE can be measured in different ways: *in vivo* by means of the skin test, based on allergen-specific mast cell degranulation in the skin, and *in vitro* with a RAST/CAP test or immunoblots, which show allergen-specific IgE in serum. The direct or indirect basophil histamine release (BHR) test is a combination of these two methods (Zuidmeer and van Ree 2006). The presence of IgE antibodies does not necessarily mean that they will always cause clinical symptoms. Even so, particularly allergens that are resistant to heat and enzymatic digestion can reach the gut intact and lead there to serious health problems.

Prevalence

The systematic review by Nwaru et al. (2014) provides current prevalence estimates in Europe for all age groups. The self-reported, lifelong prevalence of allergies to cow's milk, egg, wheat, soya, peanut, nuts, fish, and shellfish and crustaceans were 6.0%, 2.5%, 1.5%, 1.5%, 0.4%, 1.3%, 2.2%, and 1.3%, respectively. The prevalence of allergies defined with the help of food provocation tests to cow's milk, egg, wheat, soya, peanut, nuts, fish, and shellfish and crustaceans were 0.6%, 0.2%, 0.1%, 0.3%, 0.2%, 0.5%, 0.1%, and 0.1%, respectively. The prevalences of the objectively[1] determined food allergies were thus up to a factor of ten lower than the subjectively determined prevalences (Nwaru et al. 2014). Some 2-3% of infants, 1-3% of older children and 1-2% of adults has an IgE-mediated food allergy (Gezondheidsraad 2007, RIVM National Compass Public Health). The EuroPrevall consortium estimated that approximately 4-6% of children and 1-3% of adults in Europe are diagnosed with a food allergy (EuroPrevall 2010). Food allergy symptoms in infants mostly disappear within a few years, while food allergies that occur later in life normally remain (Gezondheidsraad 2007). Of all food allergies, peanut is the most frequent cause of very serious allergic reactions (Peeters 2007). More than 120 foods can cause a food allergy. Foods causing the most serious allergies are cow's milk, egg, nuts, peanut, soybean, fish, shellfish and crustaceans, and cereals that contain gluten.

Burden of disease

There are significant costs per capita associated with food-induced allergic reactions (Patel et al. 2011). One way in which to gain insight into the relative health problem of food allergies compared to other chronic and acute illnesses is to calculate the burden of disease in DALYs (Disability-Adjusted Life Years), a quantitative measurement for health loss. The DALY is made up of two components: the years lost through premature death and the years lived with a disease, weighted according to the seriousness of the disease. Based on the prevalence of a clinically-proven peanut allergy of 1% in the Netherlands, this meant that 166,000 persons suffered from a peanut allergy and the burden of

[1] An objective allergic reaction is characterised by at least one symptom observed by a clinician.

disease from peanut allergy was around 12,450 DALYs per year (Janssen and Ezendam 2012). To calculate the prevalence of cow's milk allergy, a prevalence of 2% in children aged 0-3 years and a prevalence of 0.3% in the rest of the population was assumed. Accordingly, the prevalence of cow's milk allergy in the Netherlands in 2013 was estimated at 68,035 persons. By applying a weighing factor of 0,075, the burden of disease is then 5,178 DALYs per year. In this way, for example, 36,600 DALYs can be calculated for asthma and 635 DALYs for *Campylobacter* (Janssen and Ezendam 2013). These estimates of the National Institute of Public Health and the Environment (RIVM) indicate that food allergies constitute a substantial burden of disease.

Legislation

In 1995, FAO identified the following eight food groups as the most common causes of allergy worldwide, of importance for public health: milk, egg, peanut, tree nuts, wheat, soy, fish and shellfish. These allergens are included in legislation. The main criterion for inclusion in the FAO list was the frequency of reported reactions (McClain et al. 2014). Annex II to Regulation (EU) No 1169/2011 lists the substances or foods that cause allergies or intolerances and must be declared on the label, as follows.

1. Cereals containing gluten, namely wheat, rye, barley, oats, spelt and kamut or their hybridised strains, and products thereof (there are some exceptions);
2. Crustaceans and products thereof;
3. Eggs and products thereof;
4. Fish and products thereof (there are some exceptions);
5. Peanuts and products thereof;
6. Soybeans and products thereof (there are some exceptions);
7. Milk and products thereof (including lactose) (there are some exceptions);
8. Nuts, namely: almonds (*Amygdalus communis* L.), hazelnuts (*Corylus avellana*), walnuts (*Juglans regia*), cashews (*Anacardium occidentale*), pecan nuts (C*arya illinoinensis* (Wangenh.) K. Koch), Brazil nuts (*Bertholletia excelsa*), pistachio nuts (*Pistacia vera*), macadamia or Queensland nuts (*Macadamia ternifolia*), and products thereof;
9. Celery and products thereof;
10. Mustard and products thereof;
11. Sesame seeds and products thereof;
12. Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre;
13. Lupin and products thereof;
14. Molluscs and products thereof.

As from 13 December 2014, allergen information must also be available for foods that are not pre-packed. Commission Regulation (EC) No 41/2009 came into effect for gluten-free foods on 1 January 2012. This stipulates that ‘gluten-free’ foods have a gluten content not exceeding 20 mg/kg and ‘very low gluten’ foods have a gluten content not exceeding 100 mg/kg in the food. The term ‘gluten-free’ may be used only for foods intended for normal consumption. The term ‘very low gluten’ is permitted only for diet products.

Analysis techniques for allergens

There are different analysis techniques for allergens (Diaz-Amigo and Popping 2010). After foods are processed, allergens can be denatured, hydrolysed, aggregated or bound to other foods. Assays can detect protein or DNA. There are three common analysis techniques: PCR, ELISA and MS. For most allergens, analytical tests have been developed that can detect allergens in concentrations of less than 10 µg/l. Enzyme-linked immunosorbent assay (ELISA) methods are most commonly used because they are sensitive, specific for detecting allergenic proteins and easy to use. However, commercial kits use different extraction buffers and calibration procedures and the results of the various kits, also because

of the lack of reference materials, are then not comparable. The only certified reference material available is for peanut. Egg powder (NIST RM-8445) and skimmed milk powder (NIST RM-1549) of the National Institute of Standards and Technology (NIST) are suggested as reference materials for egg and milk allergen detection methods (FAVV 2013). DNA methods detect the allergenic food and not the allergenic protein, and are complementary to immunological assays. If ELISA kits (immunological method) are not available or are not specific enough (as for celery, for example), DNA analysis is the preferred method (EFSA 2014).

Cross-contamination

Foods can be contaminated with allergenic food residues at different points in the food chain. Uncertainty about the risks of traces of allergens and unintended cross-contamination for allergic people has led food producers resorting to 'may contain'[2] warnings on food labels as a form of labelling. This is known as 'precautionary allergen labelling' (PAL) (Allen et al. 2014b). PAL or 'may contain labelling' is not a legal requirement but can be an important precautionary measure if the absence of allergens cannot be guaranteed. However, it can also result in foods that contain no allergens at all being labelled with a warning. This unnecessarily limits the food choice of allergic persons and can lead to an increased risk of developing nutrient deficiencies. Conversely, foods that have no warning may contain allergens. The use of PAL is currently regulated in four countries: Switzerland, Japan, Argentina and South Africa. Switzerland was the first country to introduce a threshold value for the use of PAL. It is compulsory in Switzerland to declare allergens in case of concentrations of 1 gram of allergen per kilogram or litre of food. Exceptions apply to sulphite (10 mg/kg or l), cereals containing gluten (10 mg of gliadin/100 g dry weight) and plant oils and fats with fully refined peanut oil (10 g of peanut oil/kg or l of prepared food) (EDI 2014). However, it is predicted that 50% of people who are allergic to peanut will have a reaction at this concentration. These threshold values are not determined on the basis of NOAELs and LOAELs. In Japan, it is compulsory to declare the food allergens wheat, buckwheat, egg, milk and peanuts in case of a value of 10 mg allergenic protein/kg of food (10 ppm) and declaring another twenty potential allergenic substances is recommended. Moreover, in Japan official reference materials must be used when analysing allergens (Allen et al. 2014b). The use of PAL is prohibited in Argentina. PAL is prohibited in South Africa, unless the producer can show the potential presence of an allergen with a documented risk assessment (Allen et al. 2014b).

Eliciting dose

The risk for the allergic consumer who eats food that may contain an allergen because of cross-contamination relates not only to the quantity of the allergen but also to the quantity of the food consumed and how much of the allergen is needed to elicit a response in that individual. This is referred to as the eliciting dose (ED). The dose of the allergen to which an individual reacts depends on a large number of factors, including the nature and quantity of the food that contains the allergen (matrix, preparation, dose, allergen content) and person-specific factors (genetic background, sport, alcohol intake, medication) (EFSA 2014). Individual minimal eliciting dose (MED) concentrations are determined with DBPCFCs[3].

The VITAL system

Although there are large differences in the individual sensitivity of food-allergic persons, a number of initiatives has been taken to establish threshold values. A

[2] Examples of 'may contain labelling' include: This product may contain traces of …; This product is made in a factory where … are also processed.

[3] DBPCFC: double-blind, placebo-controlled food challenge. This test is regarded as the best way (gold standard) to prove a food allergy.

report from 2006 by the Threshold Working Group of the US Food & Drug Administration (FDA 2006) identified four approaches that could be used to establish thresholds:

- analytical methods-based: thresholds are determined by the sensitivity of the analytical method(s) used to verify compliance;
- safety assessment-based: a safe level is calculated using the No Observed Adverse Effect Level (NOAEL) from human challenge studies and an appropriate uncertainty factor applied to account for knowledge gaps;
- risk assessment-based: examines known or potential adverse health effects resulting from human exposure to a hazard; quantifies the levels of risk associated with specific exposures and the degree of uncertainty inherent in the risk estimate;
- statutorily-derived: uses an exemption articulated in an applicable law and extrapolates from that to other potentially similar situations.

The Threshold Working Group concluded that safety assessment is a feasible way to establish threshold values for the main food allergens. LOAELs or NOAELs based on the first objective symptoms must be used and a threshold value must be determined for each allergen. If it is not possible to determine an individual threshold for each allergen, a threshold value must be determined on the basis of the most potent food allergens. An appropriate factor of uncertainty must be applied if a LOAEL is used. The working group further concluded that a quantitative risk assessment will produce the strongest, most transparent scientific analyses to determine threshold values for the main food allergens. The working group regarded the available data in 2006 to be inadequate to comply with all the requirements of this approach. Regardless of the method applied, the working group recommended periodic re-evaluation of the threshold values when new data and instruments become available (FDA 2006).

The Allergen Bureau (ABA) of Australia and New Zealand is a cooperation among industrial members such as Heinz, Kellogg's, Kraft Foods, Nestlé and Aldi. The Allergen Bureau developed the Voluntary Incidental Trace Allergen Labelling (VITAL) system in 2007. The aim of the VITAL system is to limit the use of precautionary labelling through 'action levels'. These action levels are based on the risk assessment principles of the potential exposure dose and lead to a standardised warning on the label. Initially, the so called VITAL grid was established with three action levels: green (low risk, no labelling necessary); yellow (possible risk, precautionary labelling with 'may be present: ...') and red (higher risk, labelling with 'contains ...' required). These initial VITAL action levels were established based on the threshold doses of allergenic food proteins and both subjective and objective reactions. Due to the uncertainty in the estimates, a safety factor of ten was used and the portion size was assumed to be one teaspoon (5 grams). Many green actions levels were set at <2 ppm of protein; exceptions were fish, milk, soy and gluten. In 2010, ABA decided to review the VITAL programme on the basis of new data.

In 2011, a VITAL Scientific Expert Panel (VSEP) was composed to establish the reference doses for allergenic food residues as part of the VITAL programme. Individual NOAELs and LOAELs were obtained from clinical provocations of allergic persons. Statistical parametric dose distribution models (log-normal, log-logistic and Weibull) were applied to the individual NOAELs and LOAELs to determine reference doses for each allergenic food. This approach uses the concept of a population eliciting dose (ED), in which ED_p relates to the dose of an allergen (protein) that is expected to elicit a reaction in p% of the allergenic population. Thus, a dose under which no allergic individual will react is not determined. Data on individual NOAELs and LOAELs were gathered by researchers of the Food Allergy and Research and Resource Program (FARRP) of the University of Nebraska and by TNO in accordance with the criteria set for that purpose

(Remington 2013, Taylor et al. 2009). An important criterion was that results should come from oral provocations with low doses. Previously unpublished data was also obtained from clinics in the Netherlands and Berlin (Germany) and FARRP. The first objective symptoms of an allergic reaction in an individual were used for the LOAEL (in mg total protein of the food); the NOAEL was set at the next dose in the clinical protocol. The true threshold of an individual then lies by definition between the NOAEL and LOAEL. There were sufficient low-dose provocation data for modelling the data and determining EDs. Except for cashew (children only) and shrimp (adults only), the datasets contained individual threshold values for both children and adults (Remington 2013, Taylor et al. 2014).

Based on the narrow upper and lower 95% confidence interval, the VSEP decided that datasets of threshold values with more than 200 data points were suitable for establishing reference doses based on the ED_{01} value. The upper and lower 95% confidence interval were much larger for datasets with 80 or fewer persons (particularly in the area of the curve of the low doses) and therefore, there was less statistical confidence for establishing reference doses based on the ED_{01} value. The VSEP chose in those cases the lower 95% confidence interval of the ED_{05} value. ED_{01} values were determined for peanut, milk, egg and hazelnut and the lower limits of the 95% confidence interval of the ED_{05} for soybean, wheat, cashew, mustard, lupin, sesame seed and shrimp. All statistical models deemed appropriate and relevant were used (log-logistic, log-normal and Weibull) (Taylor et al. 2014). The VSEP derived reference doses for eleven allergenic foods, varying from 0.03 mg for egg protein to 10 mg for shrimp protein. Due to lack of data, reference doses could not be established for fish and celery (Taylor et al. 2014, VITAL Scientific Expert Panel 2011). The data were not significantly influenced by the heterogeneity of the research methodology (Allen et al. 2014a). See Table 1 for the results (Taylor et al. 2014). The log-normal distribution had the best fit for peanut (Taylor et al. 2010a; Taylor et al. 2010b). Based on the Weibull model, the lowest ED values were obtained.

Table 1. Reference doses according to the VITAL Expert Panel for eleven allergenic foods based on parametric modelling of MEDs of food-allergic populations (Taylor et al. 2014)

Table 3
Reference Doses for 11 allergenic foods based parametric modeling of minimal eliciting doses from food-allergic populations.

Allergen	Distribution model		ED01 (mg protein)		95% Lower confidence interval of ED05 (mg protein)		Reference Dose (mg protein)
			Discrete dosing	Cumulative dosing	Discrete dosing	Cumulative dosing	
Peanut	LogLogistic	Children	0.14	0.18			0.2 mg
		Adults	0.21	0.26			
		Pooled	0.1	0.13			
	LogNormal	Children	0.27	0.34			
		Adults	0.57	0.72			
		Pooled	0.22	0.28			
Milk	LogLogistic	Children	0.083	0.14			0.1 mg
		Adults	4.2	4.7			
		Pooled	0.081	0.14			
	LogNormal	Children	0.22	0.35			
		Adults	5.4	5.9			
		Pooled	0.21	0.34			
Egg	LogLogistic	Children	0.13	0.12	0.69	0.66	0.03 mg
	LogNormal	Children	0.21	0.2	0.62	0.62	
	Weibull	Children	0.045	0.03	0.38	0.31	
Hazelnut	LogLogistic	Children	0.15	0.17	0.49	0.55	0.1 mg
		Adults	0.087	0.23	0.51	1.2	
		Pooled	0.11	0.21	0.69	1.3	
	LogNormal	Children	0.15	0.16	0.32	0.35	
		Adults	0.32	0.69	0.92	1.9	
		Pooled	0.25	0.42	0.84	1.4	
	Weibull	Children	0.047	0.053	0.99	0.26	
		Adults	0.011	0.033	0.48	0.36	
		Pooled	0.017	0.038	0.23	0.46	
Soy flour/infant formula	LogLogistic	Pooled			1.0	2.9	1.0 mg
	LogNormal	Pooled			2.3	5.5	
	Weibull	Pooled			0.15	0.5	
Wheat	LogLogistic	Pooled			1.5	1.3	1.0 mg
	LogNormal	Pooled			1.6	1.4	
	Weibull	Pooled			0.44	0.41	
Cashew	LogLogistic	Children			3	3.3	Provisional
	LogNormal	Children			2.6	3	2.0 mg
	Weibull	Children			1.9	2.1	
Mustard	LogLogistic	Pooled			0.09	0.1	0.05 mg
	LogNormal	Pooled			0.11	0.12	
	Weibull	Pooled			0.046	0.052	
Lupin	LogLogistic	Pooled			4.8	4.5	4.0 mg
	LogNormal	Pooled			6.5	6.1	
Sesame seed	LogLogistic	Pooled			0.45	0.56	0.2 mg
	LogNormal	Pooled			0.49	0.61	
	Weibull	Pooled			0.13	0.18	
Shrimp	LogLogistic	Adults			17.6	19.1	10 mg
	LogNormal	Adults			10.4	12.1	
	Weibull	Adults			13.1	13.9	

The ED_{01} of a food protects 99% of the allergic population against an objective reaction to that food. The use of this dose will moreover reduce the chance of serious reactions within the remaining 1% of the allergic population. However, the chance of a serious reaction in this remaining 1% cannot be fully ruled out. Ideally, this 1% of the population would be clinically identified and be given additional advice to manage their allergy (Taylor et al. 2014). The Health Council of the Netherlands believes it is desirable to draw up guidelines on the correct prescription behaviour for the epinephrine auto-injector. The auto-injector must be used by people who could have a life-threatening reaction; antihistamines can be used for mild reactions (Gezondheidsraad 2007).

If fewer than 200 data points were available, the lower 95% confidence interval of the ED_{05} was utilised as the basis for the reference dose. This dose will protect 97-98% of the relevant allergic population. The VSEP noted that some patients could have a lower minimum eliciting dose under certain conditions, such as infections, suboptimal use of medication or strain (Taylor et al. 2014). Taylor et al. (2014) state that a comparable situation exists for hypoallergenic baby food. Based on clinical trials, it can be stated with 95% certainty that 90% of babies with a milk allergy will not react to infant formula (the lower 95% confidence interval of the ED_{10}).

The data of children and adults were combined for nearly all of the allergens examined. Sufficient data were available for peanut and hazelnut to be able to compare ED estimates for children and adults. The ED estimates showed that the group of peanut-allergic children is more sensitive than the group of peanut-allergic adults, but the difference was small. No difference was found between adults and children for hazelnut (Allen et al. 2014a, Crevel et al. 2014, Taylor et al. 2014).

The current VITAL system has two action levels: if a food falls under action level 1 (intake of the allergen per meal is lower than the reference dose that applies to the quantity of the food), no warning is needed and the food can be regarded as safe for the allergic consumer. If the food falls under action level 2 (intake exceeds or is equal to the reference dose), the VITAL warning 'may be present' is used. The VITAL programme has procedures, a VITAL calculator (Excel), decision tree, reporting modules, etc. (Allergen Bureau of Australia and New Zealand). In the summer of 2015, the VITAL calculator was replaced by VITAL Online, a tool to calculate the effects of cross-contamination of ingredients and processes and to compare the results with the VITAL reference doses.

Derived initiatives
EU-VITAL states that it is an adjustment of the VITAL concept so that all requirements of European food legislation are met (EU-VITAL). This is confusing because there is no European legislation on PAL. EU-VITAL uses three action levels (in mg of allergen/kg of food, ppm) with a prescription for labelling and the accompanying wording for each action level. It is not clear who is behind EU-VITAL and how the action levels are determined.

SimplyOK has developed a pictorial trademark so the consumer can see in a glance which allergens are present in a food. The pictorial trademark is additional to the declaration of ingredients and is based on the 14 statutory allergens as ingredients. Each allergen is shown as a unique icon that always appears in the same place. 'Present' means that the allergen has been used as an ingredient. 'May be present' points only to the risk of cross-contamination that cannot be avoided. This is assessed using the VITAL 2 system. Food companies may only use the pictorial trademark after an extensive control. For this purpose, a testing scheme has been developed to assess the allergen management system of the production company in practice (SimplyOK).

EFSA opinion
An EFSA supporting publication from 2013 describes the prevalence of food allergies in Europe and shows that there are gaps in the database with regard to the prevalence of allergies for some foods, e.g. lupin and celery, and in specific age groups and countries (University of Portsmouth 2013). In 2014, EFSA published an opinion on the evaluation of allergenic foods and food ingredients in relation to labelling (EFSA 2014). EFSA indicated that around 75% of allergic reactions in children are caused by egg, peanut, cow's milk, fish and various nuts. Approximately 50% of the allergic reactions in adults are caused by fruit (of the latex group, such as kiwi and banana, and the *Rosaceae* family, such as apple, pear and plum), vegetables from the *Apiaceae* family (such as carrot and celery) and various nuts and peanut. On the basis of national registers, the EFSA panel estimated the number of deaths in the United Kingdom due to anaphylaxis (from all causes) at 0.33 deaths per million each year from 1992- 2003 (n=202). In 31% of the cases (n=63), food was mentioned as a possible cause; this corresponds to approximately 0.1 deaths per million people each year. Nuts and peanut were responsible for 50% of fatal food anaphylaxis cases. In the United States, 31 deaths (of people aged 5-50 years) were reported as a result of food anaphylaxis between 2001 and 2006; 17 cases were caused by peanut, eight by

nuts, four by milk and two by shrimps. In the German-speaking countries, 197 food anaphylactic reactions were reported between 2006 and 2009 (EFSA 2014).

The EFSA Panel described three different methods for the risk assessment of allergens: the traditional risk assessment based on the No Observed Adverse Effect Level (NOAEL) and uncertainty factors; the application of the Bench Mark Dose (BMD) and Margin of Exposure (MoE); and the application of probabilistic models. The Margin of Exposure (MoE) is the $BMDL_{10}$ of the individual threshold value distribution for an allergenic food or ingredient divided by an estimate of the exposure to that allergenic food or ingredient. The higher the MOE, the lower the chance that an allergic reaction will occur in the allergic population.

The minimum eliciting dose (MED) that EFSA uses to evaluate allergenic foods for labelling purposes is equal to the LOAEL that is used for chemical substances. A minimum observed eliciting dose (MOED) is defined as the lowest dose of an allergen at which an objective allergic reaction occurred and below which an objective adverse reaction is not expected in that individual. MED is the lowest dose of an allergen that elicits an objective or subjective reaction in an individual. In this context, the term allergic reaction is limited to IgE-mediated adverse effects, which mostly occur within two hours after administering the allergen.

The Bench Mark Dose (BMD) is the dose of an allergen that probably will elicit an allergic reaction in a certain percentage of the allergic population. The BMD lower limit (BMDL) is the lower limit of the 95% confidence interval of the BMD. ED_p represents the dose of an allergen to which p% of the allergic population will react. ED_{10} is equal to BMD_{10}. BMD and ED_p can be regarded as population threshold values (EFSA 2014). The EFSA report paid particular attention to specific allergenic foods and ingredients and focused on the description of minimal (observed) eliciting doses for individuals. These are summarised in Table 2. EFSA has not derived reference doses.

Table 2. Prevalence and minimal (observed) eliciting doses (M(O)ED) from the EFSA opinion (EFSA 2014)

Allergenic food	Prevalence	Lowest reported MED / MOED[a]	Remarks
Wheat	0.4% in young children (often disappears during adolescence)	2.6 mg of protein	
Cow's milk	1% (children) and 0.5% (adults)	0.2 mg	Reactions to lower doses cannot be ruled out; fatal reaction to 60 mg of casein and 9 µg/ml of whey protein[b]
Egg	1.5-2.5% in children <3 years and 0.1-1% in older children and adults	0.2 mg for whole egg; 14 µg for spray-dried egg protein; 0.05 g for raw, liquid egg	Processing of eggs has no effect on allergenicity; EFSA summarised that most allergic people 'are likely to react at a low mg level'
Nuts	Depends on the type of nut; hazelnut: 2.2%	MOED only for hazelnut (1 mg) and cashew (2.3 mg)	
Peanut	0.1-0.8%	100 µg with NOAEL of 30 µg	
Soy	Low	MED: 4 mg; MOED: 88 mg; NOAEL: 2 mg of soybean flour (1.1 mg of protein)	Processing leads to a reduction in allergenicity
Fish	<1%	MED: 5 mg of fish (also depends on type of fish); 1,1 mg of protein (cod)	Most common cases of serious anaphylaxis
Molluscs	0.2-0.3%	14 g for shrimps; 32 mg for shrimp extract (corresponds to 16 g of shrimps); 100 g for oysters. Value will lie around 120 mg	Three snails have led to a fatal reaction
Celery	2.7% (Germany)	0.7 g for celery root; 0,16 g for celery spice	
Lupin		MED: 50 mg of protein (265 mg for flour)	Data originates primarily from peanut-allergic people
Sesame seed		30 mg seed; oil: anaphylactic shock at 1 ml	Boiling, drying and roasting increased IgE binding capacity; microwaving and high-pressure cooking reduced IgE binding capacity
Mustard		0.8 mg protein (corresponds to 13.5 mg seeds)	
Sulphite (eq.)	Rare among non-asthmatic persons	3.7 mg SO_2 is the lowest known concentration	

[a] Very sensitive persons are often not tested. M(O)ED: minimal (observed) eliciting dose.
[b] 0.1 ml of milk corresponds to 3 mg of protein.

Proposal for reference doses

Establishing threshold values and reference doses must be based on a scientific assessment. This is followed by a risk management decision on which risks can be regarded as acceptable. EFSA has compared the strengths and weaknesses of the

BMD and NOAEL methods for establishing reference values for risk assessment (EFSA 2009). The Scientific Committee of EFSA has concluded that the BMD approach is a scientifically more advanced method than use of the NOAEL, because it makes better use of the available dose response data and better quantifies the uncertainties of the dose response data. EFSA regarded the BMD method particularly valuable in situations in which it is difficult to determine the NOAEL (EFSA 2009).

An EFSA Guidance (EFSA 2009) recommends to use various models for the BMD approach (for non-continuous data: logistic, probit, log-logistic, log-probit, Weibull, gamma and linearised multi-stage (LMS) family models) for each end point and to calculate the BMD with the accompanying confidence interval for each accepted model. This will produce a number of BMDLs. EFSA then recommends choosing the lowest BMDL, in other words the most conservative value, as the overall BMDL (EFSA 2009).

The VITAL database is unique. However, the Office for Risk Assessment and Research (BuRO) of NVWA has no access to the data from which the VITAL reference doses are derived and the VSEP does not provide any additional statistical calculations, such as confidence intervals or goodness-of-fit analyses, of the different models. There are ambiguities in VSEP's description of how reference doses are established. BuRO therefore has to rely on published data in the literature. BuRO proposes using preliminary reference doses that are based on the lowest ED_{01} value of the models used (Remington 2013). This still does not take into account the unreliability of the ED_{01} value, as EFSA advises doing. However, the ED_{01} is a reasonably strict criterion. If the ED_{01} is not available, the lower limit of the 95% confidence interval of the ED_{05} is an acceptable value. In this way, the preliminary reference doses for the main allergens, as proposed by BuRO, are approximately lower by a factor of ten than the VITAL reference doses. BuRO does not rule out adapting these preliminary reference doses if access to the VITAL database will be granted or when data become available that are gathered and recorded in an accessible European database in future.

Table 3. The preliminary reference doses, as proposed by BuRO and based on Remington 2013 and Taylor et al. 2014a, are as follows.

Allergen	**Lowest ED_{01}, mg protein**	**Lowest ED_{05}, mg protein**	**Lower limit of 95% confidence interval of ED_{05}, mg protein**	**Proposed reference dose for enforcement, mg protein**	**VITAL reference dose, mg protein**
Peanut	0.015	0.5		0.015	0.2
Milk	0.016	0.57		0.016	0.1
Egg	0.0043/0.03[b]	0.21	0.31	0.0043	0.03
Hazelnut	0.038/0.011	1.2	0.23	0.011	0.1
Soy flour	0.078	4.7	0.15	0.078	1.0
Wheat	0.14	2.0	0.41	0.14	1.0
Cashew	1.4	8.9	1.9	1.4	2.0
Mustard	0.022	0.32	0.046	0.022	0.05
Lupin	0.83	7.8	4.5[c]	0.83	4.0
Sesame	0.10	2.1	0.13	0.10	0.2
Shrimp	3.7	73.6	10.4	3.7	10

[a] In red: Remington 2013; in black: Taylor et al. 2014.
[b] There is a conspicuous discrepancy between Remington 2013 and Taylor et al. 2014. Remington (2013) notes that all three distributions should be taken into account for egg, with an emphasis on the Weibull distribution, for deriving a reference dose. The data of 206 people are marginally adequate for the use of ED_{01} in determining a reference dose.
[c] The Weibull model has been disregarded.

It should be noted that the reference doses generally lie under the detection level of most commercial analysis kits, while the VITAL reference doses seem to lie around or somewhat above the detection limits. The detection limits of commonly applied measurement methods are around 0.02 to 1 (and higher) ppm.

Coeliac disease or gluten intolerance is not the same as wheat allergy. IgE antibodies are involved in a wheat allergy and the immune system reacts to one or more wheat proteins but not to other cereals containing gluten. No IgE antibodies are involved in coeliac disease (SDU). Wheat protein consists of a number of different proteins whose properties can differ significantly. Gluten is the composite of gliadin and glutenin, which make up around 60% of wheat proteins (Žilić et al. 2011); the other proteins are albumin and globulin (SDU).
Regulation (EU) No 828/2014 will replace Regulation (EC) No 41/2009 with effect from 20 July 2016. The Regulation contains the requirements for the provision of information to consumers on the absence or reduced presence of gluten in food. The claim 'gluten-free', for example, may be used only if the food contains no more than 20 ppm of gluten.
With the exception of sulphite, the European list of allergenic ingredients that must be declared does not mention threshold values. Allergenic ingredients that are knowingly added to a food must always be labelled. This advisory report deals with establishing preliminary threshold values for allergenic ingredients that are added unknowingly or through contaminations. For example, biscuits made of wheat flour must be labelled as such. But biscuits made from oats may have come into contact with wheat. For this latter case, a threshold value for labelling is derived. 'Gluten-free' may be an applicable claim in both cases.

Prof. Antoon Opperhuizen, PhD
Director of the Office for Risk Assessment and Research

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