Parameters needed to estimate the global burden of peanut allergy

Systematic literature review

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Colophon

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Abstract

Parameters needed to estimate the global burden of disease for peanut allergy

The symptoms of peanut allergy vary from mild to severe, from swollen lips, shortness of breath to an anaphylactic shock, which is potentially fatal. The National Institute for Public Health and the Environment (RIVM) has investigated which factors have an impact on the burden of disease for peanut allergy. The most important parameters were found to be the number of people who suffer from a peanut allergy and the impact it has on their quality of life. Burden of disease is a measure to quantify the consequences of a disease by combining the loss of health from impaired quality of life and premature mortality.

This systematic literature review was performed within the framework of the Foodborne Disease Burden Epidemiology Reference Group of the World Health Organisation that is dedicated to estimating the global burden of disease for several food borne diseases. Examples are pathogens, such as parasites and bacteria or toxic chemicals that are present in food as contaminants. Peanut allergy has been included in this initiative because of the severe symptoms that can occur.

Prevalence of peanut allergy
In Western countries, peanut allergy affects 0.5 to 1.5 per cent of the population. There is a lack of prevalence data from developing countries. Geographical differences in the prevalence appear to exist, since peanut allergy is uncommon in Turkey and Israel.

Peanut allergy limits quality of life
Symptoms of the allergy are only induced when people with a peanut allergy eat products that contain peanuts. Although they can be severe, the symptoms are usually short-lasting. Consequently, they will not have an impact on the burden of disease. The number of people who die due to a peanut allergy is low; this also has a limited impact on burden of disease. The quality of life of people with a peanut allergy is impaired, for example, because they are anxious about accidentally eating products that contain peanut. This impairment of quality of life is important in the burden of disease.

Keywords:
burden of disease, peanut allergy, prevalence, quality of life

Rapport in het kort

Overzicht van gegevens die nodig zijn om de wereldwijde ziektelast van pinda allergie te berekenen

Een pinda-allergie kan milde tot ernstige klachten veroorzaken, uiteenlopend van een dikke lip en benauwdheid tot een zogeheten anafylactische shock, die potentieel dodelijk is. Het RIVM heeft onderzocht welke factoren van invloed zijn op de zogeheten ziektelast die pinda-allergie veroorzaakt. De belangrijkste parameters daarvoor blijken het aantal personen met een pinda-allergie te zijn en de invloed van een pinda-allergie op de kwaliteit van leven. Ziektelast is een maatstaf om de gevolgen van ziekten te kwantificeren en is een combinatie van gezondheidsverlies door verminderde kwaliteit van leven en door vroegtijdig overlijden.

Deze literatuurstudie is uitgevoerd in het kader van de 'Foodborne Disease Burden Epidemiology Reference Group' van de Wereldgezondheidsorganisatie die de wereldwijde ziektelast van verschillende voedingsgerelateerde aandoeningen in kaart wil brengen. Voorbeelden zijn ziekteverwekkers als parasieten en bacteriën of schadelijke stoffen die mensen via voeding binnenkrijgen. Vanwege de ernstige klachten valt pinda-allergie daar ook onder.

Aantal mensen met pinda-allergie
Tussen de 0,5 en 1,5 procent van de inwoners van westerse landen hebben een pinda-allergie. Er zijn bijna geen gegevens gepubliceerd over de mate waarin dit in niet-westerse landen voorkomt. Er lijkt sprake te zijn van geografische verschillen, omdat pinda-allergie bijvoorbeeld weinig tot niet in Turkije en Israël voorkomt.

Pinda-allergie beperkt kwaliteit van leven
Mensen met een pinda-allergie krijgen alleen allergische klachten als ze een product eten dat pinda's bevat. Hoewel ze ernstig kunnen zijn, zijn ze doorgaans van korte duur. Daardoor hebben ze weinig invloed op de ziektelast. Het aantal mensen dat aan pinda-allergie overlijdt, is laag en heeft daardoor ook weinig invloed op de ziektelast. Leven met een pinda-allergie daarentegen beperkt de kwaliteit van leven, onder andere door de angst om per ongeluk een product dat pinda's bevat te eten. Deze beperking van hun kwaliteit van leven beïnvloedt wel de ziektelast.

Trefwoorden:
ziektelast, pinda allergie, prevalentie, kwaliteit van leven

Contents

Summary

Peanuts are highly nutritious and consumed all over the world. In a small proportion of the population, consumption of peanuts can lead to peanut allergy, which is an overreaction of the immune system caused by otherwise harmless peanut proteins. Peanut allergy develops at an early age, in the majority between 14 and 24 months and it is in almost all cases a life-long problem. Peanut allergy has a large impact on the quality of life of the allergic individuals and their families, since peanuts together with tree nuts, are the most common causes of fatal or near fatal food allergic reactions in children and adolescents.

To estimate the burden of disease of peanut allergy a systematic literature review was performed to find information on the parameters needed to estimate this. A systematic literature search was conducted focusing on prevalence and incidence data, duration and severity of the disease, numbers of cases that recover and mortality rate. Prevalence data of studies assessing self-reported peanut allergy (questionnaires or interviews), peanut sensitisation (positive skin prick tests or peanut-specific IgE antibodies) or clinically confirmed peanut allergy (oral peanut challenges) were all included in this report.

Prevalence data were predominantly available from developed countries (UK, West Europe, Scandinavia, USA, Canada and Australia). There were no data from Africa and New-Zealand and limited data from East and South Europe, Asia, and South America. In Western countries the prevalence of peanut allergy ranges from 0.5%-1.5%. In some countries the prevalence was low or even zero, as has been shown for Israel and Turkey, suggesting geographical differences, possibly due to cultural or dietary differences. The symptoms that are elicited when patients accidentally eat peanuts can vary from mild to severe and occur very rapidly after exposure and have a short duration. Due to this short duration, severity of disease is considered to be irrelevant in the burden calculation. There are limited data on the mortality rate of peanut-induced anaphylaxis and studies report a case-fatality rate between 0.00125 to 0.017 deaths per 100,000 subjects per year. Hence, peanut allergy can be fatal but this occurs rarely.

To conclude, this systematic review has found relevant data that can be used to calculate the burden of disease of peanut allergens. For peanut allergy there were no incidence data obtained. Since the onset of peanut allergy is early in life and prevalence continues in older age groups, the assumption has been made to use the prevalence of peanut allergy in childhood as the incidence for all age groups. In addition, the papers that were published on the resolution of peanut allergy have shown that peanut allergy can resolve, but due to study limitations any attempt to quantitate this outcome is to uncertain. Therefore, it is assumed that peanut allergy is a life-long condition that does not resolve. The mortality rate for peanut allergens is low and probably has a limited impact on the disease burden. Peanut allergy will only induce short-term medical disabilities upon accidental ingestion of peanut, which if they are not fatal will probably not influence the burden of disease. The constant awareness of the fact that eating a small amount of peanuts might elicit severe and potentially life-threatening symptoms can have significant impact on the quality of life of patients and their families. Co-morbidities, such as other allergies, might have an impact as well. In the future it should be explored how quality of life and co-morbidities can be included in the calculation of the burden of peanut allergy.

1 Background

1.1 Aims of WHO FERG

The Foodborne Disease Burden Epidemiology Reference Group (FERG) was established by the World Health Organisation (WHO) under the leadership of Department of Food Safety, Zoonoses, and Food borne Diseases. The purpose of the FERG is to estimate the global burden of disease from food borne illness. Five task forces have been set up within the FERG – enteric (bacteria and viruses), parasites, chemicals/toxins, country studies and source attribution. This document was prepared under the auspices of the Task Force on Chemicals/Toxins.

The burden of disease (BoD) is expressed as a single metric, the Disability Adjusted Life Year (DALY). DALYs express the years of life lost to premature death (YLL) and the years lived with disability (YLD) for varying degrees of severity, making time itself the common metric for death and disability. One DALY is therefore a health gap measure, equating to one year of healthy life lost.

This report describes the available literature on parameters that are necessary to calculate the global burden of peanut allergy. Important parameters that have an impact on the burden of disease include data on incidence and/or prevalence of peanut allergy, severity and duration of symptoms, prevalence of fatal anaphylactic reactions and impact on quality of life.

1.2 Food hypersensitivities

Adverse reactions induced by food can be induced by the food itself or by contaminants present in food. Furthermore, different types of adverse reactions can be induced by food or food contaminants. Typically, toxic reactions are induced by factors inherent in the food, i.e., contaminants and will be induced in any exposed individual when ingested at an appropriate and large enough dose. In contrast, food hypersensitivities will not occur in all exposed subjects, but only affect susceptible ones. The two categories of food hypersensitivity reactions are depicted in Figure 1. Non-allergic food hypersensitivities are often caused by metabolic or pharmacological effects. An example of non-allergic food hypersensitivity is lactose tolerance, which is caused by a deficiency in the enzyme lactase. Due to this deficiency, lactose is not digested properly, leading to gastrointestinal problems.
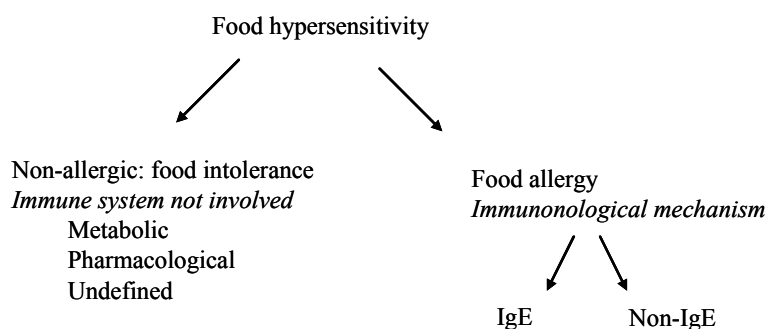

Figure 1: Food hypersensitivity reactions.

Food allergies are caused by immunological mechanisms and can be subdivided in IgE or non-IgE mediated reactions. An example of non-IgE mediated food allergy is celiac disease, which is caused by an abnormal immunological response towards gluten, leading to autoimmune-like reactions in the gastrointestinal tract. Peanut allergy on the other hand is a typical example of an IgE mediated food allergy, which is defined as an abnormal immune response directed towards harmless food proteins resulting in symptoms of immediate hypersensitivity (Johansson et al., 2001).

The human gut is exposed to an enormous amount of dietary proteins every day. The immune system of the gut has to be able to distinguish between these harmless proteins and dangerous enteric pathogens. Hence, under normal circumstances the immune system of the gut will not respond to proteins from the diet and this phenomenon is called oral tolerance (Weiner, 2000). Failure to induce oral tolerance or abrogation of oral tolerance may result in the development of food allergy. Peanut allergy, like other allergies, comprises two phases (depicted in Figure 2), the initiation phase, called sensitisation and the effector phase, called elicitation.
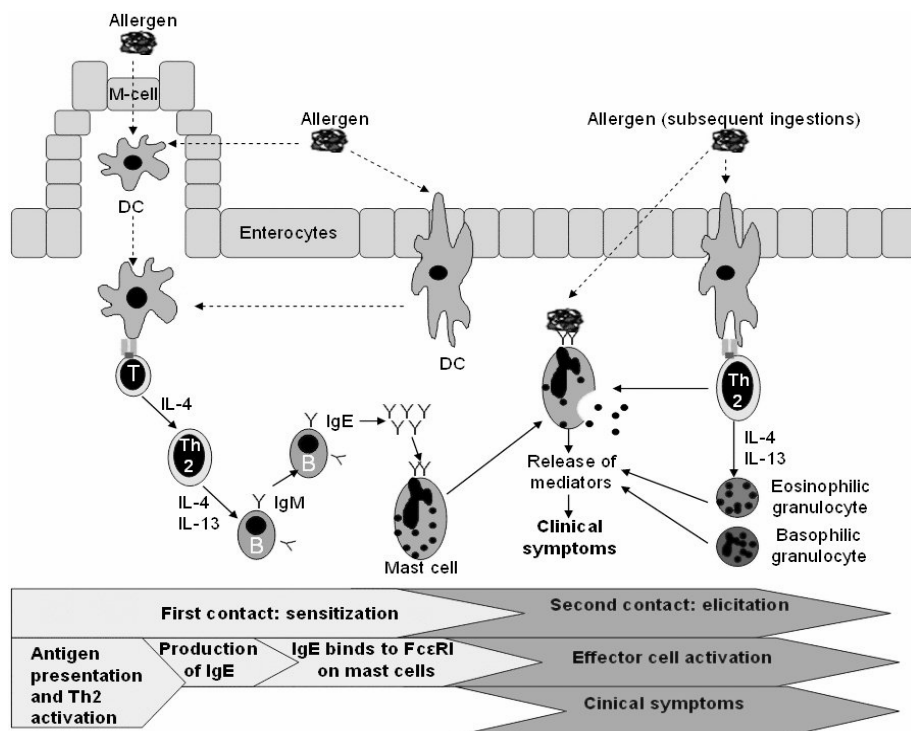
Figure 2. Schematic overview of the induction and effector phases of food allergic responses (De Jonge et al, 2009). *Food proteins are taken up via M-cells of the Peyer's Patches in the gut. After recognition and ingestion by dendritic cells the protein is digested and presented to naïve T cells in the mesenteric lymph nodes. Antigen-specific Th2 cells are generated and Th2-derived cytokines, such as IL-4 and IL-13 promote IgE production by B cells. Mast cells bind circulating IgE on their Fc receptors. Upon subsequent ingestion, antigenic fragments may interact directly with receptor-bound IgE on mast cells and cross-linking of receptors triggers the release of the preformed and newly formed inflammatory mediators responsible for clinical symptoms. Antigen-presentation may also lead to a rapid T-cell activation and the secretion of Th2 cytokines, triggering mediator release by basophilic and eosinophilic granulocytes.*

In the sensitisation phase, proteins are taken up via the gut mucosal immune system and are recognised by dendritic cells, which process and digest the proteins and migrate to the mesenteric lymph nodes. Parts of the protein (epitopes) are presented to resting immature T cells initiating T cell proliferation and maturation leading to the formation of mature effector and memory T cells. In allergy, T helper type 2 (Th2) cells play a crucial role. These cells activate B cells to mature into plasma cells that produce IgE. On the cell surface of the mast cells, IgE binds to Fc receptors. In the effector phase, peanut allergens cross-link the allergen-specific IgE on the mast cells, thereby triggering a cascade of reactions. The mast cells degranulate and release mediators such as histamine, chemokines, cytokines, prostaglandins and leukotrienes, These mediators attract circulating basophils, eosinophils, neutrophils and Th2 lymphocytes to the site of mast cell activation, where they amplify the immune reaction and mediate the symptoms of food allergy (Sampson, 1999a). Typically, clinical symptoms of peanut allergy have a rapid onset. The severity of symptoms varies from mild to severe and different organs systems can be affected, including the skin, gastrointestinal (GI) tract, upper and lower respiratory tract and cardiovascular system. The clinical symptoms are discussed in more detail in Chapter 3.

1.3 Peanut allergy

Peanut belongs to the legume family, which also includes pea, bean, soybean, lupine and lentil. Peanuts are consumed all over the world because of their high nutritious value. There are differences in the way peanuts are consumed, for instance roasted peanuts are predominantly eaten in the US and Europe, whereas in Asia peanuts are often boiled before consumption.

Peanut proteins that activate the immunological response are classified as major or minor allergens and the nomenclature (Ara h) is based on the Latin name of peanut: *Arachis hypogea*. Major allergens are recognised by more than 50% of the peanut-allergic patients and include Ara h 1 (vicilin), Ara h 2 (conglutin-homologue protein), and Ara h 3/h 4 (glycinin). The minor allergens are: Ara h 5 (pan-allergen profiling) and Ara h 6 and Ara h 7 (both conglutin-homologue proteins). Recently, Ara h 8 is identified, which is a Bet v 1 homologue, and therefore a major allergen in patients with combined birch pollen and peanut allergy (Boulay et al., 2008). Ara h 9 is, up to now, the last allergen that has been identified, and seems to be an important allergen in the Mediterranean population (Krause et al., 2009).

Peanut allergy affects both children and adults and the first peanut reaction occurs early in life (Green et al., 2007). It has been shown that 68% of the peanut allergic patients have their first reaction before the age of 2 years, whereas the majority (>95%) have their first reaction under the age of 15 years (Moneret-Vautrin et al., 1998; Mullins et al., 2009). Furthermore, peanut allergy rarely resolves, illustrating that unlike other childhood allergies, such as cow's milk and egg allergy, peanut allergy is in almost all cases a persistent and a life-long problem (Hourihane et al., 1998; Skolnick et al., 2001). Peanuts together with tree nuts are the most common causes of fatal or near fatal food allergic reactions in children and adolescents (Sampson et al., 1992; Foucard & Malmheden Yman, 1999). In highly allergic individuals, trace amounts of peanut can already provoke a reaction. Peanut allergy can have a considerable impact on the quality of life of the allergic individuals and their families (Primeau, 2000; Flokstra-de Blok et al., 2009). For patients and their families it is challenging to avoid peanuts, since they are commonly used in many different food products,

such as cookies and chocolate, and these hidden peanut allergens are often responsible for accidental ingestion. Food products that contain peanut as an ingredient should be labelled accordingly, but food products that may contain peanuts due to cross-contamination are often, but not always labelled with a 'may contain' label (Puglisi & Frieri, 2007). Not all peanut allergic patients avoid these 'may contain' products, although it is possible that these products contain amounts of peanut that can elicit an allergic reaction (Hefle et al., 2007). Approximately 56%-60% of the peanut allergic children have accidental ingestions, which occur most frequently at school, but also at home and in restaurants (Sicherer et al., 1998, Vander Leek, et al., 2000). Yu et al. report a lower incidence of accidental reactions of 14%, which might be explained according to the authors by increased awareness (Yu et al, 2006).

1.3.1 Route of exposure

The oral route is the primary route of exposure to food allergens. However, alternative routes of exposure might be possible both in the sensitisation and elicitation phase. For peanut, it has been shown that peanut sensitisation was present in children as young as 6 months of age. In most countries, children are not yet eating peanut at this early age. Possibly, exposure and sensitisation occurs via the mother, either *in utero* or during breastfeeding. In addition, application of ointments containing peanut oil has been suggested as an alternative route of exposure. In certain countries, creams containing peanut oil are commonly used in children with impaired skin barriers, i.e., atopic eczema, diaper rash. Although there is limited evidence for this theory, the skin could be an alternative route for sensitisation when the applied creams contain crude peanut oil as an ingredient (Lack et al., 2003). Furthermore, there are concerns that inhalation of peanut dust might be an alternative route of exposure. Sicherer et al. (2001a) report that in 16% of the peanut or tree nut allergic subjects, allergic sensitisation might have been triggered by inhalation. However, in these cases ingestion could not be ruled out completely, making it difficult to conclude which route of exposure is the primary route of sensitisation. According to a review of James & Crespo (2007), inhalation of peanut dusts has only been implicated in elicitation and not in induction of peanut allergic responses (James & Crespo, 2007).

1.3.2 Diagnosis and management

The diagnosis of peanut allergy comprises the medical history and physical examinations. The first important question that has to be answered is whether the complaints are related to ingestion of peanut. Therefore, it is necessary to know the onset of complaints, since food allergic symptoms occur very rapidly after ingestion. When peanut allergy is suspected, additional information is derived by determining peanut sensitisation; either by detection of peanut-specific IgE (sIgE) in the serum or by performing a skin prick test (SPT) that measures mast-cell reactivity in the skin. Sensitisation to peanut alone does not predict clinical reactivity. It is estimated that 30-60% of sensitised individuals have clinical allergy, while the others can tolerate peanut. The positive predictive value of these diagnostic tests increases when higher cut-off values are used (Roberts & Lack, 2005). Furthermore, component-resolved diagnosis might lead to a better prediction of clinical allergy in sensitised subjects. In this approach not the complete peanut extract is used for IgE diagnosis, but IgE specific for the most important peanut allergens are assessed. It was shown that the most important clinical predictor for peanut allergy was specific IgE against Ara h2 (Nicolaou et al., 2010).

The 'gold standard' for determining food allergy is the double blind placebo controlled food challenge (DBPCFC). This procedure is performed in a hospital, because it is possible that life-threatening reactions can be induced. The DBPCFC comprises of gradually feeding incremental portions of the suspected allergen (hidden in a masking vehicle) on one day and the vehicle on the placebo day. When these blinded challenges do not induce any clinical symptoms on those two days, an open challenge is performed on the second day. For this open challenge, a normal portion of the food is consumed and clinical symptoms are monitored (Sampson, 1999b; Du Toit et al., 2009).

Management of the disease generally means complete avoidance of peanuts, since there is currently no cure for peanut allergy. After accidental ingestion of peanut it is possible to relieve the clinical symptoms. Mild and local reactions can be treated with antihistamines and symptoms that involve multiple organs, but are not life-threatening, can be treated with antihistamines combined with corticosteroids. Anaphylactic shock reactions need to be treated immediately with an epinephrine injection and patients at risk for these severe reactions should always carry an autoinjector that contains epinephrine (EpiPen®) together with a written emergency plan (Sampson, 1999b).

Currently, therapies for food allergy are aiming at inducing tolerance to the allergen. These therapies are in an experimental phase and different strategies are under investigation. Oral immunotherapy (OIT) is especially under extensive research. In this approach, doses of the food protein are given in gradually increasing amounts toward a maintenance dose. In a group of 29 children with peanut allergy, OIT increased the dose that could be tolerated and some patients could eat almost 4 grams of peanut without symptoms (Jones et al., 2009). Difficulties remain in maintaining tolerance, as most studies show that when OIT is stopped, clinical reactivity to lower doses of allergen returns.

1.3.3 *Epidemiology*

A review conducted in the Europrevall project has been published that provides an overview of the relevance of genetic and environmental factors affecting peanut allergy (Boulay et al., 2008). More recently, a RIVM report provided an overview of dietary, lifestyle and environmental factors that have an impact on the risk on food allergy (Ezendam & Van Loveren, 2010). It is well-known that susceptibility to food allergy is strongly influenced by genetic constitution. A history of atopic disease in the family is an important risk factor for allergic diseases. Furthermore, there is some evidence for allergen-specific inheritance. Relatives of peanut allergic patients had a higher frequency of peanut allergy compared to the general population (Hourihane et al., 1996). In a study in twins, it has been shown that peanut allergy is shared by 64% of the monozygotic and in 7% of the dizygotic twins, suggesting a significant genetic influence (Sicherer et al., 2000). The role of ethnicity has been studied in a UK study, showing a higher rate of food allergy in non-Caucasian children compared to Caucasian children (Dias et al., 2008). Gender could also possibly play a role, since males seem to be more affected by peanut allergy. Different studies report a proportion of 63-66% of the patients being male (Sicherer et al., 1998; Sicherer et al., 2001b; Green et al., 2007).

In the UK and USA, pregnant women were advised to avoid eating peanuts during pregnancy, lactation and in the first three years of life. Recently, these recommendations have been abandoned because of lack of conclusive evidence for a protective effect (Hourihane et al., 2007). Interestingly, there is anecdotal

evidence that it might be the other way around. In some countries peanut is introduced to the diet early in life and consumed in relatively high amounts already at an early age, as is the case for example in Israel. Nevertheless, the prevalence of peanut allergy is low in this country, whereas the prevalence of other food allergies is comparable to other developed countries (Dalal et al., 2002; Du Toit et al., 2008). These observations have introduced a new hypothesis, that early life introduction of peanut might lead to oral tolerance and protects against peanut sensitisation. Currently, this is not proven in epidemiological studies, but in experimental animal studies evidence for this hypothesis has been found. In mice it was shown that low-dose peanut exposure during pregnancy and lactation reduced the risk of peanut allergy (Lopez-Exposito et al., 2009). Besides timing of introduction of peanut in the diet, there are other external factors that may have an impact on peanut allergy as well, including environmental, dietary and lifestyle factors, but scientific evidence from epidemiological studies is limited or conflicting (Ezendam & Van Loveren, 2010).

The way peanuts are processed seems to influence the allergenic properties of the peanut proteins. There are indications that roasting increases the allergenicity, while boiling and frying have less effect and perhaps even decrease allergenicity (Koppelman et al., 1999; Maleki et al., 2000; Beyer et al., 2001; Grimshaw et al., 2003). Geographical differences exist in peanut processing methods. For example in the USA, people predominantly consume roasted peanuts, whereas in China, mainly boiled peanuts are consumed. Such geographical differences in processing might have an impact on the incidence of peanut allergy, but currently there is no epidemiological evidence for this.

2 Methods

2.1 Literature search

To meet the objectives in the work statement, different search strategies were employed to find all relevant literature using PubMed and Scopus electronic databases. In addition, the databases from WHO, JECFA, NIAID, US FDA, and EFSA were searched but no reports were found.

2.1.1 Literature search on prevalence or incidence of peanut allergy.

As a starting point we used a meta-analysis on the prevalence of food allergy that was published in 2007 and included information on the prevalence of peanut allergy (Rona et al., 2007). We retrieved all 19 references regarding peanut allergy used in this meta-analysis. These papers were published between 1992 and 2004. An additional search was performed to obtain all relevant literature published between January 2004 and May 2009.[1] The search was performed for all languages.

For the PubMed and Scopus literature search we employed different search strategies:
- The major Medical Subject Headings (MeSH) terms used were: ''peanut hypersensitivity'' and ''prevalence''
- The major MeSH terms used were: ''peanut hypersensitivity'' and ''incidence''.
- The key words used were: ''peanut allergy'' and ''prevalence'' restricted to title and/or abstract
- The key words used were: ''peanut allergy'' and ''incidence'' restricted to title and/or abstract.
- The key words used were: ''food allergy'' and ''sensitisation'' and ''peanut'' restricted to title and/or abstract and human studies
- The key words used were: ''DBPCFC'' and ''peanut'' restricted to title and/or abstract and human studies.

There were only limited publications from Asia, South-America and Africa. An additional more general search was conducted to find specific papers on food allergy from these countries. For this search the key words: ''food allergy'' or ''food sensitisation'' in combination with the continent (Asia, South-America, or Africa) were used.

The following inclusion criteria were used:
i. prevalence or incidence should be assessed in a population representative for the general population, excluding studies that have included subjects with existing allergies or which are atopic
ii. peanut sensitisation should be assessed by either skin prick testing (wheal size > 3 mm) or IgE (> 0.35 IU/ml)
iii. published 1990 or later in any language

These literature searches yielded 113 Abstracts (Figure 3). The Abstracts of the retrieved papers were carefully screened for relevance and duplicates. A total of

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[1] The report has in 2012 been updated with a few relevant manuscripts published in 2010 and 2011 without performing a thorough literature review.

69 papers were rejected because they did not contain data on incidence or prevalence of peanut allergy. In addition, 13 studies were excluded because they did not meet the inclusion criteria, since prevalence was assessed in allergic or atopic subjects. These excluded studies are summarised in Table 5. Together with the papers from Rona et al. (2007), a total of 52 papers were identified for data abstraction. In addition, data from a report published on the web site of the Dutch National Institute for Public Health and the Environment was used (Ezendam et al., 2008). The literature search has been updated with a few relevant studies published in 2010 and 2011, without performing a full literature search.
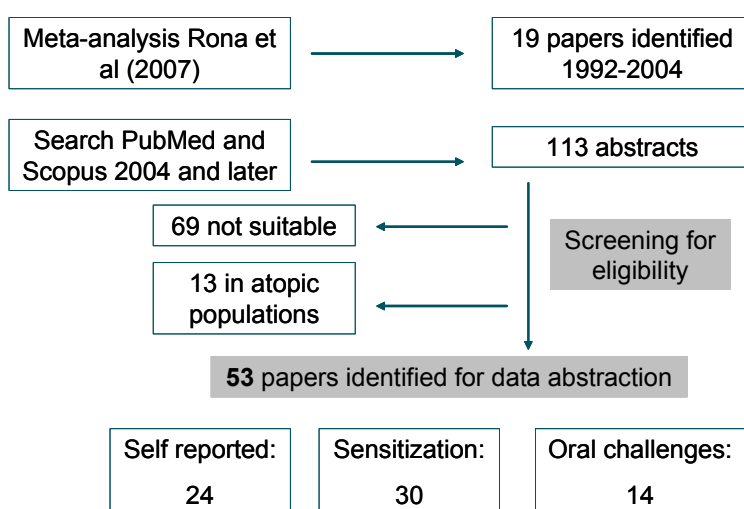
Figure 3: Data abstraction flow-chart of papers published between January 2004 and May 2009.

2.1.2   *Literature search on prevalence/incidence of clinical symptoms of peanut allergy*

To find additional literature on the distribution of different clinical symptoms of peanut allergy, different search strategies were used. It should be noted that in these searches the aim was to find selected populations, i.e., peanut allergic subjects. The following searches were conducted:

- ''Peanut hypersensitivity' was used as a major MeSH term combined with 'clinical symptoms'
- 'Peanut allergy' and 'clinical symptoms'
- 'Peanut allergy' and 'clinical aspects'
- 'Peanut allergy' and 'clinical characteristics'

A total of nine studies were found that have studied the clinical spectrum in peanut allergic subjects.

2.1.3   *Literature search on prevalence of anaphylaxis and mortality*

Information on national and worldwide data on the number of deaths from peanut allergens was obtained by using the following search strategies or key words

- 'Anaphylaxis' was used as a major MeSH term combined with the key words 'prevalence' and 'food'.

- 'Anaphylaxis' was used as a major MeSH term combined with the key words 'food' and 'incidence'.
- 'Mortality' was used as a major MeSH term combined with the key words 'peanut'
- 'Fatalities', 'peanut' were used as key words.
- 'Surveillance system', 'anaphylaxis' and 'food' were used as key words.

This search retrieved 66 publications, but after carefully screening the obtained abstracts, a total of six papers were found that contained data on the incidence of peanut-induced anaphylaxis and/or mortality.

3 Overview of parameters needed to estimate burden of peanut allergy

3.1 Clinical symptoms: severity, duration, recovery

Symptoms in peanut allergic patients can vary greatly in severity and can affect different organ systems. Furthermore, in many patients multiple organ systems are affected. The different symptoms, their severity and duration are summarised below (Sampson, 1999a; Sampson, 2005; Asero et al., 2007).

- *The oral allergy syndrome (OAS)* is characterised by contact urticaria involving lips, oral mucosa and pharynx. Symptoms include itching and/or swelling of lips, tongue, mouth, throat, ears and nose. In general, this clinical course is mild and resolves within one hour. However, in some cases a potentially fatal pharyngeal swelling can occur, which can progress towards an anaphylactic reaction.

- *Skin symptoms:* the skin is frequently involved in food allergy and various symptoms can be induced. The most common skin disorder is acute urticaria (hives). Other skin symptoms are angioedema, itching and rashes. These symptoms are known to appear very rapidly after ingestion and may last for some hours.

- *Gastrointestinal (GI) disorders* mediated by IgE include nausea, vomiting, gastric retention, intestinal hypermotility, abdominal pain and diarrhea. Symptoms usually develop within minutes to two hours after ingestion.

- *Respiratory symptoms* are rarely the only symptom in food allergic patients but occur in association with skin and GI disorders. Symptoms that can occur are rhinitis, dyspnea, throat tightness and wheezing. Certain foods, especially fish, crustaceans and legumes, can evoke respiratory symptoms following inhalation of food dusts.

- *Anaphylaxis* is defined as a 'severe life-threatening generalised or systemic hypersensitivity reaction' (Johansson et al., 2001). It is the most severe allergic reaction and along with drugs and insect stings, foods are the most common causes of anaphylaxis. It is caused by a massive release of mediators from mast cells and basophils throughout the body and involves symptoms in the skin, GI tract, respiratory tract and sometimes cardiovascular symptoms, including hypotension, collapse and arrhythmia. Patients may react within minutes or even seconds. The typical reaction is a combination of generalised urticaria, erythema, itching, nausea, vomiting, dyspnoea (caused by throat tightness and/or bronchoconstriction), dizziness, fainting or even collapse. This monophasic pattern resolves in 2 hours when appropriately treated. The more severe reactions like hypotension and bronchial constriction can be fatal. Patients with near-fatal reactions require a longer time to recover. In a small proportion of the cases, anaphylactic reactions can be biphasic or prolonged, persisting for 2-3 days with multiple recurrences interrupted by asymptomatic symptoms (Sampson et al., 1992). Criteria to diagnose anaphylaxis were defined by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network

(Sampson et al., 2006). All possible disease outcomes are schematically summarised in a disease diagram (Figure 4).
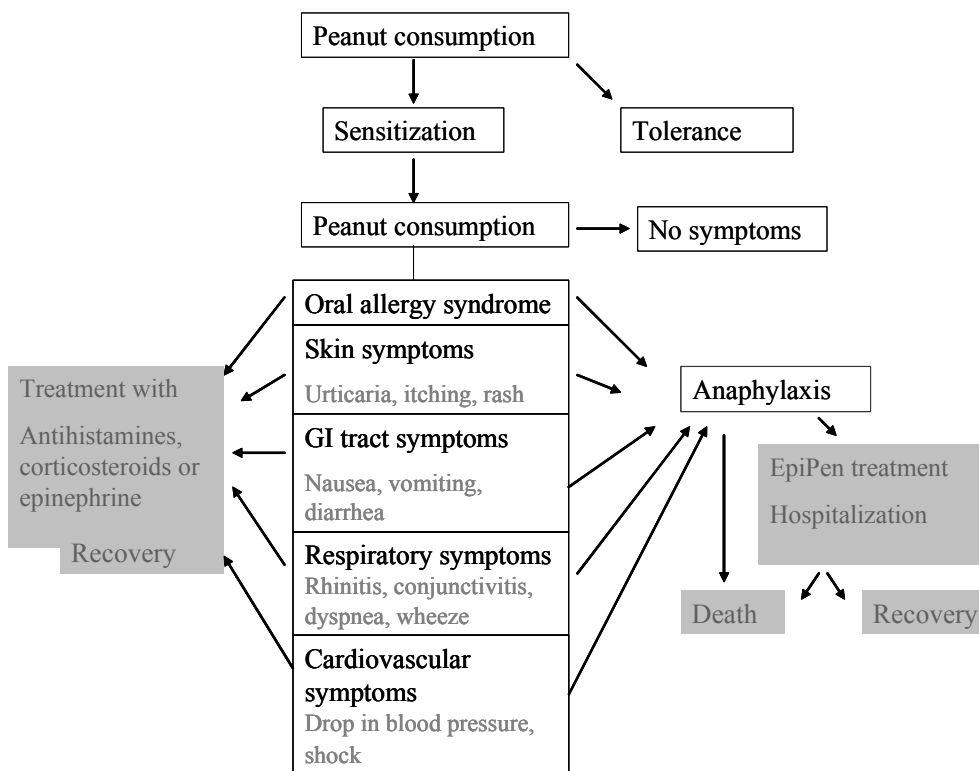
Figure 4: Disease diagram of peanut allergy.

Longitudinal studies have shown that childhood allergies, such as cow's milk and chicken egg allergy, resolve usually in the first five years of life (Host & Halken, 1990; Cantani & Micera, 2004; Savage et al., 2007). It is assumed that peanut allergy is a life-long condition, although there are limited longitudinal studies that have studied the percentage of peanut allergic subjects that outgrow their allergy. The natural course of peanut allergy has been studied in a retrospective study in 32 children aged 2-14 years with a convincing history of peanut allergy. These children underwent a double-blind, placebo-controlled, food challenge (DBPCFC) to peanut and all patients still responded to peanut with clinical symptoms. Hence, in these children peanut allergy did not resolve (Bock & Atkins, 1989). Resolution of peanut allergy has been studied in 122 children referred to a paediatric allergy clinic for evaluation of suspected peanut allergy (Hourihane et al., 1998). These children had experienced typical allergic symptoms after unequivocal exposure to peanut. In 18% (n=22) of the children this challenge was negative. This study suggest that peanut allergy has resolved in these children, but the drawback of this study is that the some of the resolvers may not have had a clinical peanut allergy, since the inclusion is based on parental observations and not on clinical examinations. So, it is possible that not all included cases were allergic to peanuts
In children aged 4 to 20 years, the resolution of peanut allergy has been studied. Patients were selected from a paediatric allergy clinic based on a convincing history of an acute reaction to peanut ingestion and on peanut sensitisation. Patients who had a reaction to peanut in the prior year were excluded. A total of 223 children aged 2-10 years were selected and 85 children underwent an open oral peanut challenge. In this study it was shown that 48

children did not respond to the oral peanut challenge, hence, 21% were not peanut allergic. However, this study has some limitations. One of them is that only 85 children were willing to participate in the peanut challenge, so the percentage might be an underestimation. Furthermore, patients with an ongoing peanut allergy were excluded, which might have biased the outcome. Also, patients were included based on an observed reaction to peanut which was not clinically confirmed at that time (Skolnick et al., 2001). These studies demonstrate that a subset of children do outgrow their peanut allergy. Due to some study limitations, it might be possible that the studies overestimate or underestimate the actual percentage that outgrows their peanut allergy.

3.2 Worldwide prevalence of peanut allergy

The prevalence and incidence data as far as available worldwide are presented in Appendix 1, Tables 2-5. Table 2 provides data on self-reported peanut allergy, Table 3 on peanut sensitisation and Table 4 on peanut allergy assessed with food challenges. Table 5 shows prevalence rates in atopic and allergic subjects. The results will be discussed for all WHO regions (see Appendix 2 for an overview). In Table 1 a summary of all data is shown for each WHO region.

3.2.1 Africa

There is no information available in the published literature on the prevalence of peanut allergy in Africa, except for one study in children with atopic eczema. In this study food sensitisation was assessed in different countries, including South Africa. In children with atopic eczema, 25% were sensitised to peanut (De Benedictis et al., 2009).

3.2.2 USA

Self-reported peanut allergy was assessed in six US studies. It is well-documented that the prevalence of perceived food allergy overestimates actual food allergy (Woods et al., 2002; Rona et al., 2007). However, the experimental design of the study, i.e., number of participants, type of questionnaires, can influence the outcome. For example, Altman and Chiaramonte (1993) used a short, simple questionnaire about food allergy to assess perceived food allergy in US citizens. They show that perceived peanut allergy is relatively high. In 1989, 5.5% reported a peanut allergy and this percentage rose to 7.2% in 1993 (Altman & Chiaramonte, 1996).
More elaborate studies performed by Sicherer et al. (1999, 2003, 2010) on self-reported peanut allergy show considerably lower prevalence rates than in the study of Altman and Chiaramonte (1993). This might be explained by the methods applied, since Sicherer et al. (1999, 2003, 2010) assessed perceived peanut allergy with telephone interviews in very large cohorts using detailed questionnaires. The prevalence of peanut allergy increased in children from 0.4%, 0.8% and 1.4% in 1997, 2002 and 2008, respectively. In adults, perceived peanut allergy did not show an increase and prevalence rates were 0.7%, 0.6% and 0.6% in 1997, 2002 and 2008, respectively (Sicherer et al., 1999, 2003, 2010).
Vierk et al. (2007) used the Food Safety Survey to assess prevalence of self-reported food allergy, including peanut allergy. The prevalence rates for peanut allergy were presented as either self-reported or self-reported doctor-diagnosed food allergy and were 0.5% and 0.3% respectively (Vierk et al., 2007). In a longitudinal survey with 2331 US mothers probable food allergy at ages 4, 8 and 12 months was assessed using detailed questionnaires. Probable peanut allergy was based on all infants that received a doctor's visit and received a diagnosis of peanut allergy or who did not receive a visit but had food-related symptoms of

swollen eyes or lips or hives. It was shown that probable peanut allergy was 0.16% at ages 4 and 8 months and increased to 0.32% at 12 months (Luccioli et al, 2008).

Peanut sensitisation was assessed in three studies. Woods et al. (2002) showed a sensitisation rate of 3.8%. Additionally, they combined the sensitisation data with information from questionnaires to estimate a probable point prevalence, which was 0.6% in 20-44 year old subjects in 1998. In the US National Health and Nutrition Examination Survey (NHANES) III a sensitisation prevalence of 0.3% was found in 6-59 year old subjects (Arbes Jr et al., 2005). In a follow-up of this study, Liu et al. (2010) reported a high rate of peanut sensitisation of 7.6%. To estimate clinical peanut allergy, they used the sIgE concentration. The probability of having a clinical peanut allergy increases at higher sIgE concentration levels. It was estimated that 1.3% would probably have clinical peanut allergy (Liu et al, 2010).

3.2.3 Canada

The prevalence of peanut allergy in Canada was assessed in two school cohorts, recruiting children (5-9 years old) between 2000-2002 (Kagan et al., 2003) and 2007-2009 (Ben-Shoshan et al., 2009). The diagnosis of peanut allergy was made if one of the following conditions was fulfilled: 1) a child that never or rarely ingested peanuts or had an uncertain clinical history of peanut allergy should have either a positive SPT to peanut and peanut-specific IgE >15 kU/l OR a positive SPT response to peanut and a positive DBPCFC or 2) a child who had a convincing history of peanut allergy together with a positive SPT to peanut or peanut-specific IgE. The prevalence of clinical peanut allergy in these school children was 1.5%.in 2000-2002 (Kagan et al., 2003) and 1.6% in 2005-2007 (Ben-Shoshan et al., 2009).

3.2.4 South America

There is limited information on the prevalence of food allergy in South America; two studies were found. In a study performed in Colombia, the prevalence of self-reported food allergy was assessed by questionnaires. In this large study, none of the 3099 participants reported peanut as a causative allergen (Marrugo et al., 2008). In a study from Brazil, sensitisation to food and inhalant allergens was assessed in atopic children and controls. In the control group the rate of peanut sensitisation was 4.8%. The group size was relatively small (n=62), so the prevalence rate is somewhat uncertain. In the atopic group the prevalence of peanut sensitisation was higher: 14.7% were sensitised (Naspitz et al., 2004).

3.2.5 Europe

United Kingdom (UK)
The prevalence of peanut allergy in the UK has been assessed in many studies and the prevalence of self-reported peanut allergy ranges from 0.48% (Emmett et al., 1999), to 2-3% (Pereira et al., 2005; Venter et al., 2006; Du Toit et al., 2008).

Emmet et al (1999) studied the prevalence in a large cohort (n=16,434) and they used a two stage protocol to assess prevalence. In the first stage at-home interviews were done and all individuals reporting peanut allergy were included in the second stage. In this stage, participants were subjected to an in-depth at-home interview. The prevalence was 0.61% in children aged 0-14 years, 0.53%

in adolescents and adults aged 15-44 years and 0.30% in adults of 45 years and older (Emmett et al., 1999).

Self-reported peanut allergy was 2-4 times higher in the other UK studies. Du Toit et al. (2008), found a prevalence rate of 2.3% in the 4-12 year-old and of 1.0% in the 12-18 year children. Only 58% of the children reporting peanut allergy participated in further clinical testing, i.e., measurement of specific IgE or SPT. The authors used cut-off values that positively predict peanut allergy with >95% accuracy (Sampson, 2001) and 77% of the children had a clinically relevant peanut allergy (Du Toit et al., 2008).

Several studies have looked at the prevalence of food allergy, including peanut allergy, on the Isle of Wight. It was possible to assess time trends by comparing three sequential birth cohorts that were performed in the same geographical area (Venter et al., 2009). Sensitisation was assessed with skin prick testing in children aged 3-4 years. It was shown that the prevalence of peanut sensitisation increased significantly from 1.3% in those born in 1989 to 3.3.% in those born between 1994 and 1996 (Grundy et al., 2002). In children born between 2001 and 2002 the prevalence of sensitisation decreased to 2%. Similarly, the increase of clinical peanut allergy increased in the first two cohorts from 0.5% to 1.4% and then decreased slightly to 1.2% (Venter et al., 2009).

In the most recently performed birth cohort study, it was shown that in children born between 2001 and 2002, peanut sensitisation increased especially between the ages of 1 and 2 and then stabilised at the age of three. The percentages of children sensitised were 0.4%, 2% and 2%, respectively. For ethical reasons, only 3 year olds were subjected to DBPCFC. In this group the prevalence of peanut allergy was 1.7% (Venter et al., 2008). In a nested cohort of the Isle of Wight birth cohort, reporting specifically on peanut sensitisation related to peanut consumption, the range of sensitisation to peanut in 543 children was reported at ages 1, 2 and 3. In this sub cohort, sensitisation was comparable to data of the full cohort: 0.55%, 2% and 1.3%, at age 1, 2 and 3 respectively (Dean et al., 2007a; Dean et al., 2007b).

The prevalence of self-reported peanut allergy in the Isle of Wight school cohort was 1.9% in children age 6 years, whereas 2.1% were sensitised to peanut. Of the 15 children sensitised to peanut, 5 refused to participate in oral peanut challenges. Of the 10 remaining children, 4 had a convincing clinical history of peanut allergy. In the remaining six children open challenges were performed and two children were positive. This means that peanut allergy was confirmed in six children. The prevalence in this cohort was estimated to be 0.86%; although a limitation of the study is that 33% did not participate in the open challenges and that none of the children was willing to undergo a DBPCFC (Venter et al., 2006).

In the second school cohort performed in the Isle of Wight, peanut allergy was assessed in 11- and 15-year old children. The prevalence of self-reported peanut allergy was 1.8% and 2.5%, in the 11 and 15 year olds, respectively. The frequency of peanut sensitisation was somewhat higher: 3.7% and 2.6% in 11 and 15 year olds, respectively. In this study food challenges were performed with several food allergens but challenges with peanut were not performed (Pereira et al., 2005).

In a school cohort of 4-5 year old children, 2.8% were sensitised to peanut. There were 30 sensitised children and 9 of them refused to undergo a DBPCFC.

However, 4 of these children had a convincing clinical history and were considered to be peanut allergic. In addition, 15 children were positive in the DBPCFC. The prevalence of clinically relevant peanut allergy in this cohort was 1.8% (Hourihane et al., 2007).

In the Avon Longitudinal Study of Parents and Children (ASLPAC study) the prevalence of peanut sensitisation was 1.4% in children aged seven years. In this study no oral peanut challenges were performed (Roberts et al., 2005).

Scandinavia
The majority of studies on peanut allergy in Scandinavia were performed in Denmark. There were a few studies on peanut allergy or sensitisation in Sweden, Norway and Iceland. Recently, a Finnish study was published on parent reported physician-diagnosed food allergy. Unfortunately, only the prevalence of allergy for legumes (peanut, peas, soy, bean, lentil) as a group was provided and not of peanut allergy (Pyrhönen et al., 2009). In addition, in a cohort of children with cow's milk allergy, it was shown that 26% were sensitised to peanuts (Klemola et al., 2005) (Table 4). So, peanut allergy is not absent in Finland, but the exact prevalence in the general population is unknown.

In the BAMSE birth cohort, conducted in Sweden, parent-reported food allergy, including doctor-diagnosed food allergy, was reported at ages 1, 2, 4 and 8. At the age of 1, the prevalence was 0.3%. At ages 2, 4 and 8, parent-reported peanut allergy was 1, 3 and 5%, respectively (Östblom et al., 2008b). In Swedish adolescents, the prevalence of self-reported peanut allergy was 5.9% (Marklund et al., 2004). Sensitisation to peanut in Swedish adults was somewhat lower than reported peanut allergy, 2.3% were sensitised. In this study sensitisation rates were compared to Norway, were peanut sensitisation was less common than in Sweden: 0.6% (Johansson et al., 2005).

The prevalence rates of peanut allergy assessed with food challenges were assessed in five Danish studies and one study performed in Iceland and Sweden. In the latter, children aged 18-19 months were included to study the prevalence of food allergy, but none of the children from Iceland or Sweden were allergic to peanut (Johansson et al., 2005). This might be explained by the relative young age of the children.

In the Danish studies, the prevalence rates of peanut allergy ranged from 0 - 0.7%, depending on the age. In a cross-sectional study it was shown that the prevalence of peanut allergy was 0% in children aged < 3 years, 0.2% in children aged 3 years, 0% in children and adolescents aged 4-22 years and 0.4% in adults (Osterballe et al., 2005). In the Danish Allergy Research Centre (DARC) birth cohort it was shown that at the age of 6, 0.5% of the children were diagnosed with peanut allergy (Kjaer et al., 2008). When the cumulative incidence from birth to 6 years of age was calculated in this cohort, the incidence was 5.2% for peanut sensitisation and 0.7% for peanut allergy (Eller et al., 2009). In Danish adolescents, similar prevalence rates were found. In the Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS) peanut sensitisation was 5.8% (specific IgE) or 3.4% (SPT). Only 44% were willing to undergo oral food challenges and it was estimated that 0.5% had clinically relevant peanut allergy (Mortz et al., 2005). Similar frequencies were demonstrated in young Danish adults aged 22 years, in which peanut allergy was confirmed in 0.6% (Osterballe et al., 2009).

France, Switzerland and Belgium
In a cross-sectional survey the prevalence of peanut allergy in French school children was assessed with questionnaires. The prevalence was 0.7% in children aged 2-5 years, 1% in children aged 6-10 years and 0.2% in children aged 11-14 years (Rancé et al., 2005). In French children aged 9-11 years old, the prevalence of self-reported peanut allergy was 0.3% (Pénard-Morand et al., 2005). In a large population based cross-sectional study including children and adults, self-reported peanut allergy was assessed in two phases. In phase 1 people with a possible food allergy were identified and these were invited for phase 2. In this phase a more extensive questionnaire was used. When inconsistencies were noted between phase 1 and phase 2 questionnaires, individuals were contacted by telephone. The prevalence rate was 0.35% (Kanny et al., 2001). Hence, the prevalence of self-reported peanut allergy in France ranges from 0.2 – 1%.

In France, an Allergy-vigilance network was established in 2001 with the aim of collecting data on allergies. In 2002, this network assessed the prevalence of peanut sensitisation in France. Peanut sensitisation was reported in four groups: 1) suspected food allergy: 23% were sensitised; 2) suffering from allergic diseases: 8.6%; 3) people sensitised to inhalant allergens: 4%; 4) non-atopics: 0.4%. It is evident that the prevalence of peanut sensitisation is higher in allergic and atopic individuals. Assuming that 25% of the French population is predisposed to atopy, the authors have calculated a rate of peanut sensitisation between 1.05-2.5% (Morisset et al., 2005). In this study, the prevalence of peanut sensitisation in Belgium and Switzerland was assessed as well. This was done in a smaller cohort (n=315) and the prevalence rates were: 2.8% in group 1, 3.8% in group 2, 2.9% in group 3 and 2.9% in group 4 (Morisset et al., 2005). It is important to note that the numbers of participants in groups 1, 3 and 4 are very low (n=35) and the percentages are therefore less reliable. In another study conducted by the Allergy-Vigilance Network, the prevalence of peanut sensitisation was 0.86% in non-atopic children and 0.6% in non-atopic adults from France and Belgium. Higher prevalence rates were reported in atopics: 4.6% in children and 2.1% in adults (Gayraud et al., 2009).

Germany
Peanut allergy was studied in three German studies, looking at reported peanut allergy and sensitisation. There were no published studies found that conducted oral peanut challenges. In a cross-sectional population-based study in German children, questionnaires and telephone interviews were used to select children with suspected food allergy. It was shown that 1.1% of the children were sensitised to peanut. In this study oral challenges with several food allergens were performed, but not with peanut (Roehr et al., 2004). In a population-based nested case-control study, the prevalence of self-reported peanut allergy in adults was 2.1%. This percentage was extrapolated to the general population by using the data of the complete cohort (n=4178) and a prevalence of 1.3% was calculated. In the nested cohort the frequency of peanut sensitisation was much higher than reported peanut allergy: 11.1% were sensitised. Hence, the majority of sensitised subjects do not have clinically relevant peanut allergy (Schäfer et al., 2009). In another German population study the prevalence of peanut sensitisation was 2.4% in a cohort consisting of children and adults. In this study food challenges were performed with several food allergens, but not with peanut (Zuberbier et al., 2004).

The Netherlands
In the Netherlands, peanut sensitisation was assessed in two year old children in the KOALA birth cohort and 4.6% of these children were sensitised to peanut (Snijders et al., 2008). To study time trends for peanut sensitisation, two cross-sectional cohorts were used. The blood samples were collected in two different time periods: 1995/96 and 2007/07. Peanut-specific IgE was measured in the sera from children and adults. It was shown that the prevalence rates increased especially in adults and these differences were significant. In children aged 0-4 years the prevalence increased from 2.1 to 5.6%. In children/adolescents from 5-18 years old no changes were observed, the prevalence rates were 8.2% and 7.5%, respectively. In adults from 19-40 years old the prevalence increased from 6.7 to 9.8% and in adults from 41-79 years old an increase from 3.6 to 5.5% was measured (Ezendam et al., 2009).

3.2.6   Israel

In a study comparing parent-reported peanut allergy in the UK and Israel it was shown that peanut allergy is not as common in Israel as compared to the UK. Parent-reported peanut allergy was 0.15% in children aged 4-12 years and 0.19% in children aged 12-18 years (Du Toit et al., 2008). Similarly, in children aged 0-2 years old the prevalence rates of parent-reported peanut allergy and peanut sensitisation were low: 0.06% and 0.4%, respectively (Dalal et al., 2002).

3.2.7   Australia and New Zealand

In two studies in Australia the prevalence of self-reported peanut allergy was assessed; peanut sensitization was also assessed in one of the studies. There were no publications on peanut allergy assessed with oral food challenges.

Allen et al. (2009) reported in a short communication on the prevalence of perceived food allergy. They used an Internet-based survey and a total of 6.9% reported to have peanut allergy (Allen et al., 2009). Lower prevalence rates were found in a cross-sectional study in five year old school-children. The prevalence of parent-reported peanut allergy was 2.4%. The prevalence rate was assessed in two phases by using questionnaires. In the follow-up phase only children with reported peanut allergy were included and a more extensive questionnaire was used (Kljakovic et al., 2009).

Mullins et al. (2009) retrospectively investigated the trends in peanut allergy between 1995 and 2007. They assessed peanut sensitisation with SPT and subsequently diagnosed peanut allergy if there was a history of acute systemic allergic reaction within 2 hours of food exposure. In the period between 1995 and 2007, 5% of the population was sensitised to peanut and 4.3% were diagnosed with peanut allergy based on clinical criteria. The incidence of peanut allergy was estimated in children born in 2001 and in 2004. At the end of 2007 the incidence for peanut sensitisation was 0.84% and 1.53%, for these two groups respectively and for peanut allergy 0.73 and 1.15%, respectively. These data suggest that the prevalence of peanut allergy is on the rise (Mullins, 2007).

There were no public data available to estimate the prevalence of peanut allergy in New Zealand (Crooks et al., 2008).

3.2.8   *Asia*

Turkey
The prevalence of peanut allergy in Turkey is assessed in two studies. In a large population-based study in adults, self-reported peanut allergy was 0% and only 0.03% of the cohort was sensitised to peanut. However, in these subjects sensitisation was not clinically relevant, because in the DBPCFC the oral challenges with peanut were negative (Gelincik et al., 2008). In a study of 6-9 year old children, parent-reported peanut allergy was 1.1%. All children reporting a food allergy were invited for SPT and 93% agreed to participate. Peanut sensitisation was confirmed in 2 children, giving a prevalence of 0.073%. DBPCFC were performed in the two sensitised children who did not respond to the peanut challenge. Hence, the prevalence of clinical peanut allergy was 0% in this study (Orhan et al., 2009). Apparently, in Turkey peanut allergy is not a common phenomenon and these two studies suggest that it may be absent.

China
Limited data are available from China and the prevalence rates differ greatly. A high frequency of peanut sensitisation of 12.3% was observed in a community-based twin study in twins aged 11 - 71 years (Kim et al., 2008). In a case-control study in Chinese children aged 6-14 years old living in Hong Kong, food sensitisation was assessed in cases (asthmatics) and controls. Subjects were only considered to be sensitised to peanut when the sIgE levels were ≥ 14 kU/L. The prevalence of peanut sensitisation in the control group was 5% (Leung et al., 2002). In another study in Chinese children aged 2-7 years old, a much lower prevalence was found. Parent-reported peanut allergy was 0.52% (Leung et al., 2009).

Korea
In a cross-sectional questionnaire survey it was demonstrated that the prevalence of parent-reported peanut allergy was low. The prevalence rates of reported peanut allergy were 0.45% in children aged 6-12 years old and 0.32% in children aged 12-15 years old (Oh et al., 2004). Hence, peanut allergy is not common in Korean children. In contrast, peanut sensitisation was more common in Korean children with atopic eczema: 16.2% were sensitised (Han et al., 2004) (Table 4).

Thailand
In a study in Thai children aged 6 months to 6 years old the prevalence of food allergy was assessed by questionnaires, SPT and food challenges. None of the parents reported that their children had a peanut allergy, so no additional diagnostic tests were performed for peanut (Santadusit et al., 2005).

Taiwan
The prevalence of peanut sensitisation is only assessed in one study in children with atopic eczema, asthma or allergic rhinitis. The highest prevalence was found in children with atopic eczema (36%); whereas in children with respiratory allergies the prevalence was lower (8.2%) (Lo et al., 2005). Hence, peanut sensitisation is not absent, but the prevalence in the general population is not known.

Japan
There is limited information on the prevalence of peanut allergy in Japan. In a cross-sectional study in 6 year old children reported peanut allergy was absent

(Iikura et al., 1999). In children suspected to have food allergy, however, it was shown that 16% were allergic to peanuts. In this group peanut was the fourth most common food allergen (Ebisawa et al., 2003). A nationwide survey on food allergy in all age groups has shown that peanut is not a frequent allergen. Only in 2.4% of the cases of food allergy, was peanut the causative allergen (Ebisawa et al., 2003).

Singapore
There are no prevalence data available from Singapore. However, peanut sensitisation is quite common in allergic children. In a cohort of children with possible food allergy, it was shown that peanut was the third most common sensitising allergen, 27% were sensitised to peanut (Chiang et al., 2007). In a cohort of children suspected of allergy, 12% was sensitised to peanut (Khoo et al., 2001) (Appendix 1, Table 5).

Table 1 Overview of the average prevalence rate for peanut allergy in different WHO regions

WHO region		Self-reported	Peanut sensitisation	Peanut allergy
EurA	**Average**	**1.3%**	**2.5%**	**0.6%**
	Min-Max	0.06 – 5.9	0.04 – 11	0 - 1.8
	Number	12	22	11
EurB	**Average**	**0.55%**	**0.05%**	**0%**
	Min-Max	0 - 1.1	0.03 – 0.07	0
	Number	2	2	2
AmrA	**Average**	**2.2%**	**0.3%**	**1.6%**
	Min-Max	0.3 – 7.2	--	1.5 – 1.6
	Number	4	1	2
AmrB	**Average**	**0%**	**4.8%**	--
	Min-Max			
	Number	1	1	0
WprA	**Average**	**3.1%**	**8.3%**	--
	Min-Max	0 – 6.9	4.3 – 12	
	Number	3	2	0
WprB	**Average**	**0.43%**	**5%**	--
	Min-Max	0.3 – 0.5		
	Number	2	1	0

For each WHO region the average prevalence is shown together with the minimum and maximum values and the number of studies that was published.

3.3 Patterns of clinical symptoms in peanut allergic subjects

The patterns of clinical symptoms in peanut allergic subjects were only assessed in five of the papers described above. Therefore, an additional search was performed to retrieve data on which symptoms occur in peanut allergic subjects and in which frequency. A total of 9 papers were retrieved (Appendix 2, Table 6).
In the studies of Eller et al. (2009) and Osterballe et al. (2009) the clinical characteristics of a small number of patients are described (n=4 and n=5, respectively) (Eller et al., 2009; Osterballe et al., 2009). It is difficult to extrapolate frequencies from these small numbers to the population of peanut allergic patients. Therefore, these studies will not be discussed further.
The studies in Table 6 differ in the method to assess clinical characteristics. Some studies have used questionnaires, sometimes combined with the

assessment of sensitisation or clinical investigations, and others used oral food challenges. The latter is a more objective method. Some studies have only included children, others only adults, while others have included both children and adults. (Hourihane et al., 1997). In general, most studies have looked at OAS, symptoms in the upper airways (rhinitis and conjunctivitis), respiratory symptoms (wheeze, asthma), skin symptoms (urticaria, atopic eczema, rash, itching), GI tract complaints (abdominal pain, vomiting) and cardiovascular symptoms (collapse, hypotension).
Only a few studies have provided data on the prevalence of anaphylaxis (Moneret-Vautrin et al., 1998; Rancé et al., 1999; Rancé et al., 2005; Mullins et al., 2009) and only in the study of Mullins et al. (2009) was this done by using the criteria described by Sampson et al. (2006). In the other studies it is not described how anaphylaxis is defined.

The overview in Appendix 2, Table 6 shows that skin symptoms are common in peanut allergic patients, 25 – 89% of the patients develop skin symptoms after eating peanuts. OAS is prevalent (32-100%) in some studies (Hourihane et al., 1997; Schäfer et al., 2001; Le et al., 2008), but low (0.5-0.7%) in two French studies (Rance & Dutau, 1999; Rancé et al., 1999). Symptoms in the upper airways are often not reported or not occurring. In contrast, in a Dutch study, rhinitis and conjunctivitis were reported by 23% and 31% of the peanut allergic patients (Le et al., 2008). The frequency of GI symptoms ranges from 15-35% in studies that have used questionnaires (Hourihane et al., 1997; Sicherer et al., 2001a; Sicherer et al., 2001b; Le et al., 2008; Kljakovic et al., 2009). In one study, only 2% reported that GI symptoms were the first symptoms they experienced after eating peanuts (Sicherer et al., 1998). When oral challenges were used, low percentages were found, less than 2% responded with GI symptoms (Moneret-Vautrin et al., 1998; Rance & Dutau, 1999; Rancé et al., 1999). It is important to note that during a food challenge, both subjective and objective symptoms occur. The observers decide which symptoms are specific for an allergic response and especially mild OAS symptoms, i.e., tingling, and GI symptoms like abdominal pain are difficult to read (Niggemann & Beyer, 2007). The prevalence of respiratory symptoms ranges from 14 – 46%. In two studies lower prevalence rates were found: 2% (Sicherer et al., 1998) and 9% (Schäfer et al., 2001). Sicherer et al (1998, 2001a, b) report on the clinical characteristics of the initial reaction to peanut. It is important to note that subsequent reactions to peanut may become more severe over time (Bock & Atkins, 1989; Hourihane et al., 1997). Hence, these initial symptoms might not be representative for the clinical characteristics in this group.
The grading of severity of the study of Mullins et al. (2009) has been done using the criteria according to the Brown classification (Brown, 2004). According to this classification symptoms are graded as mild (involving skin and subcutaneous tissues only), moderate (respiratory, cardiovascular, or gastrointestinal involvement) or severe (hypoxia, hypotension, or neurologic compromise). In this study 52% suffered from mild symptoms, 42% had moderate symptoms, and 5.8% had severe symptoms. A total of 34% of the children were anaphylactic according to the first two criteria for anaphylaxis (Table 1, Sampson et al. 2006). The prevalence of anaphylaxis is very high in this study, compared to the French studies that report percentages of 4.7-6% (Moneret-Vautrin et al., 1998; Rance & Dutau, 1999; Rancé et al., 1999). The difficulty in the interpretation of the data from Mullins et al. (2009) is that although 34% are classified as being anaphylactic, only 5.8% suffered from severe symptoms.

3.4   Peanut-induced anaphylaxis and mortality

There are limited data available on the incidence of peanut-induced anaphylaxis and mortality. Currently there are not many national registries for severe allergic reactions and the papers that were found often report only on anaphylaxis induced by food and do not report specifically on peanut. The studies that provide information on peanut are summarised in Table 7.

A recent review provides information on existing national registries of severe allergic reactions (Worm et al., 2010). In 1993 a voluntary registry was started to register life-threatening allergic reactions induced by food. For this all physicians in Sweden were asked to report those reactions. In the period from 1993-1996 a total of 61 severe allergic food reactions were reported, and 20 were caused by peanuts. Five of these cases were fatal, one was caused by peanut. The Swedish population consists of approximately 9 million people and the incidence of severe peanut allergic reactions was calculated to be 0.07 per 100,000 people per year and the mortality rate was 0.0037 per 100,000 people per year (Foucard & Malmheden Yman, 1999). In a follow-up of this registry, it was shown that in the first 15 years, four deaths were caused by peanut (Worm et al., 2010).

In Norway a National Reporting System and Register of Severe Allergic Reactions to Food was started in 2000 (Lovik et al., 2004). This registry is voluntary and collects information on reactions and circumstances, the implicated food, and serological data from the patient. This registry received 877 reports from July 200 to December 2010, approximately 70-90 reports each year. Severe reactions were defined as reactions needing medical help. From this report it was not possible to extract the number of cases that were caused by peanut ingestion and it could not be used to estimate the prevalence of anaphylaxis (Namork et al., 2011).

Other national registries have been set up, such as the French Allergy Vigilance Network, a network consisting of 456 members in French-speaking countries. Unfortunately, this network did not report specifically on anaphylaxis or death induced by peanut. They only report that peanut is a common food causing severe allergic reactions (Worm et al., 2010). Similarly, a registry of 74 allergy centres in Germany, Austria and Switzerland started a register of anaphylaxis in 2005. Up to January 2009 1163 anaphylactic reactions were reported (203 in children, 960 in adults) and in children the most frequent causes were peanuts and tree nut, while insect stings were the most frequent in adults, followed by drugs and food. At the moment, there are no specific incidence data for peanut available (Worm et al., 2010).

A study performed in the UK and Ireland searched for the number of severe and fatal peanut-induced cases of anaphylaxis in children 0-15 years. Retrospective data (1990-1998) were collected by searching death certificates and national statistics. A prospective survey from 1998-2000 was done through the British Paediatric Surveillance Unit. In the prospective study 10 severe cases were caused by peanuts. The population under 16 in the UK is 13 million and in the period from 1998-2000 the incidence was 0.038 per 100,000 children per year. The number of deaths induced by peanut between 1990 and 2000 was two. From this a mortality rate of 0.00125 per 100,000 children per year can be derived. in this age group was and the incidence of mortality due to peanut was 0.0015 per 100,000 children (Macdougall et al., 2002; Colver et al., 2005). A retrospective study conducted in the UK showed that in the period from 1992 to

2001 10 deaths were caused by peanut-induced anaphylaxis. The UK population consists of approximately 53 million people, the incidence was 0.0019 per 100,000 people (Pumphrey, 2004). In a follow-up of this study, Pumphrey et al. (2007) report a significantly higher mortality. They evaluated the medical records of all deaths associated with asthma. A total of 9 deaths were caused by peanut. The incidence was 0.017 per 100,000 subjects.

Bohlke et al. (2004) have used medical records to assess the incidence of near-fatal anaphylactic reactions in children and adolescents (< 18 years) between 1991 and 1997. The study population consisted of 229,422 children and in this group 10 cases of anaphylaxis caused by peanut were identified. The incidence was then calculated to be 1.57 per 100,000 person-years. In this study, there were no fatal reactions due to peanut (Bohlke et al., 2004).
Bock et al. report on the number of fatalities caused by food-induced anaphylaxis. A registry of the American Academy of Allergy, Asthma & Immunology and The Food Allergy and Anaphylaxis Network, report 17 fatalities due to peanut in the period of 2001-2006. Importantly, this registry does not represent a systematic or complete registration of all fatal food-induced allergic reactions. Presumably, the incidence based on this report is an underestimation of the actual incidence. The incidence for this period, assuming a population of 313 million citizens in the USA was 0.0054.

In Australia the national databases were searched to find information on the number of deaths due to anaphylactic shock. In the period from 1997 to 2005 three deaths were caused by peanut. The population of Australia consists of 22 million people giving a mortality rate of 0.0017 per 100,000 subjects per year (both children and adults) (Liew et al., 2009).

3.5   Impact on quality of life

In the case of peanut allergy, patients can live without clinical complaints when they are able to avoid eating peanuts. Avoidance is not always easy due to the frequent use of peanuts in food products, either as declared ingredients or unintended ingredients due to cross-contamination during processing and accidental ingestions occur frequently (Hourihane et al., 1997; Sicherer et al., 1998, Vander Leek et al., 2000). Therefore, having a peanut allergy can have a considerable impact on daily life, since patients and their families have to be continuously aware of the disease and which products they purchase. Joining social activities can therefore be difficult and may lead to anxiety and stress. A few studies have assessed the impact on quality of life of food allergies or more specifically of peanut allergy.

Primeau et al. (2000) have studied children and adults with peanut allergy and compared them to those with rheumatoid arthritis. Quality of life was quantified with the European Quality of Life (QoL) questionnaire and impact on the family was assessed with the Impact on Family Questionnaire. Global health status was assessed with the Child Health Questionnaire or the Medical Outcomes Study Short Form 36. The outcome of this study was that parents of children with peanut allergy reported more impairment of quality of life, disruption in family relations than parents of children with rheumatoid arthritis. In adults, there was no difference in quality of life and family relations when both diseases were compared. The higher impact on quality of life in children seems to be related to the fear of fatal reactions by the parents. Therefore, these children are often not allowed to participate in many social activities, such as birthday parties and school excursions. The physical disabilities were significantly more impaired in

the rheumatoid arthritis group than in the peanut allergic group. Hence, peanut allergy has a large impact on quality of life, which seems to be related to stress and concerns about the avoidance of the allergen rather than by disabilities or pain. One limitation of the study is the potential sampling bias, since volunteers were recruited not only from clinics, but also from a community organisation of food allergy. This could mean that people who perceive more difficulties with their allergy are overrepresented (Primeau, 2000).

The impact on quality of life of peanut allergy was studied in comparison to diabetes mellitus in 9 year old children. Quality of life was assessed with a self-designed questionnaire and a Vespid Allergy QoL questionnaire, designed for anaphylactic sensitivity to wasp stings. Quality of life was significantly poorer in peanut allergic patients than in patients with diabetes mellitus. It seemed that peanut allergic children are more aware of the fatality of their disease, whereas children with diabetes are less aware of the long-term implications. Compared to the children with diabetes, peanut allergic children were more anxious about eating outside the home, going on holidays or to birthday parties (Avery et al., 2003).

In a Swedish birth cohort, 9-year-old children with food allergies were selected and their parents were sent a questionnaire of a generic health-related quality of life instrument and disease-specific questions. In children with food allergy, the scores for the subscales physical functioning, social limitations, general health, emotional aspects, bodily pain, mental impact and parental impact were lower compared to children without allergies. On the other hand, when compared to children with other allergies, the scores were higher on the subscales physical and general health and social limitations. The impact on quality of life in food allergic children was the most pronounced in children with symptoms from the lower airways, frequent symptoms and multiple symptoms (Östblom et al., 2008a).

In a Dutch study, quality of life was assessed with the Child Health Questionnaire-Child Form (CHQ-CF87) in children (8-12 years) and adolescents (13-17 years) and with the RAND-36, which is the Dutch translation of the MOS 36-item Short-Form Health Survey. The quality of life was not impaired in children with food allergy, but adolescents with food allergy reported impairment of quality of life. These adolescents reported more often pain, limitations due to this pain and poorer perception of overall health. Furthermore, in adults, 'social functioning', 'vitality', and 'general health' scored lower than in the general population. In addition, by comparing the quality of life scores with those for asthma and diabetes mellitus, it was shown that quality of life in adolescents and adults was better than in asthma patients but worse than patients with diabetes mellitus (Flokstra-de Blok et al., 2009).

4 Discussion

A systematic literature review was performed to find all necessary parameters to calculate the burden of disease for peanut allergens. The first objective was to find prevalence and/or incidence data for peanut allergy. It was decided to include all prevalence data, i.e., self-reported, sensitisation and clinically diagnosed peanut allergy. It is important to note that prevalence assessed with a DBPCFC is considered to be the gold standard. However, only a limited number of studies have used this approach. Sensitisation data will provide prevalence data that are higher than the actual prevalence of peanut allergy, since not all sensitised subjects will have a clinical allergy. However, sensitisation is assessed quantitatively and might provide insight in geographical differences regarding the prevalence of peanut sensitisation. Therefore, these data were included as well. Self-reported peanut allergy was also included. It is known that self-reported food allergy is often an overestimation of actual food allergy but the experimental design of the study has an important impact on the reliability of the results.

The systematic review demonstrated that prevalence data stem predominantly from developed countries, with the majority originating from Western Europe, Scandinavia, North America, and Australia. There are limited data from Eastern- and Southern-Europe, Asia and South America and there are no data from African countries and New Zealand. The prevalence of self-reported peanut allergy ranges for 0%-7.2% in all countries. In Colombia, Turkey, Thailand and Japan, self-reported peanut allergy was 0%. The prevalence of peanut sensitisation varies between the obtained studies, the lowest prevalence rates were found in the Turkish studies and the highest prevalence was found in a study from Germany and one from Singapore. In general, sensitisation was between 1–6%. Only a limited number of studies have used an oral peanut challenge to assess the prevalence. These studies show that in Iceland, Sweden and Turkey the prevalence of peanut allergy is zero. In the study from Iceland and Sweden only children aged 18-19 months were included. Although peanut allergy is generally acknowledged to develop early in life, it is possible that peanut allergy may also develop later in life. In studies from the UK the prevalence ranged from 0.6-1.7%, in the Danish studies it was between 0–0.7% and in the Canadian studies, a prevalence of 1.5-1.6% was found. The prevalence of peanut allergy seems to have increased during the last decades (Mullins, 2007; Ezendam et al., 2009; Sicherer et al, 1999, 2003, 2010, Venter et al., 2009). The study from Venter et al. (2009) suggests that this increase has reached a plateau. Since there is only limited data available on time trends of peanut allergy, the point prevalence values from the retrieved papers will be used in the calculation of the burden of disease.

There are limited data on the mortality rate of peanut-induced anaphylaxis, but the majority of studies that were performed find similar rates: 0.00125, 0.0017 and 0.0019 deaths per 100,000 subjects per year. A ten-fold higher case-fatality was found in the study of Pumphrey et al. (2007). All studies that were found have their own limitations that can have an impact on the estimation of case fatality. For example, in the epidemiological studies, data obtained in a small sample size are extrapolated to incidence data for the general population. It is possible that the sample used in the study is not representative for the general population (Neugut et al., 2001). In addition, retrospective studies using

hospital admissions might underestimate the occurrence of anaphylaxis, since cases that do not need medical attention are not considered. Furthermore, fatalities that occur in the community may not be brought to the hospital (Clark & Camargo, 2007). At present, it appears that peanut allergy can be fatal but this does not occur frequently. Patients at risk for anaphylaxis will be very careful with what they eat and furthermore, these patients will carry an auto-injector that can be used in case of an anaphylactic shock.

It was not possible to assess if the severity of peanut allergy differed between countries around the world. It is well-known that peanut is an important cause of food-induced anaphylaxis, for example in the USA (Sampson et al., 1992; Bock et al., 2001; Lin et al., 2008), UK (Pumphrey & Stanworth, 1996; Macdougall et al., 2002), and France (Moneret-Vautrin et al., 2002; Moneret-Vautrin et al., 2004). Apparently, there are geographical differences in the severity of peanut allergy, since in some countries peanut is not the most important cause of anaphylaxis, for example, in Japan (Imamura et al., 2008), China (Shek & Lee, 2006; Lee et al., 2008), Italy (Novembre et al., 1998; Asero et al., 2007; Calvani et al., 2008) and Switzerland (Helbling et al., 2004), peanut rarely causes anaphylaxis. These geographical differences can have an impact on the burden of disease, but due to a lack of data on the prevalence of anaphylaxis it is currently not possible to take this into account in the burden calculation.

To conclude, this systematic review has found relevant data that can be used to calculate the burden of disease of peanut allergens. However, it is important to note that several assumptions have to be made and that it is not possible to calculate the world-wide burden of disease, due to lack of data.

5   Knowledge gaps and recommendations for the burden calculation

- There is a lack of prevalence data obtained with DBPCFC, the gold standard for assessing peanut allergy. For a burden calculation, it is important to have the most reliable prevalence data. In large epidemiological studies it is not always easy to incorporate DBPCFC and study participants (or their parents) refuse cooperation with a DBPCFC, due to fear of severe allergic reactions. Progress in the field of component-resolved diagnosis, using allergen-specific IgE measurements might lead to more clinical relevant sensitisation data and this is diagnostic tool is easier to incorporate in epidemiological studies.
- The prevalence or incidence of peanut allergy in developing countries is unknown. With the available data it is not possible to obtain full insight into geographical differences in the prevalence of peanut allergy and data from Turkey and Israel suggest that these do exist. Prevalence data from the EU project EUROPREVALL will hopefully provide some more data on the prevalence of peanut allergy, since they have assessed prevalence in Europe, Asia and Africa using a standardised methodology including DBPCFC. These studies are not published yet, but once they are they should be used to update this report.
- There is limited information on the mortality rate of peanut allergy and the available data is probably an underestimation due to several study limitations. An international registry of food-induced anaphylaxis would provide a powerful tool to obtain information on the incidence of food-induced anaphylaxis. This information can aid food allergy management and might unravel upcoming food allergens. A proposal for a pan-European register has been recently recommended by the Food Allergy Task Force of the International Life Science Institute (Worm et al., 2010).

Available parameters to calculate the burden of disease for peanut allergy

- **Incidence of disease**
  The majority of retrieved studies report on prevalence data, the incidence of peanut allergy was reported in only one study. Since the onset of peanut allergy is early in life (median age 18-24 months) (Sicherer et al., 2001b; Green et al., 2007), with continued prevalence in older age groups, it was decided to use the prevalence of peanut allergy in childhood as the incidence for that specific age-group and assume zero incidence thereafter. This assumption might not be completely true because there is some evidence that peanut allergy resolves in a subset of patients. Due to study limitations it has been decided not to include this information and assume no recovery. This means that the prevalence continues in the older age groups, as do the disease sequela. The incidence of peanut allergy in all age groups is therefore 0.5-1.5%. This percentage is in line with the study of Mullins et al. (2007), that reported an incidence of peanut allergy in children aged 0-5 years of 0.73 and 1.15% in children born in 2001 and in 2004, respectively.

- **Years with disability**
  There are no consistent data available on the percentage of peanut allergic patients in whom peanut allergy resolves. Therefore, it is assumed that peanut allergy is a life-long disease and WHO life tables will be used for burden calculations.

- **Severity of clinical symptoms**
  Peanut allergic patients will only suffer from clinical symptoms when they accidentally eat peanuts. The percentage of patients that accidentally eats peanut ranges from 56%-60% in children in the earlier studies (Sicherer et al., 1998, Vander Leek, et al., 2000). Yu et al. (2006) report a lower incidence of accidental reactions in children of 14%. In this group of children 11% suffered from a severe reaction that needed treatment with epinephrine. It is important to note that the duration of allergic symptoms is very short and since burden calculations are based on a lifetime, they will probably not affect the burden of disease. Therefore, severity of disease will not further be considered in the burden calculations.

- **Mortality**
  There is limited data available on case fatalities rates of peanut allergy and all studies have limitations. The available data is consistent and mortality rates are between 0.00125–0.017 deaths per 100,000 subjects per year. Mortality due to peanut allergy appears to be low and probably has a limited impact on the burden calculations. There is a clear need for better case-fatality data, for example, from national registries.

- **Quality of life**
  Several studies have assessed the effects of peanut allergy on quality of life and these have shown that this is impaired in peanut allergic subjects or their families. The impact on quality of life is a relevant parameter in the burden calculation of peanut allergy, especially since most patients, when they are able to avoid peanuts, will not suffer from any medical disabilities, except for co-existing co-morbidities. The daily awareness of the fact that eating a small amount of peanut might elicit severe and potentially life-threatening symptoms is a large burden for the patients and their families. In the future it should be further explored if quality of life can be included in the calculation of the burden of disease

- **Co-morbidities**
  In the burden calculations, co-morbidities might be a relevant parameter as well. Peanut allergic patients often suffer from other allergic diseases, such as atopic eczema or asthma. In the current report we have not focused on these co-morbidities but they will have an impact on the disease burden. It is therefore recommended to make an inventory of the percentage of patients that suffer from co-morbidities and use this to determine the disability weight.

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Appendix 1: Prevalence of peanut allergy

Table 2 Prevalence of self-reported peanut allergy

Reference	Assessment of prevalence	WHO region*	Country	Year	Age (yr)	N	Prevalence (%)
Altman, 1993	Questionnaire	AmrA	USA	1989	<18-70+	3950	5.5
				1993	<18-70+	3750	7.2
Sicherer, 1999	Telephone survey	AmrA	USA	1997	0 - 18	12032	0.4
					19 - 65		0.7
Sicherer, 2003	Telephone survey	AmrA	USA	2002	0 - 18	13493	0.8
					19 - 65		0.6
Sicherer, 2010	Telephone survey	AmrA	USA	2008	0 - 18	13534	1.4
					19 - 65		0.6
Vierk, 2007	Telephone survey	AmrA	USA	2001	0 - >60	4482	0.3
Luccioli, 2008	Longitudinal survey using questionnaires	AmrA	USA	2005-07	4 mo	2441	0.16
					9 mo		0.16
					12 mo		0.32
Marrugo, 2008	Questionnaire	AmrB	Colombia	NA	1-83	3099	0
Emmett, 1999	At-home interview (2 stages)	EurA	UK	1995-96	0 - >45	16430	0.48
					0-14		0.61
					15-44		0.53
					45+		0.30
Du Toit, 2008	Questionnaire	EurA	UK	NA	4-12	2395	2.34
					12-18	1458	1.03
		EurA	Israel		4-12	1992	0.15
					12-18	2573	0.19
Venter, 2006	Questionnaire	EurA	UK	2003-04	6	798	1.9
Pereira, 2005	Questionnaire	EurA	UK	2002-03	11	775	1.8
					15	757	2.5
Ostblom, 2008	Questionnaire	EurA	Sweden	1994-2004	1	3925	0.3
					2	3843	1
					4	3104	3
					8	3104	5
Marklund, 2004	Questionnaire	EurA	Sweden	2003	13-21	1451	5.9

Reference	Assessment of prevalence	WHO region*	Country	Year	Age (yr)	N	Prevalence (%)
Rancé, 2005	Questionnaire	EurA	France	NA	2-5	402	0.7
					6-10	1011	1
					11-14	1303	0.2
Pénard-Morand, 2005	Questionnaire	EurA	France	1999-2000	9-11	6672	0.3
Schäfer, 2001	Questionnaire	EurA	Germany	1997-98	24-74	4178	1.3
Dalal, 2002	Questionnaire	EurA	Israel	NA	0-2	9070	0.06
Gelincik, 2008	Questionnaire	EurB	Turkey	NA	18-79	11816	0
Orhan, 2009	Questionnaire	EurB	Turkey	2006	6-9	2739	1.1
Santadusit, 2005	Questionnaire	SearB	Thailand	NA	0.5-3	188	0
					3-6	468	0
Allen, 2009	Internet-based survey	WprA	Australia	2007	NA	1386	6.9
Kljakovic, 2009	Questionnaire	WprA	Australia	2005-06	5	3851	2.4
Iikura, 1999	Questionnaire	WprA	Japan	1996-97	<6	1336	0
Oh, 2004	Questionnaire	WprB	Korea	2000	6-12	1299	0.45
					12-15	755	0.32
Leung, 2008	Questionnaire	WprB	China	2006-07	2-7	2188	0.52

Abbreviations: yr: years; N: sample size; NA: no information available; UK: United Kingdom; USA: United States of America;
* WHO regions: see Appendix 1.

Table 3 Prevalence of peanut sensitisation (IgE and skin-prick test)

Reference	Study design	Diagnosis	WHO region*	Country	Year	Age (yr)	N	Prevalence (%)
Woods, 2002	Cross-sectional survey	SPT	AmrA	USA	1998	20-44	1141	3.8
Arbes, 2005	Cross-sectional survey	SPT	AmrA	USA	1988-94	6-59	10,863	0.3
Liu, 2010	Cross-sectional survey	sIgE	AmrA	USA	2005-06	1- >60	8203	7.6
Naspitz, 2004	Case-control study	sIgE	AmrB	Brazil	NA	1-12	69	4.8
Dean, 2007	Nested cohort in population birth cohort	SPT	EurA	UK	2001-05	1 2 3	543	0.55 2 1.3
Dean, 2007	Prospective birth cohort	SPT	EurA	UK	2001-04	2	658	2
Venter, 2008	Population-based birth cohort	SPT	EurA	UK	2002-05	1 2 3	763 658 642	0.4 2 2
Tariq, 1996	Population-based birth cohort	SPT	EurA	UK	1993-94	4	1456	1.1
Grundy, 2002	Prospective birth cohort	SPT	EurA	UK	1997-2000	3-4	1246	3.3
Hourihane, 2007	School cohort	SPT	EurA	UK	2003-05	4-5	1072	2.8
Venter, 2006	Population based cohort	SPT	EurA	UK	2003-04	6	700	2.1
Roberts, 2005	Cohort study	SPT	EurA	UK	1998- 2000	7	6213	1.4
Pereira, 2005	Cohort study	SPT, sIgE	EurA	UK	2002-03	11 15	699 649	3.7 2.6
Johansson, 2005	Cross-sectional study	sIgE	EurA EurA	Sweden Norway	NA	>18	1002 500	2.3 0.6
Eller, 2009	Prospective birth cohort	SPT, sIgE	EurA	Denmark	1998-2005	0-6	562	5.2
Mortz, 2005	Epidemiological follow-up	SPT, sIgE	EurA	Denmark	1999	16-20	702	5.8 (sIgE) 3.4 (SPT)
Morisset, 2005	Allergy Vigilance Network	SPT	EurA	France	2002	NA	757	1.1 - 2.5
Pénard-Morand 2005	Population-based cross-sectional study	SPT, sIgE	EurA	France	1999-2000	9-11	6672	1.1
Gayraud, 2009	Allergy Vigilance Network	SPT	EurA	France, Belgium	2006	<16 >16	797 990	0.87 0.6

Reference	Study design	Diagnosis	WHO region*	Country	Year	Age (yr)	N	Prevalence (%)
Morisset, 2005	Allergy Vigilance Network	SPT	EurA	Belgium, Switzerland	2002	NA	82	1.2
Roehr, 2004	Population-based cross-sectional study	SPT	EurA	Germany	1998- 2000	0-17	739	1.1
Schäfer, 2001	Population-based nested case-control	SPT	EurA	Germany	1997-98	25-74	1537	11.1
Zuberbier, 2004	Cross-sectional	SPT	EurA	Germany	1999-2000	0 - >80	4093	2.4
Snijders, 2009	Population-based birth cohort	sIgE	EurA	Netherlands	2004-05	2	789	4.6
Ezendam, 2009	Cross-sectional study	sIgE	EurA	Netherlands	1996-97	0-4	235	2.6
						5-18	440	8.2
						19-40	556	6.7
						41-79	1009	3.6
					2006-2007	0-4	217	5.6
						5-18	627	7.5
						19-40	937	9.8
						41-79	997	5.5
Dalal, 2002	Cross-sectional study	SPT	EurA	Israel	NA	0-2	9070	0.04
Gelincik, 2008	Cross-sectional survey	SPT, sIgE	EurB	Turkey	NA	18-79	11816	0.03
Orhan, 2009	Cross-sectional study	SPT	EurB	Turkey	2006	6-9	2739	0.073
Mullins, 2009	Retrospective study	SPT	WprA	Australia	1995-07	4 mo–66	18028	4.3
Kim, 2008	Cross-sectional study	SPT	WprA	Singapore	1998-05	11-71	2118	12.3
Leung, 2002	Case-control study	sIgE	WprB	China	1999-2001	10.2 ± 4.8	79	5

Abbreviations: yr: years; N: sample size; NA: no information available; UK: United Kingdom; USA: United States of America; SPT: skin prick test; sIgE: peanut-specific IgE; DBPCFC: double-blind placebo-controlled food challenge; mo: months; * WHO regions: see Appendix 1.

Table 4 Prevalence of peanut allergy assessed with oral food challenges

Reference	Study design	Diagnosis	WHO region*	Country	Year	Age (yr)	N	% that underwent oral challenge[1]	Prevalence (%)
Kagan, 2003	Cross-sectional cohort	Clinical history, SPT, sIgE and DPBCFC	AmrA	Canada	2000-02	5-9	4339	59% (10/17)	1.5
Ben-Shoshan, 2009	Cross-sectional follow-up	Clinical history, SPT, sIgE and DPBCFC	AmrA	Canada	2005-07	7	5161	60% (9/15)	1.6
Venter, 2008	Population-based birth cohort	Clinical examination, SPT, open challenges, DBPCFC	EurA	UK	2002-05	3	642	OFC: 95% (22/23) DBPCFC: 14% (1/7)	1.7
Grundy, 2002	Prospective birth cohort	Q, SPT, open challenge	EurA	UK	1994-96	3-4	1246	92% (24/26)	0.64
Hourihane, 2007	School cohort	Q, SPT, sIgE, DBPCFC	EurA	UK	2003-05	4-5	1072	70% (21/30)	1.8
Venter, 2006	Population based cohort	Q, SPT, open food challenge	EurA	UK	2003-04	6	700	61% (19/31)	0.86
Osterballe, 2005	Cross-sectional study	Q, SPT, DBPCFC	EurA	Denmark	2001-02	< 3 3 4-22 > 22	111 486 301 936	NA	0 0.2 0 0.4
Kjaer, 2008	Prospective birth cohort	Q, SPT, sIgE, DBPCFC	EurA	Denmark	1998-2005	6	404	OFC: 62% (8/13) DBPCFC: 38% (5/13)	0.5
Eller, 2009	Prospective birth cohort	Clinical history, SPT,s IgE, open food challenge	EurA	Denmark	1998-2005	0-6	562	NA	0.7
Mortz, 2005	Epidemiological follow-up study	Q, sIgE, SPT, DBPCFC	EurA	Denmark	1999	16-20	702	44% (27/61)	0.5
Osterballe, 2009	Cross-sectional study	Q, SPT, DBPCFC	EurA	Denmark	NA	22	843	26% (12/45)	0.6
Kristjansson, 1999	Prospective multicenter comparative study	Q, SPT, DBPCFC	EurA	Iceland Sweden	1994-95	18-19 mo	324 328	Not applicable	0 0

Reference	Study design	Diagnosis	WHO region*	Country	Year	Age (yr)	N	% that underwent oral challenge[1]	Prevalence (%)
Gelincik, 2008	Population based survey	Q, SPT, sIgE, DBPCFC	EurB	Turkey	NA	18-79	11816	100% (3/3)	0
Orhan, 2009	Cross-sectional study	Q, SPT, DBPCFC	EurB	Turkey	2006	6-9	2739	100% (2/2)	0

Abbreviations: yr: years; N: sample size; NA: no information available; UK: United Kingdom; SPT: skin prick test; sIgE: peanut-specific IgE; DBPCFC: double-blind placebo-controlled food challenge; mo: months; * WHO regions: see Appendix 1; [1]: the percentage of subjects that underwent an oral provocation test is based on the total number of children selected for oral provocation (mostly children suspected for peanut allergy, based on diagnostic tests or other criteria (mentioned in the column as well in brackets).

Table 5 Prevalence of peanut allergy in allergic or atopic populations

Reference	Study design	Diagnosis	WHO region	Country	Year	Age (yr)	N=	Prevalence (%)
De Benedictus 2008	Cohort study in children with atopic eczema	sIgE	--	11 countries*	2002-04	11.5-25.5 mo	2048	24.4
Hill, 2007	Cohort study in children with urticaria	sIgE	--	11 countries*	2002-04	11.5-25.5 mo	2048	31.7
Wang, 2005	Patients with asthma	sIgE	AmrA	USA	NA	4-9	504	17
Rancé, 2005	Cohort of children with food allergy	Questionnaire	EurA	France	NA	11-14	182	8.2
Klemola, 2005	Cohort of children with cow's milk allergy	sIgE	EurA	Finland	NA	4	148	25.7
Lindvik, 2008	Cohort of children with food allergy	SPT, food challenge	EurA	Norway		2.17	35	62.9
Hill, 1997	Birth cohort with atopic infants	SPT, food challenge	WprA	Australia	1990 - 1995	0 – 5	487	34
Hill, 2004	Birth cohort with atopic infants	SPT, food challenge	WprA	Australia	1990-1991	0.5 and 1	487	6.5
Ebisawa, 2003	Patients with food allergy	sIgE and elimination/ challenge	WprA	Japan	1995-2001	0-10	305	16
Chiang 2007	Cohort of children with possible food allergy	SPT, sIgE	WprA	Singapore	2003-06	0.2-15.4	413	27%
Khoo, 2001	Cohort of children with allergic symptoms	sIgE	WprA	Singapore	1995-2000	< 3	75	12
Han, 2004	Cohort study in children with atopic eczema	sIgE	WprB	Korea	2001-03	0.2- 4	266	16.2
Lo, 2005	Retrospective study in: children with atopic eczema children with asthma or rhinitis	sIgE	WprB	Taiwan	2002-2003	2-16	59 74	36% 8.2%
El-Rab, 1998	Cross-sectional study in patients with asthma, rhinitis and urticaria	sIgE	EmrB	Saudi Arabia	NA	19%	adults	23%

Abbreviations: yr: years; N: sample size; NA: no information available; USA: United States of America; SPT: skin prick test; sIgE: peanut-specific IgE; mo: months.

Appendix 2: WHO regions

AfrD	AmrA	EmrB	EurA	EurC
Algeria	Canada	Bahrain	Andorra	Belarus
Angola	United States of America	Cyprus	Austria	Estonia
Benin	Cuba	Iran	Belgium	Hungary
Burkina Faso	**AmrB**	Jordan	Croatia	Kazakhstan
Cameroon	Antigua and Barbuda	Kuwait	Czech Republic	**WprA**
Cape Verde	Argentina	Lebanon	Denmark	Brunei Darussalam
Chad	Bahamas	Libyan Arab Jamahiriya	Finland	Singapore
Comoros	Barbados	Oman	France	Australia
Equatorial Guinea	Belize	Qatar	Germany	Japan
Gabon	Brazil	Saudi Arabia	Greece	New Zealand
Gambia	Chile	Syrian Arab Republic	Iceland	**WprB**
Ghana	Colombia	Tunisia	Ireland	Malaysia
Guinea	Costa Rica	United Arab Emirates	Israel	Philippines
Guinea-Bissau	Dominica	**EmrD**	Italy	China
Liberia	Dominican Republic	Djibouti	Luxembourg	Mongolia
Madagascar	El Salvador	Somalia	Malta	Republic of Korea
Mali	Grenada	Sudan	Monaco	Cambodia
Mauritania	Guyana	Egypt	Netherlands	Lao People's Dem. Republic
Mauritius	Honduras	Iraq	Norway	Viet Nam
Niger	Jamaica	Morocco	Portugal	Cook Islands
Nigeria	Mexico	Yemen	San Marino	Fiji
Sao Tome and Principe	Panama	Afghanistan	Slovenia	Kiribati
Senegal	Paraguay	Pakistan	Spain	Marshall Islands
Seychelles	Saint Kitts and Nevis	**SearB**	Sweden	Micronesia
Sierra Leone	Saint Lucia	Indonesia	Switzerland	Nauru
Togo	Saint Vincent and the Grenadines	Sri Lanka	United Kingdom	Niue
AfrE	Suriname	Thailand	**EurB**	Palau
Botswana	Trinidad and Tobago	**SearD**	Albania	Papua New Guinea
Burundi	Uruguay	Bangladesh	Bosnia and Herzegovina	Samoa
Central African Republic	Venezuela	Bhutan	Bulgaria	Solomon Islands
Congo	**AmrD**	India	Georgia	Tonga
Cote d'Ivoire	Bolivia	Maldives	Poland	Tuvalu
Dem. Republic of the Congo	Ecuador	Nepal	Romania	Vanuatu
Eritrea	Guatemala	Dem. People's Rep. of Ko	Slovakia	
Ethiopia	Haiti	Myanmar	TFYR Macedonia	
Kenya	Nicaragua	Timor-Leste	Turkey	
Lesotho	Peru		Yugoslavia	
Malawi			Armenia	
Mozambique			Azerbaijan	
Namibia			Kyrgyzstan	
Rwanda			Tajikistan	
South Africa			Turkmenistan	
Swaziland			Uzbekistan	
Uganda				
United Rep. of Tanzania				
Zambia				
Zimbabwe				

Appendix 3: Clinical symptoms and mortality rate

Table 6 Patterns of clinical symptoms in peanut allergic subjects

Reference	Country	Diagnosis	Age (yrs)	N=	OAS	Skin	GI tract	Upper airways	Respiratory tract	Cardiovascular	Anaphylaxis
Eller, 2009	Denmark	Open challenge DBPCFC	0-6	4	NR	25%-urticaria 100%-itch	75%	0%	25%	NR	NR
Osterballe, 2009	Denmark	DBPCFC	22	5	100%	NR	NR	NR	NR	NR	NR
Hourihane1997	UK	Questionnaire	0->40	406	60%	51%	35%	NR	40% -wheeze 38% -breathing difficulty	NR	NR
Schäfer. 2001	Germany	Questionnaire	25-74	33	91%	100%	55%	NR	9%	9%	NR
Rancé & Dutau 1999	France	Open challenge DBPCFC	0.5-15	132	0.7%	43% -AD	1.5%	NR	14%	NR	6%
Rancé, 1999	France	Open challenge	0-15	192	0.5%	46% -AD 32%-urticaria	2.1%	0%	15%	NR	4.7%
Moneret-Vautrin 1998	France	DBPCFC	0.5-30	142	NR	40% -AD 37% -angio-edema	1.4%	NR	14%	NR	6%

Reference	Country	Diagnosis	Age (yrs)	N=	OAS	Skin	GI tract	Upper airways	Respiratory tract	Cardiovascular	Anaphylaxis
Le, 2008	Netherlands	Questionnaire	36.7	81	32%	46%	26%	23% - rhinitis 31% - con-junctivitis	46%	11%	NR
Sicherer, 1998	USA	Questionnaire clinical examination	8	68	NR	49%	2%	NR	2%	0%	NR
Sicherer, 2001a	USA	Questionnaire	1-63	100	NR	32%	15%	NR	15%	NR	NR
Sicherer, 2001b	USA	Questionnaire	0-65	3482	NR	89%	26%	NR	42%	4%	NR
Vander Leek, 2000	USA	Clinical anamnesis and DBPCFC	0.4 - 6.8	83		45%		54%*			14%
Kljakovic, 2009	Australia	Questionnaire	5	109	37%	46%	15-19%		30%	19%	NR
Mullins, 2009	Australia	SPT, clinical examination	0.5-66	778		NA	NA		NA	NA	34%

Abbreviations: N: sample size; OAS: oral allergy syndrome; GI tract: gastrointestinal tract; NR: not reported; NA: not available; AD: atopic dermatitis; *
Vander Leek et al. (2000) report on percentage that responds with GI and/or respiratory symptoms.

Table 7 Peanut-induced anaphylaxis: incidence, prevalence and mortality

Reference	Country	Age (yr)	Definition of anaphylaxis[1]	Incidence	Mortality rate
Macdougall, 2002, Colver, 2005	UK and Ireland	0-15	Retrospective study 1990-1998 and prospective study: 1998-2000. Initial screen for ICD-9 codes 995.0, 995.3, 988, E865 and 6931. Incidence calculated for 'Severe' cases (cardiorespiratory arrest with need for treatment with epinephrine) and 'Near fatal' cases (intubation needed)	0.038[2]	0.00125[2]
Pumphrey, 2004	UK	all	Retrospective survey using cases from the death register of the Office for National Statistics	NA	0.0019[2]
Pumphrey, 2007	UK	0-32	Retrospective study of all cases of asthma deaths caused by food, based on medical history.	NA	0.017[2]
Foucard, 1999	Sweden	all	Voluntary registry for all physicians to report life-threatening allergic reactions	0.07[2]	0.0037[2]
Bohlke, 2004	USA	0-17	Review of medical records: ICD codes: 995.0, 995.6, 999.4, 995.4	1.57[3]	0[3]
Bock, 2007	USA	5-50	Voluntary registry kept by members of the American Academy of Allergy, Asthma & Immunology and The Food Allergy and Anaphylaxis Network in the period of 2001-2006	NA	0.0054[2]
Liew, 2009	Australia	all	Retrospective study with data from the National Mortality Database (1997-2005). ICD-10 codes: T78.0, T78.2, T80.5, T88.6, T78.1, T78.3, T78.4 and data from National Hospital Morbidity Database (1994-2005) with the ICD-9 and 10 codes: 995.0 ; 995.4; 995.6; T78.0; T78.2; T80.5; T88.6	NA	0.0017[2]

[1] ICD-9 and 10 codes: 995.0 or T78.2: anaphylactic shock, 995.3: anaphylactic shock caused by allergy unspecified; 995.6 or T78.0: anaphylactic shock caused by food; 995.4 or T80.5: anaphylactic shock caused by anaesthesia; 988: toxic effect – noxious food; 999.4: anaphylactic shock caused by serum; E865: accidental poisoning – food and plants; 693.1 dermatitis caused by food ingestion; T88.6: anaphylactic shock due to adverse effects of drugs properly administered; ICD-10 codes for fatalities: T78.1: death with a cause not elsewhere classified; T78.3: angioedema; T78.4: allergy, unspecified (T78.4).

[2] Incidence is expressed as number of cases per 100,000 subjects per year [3] Incidence is expressed as the number of cases per 100,000 person-years; NA: not data available.