Systematic review of literature on early life patterns of exposure to, and avoidance of, food allergens and later development of sensitisation and clinical food allergy, with particular reference to peanut allergy.

**Document 1: Main report**

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1. Executive Summary

Introduction
Peanut allergy is one of the most common food allergies in the UK. Peanut allergy receives attention in the media because very small amounts can trigger severe, sometimes fatal, allergic reactions in susceptible people, increasing its public health impact. In 1998 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), which advises the UK Government, issued precautionary advice to mothers whose children have a family history of allergic diseases (asthma, eczema, food allergies etc), that they may wish to avoid peanut consumption during pregnancy and breastfeeding, and until the child is 3 years of age. COT’s precautionary advice (which became the UK Government advice) has since come under scrutiny, as further scientific evidence on the development of peanut allergy and other food allergies in children has emerged.

The 1998 COT advice on peanut avoidance
(i) pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy;
(ii) breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation;
(iii) a) in common with the advice given for all children, infants with a parent or sibling with an atopic disease should, if possible, be breast-fed exclusively for four to six months;
   b) during weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided;
(iv) infants or children who are allergic to peanuts should not consume peanuts or peanut products.

Methodology
On behalf of the Food Standards Agency, the British Nutrition Foundation set out to review the literature on food allergy, published since 1999, to assess the relevant evidence base since the 1998 COT advice was first issued. The review has evaluated studies on the link between dietary food allergen consumption or avoidance behaviour in early life and subsequent development of food sensitisation or food allergy, particularly peanut allergy. The review included additional specific questions on peanut allergy, firstly to look at the impact of non-dietary exposure to peanuts and peanut products on the development of peanut sensitisation or allergy; and secondly to evaluate the impact of the precautionary (COT) advice regarding peanut consumption on the behaviours of mothers and on the prevalence of peanut sensitisation and peanut allergy. The review of human studies, as described above, was conducted according to standard systematic review procedures. Studies were critically appraised and assessed on the basis of the strength of the evidence. Systematic review methodology is not routinely applied to animal or mechanistic data; however, there are published studies in these areas that are relevant to the question of whether early life exposure to peanut affects the subsequent development of peanut sensitisation. Therefore, it was considered worthwhile reviewing these studies. We present in this report non-systematic reviews of animal studies on peanut and ovalbumin exposures and the development of
sensitisation to these proteins, and on cord blood mononuclear cell responses to allergens. These reviews were carried out by experts in the relevant fields.

The review of human studies, as described above, was conducted according to standard systematic review procedures. MEDLINE, EMBASE, the Cochrane Library and CAB Abstracts were searched from 1\textsuperscript{st} January 1999 to 7\textsuperscript{th} March 2008. Data extraction forms were developed based upon the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). Twenty-four separate studies were identified. These included nine clinical trials, nine cohort studies, four case-control studies, two cross-sectional studies and two prevalence studies (some studies included more than one study design).

**Results**

The following text is structured according to the four main topic areas in relation to their possible influence on the subsequent development of sensitisation or allergy to foods: maternal dietary intake of food allergens, infant dietary intake of food allergens, infant non-dietary exposure to peanut (including topical) and the impact of the 1998 COT advice.

**Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent acquisition by the child of sensitisation, or allergy to foods?**

There is no evidence, from seven studies identified, of an association between maternal dietary intake of food allergens during pregnancy or lactation and the development of food sensitisation or food allergy in the child. One case-control study did report, in non-allergic women, a statistically significant decreased risk of sensitisation to fish with increased maternal consumption of fish during pregnancy. The results were adjusted for other factors, but these did not include breastfeeding. Another poorly designed study showed an increased sensitisation to peanut in the control group (no dietary restrictions) in comparison with the intervention group (mothers who avoided eggs, cows’ milk and fish for 3 months after delivery). This association was reported to be statistically significant for positive skin prick test, but not for allergen specific IgE production (Hattevig \textit{et al}. 1999). However, no specific advice on maternal peanut consumption had been given to either group. The systematic review identified few studies relevant to this research question, which were mainly of poor quality, and which studied a heterogeneous range of exposures.

There were no studies in animals investigating maternal diet and sensitisation to peanut in the offspring. The available animal studies which utilised ovalbumin as the exposure suggest that maternal consumption of ovalbumin may protect offspring from the development of IgE antibody mediated response to the same antigen. Research published since the 1998 COT report was published has demonstrated that it is highly likely that the fetus is exposed to small (but variable) amounts of food protein derived from the maternal diet and transported across the placenta. However, it remains unclear whether this fetal exposure results in in utero sensitisation of the fetal immune system. Moreover, it is not possible to conclude that in vitro cord blood mononuclear cell responses observed following simulation with food proteins necessarily reflect in utero exposure, in utero sensitisation, or an increased risk of clinical allergy during later life.
Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

There is no consistent evidence, from six studies identified, of an association between infants receiving cows’ milk formula compared with breast milk and the development of food sensitisation or food allergy in the child. One general population based study did find a statistically significant decreased risk of parental report of doctor diagnosed food allergy for cows’ milk formula compared with breastfeeding. However, the results were not adjusted for parental history of atopy, information on breastfeeding was poorly assessed and diagnosis of food allergy was not confirmed. There is no evidence, from eight studies identified, to show that increased duration (beyond 6 months) of breastfeeding protects against food allergy. Two studies reported that breastfeeding compared with never breastfeeding was associated with an increased risk of food allergy in general populations. However, these analyses did not adjust for other factors. There is limited evidence that, in children with (but not without) a family history of food allergy, breastfeeding for nine months or more increases the risk of food allergy.

There is no consistent evidence, from four studies identified, of an association between timing of introduction of solids into the diets of infants, either in general or for specific foods, and the development of food sensitisation or food allergy in the child. One study, conducted in a high risk population, reported a statistically significant increased risk of wheat allergy with delayed introduction of cereals until the child was over 6 months of age. Another study, conducted in a general population, reported a statistically significant increased risk of food allergy in children who had milk or egg introduced after 6 months; however, in an adjusted analysis there was no association between introduction of any foods after 6 months and food sensitisation. One study, conducted in a general population, reported that consumption of fish during the first year of life was related to a statistically significant decreased risk of food sensitisation. One case-control study reported that peanuts were introduced at an earlier age in children who subsequently developed peanut sensitisation, compared with children who did not. The results for this study were not adjusted for potential confounders. Further studies are required to confirm these findings, as the heterogeneous nature (e.g. in terms of exposure) of this evidence is a major limitation.

There is some evidence, from three studies identified, to show that multifaceted interventions (combining dietary and non-dietary interventions, such as house dust mite avoidance) aimed at mothers and infants protect against food sensitisation in the child; however, this was not confirmed when information on food allergy diagnosis was analysed. It is difficult to compare the findings of the multifaceted intervention studies owing to differences in the interventions and methods of assessing outcome.

Evidence from experimental animal studies suggests that oral exposure to peanut can inhibit the development of sensitisation (IgE antibody production) following subsequent administration with the same antigen. Such inhibition is dependent upon the amount of peanut administered and, also genetic background of the animal. Under certain conditions, however, sensitisation and IgE antibody production may be provoked by oral exposure, although oral (gavage) administration may be more effective in this respect than normal dietary exposure. The evidence suggests that oral exposure of rodents to ovalbumin serves to inhibit the subsequent development of sensitisation to the same protein delivered via another route. Much less commonly, particularly with small amounts, it has been found that oral exposure to ovalbumin may induce IgE antibody responses. Whether or not oral exposure of
rodents to ovalbumin causes priming or tolerance is affected by the dose used, genetic background and age of the animal.

**Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?**

There is very little evidence available on non-dietary exposure to peanuts and the development of sensitisation or allergy to peanuts. One small case-control study, with a high risk group and general population control group did find a statistically significant increased risk of peanut allergy in children who had used skin creams containing peanut oil. No such increased risk in children was found for maternal use of skin creams containing peanut oil. These results need to be confirmed in other studies. There is evidence from studies in animals that relatively small amount of protein allergen (peanut or ovalbumin) when applied to the skin can induce an IgE antibody response. This effect has been shown in both mice and dogs. In those studies, peanut protein was applied to damaged skin, rather than intact skin, which may be important. However, apparently healthy human skin often contains minor abrasions, and barrier function in skin from atopic individuals in particular is often compromised. Moreover, it is possible that even with intact skin, sufficient protein may cause immunological priming.

**Has the current UK Government guidance on dietary consumption of peanuts and peanut products had any impact on sensitisation and allergy rates to peanuts in the UK?**

Evidence from two studies which were designed to evaluate the impact of the COT advice found that more than 60% of women who became pregnant after the 1998 COT advice was issued, reduced their intake or avoided peanuts. There is no indication that the target group (women with a family history of atopy) were more likely to take up the advice. The overall evidence from both studies showed that of children who developed peanut sensitisation or allergy, a substantial number (77% sensitisation, 40% allergy) of mothers reported that they reduced their intake of peanuts or avoided eating them. There is some evidence that prevalence of peanut sensitisation and allergy has increased threefold in children born between 1989 and 1996 in the UK (i.e. before the COT advice); but there is no evidence of a further increase among children born in 2002 compared with 1994 in the UK. Between 1986/7 and 2000/1 peanut intake in women aged 19-40 years appears to have decreased slightly. There is no evidence to suggest that the 1998 COT advice is related to a change in peanut sensitisation or peanut allergy.

**Conclusions**

The systematic review has not provided sufficient evidence to make firm conclusions particularly in the area of non-dietary exposure to peanuts and timing of introduction of solids. None of the studies we found met the SIGN criteria for a good quality study. The few studies that were identified assessed a wide range of exposures/interventions and methods of diagnosis of sensitisation and allergy differed between studies, with few using double blind placebo controlled trials. The heterogeneous nature of the evidence makes it difficult to synthesise the evidence in order to develop firm, clear conclusions:

- The available evidence from human studies does not suggest that maternal exposure to or avoidance of food allergens during pregnancy or lactation leads to the subsequent development of food sensitisation or food allergy in the child. On the contrary, information from studies in lactating rats suggests that exposure to ovalbumin via
maternal oral intake, particularly at high doses, may protect the offspring from the development of sensitisation to ovalbumin. Studies of cord blood mononuclear cell responses and allergens published since 1998 suggest that the cord blood mononuclear cell responses observed after *in vitro* stimulation with food allergens are not necessarily the consequence of fetal exposure to, or sensitisation by maternally consumed food allergens.

- Evidence from human studies does not suggest that dietary exposure to or avoidance/delaying introduction of allergenic foods in childhood provides protection from subsequent development of sensitisation or allergy to foods. There are few studies that have investigated the timing of introduction of allergenic foods and more research is required in this area. Evidence from animal studies suggests that oral exposure to low doses of food protein may induce sensitisation; whereas high doses may result in tolerance. This would argue that attempts at avoidance of exposure to food allergens could potentially be harmful, rather than protective, if it proves impossible to avoid the relevant food allergens altogether. The results of investigations in animals need to be confirmed and their relevance to humans explored, in particular the concept of ‘small’ and ‘larger’ amounts in human terms.

- There is little information in humans available on the effects of non-dietary exposure to peanuts on the development of sensitisation and allergy. However, one study did show an increased risk of peanut allergy in children who were exposed to skin creams containing peanut oil. There is some supportive evidence from experimental animal studies examining responses to peanut or ovalbumin. Further studies in humans are required in this area.

- There appears to be confusion among the general public about the 1998 COT advice and it has not been interpreted as intended. More than 60% of women report having reduced (few totally avoided) consumption of peanuts during pregnancy and lactation, including those not targeted by the COT advice. There appears to have been a rise in the prevalence of peanut sensitisation and allergy between 1989 and 1996 but there is no evidence of any significant changes in the prevalence of peanut allergy in the UK since that time.
2. Introduction

Non-toxic adverse reactions to food have been divided into two general categories: immune-mediated reactions (namely food allergy) and non-immune mediated reactions (namely food intolerance) (COT 2000, see Figure 1). Immune-mediated reactions are further subdivided depending on whether they are mediated by immunoglobulin E (IgE) or by other immune system mechanisms. However, even within the scientific literature, there is a lack of consistency in the terms used to describe such reactions. The definitions used in this report are outlined in Box 1. Notwithstanding this confusion, food intolerance and allergy are emerging as major consumer and public health concerns and there is an overall perception that the number of food allergic individuals appears to be increasing in line with a general increase in allergic diseases, such as asthma and eczema, in the UK. In 2000, it was suggested that although around 20-30% of the population think they have food allergy or an adverse reaction to food, the prevalence of adverse reactions to foods and food ingredients was only 1.4 to 1.8% using appropriate objective tests (COT 2000). The prevalence of adverse reaction to food and food ingredients was estimated to be up to 8% in infants and young children (COT 2000). The COT working group found no systematic data that would enable an accurate calculation of prevalence, and hence it is not possible to have a definitive definition of prevalence at this time for the UK. More recent studies continue to report prevalence figures similar to those above; for example, by the age of 3 years, 5-6% of children in a survey on the Isle of Wight suffered from food allergy, diagnosed by food challenges and clinical history (Venter et al. 2008).

Peanut allergy is one of the most common food allergies in the UK and receives attention in the media because very small amounts can trigger severe, sometimes fatal, allergic reactions in susceptible people. Onset of peanut allergy typically occurs in childhood, with some children reported to react on their first known exposure to peanuts suggesting that sensitisation has already been acquired, perhaps via a different (non-dietary) route. In most cases, and unlike other common childhood allergies, peanut allergy persists into adulthood. By comparison, egg or milk allergies are typically outgrown by school age. As many as one in 55 UK children may currently react to peanuts (Hourihane et al. 2007); indeed, peanut allergy is the most common cause of severe (fatal and near fatal) allergic reaction to foods, causing 30% of all cases of anaphylaxis outside hospital (Hourihane et al. 1997).

In 1998 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), which advises the UK Government, issued precautionary advice to mothers whose children have a family history of allergic diseases (asthma, eczema, food allergies etc), that they may wish to avoid peanut consumption during pregnancy and breastfeeding and until the child is 3 years of age (Box 2 and COT 1998). This advice followed a review of the scientific evidence surrounding peanut allergy at that time. This review considered the evidence on the relationship between peanut consumption by pregnant and lactating women and the incidence of peanut allergy in their offspring to be inconclusive, but also considered the presence of a plausible mechanism of sensitisation and allergy, and so concluded that a link was possible.

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1 The full report is available to download at http://cot.food.gov.uk/cotreports/cotwgreports/cotpeanutallergy.
This advice was in part based on the idea that intrauterine immunological sensitisation can occur and is associated with subsequent atopic disease. This notion was also based in part on reports of *in vitro* responses by cord blood mononuclear cells after stimulation by allergens and that these responses were associated with the subsequent development of atopic disease in childhood. The report acknowledged that the information on the relationship between peanut consumption by pregnant women and the incidence of peanut allergy in children was inconclusive, and that the mechanisms of intrauterine sensitisation and its relationship with subsequent atopic disease were uncertain. The advice on peanut avoidance during pregnancy was based on the considered possibility of a link between maternal consumption of peanuts during pregnancy and peanut allergy in offspring.

Similarly, advice from COT to mothers during weaning recommended that toddlers who have parents or siblings who suffer from hay fever, asthma, eczema or food allergies should not eat peanuts or foods containing peanuts, including peanut butter, before they are three years old.

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**Box 1: Terminology used in this report**

COT has previously classified adverse reactions to food as outlined in Figure 1. However, there is lack of consistency in the terms used to describe adverse reactions to food and indeed, many of the studies considered for the purpose of this review have used a variety of terms to describe the development of food allergy. The definitions used in this report are as follows:

**Allergy**: The adverse health effects that may result from the stimulation of a specific immune response (e.g. hayfever, asthma, eczema).

**Atopic allergy**: Allergic sensitisation and allergic disease caused by IgE antibody.

**Food Allergy**: Allergy to food or food products resulting from allergic sensitisation to proteins found in the diet.

**Immunological tolerance**: Formerly describes specific immunological unresponsiveness or immunology hyporesponsiveness – commonly acquired during development or early in life. In the context of food allergy the term tolerance is frequently used to describe the ability to eat potentially allergenic foods without ill-effect.

**Atopy**: A predisposition toward mounting IgE antibody responses. Atopy is associated with allergic disease and, in practice, atopic individuals are commonly defined as those who exhibit sensitisation to two or more allergens.

**Sensitisation**: The act or process of inducing an acquired sensitivity or allergy. It is diagnosed by a positive skin prick test or food specific IgE levels.

**Hypersensitivity**: A state of heightened immune response to innocuous antigens that leads to symptomatic reactions upon re-exposure. There are several types of response including that associated with allergy.
Figure 1: Classification of terms as used in the advisory report to government on adverse reactions to food (COT 2000).

Box 2: The 1998 COT advice
(i) pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy;
(ii) breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation;
(iii) a) in common with the advice given for all children, infants with a parent or sibling with an atopic disease should, if possible, be breast-fed exclusively for four to six months;
    b) during weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided;
(iv) infants or children who are allergic to peanuts should not consume peanuts or peanut products.

2.1 Pre- and Postnatal Sensitisation to Foods

Predisposition plays an important role in determining susceptibility to allergic disease in general, particularly for development of childhood allergy (Rowentree et al. 1985). If one parent has allergies to grass pollen, dust mite or cat/dog dander then his/her child is more likely to become allergic to foods (in the neonatal period) and to inhaled antigens in childhood or early adult life (Burr et al. 1989). However, allergy to a particular inhalant allergen in a parent does not predict that their offspring will also react to the same antigen. In other words, the capacity to mount vigorous IgE antibody responses may be inherited, but the specific allergen against which an allergic response is mounted appears not to be genetically programmed. Other factors – notably exposure patterns (dose, timing and route) – are probably critical factors here.

Of all the factors that govern sensitisation to foods in the neonatal period, the inherited susceptibility to allergic disease is usually the most powerful. Studies have suggested that
allergy is more likely to be inherited from the mother than the father, though atopy in both parents dramatically increases the likelihood of atopy in the child (Ruiz et al. 1992).

2.1.1 Prenatal exposure
The environment experienced by the developing fetus is an extremely complex balance between factors which prevent the rejection of the developing baby (which is genetically and antigenically different from its mother due to inherited traits from the father) and those which promote its growth and development (Kemeny et al. 2002).

Evidence available at the time of the 1998 COT report suggested that fetal T-cells could be primed to common antigens during the second and third trimesters of pregnancy. In this context it is of interest that most studies involving maternal avoidance of allergen-containing foods have taken place during the third trimester i.e. potentially too late to be expected to be influential in high risk infants.

At that time, although it was well established that IgG crosses the placenta (to supply passive immunity to the developing fetal system) there was little information available about the ability of antigen or antigen fragments to cross the placenta from mother to fetus, but the potential for antibody/antigen immune complexes to travel the same path was speculated.

Research since the COT report was published has demonstrated that it is highly probable that the fetus is exposed to small (but variable) amounts of food protein derived from the mother’s diet transported across the placenta. It remains unclear, however, whether such fetal exposure results in the in utero sensitisation of the fetal immune system. Or indeed, whether it might be associated with the development of tolerance.

2.1.2 Antibody responses in early life
The infant’s immune system is immature at birth. IgA is not produced until birth and the presence of IgA in cord blood is indicative of contamination with maternal blood. There is no clear evidence that babies mount an IgE, IgG or IgA antibody response to foods in utero. Normally, it typically takes 3-6 months for babies to make their own IgE or IgG response to food antigens.

2.2 Purpose of the Review
COT’s precautionary advice published in 1998 has since come under scrutiny as further scientific evidence on the development of peanut allergy and other food allergies in children has emerged. On behalf of the Food Standards Agency, the British Nutrition Foundation set out to review the literature on food allergy published since 1999, in order to assess the relevant evidence base since the 1998 COT advice was first issued. The review has evaluated studies on the link between dietary food allergen consumption or avoidance behaviour in early life and subsequent development of food allergy, particularly peanut allergy. The review included additional specific questions on peanut allergy, firstly to look at the impact of non-dietary exposure to peanuts and peanut products and the development of food allergy; and secondly to evaluate the impact of the precautionary advice on peanut consumption on
behaviours of mothers and rates of peanut sensitisation and allergy. The review of human studies as described above was conducted according to standard systematic review procedures. Studies were critically appraised and assessed on the basis of the strength of the evidence. The research questions addressed by the systematic review of human studies are stated in full in section 2.2.1.

In order to get a full picture of the evidence on food allergy, and in particular peanut allergy, separate reviews were carried out of animal studies. Systematic review methodology is not routinely applied to animal or mechanistic data. We conducted non-systematic reviews, carried out by experts in the relevant fields; although, we did carry out a systematic search of the animal literature for peanut. The critical reviews of animal studies on peanut and ovalbumin were conducted by Dr Rebecca Dearman and the full reviews can be found in section 4.

One important aspect of the evidence available to COT in 1998 was evidence related to cord blood mononuclear cells response to allergens. It was felt that this area should be reviewed for recent information. Again, as this evidence is largely mechanistic, it was felt that a narrative review conducted by an expert in the area (Dr Graham Devereux) would be most useful (see section 5). It is intended that the compilation and interpretation of this information will enable the FSA to determine whether the precautionary advice is still appropriate and remains consistent with the best available scientific evidence.

Evidence in the report is presented under each research question. The majority of the report is devoted to the systematic review of human studies (research questions 1 to 4) and section 2 contains a full discussion of the human studies evidence. Sections 4 and 5 relate to the separate review of animal studies and evidence on cord blood mononuclear cells (research questions 5 to 8). Conclusions, based upon all aspects of the evidence, can be found in the final section (section 6).

2.2.1 Systematic review of human studies

Research question 1
Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent development of sensitisation, or allergy to foods by the child?

Research question 2
Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

Research question 3
Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?

Research question 4
Has the current UK Government guidance on dietary consumption of peanuts and peanut products had any impact on sensitisation and allergy rates to peanuts in the UK?
2.2.2 Non-systematic (expert) review of animal studies

Research question 5
Does maternal dietary/oral exposure to allergen (peanut or ovalbumin) – or avoidance of dietary consumption of allergen – during pregnancy/lactation have any impact on the subsequent acquisition by offspring of sensitisation (IgE antibody), or allergy (other signs/symptoms) to the same protein?

Research question 6
Does dietary/oral exposure to allergen (peanut or ovalbumin) – or absence of dietary/oral exposure to allergen - have any impact on the subsequent development of sensitisation (IgE antibody) or allergy (other signs/symptoms) to the same protein?

Research question 7
Does non-oral/dietary exposure to allergen (peanut or ovalbumin), for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to the same protein?

2.2.3 Non-systematic (expert) review of studies on cord blood mononuclear cell responses to allergens in vitro

Research question 8
Does intrauterine immunological sensitisation occur and is it associated with subsequent atopic disease?
3. Systematic review of human studies

3.1 Methodology for human studies

This section covers research questions 1 to 4.

3.1.1 Inclusion and exclusion criteria

Research question 1
Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent development of sensitisation, or allergy to foods by the child?

Study design
Inclusion: All types assessing the development of sensitisation or clinical food allergy.
Exclusion: Case reports; therapeutic or treatment studies, where aim is to control allergic symptoms.

Subjects
Inclusion: Women who are pregnant or breastfeeding; includes women with a family history of atopy.
Exclusion: Women who are not pregnant or breastfeeding

Exposure – comparing avoidance or reduced quantities with non-avoidance in all types of study design:
Inclusion: Maternal diet (potentially antigenic foods include peanuts, nuts (almonds, hazelnuts, walnuts, brazil nuts, cashew nuts, pecans, pistachios and macadamia nuts), cows’ milk, eggs, fish, crustaceans (such as lobster, prawns and crab), celery, cereals containing gluten (wheat, barley, rye and oats), sesame seeds, soybeans, mustard, lupin, molluscs and kiwi fruit1); includes advice to reduce quantity or avoid foods listed or food provided to participants.
Exclusion: Studies reporting dietary intake as nutrients rather than foods; vitamin and mineral supplements (unless it is specified that they contain any of the potentially allergenic foods listed; food preservatives or additives).

Outcome
Inclusion: Allergic sensitisation to foods (e.g. skin prick test/food specific IgE levels for list of foods described under exposure) or clinical allergy (positive food challenge (open and blind) - symptoms occurring shortly (within days) after eating food – vomiting, rash, diarrhoea etc). Also includes self-reports.
Exclusion: Studies with asthma, eczema, atopic dermatitis, rhinitis, atopic wheeze, and other respiratory outcomes, or that do not include any of the above will be excluded.
Foods listed are those required under EU law to be declared with reference to the allergenic source on food labels, with the exception of kiwi fruit. Kiwi fruit is added as there is emerging evidence that allergy to kiwi can be severe, especially in young children (Lucas et al. 2004).
Research question 2
Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

Study design
**Inclusion**: All types assessing the development of sensitisation or clinical food allergy.
**Exclusion**: Case reports; therapeutic or treatment studies, where aim is to control allergic symptoms.

Subjects
**Inclusion**: Infants and children, includes infants and children at a high risk of food allergy (e.g. those with other allergies or a family history of atopy).
**Exclusion**: Infants and children with food allergy at baseline for trials and prospective cohort studies. Studies in which all subjects have food allergy.

Exposure – comparing avoidance or reduced quantities with non-avoidance in all types of study design:
**Inclusion**: Infant/child diet (cows’ milk formula feeding vs. breastfeeding, timing of introduction of foods (weaning practices), potentially allergenic foods as listed above under maternal diet); includes advice to reduce quantity or avoid foods listed or food provided to participants.
**Exclusion**: Studies reporting dietary intake as nutrients rather than foods; vitamin and mineral supplements (unless it is specified that they contain any of the potentially allergenic foods listed; food preservatives or additives). Studies comparing the effects of different infant formulas e.g. Cows’ milk formula compared with extensively hydrolysed formula.

Outcome
**Inclusion**: Allergic sensitisation to foods (e.g. skin prick test/food specific IgE levels for list of foods described under exposure) or clinical allergy (positive food challenge (open and blind) - symptoms occurring shortly (within days) after eating food – vomiting, rash, diarrhoea etc). Also includes self-reports.
**Exclusion**: Studies with asthma, eczema, atopic dermatitis, rhinitis, atopic wheeze, and other respiratory outcomes, or that do not include any of the above will be excluded.
Research question 3
Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?

Study design
Inclusion: All types assessing the development of sensitisation or clinical food allergy.
Exclusion: Case reports; therapeutic or treatment studies, where aim is to control allergic symptoms.

Subjects
Inclusion: Infants and children, includes infants and children at a high risk of food allergy (e.g. those with other allergies or a family history of atopy).
Exclusion: Infants and children with food allergy at baseline for trials and prospective cohort studies. Studies where all subjects are cases i.e. have food allergy.

Exposure – comparing avoidance or reduced quantities with non-avoidance in all types of study design:
Inclusion: Infants and children exposed to non-food sources of peanuts via the respiratory tract or skin (e.g. arachis oil used in skin creams). Also included are other non-food sources of peanuts such as vitamin/mineral supplement preparations); includes advice to reduce quantity or avoid above items.
Exclusion: Creams and other products not specified as including peanuts, peanut oil.

Outcome
Inclusion: Allergic sensitisation to foods (e.g. skin prick test/food specific IgE levels for list of foods described under exposure) or clinical allergy (positive food challenge (open and blind) - symptoms occurring shortly (within days) after eating food – vomiting, rash, diarrhoea etc). Also includes self-reports.
Exclusion: Studies with asthma, eczema, atopic dermatitis, rhinitis, atopic wheeze, and other respiratory outcomes, or that do not include any of the above will be excluded.
Research question 4
Has the current UK Government guidance on dietary consumption of peanuts and peanut products had any impact on sensitisation and allergy rates to peanuts in the UK?

For this research question we have divided the evidence into two parts, direct evidence and indirect evidence. Direct evidence includes studies that report information on knowledge of, or adherence to, the 1998 COT advice, as well as information on sensitisation or allergy to peanuts in the child. As there were likely to be few studies, we also looked for other supporting information, which might help ascertain the impact of the COT advice (indirect evidence). Indirect evidence included prevalence data either on trends in peanut consumption or sensitisation or allergy to peanuts in children conceived after June 1997. Initially a June 1997 cut off was used for the indirect evidence so that prevalence data for peanut consumption and sensitisation or allergy to peanuts before and after the 1998 COT advice was issued, could be compared. As the systematic search ran from the 1st January 1999, it was thought that prevalence data for pregnant women, and infants and children conceived only as early as June 1997 would be reliably identified.

Direct evidence
Study design
Inclusion: Cohort, case-control or cross-sectional studies assessing the development of sensitisation or clinical peanut allergy in relation to adherence of COT advice.
Exclusion: Case reports, randomised controlled trials (RCTs) and other trials; therapeutic or treatment studies, where aim is to control allergic symptoms.

Subjects
Inclusion: Women who became pregnant after June 1998; infants and children conceived after June 1998; residing in the UK.

Exposure
Inclusion: Dietary and non-dietary sources of peanuts in the maternal diet and in the child’s diet up to the age of 3 years, knowledge of the COT advice.

Outcome
Inclusion: Dietary intake of peanuts; sensitisation to peanuts and peanut allergy (food challenge – symptoms occurring shortly after eating food – vomiting, rash, diarrhoea etc, also includes self-reports).

We also included what we have termed ‘indirect evidence’ in order to include information on changes in prevalence of peanut sensitisation/allergy and maternal and child peanut consumption since the 1998 COT advice to supplement the above. That is studies that report on either prevalence or intake, but do not refer directly to the 1998 COT advice.

Indirect evidence (prevalence of peanut sensitisation/allergy in children)
Study design
Inclusion: Prevalence studies or cross-sectional studies.

Subjects
Inclusion: Infants and children conceived after June 1997 (just prior to COT advice); residing in the UK.

Outcome

Inclusion: Sensitisation to peanuts and peanut allergy (food challenge – symptoms occurring shortly after eating food – vomiting, rash, diarrhoea etc). Also includes self-reports.

Indirect evidence (prevalence of peanut consumption during pregnancy, and in children aged 3 years or younger)

Study design

Inclusion: Prevalence studies or cross-sectional studies.

Subjects

Inclusion: Women who became pregnant after June 1997 (just prior to COT advice); residing in the UK; infants and children conceived after June 1997 (just prior to COT advice); residing in the UK.

Outcome

Inclusion: Dietary intake of peanuts.

[Please note that the two types of inclusion criteria for indirect evidence differ by outcome only].

Because the systematic search could only reliably identify prevalence data for pregnant women, and infants and children conceived from June 1997 onwards, additional papers which did not fulfil the inclusion criteria above, but did contain useful prevalence data on peanut intake (mother and child) or peanut sensitisation/allergy prior to 1997 (child), were used. These additional studies were identified by non-systematic methods. The identification of these additional studies allowed a comparison of trends in prevalence over a longer period of time.

3.1.2 Searches

Search strategies, based upon the inclusion criteria, were developed. It was possible to combine all the research questions for human studies into one search. A separate search strategy was developed for each database (Appendix 1). The Cochrane Library (Systematic Reviews and Central Databases), MEDLINE, EMBASE and CAB Abstracts were searched from 1st January 1999 to 7th March 2008. International literature was included; however, articles that have not been translated into English were not included. The search strategy included both MeSH terms and text terms where possible. The search was initially developed for MEDLINE and then translated for use in the other databases. The reference lists of reviews and included studies were checked for any further papers. Abstracts presented at meetings and/or conferences that were unsupported by a full published paper, were not included. A separate search, on authors of included studies, was conducted to find further articles written by these authors. The list of included studies was checked for missing studies by the Advisory Group. Any additional references identified by hand searches were added to
the ENDNOTE database and assessed against the appropriate inclusion/exclusion criteria before inclusion in the review.

Papers identified in the searches were imported into ENDNOTE (duplicate references were deleted). ENDNOTE was used to manage the papers; this included the use of custom fields to record the progress of papers included in or excluded from the review.

3.1.3 Assessing eligibility of papers
A form (IN/OUT form) was developed to assess the inclusion/exclusion of papers. No study was excluded on the basis of quality.

All titles and abstracts of papers imported to ENDNOTE were assessed by one reviewer for inclusion using the above form. Full copies of papers considered potentially relevant (not clearly excluded) were obtained. The full copies of papers were assessed for eligibility using the IN/OUT form. The assessment was carried out independently by two reviewers. Where there was disagreement between the reviewers, this was resolved by discussion between the reviewers or by assessment by a third reviewer.

3.1.4 Data extraction
Data extraction forms were developed based upon the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2008). The methodology assessment is based on a number of key questions that focus on those aspects of the study design that research has shown to have significant influence on the validity of the results reported and conclusions drawn. The key questions differ between study types and a range of checklists is used to bring a degree of consistency to the assessment process. SIGN methodology has been subjected to wide consultation and evaluation. We used checklists for RCTs, cohort studies and case-control studies. We chose to use the SIGN methodology as it was designed to be used to develop guidelines based on a range of study designs and thus the checklists are very comprehensive and include information useful both for data extraction purposes (description of studies and actual results) as well as critically appraising each study. Study design specific forms were modified to include information specific to food allergy. SIGN forms exist for RCTs, cohort and case-control studies. There are no forms for cross-sectional or prevalence studies. In order to critically appraise these studies in the same way as studies with SIGN checklists, new checklists were prepared by modifying the criteria for cohort studies. The checklists can be found in Appendix 2. As the checklists are generic it was not necessary to design separate forms for each research question. The data extraction forms included information on populations studied, exposures/interventions studied (including amount of food allergen exposed to if detailed in paper), methodologies used, quality assessment of studies, results obtained and conclusions made by the authors of the study. All data extraction forms were completed independently by two reviewers. Where there was disagreement between the reviewers, this was resolved by discussion between the reviewers.

3.2 Results of the searches
The main search was conducted on 9th November 2007. A subsequent search was conducted on 7th March 2008 to pick up any further papers that had been added to the literature databases since the main search. The results presented here include articles obtained in both searches. The search identified 5799 references in total. Table 1 shows the numbers found on each database searched and as a result of further checking (hand-search). After removal of duplicate references (those retrieved by more than one database search) 3518 references
remained; 78% (2736) were found by searching Medline. Titles and abstracts were read for each of the 3518 references and full papers were obtained for 357 of these.

Table 1: Numbers of references retrieved and included for each database searched

<table>
<thead>
<tr>
<th>Bibliographic Database</th>
<th>References downloaded from database</th>
<th>References after duplicates removed</th>
<th>Full papers obtained</th>
<th>Relevant papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>2773</td>
<td>2736</td>
<td>308</td>
<td>31</td>
</tr>
<tr>
<td>EMBASE</td>
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<td>0</td>
</tr>
<tr>
<td>Cab Abs</td>
<td>1253</td>
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<td>1</td>
</tr>
<tr>
<td>Cochrane</td>
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<td>0</td>
</tr>
<tr>
<td>Hand-search*</td>
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<td>8</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>5799</strong></td>
<td><strong>3518</strong></td>
<td><strong>357</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

*Includes papers identified after searching bibliographic databases

Each of the full papers was assessed independently by two reviewers. Disagreements were discussed between the two reviewers or referred to another reviewer for clarification of inclusion/exclusion criteria. A total of 32 papers were regarded as relevant by this process. The Kappa score for agreement was 0.63 (0.50, 0.76), this result lies in the range (0.6-0.8) for substantial agreement (McGinn et al. 2004). None of the papers obtained by hand searching were regarded as relevant when considered against the inclusion/exclusion criteria. Only one relevant paper was not found by searching Medline.

The 32 papers were reviewed to see if any of the papers came from the same study. Reference lists of included papers were checked for further papers providing information on study methodology. In addition, we also reviewed full copies of supplementary papers for relevant information e.g. letters, comments, methods papers. Study design and relevant research question was allocated before data extraction commenced. A list of the 325 papers excluded from the systematic review can be found in Appendix 3.

3.3 Interpretation and quality assessment of the evidence

Tables of evidence have been constructed in order to compare and contrast the different studies. The tables can be found in a separate document [Document 2: Tables of evidence]. The tables of evidence follow the general format of the tables used by SIGN (SIGN 2008).

The evidence is ordered firstly by review research question and, secondly by study design. The study design and quality score appear in the second and third columns. An addition has been made to the quality rating of studies compared with the standard SIGN process. Using SIGN, quality is assessed as ‘++’ if all or most criteria have been fulfilled, ‘+’ if some of the criteria have been fulfilled, and ‘-’ if few or no criteria have been fulfilled. As all the studies apart from two had a rating of ‘+’ using the existing SIGN criteria, it was therefore difficult to differentiate between studies on this basis alone. Therefore in Document 2: Tables of evidence, in addition to the SIGN notation, the actual quality score has been included. The top number refers to the number of criteria rated ‘well covered’ or ‘adequately covered’. The bottom number refers to the number of criteria that were relevant to that study.

The section on number of subjects provides information on response rate for entry into the study and follow-up (if relevant). It also includes information on numbers of subjects
included in the final analyses. This is important as in many studies the numbers of subjects with some information at follow-up (for example completed a questionnaire) is not necessarily the same (and may be much lower) as in the relevant analyses (e.g. information on SPTs). Subject characteristics are described and these include the method of recruitment, inclusion and exclusion criteria and whether the sample is from the general population or a high risk group (as defined by the authors). Information on the food allergen is provided in the next two columns. The first provides details on the exposed group, and the second on any avoidance or reduced exposure to food allergens. The columns also provide information on dietary advice given, dietary assessment methods used and compliance with the advice. Length of follow-up is given for RCTs and cohort studies and this relates to the longest follow-up. For case-control studies, the period (in time) of recall is entered. Outcome measures are described with cut-offs for SPTs or IgEs given. The results are shown in the last column and results for food allergy (report of symptoms or reactions to foods, which may or may not be confirmed by doctor’s diagnosis, open challenge or DBPCFC) and sensitisation (information on positive SPT and food specific IgEs are shown separately. At the bottom of the table, under ‘comment’, the overall findings relevant to this systematic review are stated. This section also includes relevant information on the quality of the study.

Under research question 2 some studies were set up as RCTs in order to compare the effects of different infant formulas. Our key interest, under this research question, is in understanding the influence of early dietary exposure to allergenic foods (e.g. cows’ milk) on food allergy outcomes, and hence studies comparing the use of different infant formulas were not considered relevant to the review. However, studies that included a group of infants who were breastfed compared with infants who received cows’ milk formula were regarded as relevant. In some studies, infants receiving breast milk were not randomised (as it would not have been ethical); these studies are marked RCT*. The asterisk denoting that the breastfeeding arm was not randomised; however the cows’ milk formula arm (or comparison group) was randomised. For other studies we have classified the study design by the method of analysis.

In the following sections, summary tables have been produced. These draw on information from the full tables of evidence given in [Document 2: Tables of evidence] and are used to compare and contrast studies focusing on the same food allergen exposure. These tables have been kept simple and only contain a minimum amount of data. For full information on studies please refer to ‘Document 2: Tables of evidence’.

3.4 Description of included studies

This section provides some information about the overall nature of the evidence. Thirty-two published papers met the inclusion criteria and are included in the tables of evidence (separate document [Document 2: Tables of evidence]). To these we added a further 25 methodology papers, resulting in 57 articles in total. This list of 57 papers, sorted by study, appears in section 4.7.1 References – included studies. The 32 papers meeting the inclusion criteria are indicated by an asterisk. After grouping papers by study, 24 separate studies were identified.

Whilst reading titles and abstracts of papers in the ENDNOTE database and lists of references of full papers meeting the inclusion criteria, we identified additional papers that did not fulfil the inclusion criteria but did contain useful supplementary information on prevalence of peanut sensitisation/allergy prior to 1997 in the UK. A total of five papers
(Emmett et al. 1999, Grundy et al. 2002, Lack et al. 2003, Pereira et al. 2005, Tariq et al. 1996) were identified in this way. We also conducted a search of Medline using the terms ‘peanut’ and ‘prevalence’ on 2 May 2008 and identified one further paper from the Isle of Wight study group (Venter et al. 2008). The same procedure was used to select data on prevalence of peanut sensitisation/allergy in the US (both before and after the COT advice was published). This resulted in a further four papers being identified (Bock 1987, Green et al. 2007, Kagan et al. 2003, Sicherer et al. 2003). These references are shown in section 4.7.2 References – other. The results of these studies are presented separately in section 4.5.4 Indirect evidence.

3.4.1 Study design

Twenty-four separate studies were identified with 26 study designs. Of these nine were trials, nine were cohort studies, four were case-control studies, two were cross-sectional studies and two were prevalence studies. One study included both cohort and case-control data and one study included cross-sectional and prevalence data.

Table 2 shows the study designs and research questions investigated by each of the 24 studies. Numbers do not add up to 24 studies as some studies were relevant to more than one research question. Three studies were relevant to research questions 1 and 2, one study was relevant to research questions 2 and 3, one study was relevant to research questions 1, 2 and 3, one study was relevant to research questions 2 and 4, and one study was relevant to both direct and indirect evidence for research question 4. This gives a total of 32 separate study design/research objective comparisons. Most of the evidence found (19 studies) is related to research question 2 (childhood diet) and this is largely split between trials and cohort studies. Evidence on the effect of maternal diet comes mainly from case-control studies, rather than prospectively designed studies. Only two studies looked at non-dietary exposure to peanuts, and only two studies assessed the impact of the 1998 COT advice. Research question 2 is the only research question with evidence from a number of RCTs. Although it should be noted that many of these were not true RCTs, as the breastfeeding group was not randomised.

Table 2: Study designs by relevant research question

<table>
<thead>
<tr>
<th>Research question</th>
<th>Number of studies</th>
<th>Number of studies by study design</th>
<th>Trials</th>
<th>Cohort</th>
<th>Case-control</th>
<th>Cross-sectional</th>
<th>Prevalence</th>
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</tr>
</tbody>
</table>

Note: one study may provide results relevant to more than one research question.

3.4.2 High risk or general population group

High risk populations were defined in a number of ways by different studies. ‘High risk’ is used to refer to atopic family history in parents and/or siblings, attendance of infant at an allergy clinic, or raised cord blood allergen specific IgE in the infant. Table 3 shows that more studies relevant to research question 1 (maternal diet) were carried out in high risk populations. There is a fairly even distribution of high risk/general population groups for
research question 2 (childhood diet). Overall 15/32 (47%) of studies were conducted in high risk populations.

Table 3: Population type by relevant research question

<table>
<thead>
<tr>
<th>Research question</th>
<th>Number of studies</th>
<th>High risk group</th>
<th>General Population group</th>
<th>High risk + general population group (analysed as separate groups)</th>
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<td>0</td>
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<tr>
<td>4 Indirect</td>
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</tbody>
</table>

3.4.3 Country study carried out in

Table 4 shows that most studies were carried out in Europe (75%); however there were some studies from USA/Canada, Japan and South Africa.

Table 4: Country study carried out in by relevant research question

<table>
<thead>
<tr>
<th>Research question</th>
<th>Number of studies</th>
<th>UK</th>
<th>Other Europe</th>
<th>USA/Canada</th>
<th>Japan</th>
<th>South Africa</th>
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</table>

Note the three entries for South Africa relate to the same study.

3.4.4 Date of publication

Where there was more than one paper reporting on a study, the date of the main paper (the paper contributing most to the data extraction) was used. Table 5 shows that overall there is a fairly even distribution across the years. However, more studies (3/7) relevant to research question 1 (maternal diet) were published in 1999-2000 and more studies (3/4) relevant to research question 4 (evaluation of COT advice) in 2007-2008.

Table 5: Date of publication of study by relevant research question

<table>
<thead>
<tr>
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</tbody>
</table>
3.4.5 Quality of studies

Table 6 shows the quality rating of the studies using the SIGN notation (‘-‘ a study meeting few or no criteria, ‘+‘ a study meeting some criteria, ‘++‘ a study meeting most or all criteria). There was no further information available from SIGN regarding the number of criteria required to be met for a ‘+‘ or ‘++‘ rating. We defined a rating of ‘-‘ as a score of 20% or less (i.e. 2 out of 10) and a rating of ‘++‘ as a score of 70% or more (i.e. 7 out of 10). All studies apart from two were assessed as ‘+‘ i.e. they met some of the criteria. Of note is the poor quality of the non-randomised clustered trial (we used the cohort study checklist to assess this study) for research question 1 (Hattevig et al. 1999). Overall, the quality of evidence is not high, we did not find any systematic reviews or meta-analyses covering the same time period. We did not find any high quality RCTs. Of the eight trials under research question 2, three did not adequately randomise the infants receiving breast milk. The three trials assessing the effects of multiple interventions had a slightly higher quality score than those assessing infant formulas and breast milk. About a third of the overall data comes from ‘+‘ rated case-control, cross-sectional and prevalence studies and hence is not strong evidence.

Table 6: Quality of studies using SIGN criteria by relevant research question

<table>
<thead>
<tr>
<th>Research question</th>
<th>Number of studies</th>
<th>Number of studies by study design</th>
<th>Case-control</th>
<th>Cross-sectional</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Trials</td>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>1 (-)</td>
<td>2 (+)</td>
<td>4 (+)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>8 (+)</td>
<td>9 (+)</td>
<td>1 (+)</td>
<td>1 (+)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1 (+)</td>
<td>1 (+)</td>
<td>0</td>
</tr>
<tr>
<td>4 Direct</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (+)</td>
</tr>
<tr>
<td>4 Indirect</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

We assessed which quality criteria were adequately addressed by most studies (at least 75%) and which quality criteria were adequately assessed by least studies (less than 25%) for RCTs, cohort studies and case-control studies. For all study designs, most studies addressed an appropriate and clearly focused question. In addition for RCTs, all studies used at least a skin prick test to assess outcome. For cohort studies, all groups being assessed in a study were selected from the same source population and outcomes were clearly defined. Most cohort studies had an adequate rate of follow-up (at least 80%), however, it should be noted that numbers included in final analyses could be lower. Most cohort studies reported 95% confidence intervals. For case-control studies, most studies recruited cases and controls from comparable populations and the same exclusion criteria were used for both cases and controls.

The quality criteria which were least likely to be met for RCTs, were subjects and investigators not being kept blind about treatment allocation and not using an intention to treat analysis. For cohort studies, the main shortcomings were: no comparison was made between full participants and those lost to follow-up by exposure status, the assessment of outcome was not made blind to exposure status, a reliable measure of exposure assessment was not used, and exposure level was not measured more than once. For case-control studies the main problem was not taking into account confounders in the analysis.

Summary

Twenty-four studies have been included in the tables of evidence. About two thirds of the studies come from trials and cohort studies, none of which are high quality (as
assessed by the SIGN criteria). The majority of the evidence relates to research question 2 (child’s diet), with few studies assessing non-dietary exposure or evaluating the COT advice. Much of the evidence comes from Europe, although studies from other continents, notably USA/Canada, were found. Date of publication was spread across the years examined.
3.5 Analysis of the evidence

Tables summarising the separate studies can be found in the tables of evidence (separate paper: Document 2). The results are presented under each research question. Most studies in the review have defined statistical significance as $p<0.05$, some as $p=0.05$ and for some the level of significance is not clearly reported. Throughout this report statistical significance has been referred to as $p\leq 0.05$. Results reported as $p>0.05$ are not considered statistically significant in the context of this report. Please note that where confidence intervals are reported they all refer to 95% confidence intervals.

3.5.1 Research question 1

Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent development of sensitisation, or allergy to foods by the child?

In total, seven studies were relevant to this research question. These seven studies can be found on pages 1 to 7 of the tables of evidence in Document 2. There was one non-randomised clustered trial, two cohort and four case-control studies. The results have been separated into mother’s diet during pregnancy (five studies) and mother’s diet during lactation (four studies).

**Mother’s diet during pregnancy**

Five studies assessed mothers’ diets during pregnancy and are shown in table 7. All studies, apart from one, were case-control studies. Two studies assessed intake of a number of different foods and either food sensitisation or food allergy (Sausenthaler *et al.* 2007 (LISA study from USA) and Ushiyama *et al.* 2002 (from Japan)). They both produced similar ranges of adjusted odds ratios for dairy foods, fish and eggs; and none were statistically significant. Sausenthaler *et al.* 2007 reported on sensitisation at 2 years and Ushiyama *et al.* 2002 on reported food allergy (not confirmed) up to age one year. Calvani *et al.* 2006, a case-control study from Italy, reported on maternal fish intake and risk of sensitisation to fish in children. Mothers reporting at least one of the following: asthma, hay fever or atopic eczema were defined as allergic mothers and mothers with none of these complaints were defined as non-allergic. In children with non-allergic mothers, increased maternal fish consumption was associated with a decreased risk of sensitisation to fish. No association was found in children with allergic mothers. The study also reported on maternal fish intake and sensitisation to milk or egg. It is not clear whether these data refer to the whole population or if the odds ratios were adjusted for other factors, however, the authors’ reported a statistically significant decreased risk for milk sensitisation with increased maternal fish consumption. A decreased risk of egg sensitisation and increased maternal fish consumption was also reported, but this result was not statistically significant. The study was carried out in a high risk group (infants were attending outpatient allergy clinics). Over 90% of children enrolled were included in the analysis; however it is not clear how many subjects declined to take part. The children in the study were aged up to 18 years; and hence for some mothers the period of recall was a long time and therefore prone to bias. The dietary questionnaire was self-administered and it is not clear whether it had been validated in this population. Importantly, although the results were adjusted for other factors; they were not adjusted for breastfeeding (whether the child was breastfed or duration of breastfeeding). Both Sausenthaler *et al.* 2007 and Ushiyama *et al.* 2002 presented results related to maternal fish intake (high intake vs. low intake) and food sensitisation/allergy, and neither reported a statistically significant association. Ushiyama *et al.* 2002 reported an adjusted odds ratio for maternal fish intake and parental reports of food...
allergy of 0.81 (0.30, 2.20). Sausenthaler et al. 2007 reported an adjusted odds ratio for maternal fish intake and food sensitisation (FX5: combined egg, cows’ milk, wheat, peanut, soybean and codfish) of 1.01 (0.69, 1.48).

Two case-control studies assessed consumption of peanuts during pregnancy. Frank et al. 1999 studied a high risk group (children with suspected food allergy) in South Africa. Those sensitised to peanut (established by positive specific IgE to peanut, but no food challenge tests) were compared with controls with milk or egg sensitivity (but no sensitivity to peanut). The study was small (only 25 cases) and around 90% of subjects were included in the final analyses. The results were not adjusted for other factors and the authors’ reported an odds ratio of almost 4.0 (for cases compared with controls); however this did not reach statistical significance. The other study was also small (23 cases), Lack et al. 2003 (from UK), studied a group with confirmed peanut allergy and compared these cases to atopic and non allergic controls. Results were not adjusted for other factors. There was no association with consumption of peanuts during pregnancy and peanut allergy in the child.
Table 7: Mother's diet during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dairy foods, eggs, nuts, fish</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sausenthaler et al. 2007</td>
<td>Cohort 7/13</td>
<td>General population group</td>
<td>2 years</td>
<td>Sensitisation Positive food specific IgE</td>
<td>Adjusted odds ratios (high vs. low dietary intake) between 0.89 and 1.26 NS</td>
</tr>
<tr>
<td><strong>Dairy foods, fish, eggs, tofu/natto</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ushiyama et al. 2002</td>
<td>Case-control 5/11</td>
<td>General population group</td>
<td>Up to one year</td>
<td>Food allergy Parent reported food allergy</td>
<td>Adjusted odds ratios (high vs. low dietary intake) between 0.62 and 1.16 NS</td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calvani et al. 2006</td>
<td>Case-control 7/10</td>
<td>High risk</td>
<td>Up to 18 years</td>
<td>Sensitisation Positive SPT to fish.</td>
<td>Adjusted odds ratio (high vs. low fish intake) Allergic mothers 1.13 (0.31, 4.1) NS Non-allergic mothers 0.23 (0.08, 0.69) Sig (P Trend = 0.002)</td>
</tr>
<tr>
<td><strong>Peanuts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank et al. 1999</td>
<td>Case-control 6/10</td>
<td>High risk</td>
<td>Up to 3 years and 9 months</td>
<td>Sensitisation Positive peanut specific IgE</td>
<td>Unadjusted odds ratio (peanut consumption &gt; once a week vs. &lt; once a week ) 3.97 (0.73, 24.0) NS</td>
</tr>
<tr>
<td>Lack et al. 2003*</td>
<td>Case-control 6/11</td>
<td>High risk</td>
<td>5-7 years</td>
<td>Food allergy DBPCFC to confirm peanut allergy</td>
<td>% mothers who consumed peanuts Cases – 65% Controls (atopic) – 71% Controls (normal) –61% NS</td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; IgE – immunoglobulin E; SPT – skin prick test; Sig – statistically significant (P ≤ 0.05); NS – not statistically significant (P > 0.05); values in brackets given after odds ratios refer to 95% confidence intervals; *this case-control study used two controls groups, one atopic and one normal. Quality score – the derivation of this score is described in section 3.4.5.

**Mother’s diet during lactation**

Four studies assessed mother’s diet during lactation and are shown in table 8. Most of the studies were carried out in high risk populations. The studies included one non-randomised clustered trial, one cohort study and two case-control studies. The non-randomised clustered trial was a study in which the intervention and control groups were located in two ante-natal clinics in Sweden (Hattevig et al. 1999). The rationale for deciding which one of the ante-natal clinics was the intervention group was not clear. The trial by Hattevig et al. 1999 was carried out in a high risk population (both parents with atopic disease, or one parent and one sibling with atopic disease, or single heredity and cord blood IgE ≥0.9kU/L). The allergen avoidance (diet) group was advised to follow a diet free from eggs, cows’ milk and fish from delivery for three months. The control group (non-diet) mothers were allowed to follow an unrestricted diet after birth of the infant. Results were presented on 80% of children at age 10
years. Data on parental reports of food allergy and food sensitisation showed no difference between the intervention and control groups. However, the non-diet group compared with the diet group did have a slightly higher percentage of children with food sensitisation/food allergy. The study also presented information on specific food allergens. For codfish, wheat and hazelnut there was no difference in sensitisation between the intervention and control groups. However, there was an increased sensitisation to peanut in the control group (non-diet) which was statistically significant for SPT, but not for IgE. An increased sensitisation to soy was also found in the control group; however this time it was only statistically significant for IgE and not for SPT. There was no adjustment for other factors and no information on compliance with advice given. This study was rated very poorly according to the SIGN criteria. Wetzig et al. 2000, a cohort study from Germany, assessed the effect of avoiding egg or cows’ milk. No actual results were represented in the paper apart from a statement that there were no statistically significant findings.

Two case-control studies specifically assessed consumption of peanuts during lactation. The same two studies are described under the previous section. Frank et al. 1999 found no association between consumption of peanuts during lactation and peanut sensitisation in the child. Lack et al. 2003 found that mothers of children with peanut allergy were more likely to consume peanuts at least seven times a week compared to mothers of atopic or normal controls; however when these results were adjusted for other factors (it is not clear what these factors were) the result was no longer statistically significant.

One other study made reference to maternal peanut consumption and peanut sensitisation in infants (Hourihane et al. 2007). This study is reported in full under research question 4. Authors reported there was no difference in whether mothers changed their consumption of peanuts (reduced or avoided i.e. as a response to the COT advice) and whether their children were sensitised to peanuts (no actual data reported in the paper, it is unclear whether the maternal intake related to intake during breastfeeding or lactation or both).
Table 8: Mother’s diet during lactation

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eggs, cows’ milk, fish</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hattevig et al. 1999</td>
<td>Non-randomised clustered trial 3/13</td>
<td>High risk</td>
<td>10 years</td>
<td>Food allergy</td>
<td>Food allergy</td>
</tr>
<tr>
<td></td>
<td>Diet Group was advised to follow diet free from cows’ milk, eggs and fish. Non-diet Group followed an unrestricted diet</td>
<td></td>
<td></td>
<td>Parent reported</td>
<td>Diet: 11% Non-diet: 16% NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitisation</td>
<td>Sensitisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive IgE or SPT – any food allergen</td>
<td>Any food (IgE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet: 18% Non-diet: 23% NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any food (SPT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet: 14% Non-diet: 24% NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peanut (IgE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet: 8% Non-diet: 19% NS</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Peanut (SPT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet: 2% Non-diet: 14% Sig (P=0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Soy (IgE)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Diet: 3% Non-diet: 17% Sig (P=0.02)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Soy (SPT)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Diet: 3% Non-diet: 4% NS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS for cows’ milk, egg white, cod fish, wheat and hazelnut</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hen’s egg or cows’ milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wetzig et al. 2000</td>
<td>Cohort 6/12</td>
<td>High risk</td>
<td>2 years</td>
<td>Sensitisation</td>
<td>No statistically significant difference in atopy in child and maternal egg or milk consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive food specific IgE</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peanuts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank et al. 1999</td>
<td>Case-control 6/10</td>
<td>High risk</td>
<td>Up to 3 years and 9 months</td>
<td>Sensitisation</td>
<td>Unadjusted odds ratio (peanut consumption &gt; once a week vs. &lt; once a week)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive peanut specific IgE</td>
<td>2.19 (0.39, 13.47) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack et al. 2003*</td>
<td>Case-control 6/11</td>
<td>High risk</td>
<td>5-7 years</td>
<td>Food allergy</td>
<td>% mothers who consumed peanuts at least 7 times a week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DBPCFC to confirm peanut allergy</td>
<td>Cases – 17% Controls (atopic) – 5% Controls (normal) – 5% P=0.03 NS after adjustment, unclear what factors were adjusted for</td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; IgE – immunoglobulin E; NS – not statistically significant (P> 0.05); values in brackets given after odds ratios refer to 95% confidence intervals; *this case-control study used two controls groups, one atopic and one normal. Quality score – the derivation of this score is described in section 3.4.5.
Summaries

ALL FOODS: There is no evidence, from seven studies, of an association between maternal dietary intake of food allergens during pregnancy or lactation and the development of food sensitisation or food allergy in the child. One case-control study did report in non-allergic women a statistically significant decreased risk of sensitisation to fish with increased maternal consumption of fish during pregnancy. The results were adjusted for other factors but these did not include breastfeeding (Calvani et al. 2006). Another poorly designed study showed an increased sensitisation to peanut in the control group (non-diet) which was statistically significant (P=0.02) for SPT but not for serum IgE antibody (Hattevig et al. 1999). There are few studies, which are mainly of poor quality, and a heterogeneous range of exposures was studied.

PEANUT: Evidence relating maternal diet duration pregnancy or lactation to subsequent peanut sensitisation or peanut allergy in the child, showed no association in two case-control studies in high risk populations. Most results were not adjusted for potential confounding factors.
3.5.2 Research question 2

Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

In total, 19 studies were relevant to this research question. There were eight trials, 10 cohort studies and one case-control study. Results have been grouped by type of food allergen exposure. They are shown separately for cows’ milk formula, duration of breastfeeding, timing of introduction of solids (general), and timing of introduction of solids (specific foods).

Lack et al. 2003 used the ALSPAC birth cohort and prospective information on peanut allergy and breastfeeding was available (research question 2), and thus the study is entered as a cohort study. Some information relevant to research questions 1 and 3, such as mother’s diet and use of skin cream containing peanut oil, was collected retrospectively and the results were analysed as a case-control study.

Cows’ milk formula

Six studies reported on infants fed with cows’ milk formula compared with breast milk and either food sensitisation or food allergy in the infant. These studies can be found on pages 8 to 13 in ‘Document 2: Tables of evidence’. There were 5 trials and one cohort study. As previously mentioned, it was not always possible to randomise women who wished to breastfeed. In tables 9 and 10, studies where women who breastfed were not randomised are described as controlled interventions.

Table 9 describes the three studies reporting on food sensitisation. The De Jong et al. 2002 study (from the Netherlands) is described as a RCT, and was conducted as a trial for the first two years. Subjects were, however, followed-up for a further three years beyond the period of the intervention. All infants were breastfed and the study examined the effect of brief introduction of cows’ milk (as a supplement to breastmilk) in the first three days after randomisation, which took place from birth. The avoidance/reduced exposure group received a placebo. The analysis at 5 years included about 69% of the sample and showed no association between brief early exposure and sensitisation to cows’ milk or egg. Results were not adjusted for other factors. Schoetzau et al. 2002 (from the GINI study from Germany) compared children who received cows’ milk formula with those who received exclusive breastfeeding for 16 weeks. The guidance also included avoidance of cows’ milk, dairy products, hen’s egg, soy products, fish, nuts, tomatoes and citrus fruits for the first year. This was a high risk population (1st degree relative with atopic disease) and 75% were included in the analysis at 4 months. There was no difference between the groups before or after adjustment for other factors in sensitisation to milk or egg. Szajewska et al. 2004 (from Poland) compared the effect of standard preterm cows’ milk formula with mothers’ fortified breast milk. The mothers’ breast milk was fortified with a powder supplement of extensively hydrolysed whey and casein. There was no difference between the groups at one year for sensitisation to cows’ milk. A similar result was found for the comparison of partially hydrolysed preterm whey formula and fortified breast milk. Results were not adjusted for other factors.
Table 9: Exposure to cows' milk formula and food sensitisation

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant breastfed with brief early exposure to cows’ milk or placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted odds ratios (brief exposure to cows’ milk vs. placebo)</td>
</tr>
<tr>
<td>De Jong et al. 2002</td>
<td>RCT 6/9</td>
<td>General population</td>
<td>5 years</td>
<td>Positive allergen specific IgE</td>
<td>Milk 1.77 (0.93, 3.37) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Egg 0.33 (0.04, 3.17) NS</td>
</tr>
<tr>
<td>Cows’ milk formula vs. breast milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio (breastfed vs. cows’ milk)</td>
</tr>
<tr>
<td>Schoetzau et al. 2002 (GINI)</td>
<td>Controlled intervention 6/9</td>
<td>High risk</td>
<td>1 year</td>
<td>Positive allergen specific IgE</td>
<td>Milk or egg 1.30 (0.74, 2.28) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Szajewska et al. 2004</td>
<td>Controlled intervention 5/10</td>
<td>High risk</td>
<td>1 year</td>
<td>Positive IgE for cows’ milk</td>
<td>14% Cows’ milk formula 8% Breastfed NS</td>
</tr>
<tr>
<td>Partially hydrolysed whey formula vs. breast milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szajewska et al. 2004</td>
<td>Controlled intervention 5/10</td>
<td>High risk</td>
<td>1 year</td>
<td>Positive IgE for cows’ milk</td>
<td>15% Partially hydrolysed whey formula 8% Breastfed NS</td>
</tr>
</tbody>
</table>

Abbreviations used: IgE – immunoglobulin E; NS – not statistically significant (P>0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.

Table 10 describes the four studies reporting on food allergy. Three studies compared cows’ milk formula with breast milk. In two studies food allergy was confirmed by open challenge. Saarinen et al. 1999 (from Finland) followed up virtually all subjects to 18-34 months of age. This study included women whose infants required supplementary feeding in hospital and thus, it was possible to randomise women to cows’ milk formula or pasteurised human milk from mixed donors. The supplementary feed was given as required. There was no difference between the groups in food allergy at 18-34 months. The results were not adjusted for other factors. The study reported a statistically significant increased risk of food allergy in the group receiving cows’ milk formula compared with the combined group of human breast milk and extensively hydrolysed formula after adjusting for parental atopy. Szajewska et al. 2002 (previously described) reported exactly the same percentage of children with food allergy in both groups at one year. Follow-up was poorer in this study as 69% of the cows’ milk formula group and 81% of the breast milk group were included in the final analyses. A cohort study (Hilkino et al. 2001) recorded feeding method at 4 months and related this to food allergy at 18 months and 3 years. At both time points a protective effect of formula feeding compared with breastfeeding was reported. This study was not of good quality. Results were adjusted for other factors, but these did not include parental allergy. Parental
report of doctor-diagnosed food allergy in the child was not confirmed. It is possible the parents with a history of atopic disease were more likely to breastfeed (reverse causality), thus biasing the results.

Two studies compared partially hydrolysed whey formula with breast milk (Halken et al. 2000 and Szajewska et al. 2004). Both were conducted in high risk groups; and it was not possible to randomise the breastfeeding group. In both studies open challenge was used to confirm food allergy. Both studies reported a slightly higher incidence of cows’ milk allergy among the formula fed children; however neither result was statistically significant and adjustment was not made for other factors.

Table 10: Exposure to cows’ milk formula and food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cows’ milk formula vs. breast milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saarinen et al. 1999</td>
<td>RCT 6/10</td>
<td>General population</td>
<td>18-34 months</td>
<td>Parental report followed by open challenge.</td>
<td>Unadjusted odds ratio (human vs. cows’ milk) 0.70 (0.44, 1.12) NS</td>
</tr>
<tr>
<td>Szajewska et al. 2004</td>
<td>Controlled intervention 5/10</td>
<td>High risk</td>
<td>1 year</td>
<td>Cows’ milk allergy confirmed by open challenge.</td>
<td>4% Cows’ milk formula 4% Breastfed NS</td>
</tr>
<tr>
<td>Hilkino et al. 2001</td>
<td>Cohort 5/13</td>
<td>General population</td>
<td>2 years and 8 months</td>
<td>Parental report of doctor diagnosed food allergy.</td>
<td>Adjusted odds ratios (cows’ milk formula vs. breastfed) 18 months 0.58 (0.52, 0.66) Sig 3 years 0.72 (0.55, 0.94) Sig</td>
</tr>
<tr>
<td><strong>Partially hydrolysed whey formula vs. breast milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halken et al. 2000</td>
<td>Controlled intervention 5/10</td>
<td>High risk</td>
<td>18 months</td>
<td>Parent report confirmed by open challenge</td>
<td>Milk PHW Formula 4.7% Breastfed 1.3% NS Egg PHW Formula 0% Breastfed 1.7% NS Wheat PHW Formula 0% Breastfed 0.4% NS Peanut No cases of peanut allergy in either group</td>
</tr>
<tr>
<td>Szajewska et al. 2004</td>
<td>Controlled intervention 5/10</td>
<td>High risk</td>
<td>1 year</td>
<td>Cows’ milk allergy confirmed by open challenge</td>
<td>PHW Formula 5% Breastfed 4% NS</td>
</tr>
</tbody>
</table>

Abbreviations used: IgE – immunoglobulin E; PHW – partially hydrolysed whey; Sig – statistically significant (P≤ 0.05); NS – not statistically significant (P>0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.
Summaries

ALL FOODS: There is no consistent evidence, from six studies, of an association between infants receiving cows’ milk formula compared with breast milk and the development of food sensitisation or food allergy in the child. One study (Hilkino et al. 2001) did find a statistically significant decreased risk of parent’s report of doctor diagnosed food allergy for cows’ milk formula compared with breastfeeding. However the study was not adjusted for parental history of atopy, information on breastfeeding was poorly assessed and diagnosis of food allergy was not confirmed.

PEANUT: One study assessed incidence of peanut allergy in a trial to assess the effect of partially hydrolysed whey formula and breastfeeding but no cases were found in the intervention or control groups (Halken et al. 2000).

Breastfeeding duration

Seven cohort studies and one cross-sectional study addressed either duration of breastfeeding or ever breastfeeding (yes/no) in association with food sensitisation/allergy outcomes. These studies can be found on pages 14 to 24 of the tables of evidence in Document 2. Five studies were carried out in general population samples. Length of follow-up ranged from 2 to 11 years. All studies apart from one reported on food allergy. All reports of food allergy, apart from one (Lack et al. 2003) were based on parental reports of either symptoms or of a doctor’s diagnosis. The percentage of children included in the final analyses was more than 80% for Kull et al. 2002, Lack et al. 2003, Milner et al. 2004 and Poole et al. 2006. Two studies were carried out in USA (Milner et al. 2004, Poole et al. 2006) and the rest were carried out in Europe. Information on breastfeeding was largely obtained by questionnaire and there were few details on the questions asked. It is not clear from all studies whether the comparison made was for exclusive breastfeeding or just any breastfeeding. Two studies (Gustafsson et al. 2004 and Wetzig et al. 2000) did not report actual results in the paper but stated that there were no statistically significant associations between duration of breastfeeding and subsequent development of food sensitisation or food allergy. Only Milner et al. 2004 reported that breastfeeding compared with not breastfeeding was associated with an increased risk of food allergy. Lack et al. 2003 (the only study to use DBPCFC) and Poole et al. 2006 reported a higher rate of food allergy in those breastfed for longer, but the results were not statistically significant. Kull et al. 2002 reported a lower rate of food allergy in those exclusively breastfed for at least 4 months compared with less than 4 months, again the result was not statistically significant. Pesonen et al. 2006 analysed the results by family history of allergy. At both 5 and 11 years of age those children with a family history of allergy had an increased risk of food allergy with duration of exclusive breastfeeding of 9 months or more compared with less than 9 months. It should be noted that the number of children with food allergy is relatively small and thus the 95% confidence interval around the odds ratio is large, suggesting that the results are not robust. One cross-sectional study was included, Hourihane et al. 2007 reported that children aged 4 to 5 years who were breastfed compared with bottle-fed were more likely to develop peanut allergy. Peanut allergy in this study was confirmed by DBPCFC. However, when the results were adjusted for eczema the result was no longer statistically significant.

The possible association between longer duration of breastfeeding and increased food allergy in the child may be due, at least in part, to women with a family history of allergy, or with
children who develop food allergy early in life choosing to breastfeed for longer (i.e. reverse causality).

Table 11: Breastfeeding and food sensitisation/food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/General popn.</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafsson et al. 2004</td>
<td>Cohort 5/12</td>
<td>General popn.</td>
<td>4 years</td>
<td>Food allergy</td>
<td>Parental report of symptoms (no actual results presented)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Authors report ‘no association with allergic symptoms’.</td>
<td></td>
</tr>
<tr>
<td>Hourihane et al. 2007</td>
<td>Cross-sectional 5/11</td>
<td>General popn.</td>
<td>4-5 years</td>
<td>Peanut allergy</td>
<td>DBPCFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted odds ratio (breastfed vs formula fed) 3.8 Sig (P&lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Result was not statistically significant after adjustment for eczema</td>
<td></td>
</tr>
<tr>
<td>Kull et al. 2002</td>
<td>Cohort 7/13</td>
<td>General popn.</td>
<td>2 years</td>
<td>Food allergy</td>
<td>Parental reports of symptoms and doctor's diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio (exclusive breastfeeding for ≥4 vs &lt; 4 months)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91 (0.75, 1.11) NS</td>
<td></td>
</tr>
<tr>
<td>Lack et al. 2003</td>
<td>Cohort 7/13</td>
<td>General popn.</td>
<td>Up to 38 months</td>
<td>Food allergy</td>
<td>DBPCFC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted odds ratio (≥6 vs. &lt; 6 months) 3.67 (0.80, 16.94) NS</td>
<td></td>
</tr>
<tr>
<td>Milner et al. 2004</td>
<td>Cohort 5/13</td>
<td>General popn.</td>
<td>3 years</td>
<td>Food allergy</td>
<td>Parental reports of doctor’s diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted odds ratio (breastfeeding yes vs. no) 1.39 (1.13, 1.71)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sig (P=0.002)</td>
<td></td>
</tr>
<tr>
<td>Pesonen et al. 2006</td>
<td>Cohort 7/13</td>
<td>General popn.</td>
<td>11 years</td>
<td>Food allergy</td>
<td>Parental reports of symptoms confirmed at interview</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratios (exclusive breastfeeding ≥9 vs &lt;9 months)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>At 5 years</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FH+ve: 5.3 (1.2, 24.1) Sig (P=0.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FH -ve: 1.0 (0.1, 7.5) NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At 11 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FH+ve: 7.9 (1.4, 50.0) Sig (P=0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FH -ve: 4.3 (0.1, 284) NS</td>
<td></td>
</tr>
<tr>
<td>Poole et al. 2006</td>
<td>Cohort 7/13</td>
<td>High risk</td>
<td>4 years</td>
<td>Food allergy</td>
<td>Parental reports of allergy and doctor’s diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio per one month increase in breastfeeding 1.05 (1.00, 1.11) NS</td>
<td></td>
</tr>
<tr>
<td>Wetzig et al. 2000</td>
<td>Cohort 6/12</td>
<td>High risk</td>
<td>2 years</td>
<td>Sensitisation</td>
<td>Positive IgE – egg white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Authors report no statistically significant association between length</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>of breastfeeding and sensitisation to egg white at 2 years</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; popn. – population; FH – family history; Int – intervention; OR – odds ratio; SPT – skin prick test; Sig – statistically significant (P≤ 0.05); NS – not statistically significant (P>0.05); values in brackets given after odds
ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.
One case-control study (Frank et al. 1999) reported on mean age of introduction of formula. This was 5.5 months for children with peanut sensitisation and 2.0 months for controls. The results were not adjusted for other factors. It is not reported in the paper whether this result was statistically significant.

**Summaries**

**ALL FOODS:** There is no evidence, from eight studies, to show that increased duration of breastfeeding protects against food allergy. Two studies reported that breastfeeding compared with never breastfeeding was associated with an increased risk of food allergy in general populations (Hourihane et al. 2007; Milner et al. 2004). However these analyses do not adjust for other factors. When Hourihane et al. 2007 adjusted for eczema, the result was no longer statistically significant. There is limited evidence that, in children with (but not without) a family history of food allergy, breastfeeding for nine months or more increases the risk of food allergy (Pesonen et al. 2006). This association of increased risk with longer duration of breastfeeding may be due to women with a family history of allergy, or with children who develop food allergy early in life choosing to breastfeed for longer.

**PEANUT:** One cross-sectional study reported that children who were breastfed were 3.8 times more likely to have peanut allergy compared to those bottle-fed. However, after adjustment for potential confounders this result was no longer statistically significant (Hourihane et al. 2007).

**Timing of introduction of solids (general)**

Two studies reported on either the introduction of any solids, or the introduction of cereals in association with food sensitisation and allergy outcomes. These studies can be found on pages 20 and 22 of the tables of evidence in Document 2. Both were cohort studies. Poole et al. 2006 (DAISY study from USA) reported that introduction of cereals after 6 months, compared to 6 months or earlier, was associated with a statistically significant increased risk of food allergy in a high risk population. The result was adjusted for other factors; however food allergy was based on parental reports that were confirmed at an interview. Zutavern et al. 2006 (LISA study from Germany) did not find an association between introduction of any solids after 6 months compared with before 5 months and development of food sensitisation in an analysis adjusted for potential confounders. Although, in an unadjusted analysis, children whose parents reported a doctor-diagnosed food allergy in their child, were more likely to have had milk or egg introduced after the age of 6 months compared with those without food allergy.
### Table 12: Timing of introduction of solids (general) and food sensitisation/food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poole et al. 2006</td>
<td>Cohort 7/13</td>
<td>High risk</td>
<td>4 years</td>
<td><em>Wheat allergy</em> Parental reports of allergy and doctor’s diagnosis</td>
<td>Introduction of cereals Adjusted odds ratio (&gt;6 vs. ≤ 6 months) 3.8 (1.18, 12.28) Sig (P=0.025)</td>
</tr>
<tr>
<td>Zutavern et al. 2006</td>
<td>Cohort 7/13</td>
<td>General population</td>
<td>2 years</td>
<td><em>Food allergy</em> Parental reports of doctor diagnosed food allergy</td>
<td>Introduction of milk or egg &gt; 6 months Food allergy Yes - 87% No - 76% Sig (P=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Sensitisation</em> Positive IgE – egg, cows’ milk, wheat, peanut, soybean, cod</td>
<td>Introduction of any solids Adjusted odds ratios (&gt;6 vs. &lt; 5 months) 0.83 (0.49, 1.41) NS (5-6 vs. &lt;5 months) 1.04 (0.71, 1.53) NS</td>
</tr>
</tbody>
</table>

Abbreviations used: IgE – immunoglobulin E; Sig – statistically significant (P ≤ 0.05); NS – not statistically significant (P > 0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.

### Timing of introduction of solids (specific foods)

Two studies can be found on pages 16 and 23 of the tables of evidence in Document 2. One study reported on fish consumption in the infant at one year and food sensitisation (Kull *et al.* 2006A) and reported that increased fish consumption was associated with a statistically significant lower risk of food sensitisation (cows’ milk, hen’s egg, codfish, soybean, peanut and wheat combined) after adjustment for other factors. One case-control study (Frank *et al.* 1999) reported on mean age of introduction of peanuts or peanut butter. On average peanuts were introduced earlier in cases compared with controls (12.5 vs. 17.3 months). The result was statistically significant but it was not adjusted for other factors.
Table 13: Timing of introduction of solids (specific foods) and food sensitisation/food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/General population</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kull et al. 2006A</td>
<td>Cohort 8/12</td>
<td>General population</td>
<td>2 years</td>
<td>Food sensitisation Positive food allergen specific IgE</td>
<td>Adjusted odds ratio (95% confidence interval) for fish consumption at one year (&gt;1/week vs. never) 0.47 (0.33, 0.69) Sig (P trend &lt;0.001)</td>
</tr>
<tr>
<td>Frank et al. 1999</td>
<td>Case-control 6/10</td>
<td>High risk</td>
<td>Up to 3 years</td>
<td>Peanut sensitisation Positive peanut specific IgE</td>
<td>Mean age (SD) of introduction of peanuts or peanut butter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases 12.5 (6.4) months Controls 17.3 (5.5) months Sig (P=0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age of introduction of formula (type not specified)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases 5.5 months Controls 2.0 months NS</td>
</tr>
</tbody>
</table>

Abbreviations used: IgE – immunoglobulin E; Sig – statistically significant (P≤ 0.05); NS – not statistically significant (P>0.05). Quality score – the derivation of this score is described in section 3.4.5.

Summaries

ALL FOODS: There is no consistent evidence, from four studies, of an association between timing of introduction of solids, either in general or for specific foods, and the development of food sensitisation or food allergy in the child. One study reported a statistically significant increased risk of wheat allergy with delayed introduction of cereals until the child was at least 6 months of age (Poole et al. 2006). One study reported a statistically significant increased risk of food allergy in children who had milk or egg introduced after 6 months; however in an adjusted analysis there was no association between introduction of any foods after 6 months and food sensitisation (Zutavern et al. 2006). One reported a statistically significant result for fish showing that consumption of fish during the first year of life was related to a decreased risk of food sensitisation (Kull et al. 2006A) and another that reported peanuts were introduced at an earlier age in cases of peanut sensitisation compared with controls (Frank et al. 1999). Further studies are required to confirm these findings, as the heterogeneous nature (e.g. in terms of exposure) of this evidence is a major limitation.

PEANUT: One case-control study reported peanuts were introduced at an earlier age in cases of peanut sensitisation compared with controls (Frank et al. 1999). The results for this study were not adjusted for potential confounders.
**Multifaceted interventions**

All interventions grouped in this category include dust mite avoidance measures.

Three RCTs investigated multifaceted interventions consisting of avoidance of multiple allergenic foods plus household avoidance measures (such as house dust mite avoidance, no pets, no smoking), in high risk populations. These studies can be found on pages 25 to 27 in the tables of evidence in Document 2. The interventions are described in tables 11 and 12; the comparison group was usual care (i.e. care they would have received if not taking part in the trial). In brief, Arshad *et al.* 2007 and Chang-Yeung *et al.* 2005 both included interventions regarding the mothers’ diet. For the last trimester and during lactation mothers were asked to avoid peanuts, other nuts and fish in the Chang-Yeung study (Chang-Yeung *et al.* 2005). The intervention started later in Arshad *et al.* 2007; dairy products, eggs, wheat, nuts, fish and soya were excluded from the mothers’ diet during lactation. All three studies included dietary intervention in infants. The recommended duration of breastfeeding differed for each study. It was at least 3 months for Halmerbauer *et al.* 2003, at least 9 months for Arshad *et al.* 2007 and one year for Chang-Yeung *et al.* 2005. All studies involved delayed introduction of cows’ milk, fish and peanuts.

Results on food sensitisation are shown in table 11. Arshad *et al.* 2007 (from UK) followed up children from birth for 8 years and reported a statistically significant decreased risk for food sensitisation in the intervention group after adjustment for other factors. Information on sensitisation was available for 80% of the intervention group and 93% of the control group. Compliance with the diet was assessed to be excellent. Chang-Yeung *et al.* 2005 (from Canada) followed up children from birth for 7 years and reported no difference between the intervention and control groups for sensitisation assessed by SPT to milk, egg, peanut, soy and wheat in the infant. About two thirds of subjects were included in the final analysis and results were not adjusted for other factors. There was no information on compliance. Halmerbauer *et al.* 2003 (from Austria, Germany, UK) followed up children from birth for one year and found a decreased risk for sensitisation to egg and milk if the excluded subjects were assumed not to have allergy. If they were all assumed to have allergy the results were no longer statistically significant. Results were adjusted for other factors. Compliance was assessed to be good, and about 90% of subjects were included in the analysis at 1 year.
Table 14: Multifaceted interventions and food sensitisation

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>Intervention</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arshad et al. 2007</td>
<td>RCT 6/9</td>
<td>Dairy products, eggs, wheat, nuts, fish and soya excluded from diet of infants and lactating mothers for first 9 months. Foods gradually introduced after 9 months.</td>
<td>8 years</td>
<td>Positive SPT</td>
<td>At any time in 8yr Food sensitisation (non-specific) Adjusted odds ratio (Int vs. Control) 0.15 (0.03, 0.80) Sig At age 8 years <strong>Cows’ milk</strong> Int – 0% Control: 6.5% NS <strong>Peanut</strong> Int – 0% Control – 1.6% NS</td>
</tr>
<tr>
<td>Chang-Yeung et al. 2005</td>
<td>RCT 7/10</td>
<td>Mother’s diet – in last trimester and during lactation to exclude peanuts, other nuts, fish. Infant’s diet for first year – to breastfeed for one year if possible. To delay introduction of solids until 6 months. Exclude cows’ milk, fish and peanuts for first year.</td>
<td>7 years</td>
<td>Positive SPT</td>
<td><strong>Cows’ milk</strong> Int:0.5% Control: 1.0% <strong>Egg</strong> Int: 2.0% Control: 1.5% <strong>Peanut</strong> Int: 12.4% Control: 6.9% <strong>Soy</strong> Int: 7.5% Control: 5.0% <strong>Wheat</strong> Int: 1.0% Control: 1.0% All results NS</td>
</tr>
<tr>
<td>Halmerbauer et al. 2003</td>
<td>RCT 6/10</td>
<td>Infant’s diet – Solids to be introduced gradually from 6 months. Cows’ milk, egg, fish not before one year. Peanuts and tree nuts not before 3 years. Note both groups were advised to breastfeed for at least 3 months.</td>
<td>One year</td>
<td>Positive SPT or IgE</td>
<td>Adjusted odds ratio (Int vs. Control) Assuming those lost to follow-up were not sensitised <strong>Egg</strong> 0.58 (0.39, 0.85) Sig (P=0.005) <strong>Cows’ milk</strong> 0.63 (0.41, 0.96) Sig (P=0.032)</td>
</tr>
</tbody>
</table>

Abbreviations used: IgE – immunoglobulin E; Int – intervention; RCT – randomised controlled trial; SPT – skin prick test; Sig – statistically significant (P≤ 0.05); NS – not statistically significant (P>0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.
Results on food allergy are shown in table 12. These are only available for two of the studies. Arshad et al. 2007 confirmed parental reports of food allergy by a positive specific SPT; there was no challenge test. The protective effect of the multifaceted intervention observed for food sensitisation was not apparent for food allergy. The percentage of children with food allergy was higher in the control group than the intervention group but this was not statistically significant. Halmerbauer et al. 2003 had information on parental reports of food intolerance and on parental reports of doctor diagnosed food allergy. The parental reports of subsequent food intolerance did show a protective effect of the intervention. This was statistically significant. However, when doctor diagnosed food allergy was used to assess the impact of the intervention on the incidence of food allergy; there was no statistically significant difference between the groups.

Table 15: Multifaceted interventions and food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>Intervention</th>
<th>Age of child at outcome measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arshad et al. 2007</td>
<td>RCT 6/9</td>
<td>Dairy products, eggs, wheat, nuts, fish and soya excluded from diet of infants and lactating mothers for first 9 months. Foods gradually introduced after 9 months.</td>
<td>8 years</td>
<td>Food allergy symptoms within 2 hours of eating food on 2 or more occasions + positive SPT</td>
<td>At any time in 8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio (int vs. control) 0.41 (0.11, 1.53) NS</td>
</tr>
<tr>
<td>Halmerbauer et al. 2003</td>
<td>RCT 6/10</td>
<td>Infant’s diet – solids to be introduced gradually from 6 months. Cows’ milk, egg, fish not before one year. Peanuts and tree nuts not before 3 years. Note both groups were advised to breastfeed for at least 3 months.</td>
<td>One year</td>
<td>Parent reports of intolerance</td>
<td>Assuming those lost to follow-up were not sensitised</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio (int vs. control) 0.67 (0.49, 0.92) Sig</td>
</tr>
</tbody>
</table>

Abbreviations used: Int – intervention; RCT – randomised controlled trial; SPT – skin prick test; Sig – statistically significant (P ≤ 0.05); NS – not statistically significant (P > 0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.

In these three studies it is difficult to separate the effects of maternal and infant diets and the development of food sensitisation or food allergy. Chang-Yeung et al. 2005 started the intervention in the last trimester of pregnancy and found no statistically significant association at 7 years for food sensitisation. There was no measure of food allergy. Results were not adjusted for other factors; however the univariate analysis did show a higher incidence of sensitisation to peanut and soya in the intervention group (dietary restrictions
including peanuts). Arshad et al. 2007 started the intervention at the birth of the child and dietary restriction applied to both child and lactating mother. There was a lower risk of food sensitisation and food allergy anytime in 8 years in the intervention compared with the control groups, although this was only statistically significant for food sensitisation. Results were adjusted for other factors. The other study (Halmerbauer et al. 2003), intervened in the infants only and followed up the infants for only one year. A decreased risk was observed for the intervention compared with the control group for parental report of intolerance, but not for doctor-diagnosed food allergy.

**Summaries**

**ALL FOODS:** There is some evidence, from three studies, to show that multifaceted interventions (combined dietary and non-dietary interventions, such as house dust mite avoidance) aimed at mothers and infants protect against food sensitisation in the child; however this was not confirmed when information on food allergy diagnosis was analysed. It is difficult to compare the findings of the studies due to differences in the interventions and methods of assessing outcome.

**PEANUT:** Two studies that assessed sensitisation to peanut in multifaceted interventions aimed at mothers and infants found no association, although one reported a 12% incidence of peanut sensitisation in the diet-restricted group compared with 7% in the control group (Chang-Yeung et al. 2005).
3.5.3 Research question 3

Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?

Two studies relevant to this research question were found. These studies can be found on pages 28 and 29 of the tables of evidence in Document 2. One of them is directly relevant (Lack et al. 2003) and the other peripherally relevant as it concerns the use of peanut oil to deliver a vitamin supplement (Kull et al. 2006B). These are shown in table 16 in this document. These studies assessed different exposures (vitamin preparation and skin creams) and so will be discussed separately.

Kull et al. 2006B is a cohort study from Sweden. Evidence of food allergy was based on parental reports and food sensitisation (IgE). In total 90% of children in the study received vitamin supplements, and of these most received vitamins in peanut oil. A statistically significant increased risk of food allergy and food sensitisation was found in children at four years of age (cows’ milk, egg, fish, soy, peanut and wheat combined) for vitamins in water compared with vitamins in peanut oil provided in the first year of life. When food sensitisation for single specific food allergens was tested, a statistically significant increased risk for vitamins in water compared with vitamins in oil was obtained for egg white but not for peanut or milk. The peanut oil used in this study was highly refined and thus unlikely to contain peanut protein. Those receiving supplements in water were more likely to have a family history of atopy, to be exposed to cigarette smoke and have a shorter duration of breastfeeding. Although these factors were adjusted for in the analysis, residual confounding is a possibility.

The other study was a case-control study (Lack et al. 2003). This study has been described in previous sections and reported on maternal use of breast creams containing peanut oil and found no association between their use and risk of peanut allergy. The study also reported on use of creams containing peanut oil on infants’ skin and it found that cases of peanut allergy were statistically significantly more likely to use creams with peanut oil compared with controls. This study had only 23 cases; however the result is statistically significant even after adjusting for confounders. More than 90% of cases of peanut allergy had used skin creams containing peanut oil, compared with less than 60% in the control groups. Cases of peanut allergy were also exposed to a greater number of skin creams containing peanut oil than controls; this finding was highly statistically significant (P<0.001).
Table 16: Non-dietary exposure to peanuts and food sensitisation/food allergy

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General popn.</th>
<th>Age of child at outcome measure</th>
<th>Exposure measure</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kull et al. 2006B</td>
<td>Cohort 7/13</td>
<td>General popn.</td>
<td>4 years</td>
<td>Vitamins A and D in peanut oil vs. vitamins A and D in water</td>
<td>Food allergy Parental reports of symptoms <strong>Sensitisation</strong> Positive allergen specific IgE (Adjusted odds ratios)</td>
<td>Food allergy Odds ratio (vitamins in water vs. oil) 1.87 (1.32, 2.65) Sig <strong>Sensitisation Foodmix (6 allergens)</strong> Odds ratio (vitamins in water vs. oil) 1.75 (1.20, 2.56) Sig <strong>Peanut specific</strong> Odds ratio (vitamins in water vs. oil) 1.52 (0.84, 2.75) NS <strong>Milk</strong> Odds ratio (vitamins in water vs. oil) 1.54 (0.94, 2.51) NS <strong>Egg white</strong> Odds ratio (vitamins in water vs. oil) 2.27 (1.30, 3.51) Sig</td>
</tr>
<tr>
<td>Use of creams containing peanut oil</td>
<td>Case-control 7/11</td>
<td>General popn./ High risk</td>
<td>Up to 38 months</td>
<td>Maternal and infant use of breast creams containing peanut oil in first 6 months of life vs. no use of creams containing peanut oil in mother or infant</td>
<td>Food allergy Peanut allergy cases confirmed by DBPCFC</td>
<td>Maternal use of breast creams with peanut oil Cases: 35% Atopic controls: 47% Normal controls: 24% NS <strong>Use of creams with peanut oil on infant’s skin</strong> Cases: 91% Atopic controls: 53% Normal controls: 59% Sig (P&lt;0.001) Adjusted odds ratio (Use vs. no use of creams) 8.34 (1.05, 66.1) Sig (P=0.045) <strong>Number of peanut oil preparations exposed to</strong> Cases: 1.91 Atopic controls: 0.93 Normal controls: 0.81 Sig (P&lt;0.001)</td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; popn. – population; IgE – immunoglobulin E; Sig – statistically significant (P≤ 0.05); NS – not statistically significant (P>0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.
Summary
There is very little evidence available on non-dietary exposure of peanuts and the development of sensitisation or allergy to peanuts. One small study did find a statistically significant increased risk of peanut allergy with the use of skin creams containing peanut oil on infants. No such increased risk was found for maternal use of skin creams containing peanut oil. These results need to be confirmed in other studies.
3.5.4 Research question 4
Has the current UK Government guidance on dietary consumption of peanuts and peanut products had any impact on sensitisation and allergy rates to peanuts in the UK?

We have divided the evidence into two parts, direct evidence and indirect evidence. Direct evidence includes studies that report information on knowledge of, or adherence to, the COT advice published in 1998 (see introduction for details of the COT advice) as well as information on sensitisation or allergy to peanuts in the child. As there were likely to be few studies found we also looked for other supporting information which might help ascertain the impact of the COT advice (indirect evidence). This included studies providing either prevalence information on trends in peanut consumption, or information about sensitisation or allergy to peanuts in children born after the COT advice was issued. In order to look at trends in peanut sensitisation and allergy in children born before the COT advice was issued we separately searched (not systematically) for studies with relevant prevalence data, and found a number of studies that provided such data but did not meet the inclusion criteria for the systematic review.

Direct evidence
Direct evidence includes studies that report information on knowledge of, or adherence to, the COT advice published in 1998 (see introduction for details of the COT advice) as well as information on sensitisation or allergy to peanuts in the child.

Peanut sensitisation
Two studies which address this question were identified (Dean et al. 2007A, Hourihane et al. 2007). These studies can be found on pages 30 to 32 of the tables of evidence in Document 2. Both studies were analysed as cross-sectional studies, although one (Dean et al. 2007A) utilised a birth cohort. The data in the Dean et al. 2007A study were analysed in a cross-sectional fashion and relate to one point in time and so this study is entered as a cross-sectional study.

The study by Dean et al. 2007A studied a birth cohort (658 children) from the Isle of Wight which was initially recruited whilst mothers were pregnant. The infants were born between 1 September 2001 and 31 August 2002, three years after the COT advice was first issued. A questionnaire to assess compliance with the COT advice was administered to mothers when children were aged 2 years and a SPT was requested. Mothers were asked if they had changed their diet on the basis of the advice. If they had changed their diet they were asked if they avoided peanuts completely, stopped eating obvious sources but continued to eat foods that ‘may contain peanuts’, or increased their intake of peanuts. Although around 88% of the cohort returned for the 2 year visit, only 62% of these consented to a SPT. As the children were aged less than 3 years, food challenge tests were not conducted as they would be contrary to the COT advice. In the main study, 42% of mothers who responded recalled the knowledge of the COT advice, but this was not associated with maternal atopy or family history of atopy.

Around two thirds (65%) of mothers stated they avoided peanuts during pregnancy; this was not affected by maternal atopy or family history of atopy. In a validation study (Venter et al. 2006A), 54% of mothers reported that they never ate peanuts when pregnant; a lower percentage than in the main study. Mothers having their first child were most likely to change...
their diet (either avoiding or reducing peanut consumption) during pregnancy. In the birth cohort at age 2 years, 2% of the sample were sensitised to peanut. Of the mothers with sensitised children, 77% reported that they had avoided peanuts when pregnant. The findings demonstrate that the target population (pregnant or lactating women who were atopic or where another first-degree relative of the child is atopic) did not necessarily take up the advice and that the COT advice appears to be misunderstood as women not in the target group also avoided peanuts.

A further study was conducted with 42 participants from the Isle of Wight birth cohort who agreed to take part in a qualitative study (Turke et al. 2005). The published study was not eligible for the systematic review, as it only included women who had avoided peanuts, but does add useful supplementary data. The aim of the qualitative study was to describe the experiences of mothers who had avoided peanuts during pregnancy and lactation. The main findings revealed the importance of clarity in the dissemination of advice to pregnant women with regard to the real risks associated with peanut consumption during pregnancy and lactation, and the target group to whom these risks apply. Clarification was also required with regard to which foods should be avoided and some guidance about which foods contain peanut products. Mothers thought that clear standardised labelling was required and in particular found the term ‘may contain’ unhelpful.

The study by Hourihane et al. 2007 studied 1072 mother and child pairs at age 4 to 5 years, born after the COT advice was first issued, and living in Southampton or Manchester. The response rate of this study was very low (21% of the target population). Overall, 61% of mothers recalled the COT advice, and recall was not associated with whether the mother was atopic or not. Of those who recalled the advice, 61% reported a dietary change, though few women stopped eating peanuts altogether. Most (89%) women reported reducing peanut consumption and only 10% reported eliminating peanuts during pregnancy. The study found that women with more than one child were less likely to change their diet (eliminate or reduce intake of peanuts), a similar finding to Dean et al. 2007A. Of the women who regularly ate peanuts before becoming pregnant and who breastfed their child, 46% changed their diet (eliminated or reduced intake of peanuts) while breastfeeding. Forty-one percent who breastfed thought they had eaten peanuts. Two thirds (65%) of children were reported to have consumed peanuts; the mean age of introduction was 36 months. Peanuts were introduced at similar age for those who were peanut sensitised and those who were not sensitised (32 vs. 29 months –not statistically significant). This finding is different to the small case-control study by Frank et al. 1999 who reported an earlier age of introduction of peanuts in those who were sensitised (12.5 vs. 17.3 months – statistically significant P=0.03). It should also be noted that the overall age of introduction of peanuts between the two studies is much later for Hourihane et al. 2007 than Frank et al. 1999, possibly as a result of the COT advice.

**Peanut allergy**

The study by Hourihane et al. 2007 also presented information on peanut allergy in relation to compliance with the COT advice (table 17). A total of 20 infants were identified as having peanut allergy, almost half of these had atopic mothers (9/20). Eight mothers with children with peanut allergy had reduced their intake or avoided peanuts. There was no clear relation between take up of the COT advice and atopic status of the mother.
Table 17: Studies evaluating the impact of the 1998 COT advice

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design &amp; quality score</th>
<th>High risk/ General popn.</th>
<th>Age of child at outcome measure</th>
<th>Compliance with 1998 COT advice</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean et al. 2007A</td>
<td>Cross-sectional 7/13</td>
<td>General popn.</td>
<td>2 years</td>
<td>42% of mothers recalled knowledge of COT advice 65% of mother reported avoiding peanuts during pregnancy.</td>
<td>Sensitisation</td>
<td>Positive peanut specific SPT Mothers of 77% (10/13) of the sensitised children stated they had avoided peanuts during pregnancy.</td>
</tr>
<tr>
<td>Hourihane et al. 2007</td>
<td>Cross-sectional 6/11</td>
<td>General popn.</td>
<td>4-5 years</td>
<td>61% of mothers recalled knowledge of COT advice. Of those who recalled COT advice, 61% reported a change in diet (reduced or avoided peanuts)</td>
<td>Food allergy</td>
<td>DBPCFC confirmed food allergy or strong history and skin + blood tests 20 children were considered to have peanut allergy 9/20 infants had mothers who were atopic. 7/20 mothers reduced intake of peanuts and 1/20 avoided peanuts during pregnancy 5/8 mothers who reduced/avoided intake of peanuts were atopic. Authors report no association with maternal rate of change of peanut consumption and sensitisation in the child.</td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; popn. – population; IgE – immunoglobulin E; Sig – statistically significant (P ≤ 0.05); NS – not statistically significant (P>0.05); values in brackets given after odds ratios refer to 95% confidence intervals. Quality score – the derivation of this score is described in section 3.4.5.

Indirect evidence
This included studies providing either prevalence information on trends in peanut consumption, or information about sensitisation or allergy to peanuts in children born after the COT advice was issued. In order to look at trends in peanut sensitisation and allergy in children born before the COT advice was issued we separately searched (not systematically)
for studies with relevant prevalence data, and found a number of studies that provided such data but did not meet the inclusion criteria for the systematic review.

**Prevalence of sensitisation to peanut in the UK**

Two studies were found in the systematic review that reported on prevalence of peanut sensitisation in the UK in children born after the COT advice. These studies can be found on pages 33 and 34 of the tables of evidence in Document 2. Venter *et al.* 2006B reported on prevalence of peanut sensitisation in children from the Isle of Wight at age 6 years. These children were born around the time of the COT advice, some before and some after. Two other papers, also from the Isle of Wight study team, report on sensitisation to peanuts in a birth cohort (born after the COT advice) at ages 1, 2 and 3 years (Dean *et al.* 2007B, Venter *et al.* 2008). These two analyses along with Dean *et al.* 2007A (information on the same birth cohort as Dean *et al.* 2007B) and Hourihane *et al.* 2007 are shown in the first part of table 18. It is worth noting that the Isle of Wight study is a birth cohort in which all babies born between September 2001 and August 2002 were eligible to be included. The studies identified refer to children of different ages so the results are difficult to compare. However the rate of peanut sensitisation is low in those aged 1 year and increases to 2-3% of the population for older children.

Studies reporting on prevalence of peanut sensitisation prior to the COT advice are shown in the second part of table 18. These studies are not part of the systematic review (see section 3.4 for details on how we located these studies), however, we thought it useful to look at longer term trends in peanut sensitisation/allergy. All the figures for peanut sensitisation in the UK prior to the COT advice come from Isle of Wight studies, and most are around 3-4% for ages 3-4, 11 and 15 years. Six cohorts of children have been investigated for food hypersensitivity on the Isle of Wight over the past 20 years. For one cohort (Dean/Venter), serial estimates of prevalence have been published. This provides a unique opportunity to look at trends within the Isle of Wight population over time both within cohorts and between cohorts.

Tariq *et al.* 1996 reported a prevalence of only 1.1% for 4-5 year olds (born between 1989 to 1990). If we compare the results of Tariq *et al.* 1996 and Grundy *et al.* 2002, which report on similar age groups, we can see that in those children born in 1989-1990 the prevalence of peanut sensitisation was lower (1.1%) than in children born in 1994-1996 (3.3%). Hence over a period of about 5 years, the prevalence of peanut sensitisation on the Isle of Wight appears to have increased threefold. A comparison of the the reported estimates of prevalence of peanut sensitisation published between 1981 and 2002 (see both parts of table 18) does not show evidence of a consistent increase in peanut sensitisation in children born before the COT advice compared to those born after. Before the COT advice, prevalence of peanut sensitisation was 1.1-3.7% and after the COT advice it was 0.4 to 2.8%. If we again compare similar age groups (age 3 to 5 years), in all but one study, the prevalence in children born between 1994 and 2001 was 2 to 3%, but in the study by Tariq *et al.* (1996) prevalence was 1.1%. All results were based on SPT. Hence there may have been an increase in peanut sensitisation in 3-5 years olds between 1989 and 1996, but there is no evidence of an increase between 1994 and 2002. The updated analysis from the Isle of Wight cohort (Venter *et al.* 2008) indicates that prevalence has in fact remained at 2% in 2 and 3 year olds, rather than having fallen as was initially indicated in the earlier analysis (Dean *et al.* 2007B).

**Prevalence of peanut allergy in the UK**
Two studies were found in the systematic review that reported on prevalence of peanut allergy in the UK in children born after the COT advice. These studies can be found on pages 33 and 34 of the tables of evidence in Document 2. A summary of the prevalence data is shown in table 18. Venter et al. 2006B reported on prevalence of peanut allergy in children from the Isle of Wight at age 6 years. These children were born around the time of the COT advice, some before and some after. The study reports on food allergy and not specifically peanut allergy. We calculated the prevalence of peanut allergy to be 0.6%; which includes children with a positive open challenge to peanuts (no parents agreed to DBPCFC) and those with known peanut allergy. All cases of peanut allergy had a positive SPT for peanut. There appears to be a difference in prevalence rate between Hourihane et al. 2007 and Venter et al. 2006B, rates of sensitisation are similar but prevalence figures for peanut allergy are much lower for Venter et al. 2006B (0.6% compared with 1.8%). Both of these studies included children whose parents did not agree to challenge tests but had a strong history and a positive SPT for peanut. The children in the Isle of Wight study were slightly older (6 compared with 4-5 years) and there was a higher response rate (55% compared with 21%) compared with Hourihane et al. 2007. A more recent analysis of the Isle of Wight data (Venter et al. 2008) of children aged 3 years shows a similar prevalence of peanut allergy to Hourihane et al. 2007 (1.7%).

Studies reporting on prevalence of allergy prior to the COT advice are shown in the second part of table 18 (as with the studies on sensitisation, this information was not collected systematically). The highest prevalence figure is reported by Grundy et al. 2002 from the Isle of Wight and is for peanut allergy at 3-4 years of age (1.5%). All other estimates of peanut allergy are less than 1%. As seen with peanut sensitisation, if we compare Tariq et al. 1996 and Grundy et al. 2002, we observe a threefold increase in peanut allergy from 0.5 to 1.5% in 5 years in the Isle of Wight population (Also see table 19). A comparison of the the reported estimates of prevalence of peanut sensitisation published between 1981 and 2002 (see both parts of table 18) does not show evidence of a consistent increase in peanut sensitisation in children born before the COT advice compared to those born after. Table 18 shows that children (all age groups of children combined), born before the COT advice was issued, the prevalence of peanut sensitisation was 0.2 to 1.5%, and in children born after the COT advice it was 0.6 to 1.8%. However it is important to compare similar age groups of children. If we again compare similar age groups (age 3 to 5 years), with the exception of Tariq et al. 1996 prevalence of peanut allergy is 1.5 to 1.8% for children born between 1994 and 2002. Hence there may have been an increase in peanut allergy in 3-5 years olds between 1989 and 1996, but there is no evidence of a further increase between 1994 and 2002.

Many of the studies that have investigated prevalence of peanut allergy in the UK have been conducted on the Isle of Wight. Table 19 shows temporal trends in reported prevalence of peanut allergy and sensitisation in the Isle of Wight population in children aged 3 to 6 years. The format of the table is the same as table 18. Part 2 of the table clearly shows the previously noted threefold increase in prevalence of peanut sensitisation and allergy between 1989 and 1996. Prevalence of sensitisation in the more recent cohorts by Venter et al. is a little less than Grundy et al. 2002 but is higher than Tariq et al. 1996. The picture is a little different with regard to the prevalence of peanut allergy; the most recent cohort (Venter et al. 2008) has a very similar prevalence to Grundy et al. 2002. It is not clear why the study of 6 year olds had a lower prevalence of peanut allergy. It is also worth noting here than the cohort conducted in Southampton (located on the mainland from the Isle of Wight) and Manchester (Hourihane et al. 2007) reported a similar prevalence of peanut allergy to the most recent Isle of Wight birth cohort (Venter et al. 2008).
As prevalence of peanut allergy is low, large studies are required in order to obtain a sufficient number of cases. Most of these studies have few cases despite large study numbers because of the low prevalence of peanut allergy, and so a difference of 1 or 2 cases between studies can result in a different estimate of prevalence. Hourihane *et al.* 2007 identified 30 cases and Grundy *et al.* 2002 identified 41 cases of sensitisation to peanuts. Other studies had fewer cases. For peanut allergy the numbers of cases were 20 and 18 for Hourihane *et al.* 2007 and Grundy *et al.* 2002 respectively. Assuming these studies are more reliable due to the larger number of cases, they appear to show no increase in either peanut sensitisation or allergy in a five year period. These results should be interpreted with caution, owing to the low response rates. Response rates (shown in table 18) are no more than 60% for most studies. If children with allergy were more likely to be tested then this would result in a higher prevalence; however if children with allergy were less likely to be tested then the reported prevalence would be an underestimate of true prevalence. Thus it is difficult to get a true picture of prevalence of peanut allergy at any one time.
# Table 18: Prevalence of peanut sensitisation and allergy in children in the UK

1. Studies included in the systematic review under indirect evidence: prevalence of peanut allergy in children conceived after June 1997

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Birth of infant</th>
<th>Age yrs</th>
<th>% complete data (total sample)</th>
<th>Test used</th>
<th>Prevalence of peanut sensitisation (%)</th>
<th>Prevalence of peanut allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venter et al. 2006B</td>
<td>Isle of Wight</td>
<td>1997-1998</td>
<td>6</td>
<td>55% (1440)</td>
<td>SPT/ Open challenge/ known peanut allergy</td>
<td>2.6% (18/700)</td>
<td>0.6% (5/798)</td>
</tr>
<tr>
<td>Hourihane et al. 2007</td>
<td>Southampton, Manchester</td>
<td>1999-2000</td>
<td>4-5</td>
<td>21% (5072)</td>
<td>SPT, IgE, DBPCFC, Symptoms + SPT</td>
<td>2.8% (30/1072)</td>
<td>1.8% (20/1072)</td>
</tr>
<tr>
<td>Dean et al. 2007B</td>
<td>Isle of Wight</td>
<td>2001-2002</td>
<td>3</td>
<td>51% (1063)</td>
<td>SPT</td>
<td>1.3% (7/543)</td>
<td></td>
</tr>
<tr>
<td>&quot;Venter et al. 2008&quot;</td>
<td>Isle of Wight</td>
<td>2001-2002</td>
<td>3</td>
<td>60% (1063)</td>
<td>SPT, Open challenge</td>
<td>2.0% (13/642)</td>
<td>1.7%* (11/642)</td>
</tr>
<tr>
<td>Dean et al. 2007A</td>
<td>Isle of Wight</td>
<td>2001-2002</td>
<td>2</td>
<td>62% (1063)</td>
<td>SPT</td>
<td>2.0% (13/653)</td>
<td></td>
</tr>
<tr>
<td>Venter et al. 2006C</td>
<td>Isle of Wight</td>
<td>2001-2002</td>
<td>1</td>
<td>72% (1063)</td>
<td>SPT</td>
<td>0.4% (3/763)</td>
<td></td>
</tr>
</tbody>
</table>

*We have added Venter et al. 2008 to the table; this article was identified in a search on prevalence and peanuts conducted in May 2008. It updates incomplete figures published by Dean et al. 2007B for children aged 3 years.

2. UK Studies of children conceived before July 1997 (information collected non-systematically)

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Birth of infant</th>
<th>Age yrs</th>
<th>% complete data (total sample)</th>
<th>Test used</th>
<th>Prevalence of peanut sensitisation (%)</th>
<th>Prevalence of peanut allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pereira et al. 2005</td>
<td>Isle of Wight</td>
<td>1987-1988</td>
<td>15</td>
<td>43% (1508)</td>
<td>SPT</td>
<td>2.6% (17/649)</td>
<td>0.7% males 0.5% females</td>
</tr>
<tr>
<td>Emmett et al. 1999</td>
<td>Great Britain</td>
<td>1981-1985</td>
<td>10-14</td>
<td>?</td>
<td>Interview</td>
<td></td>
<td>0.8% males 0.6% females</td>
</tr>
<tr>
<td>Pereira et al. 2005</td>
<td>Isle of Wight</td>
<td>1991-1992</td>
<td>11</td>
<td>43% (1636)</td>
<td>SPT</td>
<td>3.7% (26/699)</td>
<td></td>
</tr>
<tr>
<td>Emmett et al. 1999</td>
<td>Great Britain</td>
<td>1986-1990</td>
<td>5-9</td>
<td>?</td>
<td>Interview</td>
<td></td>
<td>0.5% males 0.3% females</td>
</tr>
<tr>
<td>Tariq et al. 1996</td>
<td>Isle of Wight</td>
<td>1989-1990</td>
<td>4-5</td>
<td>64% (1536)</td>
<td>SPT + history</td>
<td>1.1% (11/981)</td>
<td>0.5% (6/1218)</td>
</tr>
<tr>
<td>Grundy et al. 2002</td>
<td>Isle of Wight</td>
<td>1994-1996</td>
<td>3-4</td>
<td>43% (2878)</td>
<td>SPT, Open challenge Known allergy</td>
<td>3.3% (41/1246)</td>
<td>1.5% (18/1273)</td>
</tr>
<tr>
<td>Lack et al. 2003</td>
<td>Avon</td>
<td>1991-1992</td>
<td>2-3</td>
<td>61% (14541)</td>
<td>DBPCFC</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Emmett et al. 1999</td>
<td>Great Britain</td>
<td>1991-1995</td>
<td>0-4</td>
<td>?</td>
<td>Interview</td>
<td>0.5% males 0.3% females</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; IgE – immunoglobulin E; SPT – skin prick test

*Prevalence figure of 1.7% calculated using number of children who underwent SPT at age 3 as the denominator (n=642). This is the approach employed by all other studies reported in table 18. Venter et al. (2008) have reported a prevalence figure of 1.2%. This is calculated using all children who took part in the study at age 3 years (n=891).
Table 19: Prevalence of peanut sensitisation and allergy in children born on the Isle of Wight and aged between 3 and 6 years at the time of allergy testing

1. Studies included in the systematic review under indirect evidence: prevalence of peanut allergy in children conceived after June 1997

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Birth of infant</th>
<th>Age yrs</th>
<th>% complete data (total sample)</th>
<th>Test used</th>
<th>Prevalence of peanut sensitisation (%)</th>
<th>Prevalence of peanut allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venter et al. 2008</td>
<td>Isle of Wight</td>
<td>2001-2002</td>
<td>3</td>
<td>60% (1063)</td>
<td>SPT</td>
<td>2.0 (13/642)</td>
<td>1.7% (11/642)</td>
</tr>
<tr>
<td>Venter et al. 2006B</td>
<td>Isle of Wight</td>
<td>1997-1998</td>
<td>6</td>
<td>55% (1440)</td>
<td>SPT/Open challenge/Known peanut allergy</td>
<td>2.6% (18/700)</td>
<td>0.6% (5/798)</td>
</tr>
</tbody>
</table>

*We have added Venter et al. 2008 to the table; this article was identified in a search on prevalence and peanuts conducted in May 2008. It updates incomplete figures published by Dean et al. 2007B for children aged 3 years.

2. UK Studies of children conceived before July 1997

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Birth of infant</th>
<th>Age yrs</th>
<th>% complete data (total sample)</th>
<th>Test used</th>
<th>Prevalence of peanut sensitisation (%)</th>
<th>Prevalence of peanut allergy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grundy et al. 2002</td>
<td>Isle of Wight</td>
<td>1994-1996</td>
<td>3-4</td>
<td>43% (2878)</td>
<td>SPT, Open challenge/Known allergy</td>
<td>3.3% (41/1246)</td>
<td>1.5% (18/1273)</td>
</tr>
<tr>
<td>Tariq et al. 1996</td>
<td>Isle of Wight</td>
<td>1989-1990</td>
<td>4-5</td>
<td>64% (1536)</td>
<td>SPT + history</td>
<td>1.1% (11/981)</td>
<td>0.5% (6/1218)</td>
</tr>
</tbody>
</table>

Abbreviations used: DBPCFC – double blind placebo controlled food challenge; IgE – immunoglobulin E; SPT – skin prick test

For a further comparison of time trends in prevalence of peanut allergy, we compared the UK data with some studies from USA and Canada (see page 25 for a description of how studies were identified). Bock 1987 reported that, in 3 year old children born in 1980, the prevalence of peanut allergy confirmed by DBPCFC was 0.6% (3/480). A random digit dial telephone survey in the USA found a reported prevalence of peanut allergy in children (<18 years) was 0.4% in 1997 and 0.8% in 2002 (Sicherer et al. 2003). This was not confirmed by SPT or DBPCFC. Age specific rates for peanut allergy were also reported from the 2002 survey and were 0.8% (0.2, 1.4) for 0-5 year olds, 0.6% (0.1, 1.1) for 6-10 year olds and 0.2% (0.0, 0.4) for 11-17 year olds. A study from Montreal, Canada reported a prevalence of peanut allergy of 1.5% in 1999-2000 in children, mean age 7 years. Peanut allergy was initially assessed by questionnaire and then later confirmed by clinical history, peanut specific IgE or DBPCFC (Kagan et al. 2003). Most of the figures for USA and Canada relate to a period before the COT advice and are comparable with UK data. Data from hospital admissions/clinical registers for peanut allergy reaction cases are not typically available either nationally or internationally, by which to analyse time trends in the prevalence of reactions to peanut (or any other individual food allergen).

Prevalence of peanut consumption in general populations

In the Hourihane et al. 2007 study, peanuts were first introduced at 36 months. However, in the Tariq et al. 1996 study (prior to COT advice) peanuts were first introduced at 12.6
months. The prevalence of peanut allergy was lower in the Tariq et al. study, 0.5% compared with 1.8%. A different finding was reported in a recent study from the USA which compared the clinical characteristics of peanut-allergic children. Those children born between 1988 and 1999 were first introduced to peanuts at a mean age of 28.6 months; whereas those children born between 2000 and 2005 were first introduced peanuts at a mean age of 14.7 months (Green et al. 2007).

The Food Standards Agency provided us with information on peanut consumption from the National Diet and Nutrition Surveys (NDNS). The full report can be found as appendix 4. A summary of the results is shown in table 20. Information on young children (1.5 to 4.5 years) is only available for the period before the COT advice was issued (1992-1993) and shows that a group of this population did consume peanuts (15%). Owing to different methodologies used in the surveys it is not possible to make direct comparisons between the data for younger (1.5 to 4.5 years) and older children (4 to 18 years). At around 1997 to 1998, the time when the COT advice was issued, about 30% of children aged 4-18 years consumed peanuts.

In adults, it is possible to compare the results from the 1986/7 and 2000/1 NDNS surveys. It should be noted that pregnant women were excluded from the surveys. The data for females aged 19-40 years gives information on peanut consumption in women who might become pregnant. The percentage of women, in this age group, consuming peanuts has declined from 28.5 in 1986/7 to 22.1% in 2000/1. This compares with a slight increase in consumption rates in the general adult population aged 16-64 years. The amount consumed, by women aged 19 to 40 years, has also reduced from 5.3 to 4.6g per person per day. It is not possible to determine whether this is related to the 1998 COT advice.

Table 20: Peanut consumption rates - NDNS survey analysis

<table>
<thead>
<tr>
<th>NDNS Survey Age/gender group</th>
<th>Date of survey</th>
<th>% of survey consuming peanuts or peanut products</th>
<th>Average consumption of those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile of consumers (g/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 months*</td>
<td>1986</td>
<td>3.4</td>
<td>2.5</td>
<td>5.5</td>
</tr>
<tr>
<td>1.5 to 4.5 years*</td>
<td>1992/1993</td>
<td>15.2</td>
<td>4.6</td>
<td>17.6</td>
</tr>
<tr>
<td>4-6 years</td>
<td>1997/1998</td>
<td>31.5</td>
<td>3.0</td>
<td>16.8</td>
</tr>
<tr>
<td>7-11 years</td>
<td>1997/1998</td>
<td>32.9</td>
<td>4.8</td>
<td>21.5</td>
</tr>
<tr>
<td>12-18 years</td>
<td>1997/1998</td>
<td>30.4</td>
<td>4.7</td>
<td>25.4</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-64 years</td>
<td>1986/7</td>
<td>24.1</td>
<td>6.1</td>
<td>28.4</td>
</tr>
<tr>
<td>19-64 years</td>
<td>2000/1</td>
<td>25.2</td>
<td>6.3</td>
<td>31.8</td>
</tr>
<tr>
<td>Females 19-40 years</td>
<td>1986/7</td>
<td>28.5</td>
<td>5.3</td>
<td>24.9</td>
</tr>
<tr>
<td>Females 19-40 years</td>
<td>2000/1</td>
<td>22.1</td>
<td>4.6</td>
<td>24.9</td>
</tr>
</tbody>
</table>

Summary

Evidence from two studies designed to evaluate the impact of the COT advice found that more than 60% of pregnant women reduced their intake or avoided peanuts. There is no indication that the target group (women with a family history of allergy) were more likely to take up the advice. Of children who developed peanut sensitisation or allergy, a significant number (77% sensitisation, 40% allergy) of mothers reported that they reduced their intake or avoided peanuts. There is some evidence that prevalence of peanut sensitisation and allergy has increased threefold in children born between 1989 and 1996 in the UK; but there is no evidence of a further increase among children born in 2002 compared with 1994 in the UK. Between 1986/7 and 2000/1 peanut intake in women aged 19-40 years appears to have decreased slightly. There is no evidence to suggest that the COT advice is related to a change in peanut sensitisation or allergy.
3.6 Discussion of the systematic review

3.6.1 Main findings

The main findings for each research question for the human studies systematic review are shown below. Research questions 1 and 2 related to food sensitisation and food allergy as well as peanut sensitisation/allergy; whereas research questions 3 and 4 are specific to peanuts. Therefore for research questions 1 and 2 we have provided an overall summary and a peanut specific summary. This discussion relates to the evidence presented in the systematic review.

Research question 1

Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent development of sensitisation, or allergy to foods by the child?

ALL FOODS

There is no evidence, from seven studies, of an association between maternal dietary intake of food allergens during pregnancy or lactation and the development of food sensitisation or food allergy in the child. One case-control study did report in non-allergic women a statistically significant decreased risk of sensitisation to fish with increased maternal consumption of fish during pregnancy. The results were adjusted for other factors but these did not include breastfeeding (Calvani et al. 2006). Another poorly designed study showed an increased sensitisation to peanut in the control group (no dietary restrictions) which was statistically significant (P=0.02) for SPT but not for serum IgE antibody (Hattevig et al. 1999). There are few studies, which are mainly of poor quality, and a heterogeneous range of exposures was studied.

PEANUT

Evidence relating maternal diet duration pregnancy or lactation to subsequent peanut sensitisation or peanut allergy in the child, showed no association in two case-control studies in high risk populations. Most results were not adjusted for potential confounding factors.

Seven studies were relevant to research question 1 and four of these studies were case-control studies, rather than cohort studies and RCTs, and hence the evidence is quite weak. The one trial related to mother’s diet during lactation was a non-randomised cluster trial of two towns in Sweden, where one acted as the intervention town and the other the control town (Hattevig et al. 1999). No one exposure/intervention was evaluated by more than two studies, and hence comparison between studies is limited. This study reported an increased sensitisation to peanut using the SPT in the group with an unrestricted diet. No difference between intervention and control groups was found if serum IgE antibody was used as the assessment method. However, no specific advice on maternal peanut consumption had been given to either group. This study had the lowest SIGN score of all studies included in the review. Two case-control studies investigated peanut sensitisation and allergy (Frank et al. 1999 and Lack et al. 2003). It is difficult to compare the studies for mother’s diet during pregnancy as one calculated an unadjusted odds ratio for consumption of peanuts (> once a week vs. < once a week) and sensitisation in children under 4 years of age (Frank et al. 1999) and the other
study reported percent of cases (peanut allergy confirmed by DBPCFC) and controls whose mothers had consumed peanuts. Both studies reported no statistically significant effect for mother’s diet during pregnancy when assessing a high risk group, although the direction of effect differed (Frank et al. 1999 reported increased risk in higher consumers of peanuts, and Lack et al. 2003 reported a lower risk in children whose mothers had consumed peanuts). For mother’s diet during lactation, Frank et al. 1999 compared peanut consumption of more than once a week with less than once a week, whereas Lack et al. 2003 calculated the percent of mothers consuming peanuts at least 7 times a weeks; a much higher intake. Frank et al. 1999 reported an increased risk in higher consumers of peanuts that was not statistically significant. Lack et al. 2003 did find a statistically significant increased risk, but this was no longer statistically significant after adjustment for other factors. Both the studies had few cases of peanut sensitisation/allergy. However, as peanut allergy is not common, in order to obtain an appreciable number of cases a huge sample of subjects would need to be assessed.

Further studies are required to determine if there is any impact of mother’s diet on development of food sensitisation/allergy. At present no firm conclusions can be made.

**Research question 2**

Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

---

**ALL FOODS**

There is no consistent evidence, from six studies, of an association between infants receiving cows’ milk formula compared with breast milk and the development of food sensitisation or food allergy in the child. One study (Hilkino et al. 2001) did find a statistically significant decreased risk of parent’s report of doctor diagnosed food allergy for cows’ milk formula compared with breastfeeding. However the study was not adjusted for parental history of atopy, information on breastfeeding was poorly assessed and diagnosis of food allergy was not confirmed.

There is no evidence, from eight studies, to show that increased duration of breastfeeding protects against food allergy. Two studies reported that breastfeeding compared with never breastfeeding was associated with an increased risk of food allergy in general populations (Hourihane et al. 2007; Milner et al. 2004). However these analyses do not adjust for other factors. When Hourihane et al. 2007 adjusted for eczema, the result was no longer statistically significant. There is limited evidence that, in children with (but not without) a family history of food allergy, breastfeeding for nine months or more increases the risk of food allergy (Pesonen et al. 2006). This association of increased risk with longer duration of breastfeeding may be due to women with a family history of allergy choosing to breastfeed for longer.

There is no consistent evidence, from four studies, of an association between timing of introduction of solids, either in general or for specific foods, and the development of food sensitisation or food allergy in the child. One study reported a statistically significant increased risk of wheat allergy with delayed introduction of cereals until the child was at least 6 months of age (Poole et al. 2006). One study reported a statistically significant increased risk of food allergy in children who had milk or egg introduced after 6 months; however in an adjusted analysis there was no association between introduction of any foods after 6 months and food sensitisation (Zutavern et al. 2006).
One reported a statistically significant result for fish showing that consumption of fish during the first year of life was related to a decreased risk of food sensitisation (Kull et al. 2006A) and another that reported peanuts were introduced at an earlier age in cases of peanut sensitisation compared with controls (Frank et al. 1999). Further studies are required to confirm these findings, as the heterogeneous nature (e.g. in terms of exposure) of this evidence is a major limitation.

There is some evidence, from three studies, to show that multifaceted interventions (combining dietary and non-dietary interventions, such as house dust mite avoidance) aimed at mothers and infants protect against food sensitisation in the child; however this was not confirmed when information on food allergy diagnosis was analysed. It is difficult to compare the findings of the studies due to differences in the interventions and methods of assessing outcome.

### PEANUT

One study assessed incidence of peanut allergy in a trial to assess the effect of partially hydrolysed whey formula and breastfeeding but no cases were found in the intervention or control groups (Halken et al. 2000).

One cross-sectional study reported that children who were breastfed were 3.8 times more likely to have peanut allergy compared to those bottle-fed. However, after adjustment for potential confounders this result was no longer statistically significant (Hourihane et al. 2007).

One case-control study reported peanuts were introduced at an earlier age in cases of peanut sensitisation compared with controls (Frank et al. 1999). The results for this study were not adjusted for potential confounders.

Two studies that assessed sensitisation to peanut in multifaceted interventions aimed at mothers and infants found no association, although one reported a 12% incidence of peanut sensitisation in the diet-restricted group compared with 7% in the control group (Chang-Yeung et al. 2005).

In total 19 studies were relevant to research question 2 and 18 of these were trials and cohort studies. Therefore, compared with research question 1, there is more evidence and the study designs used were more robust. However, when the quality of the studies was assessed using the SIGN criteria most studies were relatively poor, particularly those RCTs investigating exposure to cows’ milk formula. Rates of follow-up and methods of analysis were often poor. Only one of six studies reported a benefit of cows’ milk formula compared with breastfeeding; however this was not a good quality study, as the results were not adjusted for parental allergy and parental report of doctor-diagnosed food allergy was not confirmed (Hilkino et al. 2001). Most studies, but not all, tended to report non-statistically significant findings showing an increased risk for cows’ milk formula compared with breastfeeding. It’s difficult to make a comparison between the studies as the age when children were assessed for sensitisation or allergy differed across the studies, as well as the outcome measures used. Duration of breastfeeding may be important and several studies have addressed this question. Seven cohort studies evaluated the effect of duration of breastfeeding. Again it is difficult to make comparisons between the studies owing to poor quality, the different age of assessment.
of sensitisation or allergy and methods of ascertainment of allergy (parental report, reported doctor’s diagnosis, DBPCFC) and adjustment for other factors (not carried out in all studies). There was no evidence to suggest that breastfeeding protects against development of food sensitisation or allergy in the child. In fact, there was some evidence to suggest prolonged breastfeeding may increase the risk of parent reports of food allergy in children with a family history of atopy (Pesonen et al. 2006). However, this could be explained by mothers with a family history of atopy choosing to delay introduction of solids to the infant and to breastfeed for longer.

Four studies investigated the timing of introduction of solids into the diets of infants and each assessed a different food/food group, and hence comparisons between studies cannot be made. One study reported that delayed introduction of cereals, to after 6 months, increased the risk of wheat allergy in a high risk population. However, in the study wheat allergy was not confirmed by DBPCFC. One study reported a statistically significant result for fish, showing that consumption of fish was related to a decreased risk of food sensitisation (Kull et al. 2006A). Although fish is considered as an allergenic food, certain types of fish are high in n3 long chain polyunsaturated fatty acids and this type of fat may protect against allergy (Calder et al. 2006). A case-control study reported that peanuts were introduced at an earlier age in cases of peanut sensitisation compared with controls (Frank et al. 1999); however results were not adjusted for other factors.

Three RCTs of multifaceted interventions (included household measures to decrease exposure to other allergens, such as house dust mites) were identified. These trials were generally of slightly higher quality compared with those discussed above under cows’ milk formula. One trial (Arshad et al. 2007) did report a protective effect of the intervention on food sensitisation at any time in the 8 year follow-up period. When results were analysed in a similar way to another study (Chang-Yeung et al. 2005), that is for specific food allergens, no statistically significant findings were found. However, Chang-Yeung et al. 2005, but not Arshad et al. 2007, reported an increased percent of children in the intervention group compared with the control group with sensitisation to peanut. As these trials were multifaceted it is not possible to determine which of the interventions had the greatest effect on development of food sensitisation or allergy.

Further studies are required to evaluate the effect of delayed introduction of allergenic foods, in particular peanuts. The evidence on breastfeeding compared with formula feeding, and on duration of breastfeeding is not clear; but there is no evidence to support extended exclusive breastfeeding beyond the current guidelines of 6 months.

**Research question 3**

Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?

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There is very little evidence available on non-dietary exposure of peanuts and the development of sensitisation or allergy to peanuts. One small study did find a statistically significant increased risk of peanut allergy with the use of skin creams containing peanut oil on infants. No such increased risk was found for maternal use of skin creams containing peanut oil. These results need to be confirmed in other studies.
Only two studies were found, one related the use of peanut oil in vitamin supplements and found an increased risk of food allergy in the vitamins in water compared with those in peanut oil; similar findings were observed for food sensitisation, although it was not statistically significant for peanut sensitisation (Kull et al. 2006). A possible reason to explain the results includes incomplete control of confounding, with infants with a family history of allergy more likely to use vitamins in water. The other study, a case-control study (Lack et al. 2003), did report an increased risk in children with use of skin cream containing peanut oil when applied to infants, but not for maternal use. This is potentially a very interesting finding, but it needs to be replicated in other studies. The authors hypothesised that exposure to low doses of peanut antigens through inflamed skin could cause allergy. The creams used were largely emollients for the treatment of nappy rashes, eczema, dry skin and inflammatory cutaneous conditions in infancy.

Further studies are required and are underway to assess the impact of non-dietary exposure to peanuts. Possible routes of exposure include skin, respiratory and other non-dietary oral exposure such as through vitamin supplements and medicines.

**Research question 4**

Has the current UK Government guidance on dietary consumption of peanuts and peanut products had any impact on sensitisation and allergy rates to peanuts in the UK?

**Evidence from two studies designed to evaluate the impact of the 1998 COT advice**

Evidence from two studies designed to evaluate the impact of the 1998 COT advice found that more than 60% of pregnant women reduced their intake or avoided peanuts. There is no indication that the target group (women with a family history of allergy) were more likely to take up the advice. Of children who developed peanut sensitisation or allergy, a significant number (77% sensitisation, 40% allergy) of mothers reported that they reduced their intake or avoided peanuts. There is some evidence that prevalence of peanut sensitisation and allergy has increased threefold in children born between 1989 and 1996 in the UK; but there is no evidence of a further increase among children born in 2002 compared with 1994 in the UK. Between 1986/7 and 2000/1 peanut intake in women aged 19-40 years appears to have decreased slightly. There is no evidence to suggest that the COT advice is related to a change in peanut sensitisation or allergy.

Two studies designed to evaluate the impact of the COT advice were found (Dean et al. 2007 and Hourihane et al. 2007). With regard to the advice, more than 60% of pregnant women reported they that reduced their consumption of peanuts, if not avoided them altogether. The COT advice is directed at mothers whose children have a parent or sibling with an atopic disease (asthma, eczema, food allergies etc); but this targeting does not appear to be understood by the majority of the population. Even in those who were targeted, not all women took up the advice. One potential problem is that around 30% of people perceive they have a food allergy when in fact the prevalence is much lower. Also evidence from a qualitative study showed that pregnant women were unclear about to whom the advice was directed (Turke et al. 2005). The advice was to avoid, rather than reduce intake of peanuts and few women actually reported avoiding peanuts. Hence the advice has not been interpreted by the general public in the manner intended by COT. It is therefore difficult to assess whether avoiding peanuts has had any impact on peanut sensitisation or allergy. In addition these studies were analysed as cross-sectional studies and hence information on peanut consumption was collected at the same time as ascertainment of sensitisation and allergy, and this may introduce bias. Both studies concluded that there is no evidence to
suggest that the COT advice has affected the prevalence of peanut allergy (either increase or decrease).

In addition to these two studies, we have looked for other sources of information that might be useful in assessing whether the COT advice has had an effect on peanut consumption or prevalence of peanut allergy. There is little information on peanut consumption, and we found no further specific data on intake during pregnancy. What little data there is suggests that, in women aged 19-40 years, there may have been a small decrease in the amount of peanuts consumed, both in the percent of women consuming peanuts and the amount consumers ate between 1986/7 and 2000/1. With regard to prevalence of peanut sensitisation, we feel this is difficult to assess as peanut allergy is not common and there is a low response rate for take up of allergy testing. Also, in children under 3 years food challenges with peanut are contrary to the COT advice. In the period before the COT advice was issued there does appear to be a rise in prevalence of peanut sensitisation or allergy, possibly by threefold. However in the period after the COT advice was issued there is no clear change in prevalence, although a change cannot be ruled out.

Hence the evidence we found suggests that a large number of women, including those not targeted by the COT advice, changed their peanut consumption (mainly reduced their intake). It is not clear whether the reported change in intake of peanuts has resulted in a change in prevalence of peanut sensitisation or allergy. But on balance it seems unlikely that prevalence of peanut sensitisation/allergy has changed. It has been suggested that prevalence of asthma and atopic disease may have levelled off in recent years and in some countries may be in decline (Ronchetti et al. 2001, Zollner et al. 2005). It is possible we are also seeing a levelling off with respect to peanut allergy.

3.6.2 Limitations of the systematic review

The systematic review was conducted in a robust fashion similar to that of a Cochrane review. Decisions on inclusion and exclusion of studies and data extraction were carried out by two reviewers independently. The systematic review covered only studies published between January 1999 and March 2008, in order to capture the scientific evidence published since the previous review by COT, in 1998. It has not included unpublished literature as this would have been difficult to identify in a systematic way. However there may be other studies that have been carried out and never published, possibly because they did not find any statistically significant results. We restricted the literature to that that was available in English language and hence may have missed relevant studies published in languages other than English. We have not carried out any meta-analyses as we do not consider the evidence suitable for meta-analysis. Studies assessed a heterogeneous range of exposures and interventions that were measured in a number of ways; there was also heterogeneity in the ascertainment of outcome (sensitisation and allergy).

The heterogeneity of the evidence and the poor quality of the studies (see section 3.4.5 Quality of Studies) has also made it difficult to reach any firm conclusions. Few studies included peanut as an exposure and this has limited our ability to draw conclusions.
3.6.3 Comparison with other studies

A review of breastfeeding and allergic disease from 1966 to 2001 was published in 2003 (van Odijk et al. 2003). The review concluded that breastfeeding seems to protect children from the development of atopic disease and that the effect was stronger in children with a family history of atopy. Few studies included in the review assessed food allergy.

The Australian Society of Clinical Immunology and Allergy published a position statement in 2005 (Prescott & Tang 2005). They concluded that dietary restrictions in pregnancy and lactation are not recommended. They recommend breastfeeding, but state that the protection breastfeeding confers against allergic diseases in the early years is relatively small. They report that there are inherent limitations in published studies and that studies do not differentiate between ‘exclusive breastfeeding’ and ‘any breastfeeding’. However, much of this evidence relates to all allergic disease and is not specific to food allergy. They found no evidence that delaying the introduction of potentially allergenic foods such as eggs and milk, until after the age 4-6 months has a protective effect. They suggest that avoidance of peanut, nut and shellfish for the first 2-4 years of life might be of value in high risk children and is unlikely to cause harm, however they emphasise that there is no evidence to support this.

A consensus document from USA (Fiocchi et al. 2006), on food allergy and the introduction of solid foods to infants, suggested that paediatricians and allergists should assess infants with an increased risk of allergy on a case by case basis. They suggested the optimal age for introduction of selected foods was 6 months, dairy products was 12 months, hen’s egg was 24 months and peanut, tree nuts, fish and seafood were at least 36 months. A systematic review on the relationship between early introduction of solid foods and the development of allergic disease concluded that there were few data supporting an association between early solid feeding and allergy with the exception of eczema (Tarini et al. 2006).

A recent report from the American Academy of Pediatrics (Greer et al. 2007) on the effects of early nutritional interventions on the development of atopic disease in infants and children, which considered the available evidence on the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas, also stated that current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation. They also reported that firm conclusions about the role of breastfeeding in either preventing or delaying the onset of specific food allergies are not possible at this time. With regard to introduction of solids, they were also unable to reach any conclusions about an effect of timing of introduction of solids on development of atopic disease. They questioned the benefit of delaying introduction of solids and said further studies are required.

These recently published papers are consistent with the results of our systematic review. They conclude that there is little evidence to support maternal dietary restriction during pregnancy or lactation. The role of breastfeeding in preventing food allergy is also unclear. They also found little evidence to support a delay in the introduction of solids. There appears to be more evidence available for other atopic diseases such as asthma and eczema but the information on food allergy is limited both in amount and quality of the data.
3.6.4 Conclusions

**Food sensitisation and allergy**
At present there is no evidence to suggest that maternal diet during pregnancy and lactation has an impact on development of food sensitisation or allergy in the child. It should be noted that there are few studies and most of these are of poor quality.

At present there is no evidence to suggest that delaying the introduction of solids and prolonging breastfeeding beyond the current recommendation of 6 months have an impact on development of food sensitisation or allergy in the child. There is also no clear evidence that using a cows’ milk formula increases the risk of food sensitisation compared with breastfeeding; however breastfeeding should still be recommended in preference to formula feeding where possible because of its other benefits. It should be noted that very few studies assessed the impact of delaying solids.

**Peanut sensitisation and allergy**
Few studies have assessed peanut sensitisation and allergy and no firm conclusions can be made. More work is required in this area particularly in relation to non-dietary routes of exposure. There is limited evidence to suggest that application to infants of skin creams containing peanut oil may increase the risk of peanut allergy.

There appears to be confusion among the general public about the 1998 COT advice and it has not been interpreted as the committee intended. More than 60% of women report having reduced (rather than avoided) consumption of peanuts during pregnancy and lactation, including those not targeted by the COT advice. There appears to have been a rise in the prevalence of peanut sensitisation and allergy between 1989 and 1996 but there is no clear evidence of a change (increase or decrease) in the prevalence of peanut allergy as a result of the COT advice.
3.7 References

3.7.1 References – included studies

References grouped by study design and study

Papers marked with * have undergone data extraction and appear in ‘Document 2: Tables of evidence’. Other papers have relevant information on methodologies used

Trials (9 studies)


Mellis C (2007) Reducing infant exposure to food and dust mite allergens reduced the incidence of asthma and allergy at age 8 years. Evidence Based Medicine, 12, 117.


Schoetzau A, Filipiak-Pittoff B, Franke K, et al. (2002A) Effect of exclusive breast-feeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. Pediatric Allergy & Immunology, 13, 234-42.


Cohort studies (9 studies)


*Kull I, Bergstrom A, Lilja G, Pershagen G and Wickman M (2006A) Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy, 61, 1009-15.\n


**Case-control studies (4 studies)**


*Lack G, Fox D, Northstone K, Golding J and Avon Longitudinal Study of Parents and...


Cross-sectional studies (2)


UK Prevalence data for peanut allergy for children born from 1997 onwards (2 studies)
*Dean T, Venter C, Pereira B, et al. (2007B) Patterns of sensitization to food and aeroallergens in the first 3 years of life. *Journal of Allergy & Clinical Immunology*, **120**, 1166-71.


3.7.2 References – other


Greer FR, Sicherer SH, Burks AW and the Committee on Nutrition and Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolysed formulas. Pediatrics, 121, 183-91


4. Review of animal evidence

4.1 Introduction

The systematic review conducted by the British Nutrition Foundation (“T07052-Systematic review of the literature on early life patterns of exposure and of avoidance to food allergens and later development of sensitisation and clinical allergy, with particular reference to peanut allergy”) on consequences of early life exposure to peanut had as its original remit consideration of both data from clinical studies and, where available, evidence from experimental animal models that utilised peanut proteins. Although the main focus of the systematic review was peanut proteins, it was decided that animal studies using ovalbumin (from hens’ eggs) as the model allergen should also be included. This was due to the relatively limited number of animal studies that have been published using peanut and that have utilised routes of exposure relevant to the research questions. As a result it is possible to draw conclusions about the effects of maternal dietary exposure to allergen on subsequent sensitisation responses in offspring, using the studies conducted with ovalbumin.

Due to the rather limited number of studies published using peanut allergen, a comprehensive review was undertaken that encompassed all available data on administration of peanut and sensitisation outcomes in animal models. Conversely, for ovalbumin a more selective approach was employed owing to the very large number of publications on sensitisation outcomes following the administration of ovalbumin to animals.

One other factor for consideration is the type of allergen preparation used in the different studies. Ovalbumin is available commercially as a purified and relatively homogenous protein whereas peanut proteins are not available commercially in purified form. For the peanut studies, individual groups of investigators generally prepare crude extracts of a heterogeneous group of proteins in house that will differ substantially between laboratories. It is therefore more difficult to compare between laboratories for the peanut studies.

4.2 Peanut

This section covers the following research questions:

**Research question 5**
Does maternal dietary/oral exposure to peanut – or avoidance of dietary consumption of allergen – during pregnancy/lactation have any impact on the subsequent acquisition by offspring of sensitisation (IgE antibody), or allergy (other signs/symptoms) to the same protein?

**Research question 6**
Does dietary/oral exposure to peanut – or absence of dietary/oral exposure to allergen - have any impact on the subsequent development of sensitisation (IgE antibody) or allergy (other signs/symptoms) to the same protein?

**Research question 7**
Does non-oral/dietary exposure to peanut, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to the same protein?

The systematic search for publications was carried out by the British Nutrition Foundation using the search strategy shown in appendix 1. The 35 potentially relevant papers and 3 reviews were given to Dr Rebecca Dearman to conduct a non-systematic analysis of the studies. Details of the search conducted by the British Nutrition Foundation are shown in section 4.2.1. The work conducted by Rebecca Dearman can be found in section 4.2.2.
4.2.1 Systematic search for papers

Inclusion and exclusion criteria for the peanut allergy studies

Study design

*Inclusion:* All types assessing the development of sensitisation or clinical peanut allergy.

*Exclusion:* Therapeutic or treatment studies, where intervention for control of allergic symptoms are evaluated in offspring with peanut allergy. Studies without a control group will be excluded.

Subjects

*Inclusion:* Animal models all types – in vivo and ex vivo.

Exposure

*Inclusion:* To peanuts or peanut extract via different routes of administration. Includes use of adjuvants to boost immune responses e.g. cholera toxin or alum.

Research question 5

a) maternal diet

OR

Research question 6

b) offspring diet – (include all ages – a rat is considered an adult at 6 weeks).

OR

Research question 7

c) Offspring – non food sources of peanuts e.g. in contact with skin – e.g. arachis oil – creams, peanut fractions.

Outcome

*Inclusion:* Allergic sensitisation to foods (e.g. antibodies and cytokines), anaphylaxis or other response after exposure to peanut fractions.
Methodology for peanut allergy animal studies

Searches

Search strategies were developed based upon the inclusion criteria. It was possible to combine all the research questions for the animal studies into one search. Hence one search strategy was developed for each database. The Cochrane Library (Systematic Reviews and Central Databases), MEDLINE, EMBASE and CAB Abstracts were searched from 1st January 1999 to 9th November 2007. International literature was included; however, articles which have not been translated into English were not included. A separate search was conducted on authors of included studies to find further articles written by these authors. The search strategy included both MeSH terms and text terms where possible. The search was initially developed for MEDLINE and then translated for use in the other databases. The reference lists of reviews and included studies were checked for any further papers. Abstracts presented at meetings and/or conferences, where there is not yet a full paper, were not included. The list of included studies was checked for missing studies by the Advisory Group. Any additional references identified by hand searches were added to the ENDNOTE database.

Papers identified in the searches were imported into ENDNOTE (duplicate references were deleted). ENDNOTE was used to manage the papers; this included the use of custom fields to record the progress of papers included in or excluded from the review.

Assessing eligibility of papers

A form (IN/OUT form) was developed to assess the inclusion/exclusion of papers. No study was excluded on the basis of quality of the methodology.

All titles and abstracts of papers imported to ENDNOTE were assessed by one reviewer for inclusion using the above form. Full copies of papers that were considered potentially relevant (not clearly excluded) were obtained. The full copies of papers were passed onto Dr. Rebecca Dearman to conduct the review of the evidence.

Results of the search

The search for animal studies identified 240 references in total. Table 17 shows the numbers found on each database searched. After removal of duplicate references (those retrieved by more than one database search) 159 references remained. Of these 94% (150/159) were found by searching Medline. Titles and abstracts were read for each of the 159 references and full papers were obtained for 35 of these. In addition 3 review articles were found. In order to check potentially relevant papers were not missed the reference lists of reviews and supplementary papers we obtained were checked. No further articles were identified.

Table 21: Animal studies – research questions – 5, 6, and 7

<table>
<thead>
<tr>
<th>Bibliographic Database</th>
<th>References downloaded from database</th>
<th>References after duplicates removed</th>
<th>Full papers obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>150</td>
<td>150</td>
<td>31</td>
</tr>
<tr>
<td>EMBASE</td>
<td>48</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Cab Abs</td>
<td>42</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cochrane</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand-search</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>240</strong></td>
<td><strong>159</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>
4.2.2 Further searches

Conducted by Rebecca Dearman

SEARCHES CONDUCTED IN PUB MED

Thirty eight references for responses to peanut in animal models were sourced by the British Nutrition Foundation (BNF) following a systematic literature review conducted with the assistance of Dr Jessica Strid. The following references were excluded from the final document for the following reasons:

(a) review articles that did not present new data (Finkelman, 2007; Kimber et al. 2003; Strid and Strobel, 2005)
(b) the route of sensitisation was inappropriate : systemic (intraperitoneal) immunisation which is a non-physiological route of exposure (Birmingham et al. 2002; Dearman et al. 2003; Helm et al. 2002; Lehrer et al. 2004), subcutaneous injection in the presence of adjuvant (Cardoso et al. 2008) or immunisation by intramuscular injection of plasmid DNA (Li et al. 1999)
(c) the end points measured were inappropriate and did not incorporate IgE antibody production or immediate type hypersensitivity reactions (Chambers et al. 2004; Knippels and Penninks, 2003; Kopper et al. 2006).
(d) Exposure was to peanut oil rather than to peanut proteins, the peanut oil was simply being used as a vehicle control in this study and sensitisation relevant end points were not measured (Ikeda et al. 2005)

In addition, a second search was made using the terms described below:

1. peanut, oral/diet, maternal/lactation
2. peanut, oral/diet, IgE/sensitisation
3. peanut, skin/respiratory, sensitisation/IgE
4. peanut, neonatal, sensitisation/IgE

This second review was not conducted according to the principles of a full systematic review. Studies identified from the search were then assessed for inclusion. Studies were included if appropriate control groups and end points for allergic sensitisation were used and the year of publication (1980 being the cut off year). A systematic listing of rejected publications, and the reasons for rejection, is not provided. This additional search provided a further 3 references which are marked with an asterisk in the references section and also where included in summary tables. Two of these references were published after the BNF search and the third was identified by the BNF search, but was not deemed relevant enough to the research questions.
4.2.3 Research question 5

Does maternal dietary consumption of peanut – or avoidance of dietary consumption of peanut – during pregnancy/lactation have any impact on the subsequent acquisition by offspring of sensitisation to peanut (IgE antibody), or allergy to peanut (other signs/symptoms)?

The searches on peanut and oral/diet and maternal/lactation did not yield any published papers using animal models. In addition, none of papers provided by the original search conducted by the BNF yielded any information on the effects of maternal exposure to peanut on sensitisation responses of offspring. It is not possible, therefore, to draw any conclusions from animal models about the effects of maternal consumption of peanuts on the development of sensitisation of offspring.
4.2.4 Research question 6

Does dietary/oral exposure to peanut – or absence of dietary/oral exposure to peanut - have any impact on the subsequent development of sensitisation to peanut, or allergy to peanut?

There are relatively few animal studies in which the impact of oral exposure to peanut upon the subsequent development of sensitisation has been examined.

It has been demonstrated that a single relatively low dose of peanut extract (0.02 to 0.2 mg) administered orally by gavage (bolus administration of liquid by syringe into the stomach) to BALB/c strain mice enhanced subsequent anti-peanut IgE responses to subcutaneous immunisation with peanut extract and adjuvant (complete Freund’s adjuvant; CFA) (Strid et al. 2004A; 2005). The function of the adjuvant (from the Latin “ad-juvare”: to help) in this type of experimental design is to boost immune responses to the reference allergen peanut. However, higher doses (100 mg) of peanut extract resulted in oral tolerance, with marked inhibition of specific IgE antibody responses recorded following subsequent challenge by subcutaneous injection of peanut protein and CFA adjuvant (Strid et al. 2004A). The dose response pattern was different from that observed for the allergen ovalbumin, where considerably lower doses can result in tolerance (Strid et al. 2004A).

It should be noted, however, that under other circumstances exposure to peanut by the oral route can result in sensitisation with respect to induction of specific IgE antibody responses. In general, this is associated with repeated exposure to relatively low doses of peanut protein in the absence of adjuvant. Oral (gavage) administration of peanut protein (1 mg daily for 42 days) to BALB/c strain mice (8-12 weeks old) in the absence of adjuvant resulted in the production of specific IgE antibody over a 42 day period (Dearman et al. 2001). A less vigorous dosing regimen (3 consecutive daily gavage exposures of 6 mg followed by 4 weekly gavage exposures) failed to stimulate detectable IgE antibody responses in C3H/HeJ mice (van Wijk et al. 2005A; van Wijk et al. 2005B). Similarly, two or four once weekly doses of 2 mg of peanut extract to C3H/HeJ strain mice by oral (gavage) exposure in the absence of adjuvant failed to stimulate detectable specific IgE antibody (Bowman and Selgrade, 2008). A recent publication has demonstrated that a single high dose gavage administration of peanut extract (80 mg) in the absence of adjuvant to C3H/HeJ mice resulted in a severe anaphylactic response on systemic (intraperitoneal) challenge associated with serum specific IgE (Proust et al. 2008).

There were many papers identified in the systematic review conducted by the BNF that demonstrated that oral (intragastric) administration of peanut extracts to BALB/c, C57BL/6 or C3H/HeJ strain mice induces the production of IgE antibody (Adel-Patient et al. 2005; Cardoso et al. 2008; Bowman and Selgrade, 2008; Fischer et al. 2005; 2007; Lee et al. 2001; Li et al. 2000; Li et al. 2001; Morafò et al. 2003; Qu et al. 2007; Temblay et al. 2007; van Wijk et al. 2004; van Wijk et al. 2005A; van Wijk et al. 2005B; van Wijk et al. 2007A; van Wijk et al. 2007B; Zhu et al. 2007). However, the main aim of these studies was to develop animal models of peanut allergy, and they were not designed to replicate sensitisation in a human population. Therefore, these observations are difficult to extrapolate with respect to the relevance of oral exposure of the human population and the development of sensitisation to peanut proteins due to the experimental design. In this protocol, repeated exposure to peanut protein during the sensitisation phase has been performed with concurrent administration of adjuvant (cholera toxin). In the context of these experiments, the question is
effectively “Does oral exposure to peanut induce sensitisation?” Given that the studies described above have used oral exposure concurrently with adjuvant to boost immune immune responses (a very vigorous immunisation protocol) these data are not directly relevant to human exposure to the allergen.

It is important to emphasise that the studies using adjuvant that have been cited elsewhere in this review, are considered to be relevant because the adjuvant has been used only in the challenge phase of the protocol. In this context, the challenge phase is designed to be as vigorous as possible in order to determine if the previous exposure (performed in the absence of adjuvant) has impacted on the ability to induce immune responses to the subsequent challenge. That is, the question addressed in these studies is “Does exposure to allergen in the absence of adjuvant (by a route relevant to human exposure) impact on the ability of the animal to mount immune responses to subsequent challenge with the same allergen?”

Daily oral (gavage) administration of crude peanut preparation to Brown Norway (BN) rats (3-4 weeks old) in the absence of adjuvant resulted in the production of detectable specific IgE antibody (de Jonge et al. 2007A and B). These studies also demonstrated the importance of raising experimental animals on peanut free diets for several generations, with animals raised on peanut- and soy-free diets showing higher specific IgE titres and inflammatory responses on challenge than those raised on peanut-free diets alone (de Jonge et al. 2007B).

Other investigators have demonstrated that exposure of various mouse strains including BALB/c to peanut proteins in the diet failed to provoke anti-peanut IgE antibody production (Lifrani et al. 2005).

Taken together these results indicate that oral exposure to peanut can inhibit sensitisation (IgE) to subsequent immunisation with the same antigen. Such inhibition is dependent upon the amount of peanut administered and, in mice, strain dependence in susceptibility appears to play a role. Under certain conditions, however, sensitisation and IgE antibody production may be provoked by oral exposure, although oral (gavage) administration may be more effective in this respect than dietary exposure.
### Table 22: Summary table: dietary/oral exposure to peanut – or absence of dietary/oral exposure to peanut

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dosing regimen</th>
<th>Animal model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strid <em>et al</em>. 2004A</td>
<td>Gavage (single high dose)</td>
<td>BALB/c mice</td>
<td>Inhibited IgE on challenge</td>
</tr>
<tr>
<td>Strid <em>et al</em>. 2004A; 2005</td>
<td>Gavage (single low dose)</td>
<td>BALB/c mice</td>
<td>Enhanced IgE on challenge</td>
</tr>
<tr>
<td>Dearman <em>et al</em>. 2001</td>
<td>Gavage (repeated low dose)</td>
<td>BALB/c mice</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>van Wijk <em>et al</em>. 2005A and B</td>
<td>Gavage (repeated low dose)</td>
<td>C3H/HeJ mice</td>
<td>No induction of IgE</td>
</tr>
<tr>
<td>*Bowman and Selgrade, 2008</td>
<td>Gavage (repeated low dose)</td>
<td>C3H/HeJ mice</td>
<td>No induction of IgE</td>
</tr>
<tr>
<td>*Proust <em>et al</em>. 2008</td>
<td>Gavage (single high dose)</td>
<td>C3H/HeJ mice</td>
<td>Induction of IgE and anaphylaxis</td>
</tr>
<tr>
<td>de Jonge <em>et al</em>. 2007A and B</td>
<td>Gavage (repeated low dose)</td>
<td>BN rats</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Lifrani <em>et al</em>. 2005</td>
<td>Dietary (repeated)</td>
<td>BALB/c mouse</td>
<td>No induction of IgE</td>
</tr>
</tbody>
</table>

4.2.5 Research question 7

Does non-oral/dietary exposure to peanut (via skin or respiratory tract) have any impact on the subsequent development of sensitisation to peanut, or allergy to peanut?

There is a number of animal studies that have demonstrated that the topical route of exposure to protein allergens, including peanut, may be effective for the induction of IgE-mediated immune responses. Topical exposure to relatively low dose peanut extract (100 µg) through depilated intact skin of BALB/c strain mice primed for subsequent specific IgE antibody responses to oral challenge with peanut and adjuvant (cholera toxin) (Adel-Patient et al. 2007). After removal of the stratum corneum by tape stripping, topical application of low doses of peanut extract (100 µg) to the skin of several different mouse strains (BALB/c, C57BL/6 and CBA/C9) resulted in the production of specific IgE antibody (Strid et al. 2004B; 2005). Furthermore, prior exposure to peanut through abraded skin was able to reverse the tolerogenic effects of high dose (100 mg) oral exposure to peanut in BALB/c strain mice (Strid et al. 2005). In these experiments it was shown that gavage (oral) administration of peanut extract (100 mg) inhibited subsequent specific IgE antibody responses provoked by subcutaneous immunisation with peanut in the presence of adjuvant (CFA) (Strid et al. 2004B; 2005). However, topical pretreatment of mice through abraded skin with peanut protein (100 µg; 3 consecutive daily exposures) not only prevented the ability of oral exposure to inhibit IgE responses to subsequent immunisation, but also resulted in enhanced IgE responses to the subcutaneous challenge (Strid et al. 2005). Similar effects were observed when the epicutaneous dosing was performed 6 or 20 days before the oral exposure (Strid et al. 2005). The same authors also demonstrated that epicutaneous administration of peanut proteins through abraded skin was able to partially reverse established tolerance (Strid et al. 2005). Thus, oral gavage exposure to peanut down-regulated IgE responses to subsequent subcutaneous challenge, whereas topical application of peanut through abraded skin one week after the oral treatment significantly increased specific IgE antibody production (Strid et al. 2005).

There is other evidence that exposure through the skin may be effective in the induction of IgE antibody responses. In BALB/c strain mice, intradermal injection of purified peanut protein in the absence of adjuvant induced marked anti-peanut IgE antibody responses (Betts et al., 2004) and subcutaneous injection of peanut protein extract to C3H/HeJ strain mice resulted in specific IgE antibody responses (Bowman and Selgrade, 2008). The subcutaneous route of exposure was also effective for sensitisation of dogs to peanut extract, with marked specific IgE antibody responses, skin prick test positivity and gastric responses on oral challenge observed (Schiessel et al. 2003; Teuber et al. 2002). It should be noted, however, that this exposure regimen (for immunisation of the dogs) comprises repeat injections in the presence of adjuvant (aluminium hydroxide; alum) over a period of some months and responses are recorded after 6 months to 1 year. Given such a vigorous immunisation protocol, the direct relevance of these data for human exposure is difficult to ascertain.

Although it could be argued that tape stripping or depilation does not reflect normal conditions for human exposure, apparently healthy human skin often contains minor abrasions, and barrier function in skin from atopic individuals in particular is often compromised (Elias et al. 2008). Moreover, it may be that abrasion, occlusion or impaired barrier function is not in fact necessary for the induction of allergic responses to proteins encountered at skin surfaces. Taken together with the relatively low doses of allergen required for sensitisation through the skin, these data suggest that routes of exposure other
than the gastrointestinal tract may play an important role in the development of food allergic responses.

Table 23: Summary table: non-oral/dietary exposure to peanut via skin or respiratory tract

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dosing regimen</th>
<th>Animal model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betts et al. 2004</td>
<td>Intradermal</td>
<td>BALB/c mice</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Bowman and Selgrade, 2008</td>
<td>Subcutaneous</td>
<td>C3H/HeJ mice</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Schiessel et al. 2003; Teuber et al. 2002</td>
<td>Subcutaneous (adjuvant)</td>
<td>Dogs</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Schiessel et al. 2003; Teuber et al. 2002</td>
<td>Subcutaneous (adjuvant)</td>
<td>Dogs</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Adel-Patient et al. 2007</td>
<td>Topical (low dose) (depilated skin)</td>
<td>BALB/c mice</td>
<td>Enhanced IgE on challenge</td>
</tr>
<tr>
<td>Strid et al. 2004B; 2005</td>
<td>Topical (low dose) (tape stripped skin)</td>
<td>BALB/c, C57BL/6 and CBA/C9</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Strid et al. 2005</td>
<td>Topical (low dose) (tape stripped skin)</td>
<td>BALB/c</td>
<td>Overrides oral tolerance</td>
</tr>
</tbody>
</table>

4.2.6 References

Adel-Patient K, Ah-Leung S, Bernard H, et al. (2007) Oral sensitization to peanut is highly enhanced by application of peanut extracts to intact skin, but is prevented when CpG and cholera toxin are added. *International Archives of Allergy & Immunology*, 143, 10-20.


de Jonge JD, Ezendam J, Knippe LAM, et al. (2007A) Bis(tributyltin)oxide (TBTO) decreases the food allergic response against peanut and ovalbumin in Brown Norway rats. *Toxicology*, 239, 68-76.


* Proust B, Astier C, Jacquenet S et al. (2008). A single oral sensitization to peanut without adjuvant leads to anaphylaxis in mice. International Archives of Allergy and Immunology, 146, 212-218.


van Wijk F, Wehrens EJM, Nierkens S, et al. (2007A) CD4+CD25+ T cells regulate the intensity of hypersensitivity responses to peanut, but are not decisive in the induction of oral sensitization. *Clinical & Experimental Allergy, 37*, 572-81.


References identified by the systematic literature search conducted by BNF which have not been included in the current review


4.3. Ovalbumin

This section covers research questions 5 to 7 for ovalbumin. Ovalbumin derives from hens’ egg.

Conducted by Rebecca Dearman

SEARCHES CONDUCTED IN PUB MED
1. ovalbumin, oral/diet, maternal/lactation
2. ovalbumin, oral/diet, IgE/sensitisation
3. ovalbumin, skin/respiratory, sensitisation
4. ovalbumin, neonatal, sensitisation

This review was not conducted according to the principles of a full systematic review. Searches were conducted using the above terms, then relevant papers were selected according to whether appropriate control groups and end points for allergic sensitisation were used and the year of publication (1980 being the cut off year). In addition, a systematic listing of rejected publications, and the reasons for rejection, is not provided.

4.3.1 Research question 5
Does maternal dietary consumption of ovalbumin – or avoidance of dietary consumption of ovalbumin – during pregnancy/lactation have any impact on the subsequent acquisition by offspring of sensitisation to ovalbumin (IgE antibody), or allergy to ovalbumin (other signs/symptoms)?

There are few studies that have directly examined the impact of maternal dietary consumption or avoidance of ovalbumin (OVA) on the subsequent acquisition by offspring of sensitisation. However, there is one study in which pregnant rats were fed high doses of OVA in the diet (21.5% of dietary composition) during gestation and/or lactation (Nicklin and Miller, 1987). In the offspring (7 weeks old at challenge) from the OVA treated animals, specific IgE antibody responses to intraperitoneal immunisation of OVA in the presence of adjuvant (carrageenan) were profoundly suppressed compared with the offspring of animals that had not received OVA in the diet at any time. This is a vigorous immunisation protocol and as such is not directly relevant to human exposure to the allergen. However, the use of adjuvant is relevant in this context because the adjuvant is being used at the challenge phase only, in order to determine if the previous exposure (performed in the absence of adjuvant) has impacted on the ability to induce immune responses to the subsequent challenge. That is, the question addressed in these studies is “Does exposure to allergen (OVA) in the absence of adjuvant (by a route relevant to human exposure) impact on the ability of the animal to mount immune responses to subsequent challenge with the same allergen?”

In an independent series of studies, rats were exposed to relatively high dose OVA (80mg/day) in the drinking water during lactation; the offspring of these animals exhibited suppressed specific IgE antibody responses following subsequent subcutaneous immunisation with OVA and adjuvant (complete Freund’s adjuvant [CFA]), but only if they were fed on a diet containing high levels of n-3 fatty acids during late gestation and lactation (Korotkova et al. 2004).
In addition, a very recent study in mice has demonstrated that intranasal or intragastric exposure of lactating mice to OVA (0.1 to 0.5mg/day) resulted in protection of offspring from subsequent systemic (intraperitoneal) immunisation with OVA and adjuvant (aluminium hydroxide [alum]) with respect to reduced specific IgE antibody and respiratory hypersensitivity responses on inhalation challenge (Verhasselt et al. 2008).

Taken together these data suggest that maternal oral or mucosal exposure to OVA (during gestation and or lactation), possibly with high doses of allergen, may protect offspring from the development of IgE-mediated responses to the same antigen.

Table 24: Summary table: maternal dietary consumption of ovalbumin – or avoidance of dietary consumption of ovalbumin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dosing regimen</th>
<th>Animal model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklin and Miller, 1987</td>
<td>Dietary (high dose)</td>
<td>Pregnant/lactating rats</td>
<td>Inhibited IgE on challenge in offspring</td>
</tr>
<tr>
<td>Korotkova et al. 2004</td>
<td>Drinking water (high dose)</td>
<td>Lactating rats (n-3 fatty acids-rich diet)</td>
<td>Inhibited IgE on challenge in offspring</td>
</tr>
<tr>
<td>Verhasselt et al. 2008</td>
<td>Intranasal/intragastric (low dose)</td>
<td>Lactating rats</td>
<td>Inhibited IgE and respiratory responses on challenge in offspring</td>
</tr>
</tbody>
</table>
4.3.2 Research question 6

‘Does dietary/oral exposure to ovalbumin – or absence of dietary/oral exposure to ovalbumin - have any impact on the subsequent development of sensitisation to ovalbumin, or allergy to ovalbumin?’

There is a large number of animal studies in which the impact of oral exposure to OVA upon the subsequent development of sensitisation has been examined, although many of the early studies did not examine effects on IgE-mediated responses, focusing instead on cell-mediated delayed type hypersensitivity (DTH) responses (Lamont et al, 1988; 1989). There are many reports that oral (gavage) exposure of mice to a single high dose of OVA (20-100mg) in the absence of adjuvant inhibits subsequent specific IgE antibody production and/or immediate hypersensitivity reactions upon systemic (intraperitoneal) immunisation with OVA in the presence of alum (Ando et al. 2007; Nakao et al. 1998; Oliveira et al. 2005), CFA (Strid et al. 2004) or cholera toxin (Wakabayashi et al. 2006) adjuvants. It is also reported that exposure of mice to high dose OVA (30-50mg) in drinking water followed by subcutaneous immunisation with OVA and adjuvant (alum) inhibits anti-OVA IgE antibody production (Russo et al. 2001). However, the development of this “oral tolerance” is very markedly affected by the dose of OVA, such that less than 20mg OVA failed to inhibit specific IgE antibody responses (Strid et al. 2004). Earlier reports in which the endpoints were IgG antibody production and DTH responses noted that doses of less than 1mg OVA not only did not induce tolerance but rather primed for responses to the same antigen (Lamont et al. 1989). It was also observed that different mouse strains exhibited different degrees of tolerance to high dose (25mg) OVA (Lamont et al. 1988).

Rodents are not the only species in which oral tolerance has been observed. In dogs, administration of high dose OVA in drinking water (10mg) inhibited anti-OVA IgE antibody production and challenge symptoms (conjunctivitis) in response to subsequent subcutaneous immunisation with OVA in the presence of adjuvant (alum) (Zemann et al. 2003). It should be noted, however, that under other circumstances exposure to OVA by the oral route can result in sensitisation with respect to induction of specific IgE antibody responses. In general, this is associated with repeated exposure to relatively low doses of OVA in the absence of adjuvant. In Brown Norway (BN) rats, daily oral (gavage) administration of OVA (1mg) induced anti-OVA IgE antibody in approximately 50% of animals (young adult stage of development) (Pilegaard and Madsen, 2004). Similarly, in BN rats, but not in three other rat strains, oral (gavage) administration of OVA (1mg) induced specific IgE antibody in all animals (at the young adult stage of development) (Knippels et al. 1999) and exposure via the drinking water (5mg/ml) also resulted in IgE production (Akiyama et al. 2001). Exposure of BALB/c strain mice to 1mg of OVA via oral (gavage) also resulted in the induction of specific IgE antibody, although such was considerably less vigorous than that provoked by intraperitoneal administration (Dearman et al. 2001).

Taken together these results indicate that oral exposure to OVA can inhibit sensitisation (IgE and immediate type hypersensitivity reactions) to subsequent immunisation with the same antigen. However, such inhibition is dependent upon the amount of OVA administered and in rodents marked strain dependence in susceptibility is observed. Under certain conditions, particularly with relatively low dose OVA, however, sensitisation and IgE antibody production may be provoked by oral exposure. Moreover, although it has not been investigated in a systematic way, the assumption is that the age of animals at which a protein
is first encountered via dietary or gavage exposure will impact on the effectiveness with which oral tolerance is induced (Akiyama et al. 2001).

Table 25: Summary table: dietary/oral exposure to ovalbumin – or absence of dietary/oral exposure to ovalbumin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dosing regimen</th>
<th>Animal model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strid et al. 2004</td>
<td>Gavage (low dose)</td>
<td>Mice</td>
<td>No inhibition of IgE on challenge</td>
</tr>
<tr>
<td>Lamont et al. 1989</td>
<td>Gavage (low dose)</td>
<td>Mice</td>
<td>Priming for IgE on challenge</td>
</tr>
<tr>
<td>Lamont et al. 1988</td>
<td>Gavage (high dose)</td>
<td>Mice</td>
<td>Strain dependent inhibition of IgE on challenge</td>
</tr>
<tr>
<td>Ando et al. 2007; Nakao et al. 1998; Oliveira et al. 2005; Strid et al. 2004; Wakabayashi et al. 2006</td>
<td>Gavage (single high dose)</td>
<td>Mice</td>
<td>Inhibited IgE on challenge</td>
</tr>
<tr>
<td>Russo et al. 2001</td>
<td>Gavage (single high dose)</td>
<td>Mice</td>
<td>Inhibited IgE on challenge</td>
</tr>
<tr>
<td>Zemann et al. 2003</td>
<td>Drinking water (high dose)</td>
<td>Dogs</td>
<td>Inhibited IgE on challenge</td>
</tr>
<tr>
<td>Pilegaard and Madsen, 2004</td>
<td>Gavage (repeated low dose)</td>
<td>BN rats</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Knippels et al. 1999</td>
<td>Gavage (repeated low dose)</td>
<td>BN rats 3 other rat strains</td>
<td>Induction of IgE only in BN rats</td>
</tr>
<tr>
<td>Akiyama et al. 2001</td>
<td>Drinking water (low dose)</td>
<td>BN rats</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>Dearman et al. 2001</td>
<td>Gavage (low dose)</td>
<td>BALB/c mice</td>
<td>Induction of IgE</td>
</tr>
</tbody>
</table>
4.3.3 Research question 7

‘Does non-oral/dietary exposure to ovalbumin (via skin or respiratory tract) have any impact on the subsequent development of sensitisation to ovalbumin, or allergy to ovalbumin?’

There is a number of animal studies that have demonstrated that the topical route of exposure to protein allergens, including OVA, may be effective for the induction of IgE-mediated immune responses. Mice exposed to relatively low dose OVA (10 to 100µg) via an occlusive patch on shaved skin (Spergel et al. 1998) exhibited substantially more vigorous specific IgE antibody responses than did mice immunised by intraperitoneal injection to the same antigen in the presence of adjuvant (alum). Other authors have confirmed these findings using similar exposure regimens (Aeki et al. 2005; Herrick et al. 2000; Hsieh et al. 2003; Nedle et al. 2001), with the latter group also demonstrating anaphylactic reactions on challenge. Alternative dosing regimens have incorporated tape stripping of the stratum corneum in addition to the application of an adhesive patch (Wang et al. 2007; Vaali et al. 2006), or tape stripping alone (Strid et al. 2004), with similar findings.

Although it could be argued that tape stripping and/or the application of an occlusive patch do not reflect normal conditions for human exposure, apparently healthy human skin often contains minor abrasions, and barrier function in skin from atopic individuals in particular is often compromised (Elias et al. 2008). Moreover, it may be that abrasion, occlusion or impaired barrier function is not in fact necessary for the induction of allergic responses to proteins encountered at skin surfaces. Taken together with the relatively low doses of allergen required for sensitisation through the skin, these data suggest that routes of exposure other than the gastrointestinal tract may play an important role in the development of food allergic responses.

Table 26: Summary table: non-oral/dietary exposure to ovalbumin via skin or respiratory tract

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dosing regimen</th>
<th>Animal model</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aeki et al. 2005; Herrick et</td>
<td>Topical (occlusion)</td>
<td>Mice</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>al. 2000; Hsieh et al. 2003;</td>
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<tr>
<td>Spergel et al. 1998</td>
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<td></td>
</tr>
<tr>
<td>Nedle et al. 2001</td>
<td>Topical (occlusion)</td>
<td>Mice</td>
<td>Induction of IgE and anaphylaxis</td>
</tr>
<tr>
<td>Wang et al. 2007; Vaali et</td>
<td>Topical (occlusion and tape stripping)</td>
<td>Mice</td>
<td>Induction of IgE</td>
</tr>
<tr>
<td>al. 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strid et al. 2004</td>
<td>Topical (tape stripping)</td>
<td>Mice</td>
<td>Induction of IgE</td>
</tr>
</tbody>
</table>
4.4.4 References


5. Cord blood mononuclear cells and allergy: progress since 1999

Conducted by Dr. Graham Devereux

This section covers research question 8.

Methodology

The search strategy used for the Cord Blood Mononuclear Cell (CBMC) responses included studies that investigated fetal exposure to allergens and studies relating CBMC responses to maternal allergen exposure. The allergen exposures of interest were peanut, food allergens (ovalbumin, beta-lactoglobulin) and aeroallergens (house dust mite, timothy grass, birch, cat). The search terms included CBMC, cord blood, allergens, peanut, ara h$, ovalbumin, beta-lactoglobulin, food, house dust mite, cat, birch, timothy grass, placenta, amniotic fluid, cytokine, peanut allergy, allergy. The Cochrane Library (Systematic Reviews and Central Databases), MEDLINE, EMBASE and CAB Abstracts were searched from 1st January 1999 to 31st March 2008. Animal studies were excluded, as were studies that related CBMC responses to non-allergenic ante-natal exposure and subsequent atopic disease. International literature was included; however, articles which have not been translated into English were not included. A separate search was conducted on authors of included studies to find further articles written by these authors. The search strategy included both MeSH terms and text terms where possible. The search was initially developed for MEDLINE and then translated for use in the other databases. The reference lists of reviews and included studies were checked for any further papers. Abstracts presented at meetings and/or conferences, where there is not yet a full paper, were not included.

The abstracts of the identified papers were reviewed by Graham Devereux to assess their relevance to the research questions:

Is the fetus is exposed to maternally derived allergen?
Have allergen responsive CBMC been exposed to allergen in utero?
Have allergen responsive CBMC been primed by allergen in utero?

Sixteen papers were identified as being relevant and were read in full.

Does intrauterine immunological sensitisation occur and is it associated with subsequent atopic disease?

The 1998 COT report on peanut allergy advised that pregnant women who are atopic, or for whom the father or any sibling of the unborn child has atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy. This advice was in part based on the idea that intrauterine immunological sensitisation can occur and is associated with subsequent atopic disease. This notion was based on reports of in vitro proliferative and cytokine responses by cord blood mononuclear cells (CBMC) after stimulation by mitogen, aeroallergens and food allergens (typically β-lactoglobulin and ovalbumin) (Miles et al. 1996) and that these responses were associated with the subsequent development of atopic
disease in early childhood (Warner et al. 1994). The report acknowledged that the data on the relationship between peanut consumption by pregnant women and the incidence of peanut allergy in children were inconclusive and that the mechanisms of intrauterine sensitisation and its relationship with subsequent atopic disease were uncertain. The advice on peanut avoidance during pregnancy was based on the considered possibility of a link between maternal consumption of peanuts during pregnancy and peanut allergy in offspring.

Since the COT report in 1998 there has been ongoing speculation about whether:
1). the fetus is exposed to maternally derived allergen,
2). allergen responsive CBMC have been exposed to allergen in utero
3). allergen responsive CBMC have been primed by allergen in utero

The majority of studies upon which the COT advice was based focused on aeroallergens and certain food allergens such as β-lactoglobulin and ovalbumin. Unfortunately there remains a paucity of data specific for peanuts and as for the COT report the following description of work since the report focuses on aeroallergens and certain food allergens.

In utero exposure of the fetus to allergens

*Ex vivo* perfusion experiments with fresh placentas from term and pre-term deliveries have demonstrated almost universal rapid transplacental transfer of the food allergens β-lactoglobulin and ovalbumin, however transfer of the aeroallergen Bet v1 only occurred in 20% of placentas and required the addition of serum, suggesting an IgG mediated mechanism (Szepfalusi et al. 2000; Edelbauer et al. 2004). Further work using this model suggests that approximately 1 in 10,000 molecules of β-lactoglobulin and ovalbumin in the maternal circulation cross the placenta into the fetal circulation (Loibichler et al. 2002). This experimental work is supported by the detection of β-lactoglobulin and ovalbumin (Edelbauer et al. 2004; Vance et al. 2005) in umbilical cord blood at birth. The house dust mite allergen der p1 has been detected in cord blood (60% of births) and amniotic fluid (10% of pregnancies) suggesting diaamniotic transfer of allergens in addition to transplacental transfer (Holloway et al. 2000). The cat allergen fel d1 complexed to immunoglobulin has been detected in cord blood at birth (Casas & Bjorksten 2001).

These studies suggest that the fetus is exposed to tiny amounts of ubiquitous nutrient allergens derived from the mother, however the placental transfer of aeroallergens appears to be less efficient and much less frequent. Since the COT report several studies have cast doubt on the assertion that CBMC responses after stimulation with allergen are a consequence of maternal exposure to that allergen during pregnancy.

**CBMC responses and maternal exposure to allergen**

It is clear that more work is needed to clarify the association between maternal consumption of food allergens, (especially peanuts) and offspring immune responses to the allergens. From work based predominantly on aeroallergens it appears that maternal allergen exposure during pregnancy does not have a major influence on infant immune development,

A study single has reported a weak association between maternal exposure to aeroallergen and CBMC responses of offspring (Hagendorens et al. 2004). In a study of 22 neonates, higher levels of house dust mite allergen der p1 vacuumed from the maternal mattress during early to mid-pregnancy were associated with a statistically significant reduction in the proportion of IFN-γ producing CD4+ T-cells after mitogenic stimulation (p=0.03) (Hagendorens et al. 2004). No associations were reported for numbers of IL-2, IL-4 secreting
CD4+ and CD8+ T-cells after stimulation or numbers of IL-2, IL-4, IFN-γ secreting CD4+ and CD8 T-cells. The reported association needs to be interpreted cautiously because of the multiple comparisons during the analysis of this study. In contrast the vast majority of studies have demonstrated no association between maternal allergen exposure during pregnancy and CBMC responses (Smillie et al. 2001; Chan-Yeung et al. 1999; Marks et al. 2002; Miller et al. 2001). Smillie et al. reported no association between levels of Der p1 in the maternal mattress during pregnancy and CBMC proliferative responses after stimulation with Der p1 in 225 neonates participating in an allergen avoidance study in Manchester, UK, of note there was a 21,000 fold difference in the range of exposure to der p1 between the highest and lowest exposures (Smillie et al. 2001). Similarly Miller et al. reported no association between measured levels of house dust mite, mouse and cockroach allergens during pregnancy and CBMC responses, furthermore CBMC responses were observed in the absence of maternal allergen induced peripheral mononuclear cell responses (Miller et al. 2001).

Szepfalusi et al. also concluded that maternal allergen exposure during pregnancy only partly explain corresponding CBMC responses to that allergen (Szepfalusi et al. 2000). For the seasonal allergens birch pollen and timothy grass 6/62 (9%) of CBMC samples proliferated after stimulation with Bet v1 (birch allergen) and 15/62 (15%) responded after stimulation with Phl p1 (timothy grass allergen). By analysing allergen exposure during pregnancy only 3 of the 6 (50%) CBMC samples responding to Bet v1 came from pregnancies exposed to birch pollen and 12/15 (80%) CBMC samples responding to Phl p1 came from pregnancies exposed to timothy grass pollen. Clearly CBMC samples were responding in the absence of previous exposure. Conversely 32 of 45 CBMC samples not responding to Bet v1 came from pregnancies exposed to birch pollen and 37 of 45 CBMC samples not responding to Phl p1 came from pregnancies exposed to timothy grass pollen. This work suggests that CBMC responses after stimulation with aeroallergens do not reflect in utero exposure to the allergen (Szepfalusi et al. 2000).

A single study has determined the CD45 isoform of neonatal Th-cells that respond to allergen stimulation (15). This approach is well-established in adults; with primary T-cell responses in vitro being mediated by T-cells bearing the CD45RA<sup>high</sup> isoform and recall responses are mediated by T-cells expressing the CD45RO<sup>high</sup> isoform. Devereux et al. demonstrated that 50% of CBMC proliferative responses after stimulation with timothy grass allergen are mediated by T-cells expressing CD45RA<sup>high</sup> and 50% are mediated by T-cells expressing the CD45RO<sup>high</sup> isoforms (Devereux et al. 2001). It was concluded that timothy grass allergen specific fetal Th-cells can be sensitised in utero, but that this priming does not occur in all individuals even if their CBMC are able to respond to the allergen. The validity of assuming that neonatal CD45RA<sup>high</sup> and CD45RO<sup>high</sup> isoforms are equivalent to adult ‘naïve’ and ‘memory’ cells has been questioned (Prescott & Jones 2001).

At the time of the COT report, it was widely held that CBMC responses are a reliable indicator of in utero exposure to, and sensitisation by, allergens. More recent data suggest that the association between antenatal allergen exposure and CBMC responses are complex and that it is not sustainable to assume that CBMC responses are a reliable indicator of in utero sensitisation.

The characteristics of the CBMC responding to allergens

Two recent detailed investigations of CBMC responses and the timing of allergen sensitisation question the scientific basis for existing recommendations for allergen avoidance by high-risk women during pregnancy (Thornton et al. 2004; Rowe et al. 2007). After a
detailed investigation of CBMC responses Thornton et al concluded that neonatal T-cell responses to allergens differ markedly from those occurring later in life (Thornton et al. 2004). Neonatal T-cell responding to allergens express CD45RA and CD38 and the majority undergo apoptosis after stimulation. Thornton et al concluded that responding neonatal cells are naïve immature thymic emigrants with modified antigen receptors that interact nonspecifically with protein antigens, providing short lived cellular immunity that does not generate conventional T-cell memory. More recent work from this group concluded that stable IgE associated Th2-cell memory to house dust mite and peanut occurs entirely postnatally and does not appear until after 6 months of age (Rowe et al. 2007). The evolutionary advantage of non-specific neonatal T-cell responses that fail to generate T-cell memory during the first exposures of the immune system to antigens is not clear.

Research since the COT report was published has demonstrated that it is highly probable that the fetus is exposed to small (but variable) amounts of food protein derived from the mother’s diet transported across the placenta. It remains unclear however, whether such fetal exposure results in the in utero sensitisation of the fetal immune system. It is certainly not possible to conclude that the in vitro CBMC responses observed after stimulation by food proteins necessarily reflects in utero exposure and/or sensitisation to food proteins. Furthermore, even if it could be established that in utero priming of fetal T-cells by maternal dietary proteins takes place at the present time it is not possible to conclude that such priming will result in clinical allergy in the infant.
References

Terms CBMC, cord blood, peanut, ara h$, peanut allergy, allergy

Casas R and Bjorksten B (2001) Detection of Fel d 1-immunoglobulin G immune complexes in cord blood and sera from allergic and non-allergic mothers. Pediatric Allergy & Immunology, 12, 59-64.


Vance GHS, Lewis SA, Grimshaw KEC, et al. (2005) Exposure of the fetus and infant to hens’ egg ovalbumin via the placenta and breast milk in relation to maternal intake of

6. Final conclusions - human and animal evidence on food sensitisation and food allergy

This section aims to draw together the different elements of the review (systematic review of human studies, and non-systematic (expert) reviews of animal evidence and cord blood mononuclear cells responses to allergens). The following text is structured according to the three main topic areas in relation to subsequent development of sensitisation or allergy to foods: maternal dietary intake of food allergens (section 6.1), infant dietary intake of food allergens (section 6.2), and infant non-dietary exposure to peanut (including topical) (section 6.3).

6.1 Does maternal dietary consumption of food allergens - or avoidance of dietary consumption of food allergens - during pregnancy/lactation have any impact on the subsequent acquisition by the child of sensitisation, or allergy to foods?

The systematic review of human studies found no evidence to support an association between maternal dietary intake of food allergens during pregnancy or lactation, and the development of sensitisation or allergy to foods in the child. Avoidance of food allergens was investigated in only two studies, and both showed no evidence of an association between maternal diet during pregnancy or lactation and sensitisation or allergy in the child. In total, there were only seven studies available. These were not well designed (no RCTs) and investigated a heterogeneous range of exposures. Therefore, comparisons between studies were difficult to make. Most studies were carried out in high risk populations. One case-control study reported a statistically significant decreased risk of sensitisation to fish associated with increased maternal consumption of fish during pregnancy by non-allergic women (Calvani et al. 2006). One non-randomised clustered trial, studying the diet of mothers during lactation, showed an increased rate of sensitisation to peanut in the control group (mothers with no dietary restrictions) in comparison with the intervention group (mothers who avoided eggs, cows’ milk and fish for 3 months after delivery). This association was reported to be statistically significant for positive SPT, but not for serum specific IgE antibody (Hattevig et al. 1999). However, no specific advice on maternal peanut consumption had been given to either group.

We found no peer reviewed studies in animals that assessed the impact of maternal dietary exposure to peanuts and the subsequent development of sensitisation or allergy to peanuts in the offspring. However, three different animal studies assessing maternal intake of ovalbumin and its effect on specific IgE antibody in the offspring were found. Each of these investigated lactating rats (one also used pregnant rats) and all found that administration of ovalbumin to the mother resulted in an inhibition of specific IgE antibody production in the offspring, compared with offspring whose mothers had not received ovalbumin. The effect was shown with both low and high doses of ovalbumin. Thus, the available animal studies of ovalbumin suggest that maternal consumption of ovalbumin may protect offspring from the development of IgE antibody mediated response to the same antigen.

The 1998 COT advice on peanut avoidance during pregnancy and lactation was in part based on the findings of published in vitro studies of cord blood mononuclear cells that were available at that time. The COT report concluded that sensitisation in utero or of the neonate
during breast-feeding is possible, although there were no data supporting this mechanism with regard to peanut allergens. Research published since the COT report has demonstrated that it is highly likely that the fetus is exposed to small (but variable) amounts of food protein derived from the maternal diet and transported across the placenta. However, it remains unclear whether this fetal exposure results in in utero sensitisation of the fetal immune system. Moreover, it is not possible to conclude that in vitro cord blood mononuclear cell responses observed following simulation with food proteins necessarily reflect in utero exposure, in utero sensitisation, or an increased risk of clinical allergy during later life.

Therefore, the available evidence from human studies does not suggest that maternal exposure to, or avoidance of, food allergens favours the subsequent development of food sensitisation or allergy in the child. In fact, what information there is available from studies in rats suggests that maternal oral exposure to allergen (ovalbumin), particularly at high doses, may protect the offspring from the development of sensitisation to ovalbumin.

6.2 Does dietary consumption of food allergens - or avoidance of dietary consumption of food allergens in childhood - have any impact on the subsequent development of sensitisation or allergy to foods?

The systematic review of human studies found no clear evidence of an association between dietary intake of food allergens in childhood and the subsequent development of sensitisation or allergy to foods. There was also no evidence of an association between avoidance of food allergens in the diet of children and later sensitisation or allergy to foods. In total, 19 studies were identified that investigated this question and, at present, there is no evidence to suggest that delaying the introduction of solids and/or prolonging breastfeeding beyond the current World Health Organization recommendation of six months has a beneficial impact on the development of food sensitisation or allergy in the child. One study reported an increased risk of parental reports of food allergy in children (with a family history of allergy) who were breastfed for at least nine months, compared with those who were breastfed for less than nine months (Pesonen et al. 2006). There is also no clear evidence that using a cows’ milk formula compared with breastfeeding increases the risk of sensitisation to foods. Several studies (of variable quality) have, in fact, reported an increased risk of food allergy among children who were breastfed compared with formula fed infants (Hilkino et al. 2001; Hourihane et al. 2007; Milner et al. 2004). However, the associations observed could have been confounded by mothers with a family history of allergic disease choosing to breastfeed as a potential preventative measure. Nevertheless, breastfeeding should still be recommended in preference to formula feeding where possible, because of other known health benefits. It should be noted that very few studies assessed the impact of delaying the introduction of solids into the diets of infants on sensitisation/allergy to foods. Those that did investigated different exposures, making comparisons between studies difficult. From the little information available, there is no evidence to suggest that delaying the introduction of solids, beyond the current recommendation of 6 months, is associated with a reduction in food sensitisation or food allergy.

Two studies that considered peanut intake by infants are worthy of mention. One case-control study reported that among children who subsequently developed peanut sensitisation, peanuts had been introduced at an earlier age compared with children who did not subsequently
develop sensitisation to peanut (Frank et al. 1999). The results of this study were statistically significant; however, they were not adjusted for other potential confounders. One RCT, which assessed sensitisation to peanut in a multifaceted intervention (which as well as dietary avoidance measures also included household measures to decrease exposure to other allergens such as house dust mites) aimed at mothers and infants, reported a 12% incidence of peanut sensitisation in the diet-restricted group compared with 7% in the control group (Chang-Yeung et al. 2005). However, this difference was not statistically significant. In this trial, mothers in the diet-restricted group were asked, in addition to other requirements, to avoid peanut in the last trimester of pregnancy and during lactation, and peanuts were excluded from the diet of children until the age of one year. Another study (Arshad et al. 2007), in which nuts were excluded from the diet of both the child and the lactating mother, reported a very low rate of sensitisation to peanut at 8 years of age (0% in intervention and 1.6% in the control groups).

More than 20 studies investigating oral exposure to peanut and subsequent development of sensitisation in experimental animals were found. The evidence suggests that oral exposure to peanut can inhibit the development of sensitisation (IgE antibody production) following subsequent administration with the same antigen. Such inhibition is dependent upon the amount of peanut administered, and also genetic background. Under certain conditions, however, sensitisation and IgE antibody production may be provoked by oral exposure, although oral (gavage) administration may be more effective in this respect than normal dietary exposure.

Compared with the information on peanut exposure in animals, there is more evidence available on the effect of dietary exposure of animals to ovalbumin and the subsequent development of sensitisation. Overall, the data indicate that oral exposure of rodents to ovalbumin serves to inhibit the subsequent development of sensitisation to the same protein delivered via another route. Much less commonly, particularly with low doses, it has been found that oral exposure to ovalbumin may induce IgE antibody responses. Whether or not oral exposure of rodents to ovalbumin causes priming or tolerance is affected by the dose used, genetic background and age of the animal.

To conclude, human studies provide no evidence that consumption or avoidance of food allergens in the childhood diet will lead to a reduced risk of subsequent food sensitisation and allergy. There was also no evidence that delaying the timing of introduction of food allergens into the diet is associated with reduced risk of subsequent food sensitisation and allergy. The ability to draw clear conclusions is limited by the insufficient quantity and quality of studies reporting on any particular food allergen. The animal model studies were able to examine the impact of dose on the influence of dietary exposure to food allergens in a way that is not normally possible in human studies. In the case of ovalbumin, for which a relatively substantive amount of information exists, studies in rodents suggest that the dose of protein encountered by oral exposure can influence whether the outcome is tolerance or immunological priming (sensitisation), with high doses generally being tolerogenic.
6.3 Does non-dietary exposure to peanut in childhood, for instance via skin or the respiratory tract, have any impact on the subsequent development of sensitisation or allergy to peanuts?

There is very little human evidence available on non-dietary exposure to peanuts in childhood and the impact of this on the development of sensitisation or allergy to peanuts. However, one small case-control study did find a statistically significant increased risk of peanut allergy in children following their previous exposure to skin creams containing peanut oil (Lack et al. 2003). Use of creams occurred commonly when the children were suffering from rashes. However, the association remained significant even after adjustment for rashes where abrasion might be expected to result in increased absorption through the skin. There was no association between maternal exposure to skin creams containing peanut oil and increased risk of peanut allergy in their children. There is as yet no independent confirmation of these findings.

There is evidence from studies in animals that relatively small amounts of protein allergen (peanut or ovalbumin) when applied to the skin can induce an IgE antibody response. This effect has been shown in both mice and dogs. In those studies, peanut protein was applied to damaged skin, rather than intact skin, which may be important. However, apparently healthy human skin often contains minor abrasions, and barrier function in skin from atopic individuals in particular is often compromised (Elias et al. 2008). Moreover, it is possible that even with intact skin, sufficient protein may gain access to cause immunological priming.

The animal evidence presented on topical exposure to food allergens is in principle consistent with the study reported by Lack et al. (2003). Further studies in humans are required in order to confirm the importance of topical exposure to food allergens for the acquisition of sensitisation.

No published evidence, meeting the review criteria, was found investigating other non-dietary sources of exposure to peanut and their possible impact on the development of sensitisation or allergy to peanut (such as exposure via the respiratory tract).

6.4 Ongoing research

The systematic review of human studies included only published peer reviewed publications. It did not include ongoing studies or recently completed studies that have not yet been published in peer-reviewed publications. In order to identify ongoing studies that may yield relevant data on peanut sensitisation/allergy, we searched meta-register, a database of controlled trials in progress. This database includes studies supported by major funders such as the Medical Research Council and The Wellcome Trust. Using the term ‘peanut’ we found one RCT, the LEAP (Learning Early About Peanut allergies) study (www.leapstudy.co.uk). The aim of this study is to evaluate whether during childhood early avoidance of, or exposure to, peanuts in the diet promotes tolerance and provides protection from the subsequent development of peanut allergy in children that are at high risk of developing peanut allergy. The study aims to recruit at least 480 children aged between 4 and 10 months who are at high risk as determined by allergy to eggs or severe eczema (or both). These children will be assigned randomly to the intervention group or control group. Those in the intervention group
will be asked to consume an age-appropriate peanut snack three times a week for the duration of the 5 year trial. Children assigned to the control group will be asked to avoid peanuts for the first three years of life. The study started in 2006 and is due to finish in 2013. This study should provide very useful information on the effect of early dietary introduction of peanut on the development of peanut allergy by 5 years of age.

### 6.5 Final conclusions

The available evidence from human studies does not suggest that maternal exposure to or avoidance of food allergens during pregnancy or lactation leads to the subsequent development of food sensitisation or food allergy in the child (See section 3.5.1 research question 1). On the contrary, information from studies in lactating rats suggests that exposure to ovalbumin via maternal oral intake, particularly at high doses, may protect the offspring from the development of sensitisation to ovalbumin. Studies of cord blood mononuclear cell responses and allergens published since 1998 suggest that the cord blood mononuclear cell responses observed after *in vitro* stimulation with food allergens are not necessarily the consequence of fetal exposure to, or sensitisation by maternally consumed food allergens.

Evidence from human studies does not suggest that dietary exposure to or avoidance/delaying introduction of allergenic foods in childhood provides protection from subsequent development of sensitisation or allergy to foods. There are few studies that have investigated the timing of introduction of allergenic foods and more research is required in this area (See section 3.5.2 research question 2). Evidence from animal studies suggests that oral exposure to low doses of food protein may induce sensitisation; whereas high doses may result in tolerance. This would argue that attempts at avoidance of exposure to food allergens could potentially be harmful, rather than protective, if it proves impossible to avoid the relevant food allergens altogether. The results of investigations in animals need to be confirmed and their relevance to humans explored, in particular the concept of ‘small’ and ‘larger’ amounts in human terms

There is little information in humans available on the effects of non-dietary exposure to peanuts on the development of sensitisation and allergy. However, one study did show an increased risk of peanut allergy in children who were exposed to skin creams containing peanut oil. There is some supportive evidence from experimental animal studies examining responses to peanut or ovalbumin. Further studies in humans are required in this area (See section 3.5.3 research question 3).

There appears to be confusion among the general public about the COT advice and it has not been interpreted as intended. More than 60% of women report having reduced (few avoided) consumption of peanuts during pregnancy and lactation, including those not targeted by the COT advice. There appears to have been a rise in the prevalence of peanut sensitisation and allergy between 1989 and 1996, but there is no evidence of any significant changes in the prevalence of peanut allergy since that time (See section 3.5.4 research question 4).

### 6.6 References


Proust B, Astier C, Jacquenet S *et al.* (2008). A single oral sensitization to peanut without adjuvant leads to anaphylaxis in mice. International Archives of Allergy and Immunology, **146**, 212-218.

Appendix 1 : Search strategies

1.1 Human studies

MEDLINE

1. Arachis hypogaea/
2. arachis oil.ab,ti.
3. peanut$.ab,ti.
4. 1 or 2 or 3
5. limit 4 to (humans and english language and yr="1999 - 2007")
6. limit 5 to (“newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)” or “child (6 to 12 years)”)
7. limit 5 to female
8. 6 or 7
9. exp Food Hypersensitivity/
10. peanut$.ab,ti.
11. milk.ab,ti.
12. fish.ab,ti.
13. nut.ab,ti.
14. nuts.ab,ti.
15. egg.ab,ti.
16. eggs.ab,ti.
17. food.ab,ti.
18. foods.ab,ti.
19. breastfeed$.ab,ti.
20. breastfed.ab,ti.
21. breast fed.ab,ti.
22. weaning.ab,ti.
23. weaning.ab,ti.
24. infant feeding.ab,ti.
25. celery.ab,ti.
26. wheat.ab,ti.
27. barley.ab,ti.
28. rye.ab,ti.
29. oats.ab,ti.
30. crustacean$.ab,ti.
31. almonds.ab,ti.
32. hazelnuts.ab,ti.
33. walnuts.ab,ti.
34. pecans.ab,ti.
35. pistachios.ab,ti.
36. lobster.ab,ti.
37. crab.ab,ti.
38. shellfish.ab,ti.
39. mustard.ab,ti.
40. sesame.ab,ti.
41. soy$.ab,ti.
42. kiwi fruit$.ab,ti.
43. lupin.ab,ti.
44. molluscs.ab,ti.
EMBASE
1. ARACHIS OIL/
2. arachis oil.ab,ti.
3. peanut$.ab,ti.
4. 1 or 2 or 3
5. limit 4 to (human and english language and yr="1999 - 2007")
6. limit 5 to (infant or preschool child <1 to 6 years> or school child <7 to 12 years>)
7. limit 5 to female
8. 6 or 7
9. exp Food Allergy/
38. shellfish.ab,ti.
39. mustard.ab,ti.
40. sesame.ab,ti.
41. soy$.ab,ti.
42. kiwi fruit$.ab,ti.
43. lupin.ab,ti.
44. molluscs.ab,ti.
45. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. allerg$.ab,ti.
47. atopy.ab,ti.
48. atopic.ab,ti.
49. intolerance.ab,ti.
50. hypersensitivit$.ab,ti.
51. 46 or 47 or 48 or 49 or 50
52. 45 and 51
53. 9 or 52
54. limit 53 to (human and english language and yr="1999 - 2007")
55. limit 54 to (infant or preschool child <1 to 6 years> or school child <7 to 12 years>)
56. 8 or 55

**CAB Abstracts**
1. arachis oil.ab,ti.
2. peanut$.ab,ti.
3. 1 or 2
4. limit 3 to (english language and yr="1999 - 2007")
5. child$.ab,ti.
6. infant$.ab,ti.
7. 5 or 6
8. 4 and 7
9. maternal.ab,ti.
10. pregnant$.ab,ti.
11. 9 or 10
12. 4 and 11
13. 8 or 12
14. exp food allergies/
15. peanut$.ab,ti.
16. milk.ab,ti.
17. fish.ab,ti.
18. nut.ab,ti.
19. nuts.ab,ti.
20. egg.ab,ti.
21. eggs.ab,ti.
22. food.ab,ti.
23. foods.ab,ti.
24. breastfeed$.ab,ti.
25. breastfed.ab,ti.
26. breast fed.ab,ti.
27. breast feed$.ab,ti.
28. weaning.ab,ti.
29. infant feeding.ab,ti.
30. celery.ab,ti.
31. wheat.ab,ti.
32. barley.ab,ti.
33. rye.ab,ti.
34. oats.ab,ti.
35. crustacean$.ab,ti.
36. almonds.ab,ti.
37. hazelnuts.ab,ti.
38. walnuts.ab,ti.
39. pecans.ab,ti.
40. pistachios.ab,ti.
41. lobster.ab,ti.
42. crab.ab,ti.
43. shellfish.ab,ti.
44. mustard.ab,ti.
45. sesame.ab,ti.
46. soy$.ab,ti.
47. kiwi fruit$.ab,ti.
48. lupin.ab,ti.
49. molluscs.ab,ti.

50. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. allerg$.ab,ti.
52. atopic.ab,ti.
53. intolerance.ab,ti.
54. hypersensitivity$.ab,ti.
55. atopy.ab,ti.
56. 51 or 52 or 53 or 54 or 55
57. 50 and 56
58. 14 or 57
59. limit 58 to (english language and yr="1999 - 2007")
60. 7 and 59
61. 13 or 60

**COCHRANE LIBRARY**

1. MeSH descriptor Arachis hypogaea explode all trees
2. arachis oil
3. peanut*
4. infant*
5. child*
6. maternal
7. pregnant*
8. (1 OR 2 OR 3)
9. (4 OR 5)
10. (6 OR 7)
11. (8 AND 9)
12. (6 AND 10)
13. (11 OR 12), from 1999 to 2008
14. MeSH descriptor Food Hypersensitivity explode all trees
15. peanut*:ti,ab
16. milk:ti,ab
17. fish:ti,ab
18. nut:ti,ab
19. egg:ti,ab
20. food:ab,ti
21. breastfeeding:ti,ab
22. breast fed:ab,ti
23. weaning:ti,ab
24. infant feeding:ti,ab
25. celery:ti,ab
26. wheat:ti,ab
27. barley:ab,ti
28. rye:ab,ti
29. oats:ab,ti
30. crustacean:ti,ab
31. almonds:ab,ti
32. hazelnuts:ab,ti
33. walnuts:ab,ti
34. pecans:ab,ti
35. pistachios:ab,ti
36. lobster:ab,ti
37. crab:ab,ti
38. shellfish:ab,ti
39. mustard:ab,ti
40. sesame:ab,ti
41. soy:ab,ti
42. kiwi fruit:ab,ti
43. lupin:ab,ti
44. molluscs:ab,ti
45. (15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44)
46. allerg*:ab,ti
47. atopy:ab,ti
48. atopic:ab,ti
49. intolerance:ab,ti
50. hypersensitiv*:ab,ti
51. (46 OR 47 OR 48 OR 49 OR 50)
52. (45 AND 51)
53. (14 OR 52)
54. (53), from 1999 to 2008
55. (9 AND 54)
56. (13 OR 55)
1.2 Animal studies

**MEDLINE**
1. peanut$.ab,ti.
2. arachis oil.ab,ti.
3. Arachis hypogaea/  
4. Peanut Hypersensitivity/  
5. allerg$.ab,ti.
6. atopy.ab,ti.
7. atopic.ab,ti.
8. intolerance.ab,ti.
9. hypersensitiv$.ab,ti.
10. 1 or 2 or 3
11. 5 or 6 or 7 or 8 or 9
12. 10 and 11
13. 4 or 12
14. limit 13 to (english language and yr="1999 - 2008")  
15. limit 14 to animals

**EMBASE**
1. ARACHIS OIL/  
2. arachis oil.ab,ti.
3. peanut$.ab,ti.
4. allerg$.ab,ti.
5. atopy.ab,ti.
6. atopic.ab,ti.
7. intolerance.ab,ti.
8. hypersensitiv$.ab,ti.
9. Peanut Allergy/  
10. 1 or 2 or 3
11. 4 or 5 or 6 or 7 or 8
12. 10 and 11
13. 9 or 12
14. limit 13 to (english language and yr="1999 - 2008")  
15. Animal Model/ 
16. Animal Experiment/  
17. 15 or 16
18. 14 and 17
19. from 18 keep 1-10
20. from 18 keep 1-48

**CAB Abstracts**
1. peanut$.ab,ti.
2. arachis oil.ab,ti.
3. allerg$.ab,ti.
4. atopy.ab,ti.
5. atopic.ab,ti.
6. intolerance.ab,ti.
7. hypersensitiv$.ab,ti.
8. 1 or 2
9. 3 or 4 or 5 or 6 or 7
10. 8 and 9
11. limit 10 to (english language and yr="1999 - 2008")
12. animal. cw.
13. 11 and 12
Appendix 2: SIGN checklists

<table>
<thead>
<tr>
<th>SIGN Methodology Checklist 1: Randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study identification (author, year of publication, study name (if applicable))</td>
</tr>
<tr>
<td>Research question:</td>
</tr>
<tr>
<td>Checklist completed by:</td>
</tr>
</tbody>
</table>

### Section 1: Internal validity

**In a well conducted RCT study.....**

| 1.1 | The study addresses an appropriate and clearly focused question.  
Population, intervention, control, outcome | Well covered  
Adequately addressed  
Poorly addressed  
Not reported  
Not applicable |
| :--: | :--: | :--: | :--: | :--: |
| 1.2 | The assignment of subjects to treatment groups is randomised | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.3 | An adequate concealment method is used | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.4 | Subjects and investigators are kept ‘blind’ about treatment allocation | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.5 | The treatment and control groups are similar at the start of the trial | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.6 | The only difference between groups is the treatment under investigation | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.7 | All relevant outcomes are measured in a standard, valid and reliable way  
*Well covered – DBPCFC, Adequate – SPT, specific IgE-Ab in serum, poorly – other skin tests, self-reports, but consider if DBPCFC is suitable – peanut/infancy* | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.8 | What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| 1.9 | All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)  
*Not per protocol* | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Rating</th>
<th>Subsection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
<td>Well covered</td>
<td>Adequately addressed            Poorly addressed            Not addressed            Not reported            Not applicable</td>
</tr>
<tr>
<td>SECTION 2: OVERALL ASSESSMENT OF THE STUDY</td>
<td>2.1 How well was the study done to minimise bias? Code ++, +, or –</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.2 If coded as +, or – what is the likely direction in which bias might affect the study results?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.3 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.4 Are the results of this study directly applicable to the patient group targeted by this guideline?</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>SECTION 3: DESCRIPTION OF THE STUDY</td>
<td>3.1 How many participants are included in this study? Please indicate total number randomized and numbers in each group at baseline. Is there a sample size calculation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2 What are the main characteristics of the population? Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based, and country study carried out in. How were they recruited? Response rate?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Country carried out in/ ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>General population</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk group (describe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family history of atopy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 3.3 | What intervention is being investigated in this study?  
*List all interventions covered by the study. Include duration of intervention.* |
| 3.4 | What comparisons are made in the study?  
*Are comparisons made between treatments, or between treatment and placebo / no treatment?*  
*Describe the advice/treatment of control group* |
| 3.5 | How long are patients followed-up in the study?  
*Length of time patients are followed from beginning* |
participation in the study. Note specified end points used to decide end of follow-up (e.g. death, complete cure). Note if follow-up period is shorter than originally planned. Include number of follow-ups and timings.

<table>
<thead>
<tr>
<th>3.6</th>
<th>What outcome measure(s) are used in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>List all food allergy outcomes that are used to assess effectiveness of the interventions used. Details on tests carried out and quality control - validity</strong></td>
</tr>
<tr>
<td></td>
<td><em>Food sensitisation</em></td>
</tr>
</tbody>
</table>

|     | **Food allergy** |

<table>
<thead>
<tr>
<th>3.7</th>
<th>What size of effect is identified in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>List all measures of effect in the units used in the study – e.g. absolute or relative risk, NNT, etc. Include p values and any confidence intervals that are provided.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>How were missing data (drop-outs) treated? Subjects excluded/values imputed etc</strong></td>
</tr>
</tbody>
</table>

<p>|     | <em>Food sensitisation</em> |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 3.8 | How was this study funded?  
*List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.* |   |
| 3.9 | Does this study help to answer your key question?  
*Summarise the main conclusions of the study and indicate how it relates to the key question.* |   |

Any other comments.

Any relevant information on breastfeeding and weaning? Either as a descriptive variable or in the analysis
Methodology Checklist 2: Cohort studies

Study identification  (*Include author, year of publication, study name (if applicable)*)

Research question:  

Question being addressed by study:

Checklist completed by:

**Section 1: Internal validity**

*In a well conducted cohort study:*

<table>
<thead>
<tr>
<th>Item</th>
<th>Plurality</th>
<th>Status</th>
</tr>
</thead>
</table>
| 1.1  | The study addresses an appropriate and clearly focused question.  
*Population, exposure, outcome* | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.2  | The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.3  | The study indicates how many of the people asked to take part did so, in each of the groups being studied. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.4  | The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.5  | What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.6  | *Comparison is made between full participants and those lost to follow up, by exposure status.* | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.7  | The outcomes are clearly defined. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.8  | The assessment of outcome is made blind to exposure status. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.9  | Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. | Well covered | Not addressed |
|      |            | Adequately addressed | Not reported |
|      |            | Poorly addressed | Not applicable |
| 1.10 | The measure of assessment of exposure is reliable. 
Dietary assessment methods, measure of validity | Well covered
Adequately addressed
Poorly addressed | Not addressed
Not reported
Not applicable |
| 1.11 | Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable. 
Well covered – DBPCFC, Adequate – SPT, specific Ig-AB serum, poorly – other skin tests, self reports, but consider if DBPCFC is suitable – peanut/infancy. | Well covered
Adequately addressed
Poorly addressed | Not addressed
Not reported
Not applicable |
| 1.12 | Exposure level or prognostic factor is assessed more than once. | Well covered
Adequately addressed
Poorly addressed | Not addressed
Not reported
Not applicable |
| CONFOUNDING | | | |
| 1.13 | The main potential confounders are identified and taken into account in the design and analysis. | Well covered
Adequately addressed
Poorly addressed | Not addressed
Not reported
Not applicable |
| STATISTICAL ANALYSIS | | | |
| 1.14 | Have confidence intervals been provided? | | |

### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

| 2.1 | How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? 
*Code ++, +, or –* | |
| 2.2 | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated? | |
| 2.3 | Are the results of this study directly applicable to the patient group targeted in this guideline? | N/A |
SECTION 3: DESCRIPTION OF THE STUDY (Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).

**PLEASE PRINT CLEARLY**

| 3.1 | How many patients are included in this study? List the number in each group separately. Is there a sample size calculation? |
| 3.2 | What are the main characteristics of the study population? Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based, and country study carried out in. Inclusion/exclusion criteria. How and when were they recruited? Response rate? |

**Age:**
**Gender:**
Country study carried out in/ethnicity

General population
High risk group (describe)

Family history of atopy

Comorbidity/disease status

Other inclusion/exclusion criteria

<p>| 3.3 | Which exposures are being investigated in this study? (eg. Eggs, breastfeeding, weaning). Include timing of exposure to allergen, frequency and dose. How measured? Valid |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.4</strong></td>
<td>What comparisons are made in the study?</td>
<td>Are comparisons made between presence or absence of an exposure, or different levels of the factor?</td>
</tr>
<tr>
<td><strong>3.5</strong></td>
<td>For how long are patients followed-up in the study?</td>
<td>Timing of follow-up appointments</td>
</tr>
<tr>
<td><strong>3.6</strong></td>
<td>What outcome measure(s) are used in the study?</td>
<td>List all outcomes that are used to assess the impact of the chosen food allergen and timing of assessment. Are they valid?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food sensitisation</td>
</tr>
<tr>
<td></td>
<td>Food sensitisation</td>
<td></td>
</tr>
<tr>
<td><strong>3.7</strong></td>
<td>What size of effect is identified in the study?</td>
<td>List all measures of effect in the units used in the study – e.g. absolute or relative risk. Include p values and any confidence intervals that are provided. <strong>Note:</strong> Be sure to include any adjustments made for confounding factors, differences in prevalence, etc.</td>
</tr>
<tr>
<td></td>
<td>Food sensitisation</td>
<td></td>
</tr>
</tbody>
</table>

Food allergy
### 3.8 How was this study funded?
*List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*

<table>
<thead>
<tr>
<th>3.9 Does this study help to answer your key question?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summarise the main conclusions of the study and indicate how it relates to the key question?</td>
</tr>
</tbody>
</table>
Any other comments.

Any relevant information on breastfeeding and weaning?
# Methodology Checklist 3: Case-control studies

**Study identification**  *(Include author, year of publication, study name (if applicable))*

**Research question:**

**Question being addressed by study:**

**Checklist completed by:**

## Section 1: Internal validity

**In an well conducted case control study:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
<th>Not reported</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1</strong> The study addresses an appropriate and clearly focused question</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Population, exposure, outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.2</strong> The cases and controls are taken from comparable populations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.3</strong> The same exclusion criteria are used for both cases and controls</td>
<td></td>
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</tr>
<tr>
<td><strong>1.4</strong> What percentage of each group (cases and controls) participated in the study?</td>
<td></td>
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</tr>
<tr>
<td><strong>1.5</strong> Comparison is made between participants and non-participants to establish their similarities or differences</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.6</strong> Cases are clearly defined and differentiated from controls</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Well covered – DBPCFC, Adequate – SPT, specific Ig-AB serum, poorly – other skin tests, self reports, but consider if DBPCFC is suitable – peanut/infancy.</strong></td>
<td></td>
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<tr>
<td><strong>1.7</strong> It is clearly established that controls are non-cases</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>1.8</strong> Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment</td>
<td></td>
<td></td>
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<tr>
<td><strong>1.9</strong> Exposure status is measured in a standard, valid and reliable way</td>
<td></td>
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</tr>
</tbody>
</table>

## Selection of Subjects

<table>
<thead>
<tr>
<th><strong>SELECTION OF SUBJECTS</strong></th>
</tr>
</thead>
</table>

## Assessment

<table>
<thead>
<tr>
<th><strong>ASSESSMENT</strong></th>
</tr>
</thead>
</table>

## Confounding
### STATISTICAL ANALYSIS

<table>
<thead>
<tr>
<th>1.10</th>
<th>The main potential confounders are identified and taken into account in the design and analysis</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
<th>Not reported</th>
<th>Not applicable</th>
</tr>
</thead>
</table>

### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

| 2.1 | *How well was the study done to minimise the risk of bias or confounding?*<br>Code ++, +, or – |  |
| 2.2 | *Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?* |  |
| 2.3 | *Are the results of this study directly applicable to the patient group targeted by this guideline?* | N/A |
### SECTION 3: DESCRIPTION OF THE STUDY (Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available).

**PLEASE PRINT CLEARLY**

<table>
<thead>
<tr>
<th>3.1</th>
<th><strong>How many patients are included in this study?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>List the number cases and controls separately. Is there a sample size calculation?</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.2</th>
<th><strong>What are the main characteristics of the study population?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Include all characteristics used to identify both cases and controls – e.g. age, sex, social class, disease status, community/hospital based, and country study carried out in.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>How and when were they recruited?</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cases (description)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (description)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Country study carried out in/ ethnicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family history of atopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidity/disease status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other inclusion/exclusion criteria</td>
<td></td>
</tr>
</tbody>
</table>
| 3.3 | **Which exposures are being investigated in this study?**  
(eg. Eggs, breastfeeding, weaning). **Include timing of exposure to allergen, frequency and dose.**  
**How measured? Valid** |
| 3.4 | **What comparisons are made in the study?**  
Normally only one factor will be compared, but in some cases the extent of exposure may be stratified – e.g. non-smokers v. light, moderate, or heavy smokers.  
**Note all comparisons here.** |
| 3.5 | **For how long are patients followed-up in the study?**  
Length of time participant histories are tracked in the study. |
| 3.6 | **What outcome measures are used in the study?**  
List all outcomes that are used to assess the impact of the chosen exposures. **Valid?**  
*Food sensitisation*  

*Food allergy* |
3.7 What size of effect is identified in the study?  
*Effect size should be expressed as an odds ratio.* If any other measures are included, note them as well. Include p values and any confidence intervals that are provided.

*Food sensitisation*

*Food allergy*
3.8 How was this study funded?
_List all sources of funding quoted in the article, whether Government, voluntary sector, or industry._

3.9 Does this study help to answer your key question?
_Summarise the main conclusions of the study and indicate how it relates to the key question._

Any other comments.

Any relevant information on breastfeeding and weaning?
## Methodology Checklist 4: Cross-sectional studies

### Study identification

INCLUDE AUTHOR, YEAR OF PUBLICATION, STUDY NAME (IF APPLICABLE)

<table>
<thead>
<tr>
<th>Research question</th>
<th>Question being addressed by study:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Checklist completed by:

### Section 1: Internal validity

**In a well conducted cohort study:**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
<th>Not reported</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The study addresses an appropriate and clearly focused question.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 Are the subjects representative of a larger population?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.3 The study indicates how many of the people asked to take part did so.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1.4 Information about people that did not take part.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 The outcomes are clearly defined.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6 The assessment of outcome is made blind to exposure status.</td>
<td></td>
<td></td>
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<tr>
<td>1.7 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.</td>
<td></td>
<td></td>
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<tr>
<td>1.8 The measure of assessment of exposure is reliable.</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1.9 Method of outcome assessment is valid and reliable.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Well covered – DBPCFC, Adequate – SPT, specific Ig-AB serum, poorly – other skin tests, self reports, but consider if DBPCFC is suitable – peanut/infancy.**

### Confounding
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</thead>
</table>
| **1.10** | The main potential confounders are identified and taken into account in the design and analysis. | Well covered  
Adequately addressed  
Poorly addressed  
Not addressed  
Not reported  
Not applicable |
| **STATISTICAL ANALYSIS** |   |   |
| **1.11** | Have confidence intervals been provided? |   |
| **SECTION 2: OVERALL ASSESSMENT OF THE STUDY** |   |   |
| **2.1** | How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect?  
*Code ++, +, or –* |   |
| **2.2** | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated? |   |
| **2.3** | Are the results of this study directly applicable to the patient group targeted in this guideline? | N/A |
### SECTION 3: DESCRIPTION OF THE STUDY

(Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available.)

| 3.1 | **How many patients are included in this study?** |  
| **Is there a sample size calculation?** |
| 3.2 | **What are the main characteristics of the study population?**  
*Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based, and country study carried out in.* |  
| **How and when were they recruited? Response rate?** |
| **Age:** |  
**Gender:** |  
**Country study carried out in/ethnicity** |  
**General population** |  
**High risk group (describe)** |  
**Family history of atopy** |  
**Comorbidity/disease status** |  
**Other inclusion/exclusion criteria** |
| 3.3 | **Which exposures are being investigated in this study?**  
*(e.g. Eggs, breastfeeding, weaning). Include timing of exposure to allergen, frequency and dose.*  
*How measured? Valid* |
| 3.4 | **What comparisons are made in the study?**  
**Are comparisons made between presence or** |
| 3.5 | What outcome measure(s) are used in the study?  
List all outcomes that are used to assess the impact of the chosen food allergen. Are they valid?  
Food sensitisation |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

Food allergy
3.6 What size of effect is identified in the study? List all measures of effect in the units used in the study – e.g. absolute or relative risk. Include p values and any confidence intervals that are provided. **Note:** Be sure to include any adjustments made for confounding factors, differences in prevalence, etc.

*Food sensitisation*


*Food allergy*
3.7 How was this study funded? 
*List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.*

3.8 Does this study help to answer your key question? 
*Summarise the main conclusions of the study and indicate how it relates to the key question.*

Any other comments.

Any relevant information on breastfeeding and weaning?
## Methodology Checklist 5: Prevalence studies

Study identification *(Include author, year of publication, study name (if applicable))*

<table>
<thead>
<tr>
<th>Research question:</th>
<th>Question being addressed by study:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Checklist completed by:

### Section 1: Internal validity

**In a well conducted cohort study:**

<table>
<thead>
<tr>
<th>1.1</th>
<th>The study addresses an appropriate and clearly focused question.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tbody>
</table>

**SECTION OF SUBJECTS**

<table>
<thead>
<tr>
<th>1.2</th>
<th>Are the subjects representative of a larger population?</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1.3</th>
<th>The study indicates how many of the people asked to take part did so.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1.4</th>
<th>Information about people that did not take part.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
</thead>
<tbody>
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</table>

**ASSESSMENT**

<table>
<thead>
<tr>
<th>1.5</th>
<th>The outcomes are clearly defined.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1.6</th>
<th>Method of outcome assessment is valid and reliable.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Well covered – DBPCFC, Adequate – SPT, specific Ig-AB serum, poorly – other skin tests, self reports, but consider if DBPCFC is suitable – peanut/infancy.</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STATISTICAL ANALYSIS**

<table>
<thead>
<tr>
<th>1.7</th>
<th>Have confidence intervals been provided?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

<table>
<thead>
<tr>
<th>2.1</th>
<th>How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect?</th>
<th>Code ++, +, or −</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 2.2 | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being |
|-----|---------------------------------------------------------------------------------------------------------------------------------|-----------------|
|     |                                                                                                                                 |                 |
### 2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?

| N/A |

---

### SECTION 3: DESCRIPTION OF THE STUDY

*Note: The following information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available.*

**PLEASE PRINT CLEARLY**

### 3.1 How many patients are included in this study?

<table>
<thead>
<tr>
<th>Is there a sample size calculation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

### 3.2 What are the main characteristics of the study population?

*Include all relevant characteristics – e.g. age, sex, ethnic origin, comorbidity, disease status, community/hospital based, and country study carried out in.*

- How and when were they recruited? Response rate?

  - Age:
  - Gender:
  - Country study carried out in/ ethnicity
  - General population
  - High risk group (describe)
  - Family history of atopy
  - Comorbidity/disease status
  - Other inclusion/exclusion criteria

### 3.3 What outcome measure(s) are used in the study?

*List all outcomes that are used to assess the impact of the chosen food allergen. Are they valid?*

*Food sensitisation*
Food allergy
<table>
<thead>
<tr>
<th>3.6</th>
<th>What size of effect is identified in the study? List all measures of effect in the units used in the study – e.g. absolute or relative risk. Include p values and any confidence intervals that are provided. <strong>Note:</strong> Be sure to include any adjustments made for confounding factors, differences in prevalence, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food sensitisation</td>
<td></td>
</tr>
<tr>
<td>Food allergy</td>
<td></td>
</tr>
</tbody>
</table>
| 3.7 | How was this study funded?  
*List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.* |

| 3.8 | Does this study help to answer your key question?  
*Summarise the main conclusions of the study and indicate how it relates to the key question.* |

Any other comments.

Any relevant information on breastfeeding and weaning?
Appendix 3: Papers excluded from the human studies systematic review

List of papers excluded after reading full copies of papers.

Almqvist C, Garden F, Xuan W, et al. (2007) Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years. Journal of Allergy & Clinical Immunology, 119, 1438-44.
Arshad SH and Gant C (2001) Allergy to nuts: how much of a problem really is this? Clinical & Experimental Allergy, 31, 5-7.


Clark AT and Ewan PW (2003) Interpretation of tests for nut allergy in one thousand patients, in relation to allergy or tolerance. Clinical & Experimental Allergy, 33, 1041-5.


Dixon V, Habeeb S and Lakshman R (2007) Did you know this medicine has peanut butter in it, doctor? Archives of Disease in Childhood, 92, 654.


Gustafsson D, Sjoberg O and Foucard T (2003) Sensitization to food and airborne allergens in children with atopic dermatitis followed up to 7 years of age. Pediatric Allergy & Immunology, 14, 448-52.


Hadley C (2006) Food allergies on the rise? Determining the prevalence of food allergies, and how quickly it is increasing, is the first step in tackling the problem. EMBO Reports, 7, 1080-3.


Host A (2001) Primary and secondary dietary prevention. Pediatric Allergy & Immunology, 12 Suppl 14, 78-84.


Host A (2001) Primary and secondary dietary prevention. Pediatric Allergy & Immunology, 12 Suppl 14, 78-84.


Huang JL, Chen CC, Kuo ML and Hsieh KH (2001) Exposure to a high concentration of mite allergen in early infancy is a risk factor for developing atopic dermatitis: a 3-year follow-up study. Pediatric Allergy & Immunology, 12, 11-6.


Kerkhoff M, Koopman LP, van Strien RT, et al. (2003) Risk factors for atopic dermatitis in infants at high risk of
allergy: the PIAMA study. *Clinical & Experimental Allergy*, 33, 1336-41.


Kmietowicz Z (2007) Advice to pregnant women to avoid eating peanuts should be withdrawn, says Lords committee. *BMJ*, 335, 633.


Maloney JM, Sampson HA, Sicherer SH and Burks WA (2006) Food allergy and the introduction of solid foods to infants: a consensus document. Annals of Allergy, Asthma, & Immunology, 97, 559-60; author reply 61-2.


Mellis C (2007) Reducing infant exposure to food and dust mite allergens reduced the incidence of asthma and allergy at age 8 years. Evidence-Based Medicine, 12, 117.


vitamin supplementation is associated with increased risk for food allergy. 


Sariachvili M, Droste J, Dom S, *et al.* (2007) Is breast feeding a risk factor for eczema during the first year of lif...
life? Pediatric Allergy & Immunology, 18, 410-7.
Tay SS, Clark AT, Deighton J, King Y and Ewan PW (2007) Patterns of immunoglobulin G responses to egg and peanut allergens are distinct: ovalbumin-specific immunoglobulin responses are ubiquitous, but peanut-specific immunoglobulin responses are up-regulated in peanut allergy. Clinical & Experimental Allergy, 37, 1512-8.


Vander Leek TK, Liu AH and Stefanski K (2001) Subsequent reactions were common and often more serious than the initial reactions of children with peanut allergy. Evidence-Based Medicine, 6, 126.


von Mutius E, Schwartz J, Neas LM, Dockery D and Weiss ST (2001) Relation of body mass index to asthma


Appendix 4: Peanut consumption rates – NDNS Survey Analysis

Conducted by Josh Atkinson a statistician at the Food Standards Agency

Introduction

Comparability of Data Sets

The three data sets used for the statistics on peanut consumption are (chronologically):
- NDNS 1997/1998 Young persons 4-18
- NDNS 1986/1987 Adults 19-64
- NDNS 2000/2001 Adults 19-64

If the user wants to compare the statistics from this analysis to assess how peanut consumption rates have changed over time then the 1997 Young Person’s survey analysis must be ignored. This data set uses a different population from the 86/87 and 00/01 adult surveys (different age groups). Therefore it is not possible to separate whether the differences seen between the surveys are due to changes over time or the difference in populations.

This is not the case for the 1986/87 and 2000/01 adult surveys. These both use 19-64 year olds and so any changes seen between these surveys should be due to variation in consumption over time.

Limitations

Adults 1986/87 and 2000/01: Pregnant women are excluded from the surveys

Intake2 (the software that analyses the NDNS data) has a bug that effects the calculation of some statistics. In this report, the statistics affected by this bug are the ‘average of max amount of peanuts consumed on one occasion’ and ‘average highest amount recorded for consumption of peanuts in one day for those eating peanut products’. This only has a mild effect, but does mean that the acute calculations will not be exact.

Explanation of columns:

Average of max amount of peanuts consumed in one meal (g/person/occasion)

This takes each subject that has consumed the peanut product, produces a distribution from their maximum consumption in any one meal (across the whole food diary period) and averages these maximum values.

Highest amount recorded for consumption of peanuts in one day (g)

The highest amount of peanuts in a product consumed in one day by one individual from the surveys.

This value is not representative of the population as it is only from a single individual, because of this I have included the statistic ‘average highest amount recorded for consumption of peanuts in one day’ which better represents the acute eating habits of the population.
Average highest amount recorded for consumption of peanuts in one day (g/person/d)

Similar to the ‘average of max amount of peanuts consumed on one occasion’, but for the consumption rate over a day instead. This takes each subject that has consumed the peanut product, produces a distribution from their maximum rate of consumption on any one day (across the whole food diary period) and averages these maximum values.
Table 1: Consumption rates – NDNS Survey 1986/1987 Adults (ages 19-64) n= 2197

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g)</th>
<th>Average highest amount recorded for consumption of peanuts in one day for those eating peanut products (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>9.8</td>
<td>0.88</td>
<td>9.00</td>
<td>29.25</td>
<td>49.34</td>
<td>224</td>
<td>51.14</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>3.0</td>
<td>0.12</td>
<td>4.13</td>
<td>23.4</td>
<td>17.15</td>
<td>100.5</td>
<td>18.1</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>4.0</td>
<td>0.27</td>
<td>6.67</td>
<td>23.79</td>
<td>24.44</td>
<td>95.8</td>
<td>25.94</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>0.1</td>
<td>0.002</td>
<td>1.67</td>
<td>n/a</td>
<td>11.69</td>
<td>20</td>
<td>11.69</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>9.7</td>
<td>0.13</td>
<td>1.32</td>
<td>8.46</td>
<td>5.22</td>
<td>90.3</td>
<td>8.53</td>
</tr>
<tr>
<td>TOTAL*</td>
<td>24.1</td>
<td>1.47</td>
<td>6.1</td>
<td>28.4</td>
<td>28.06</td>
<td>224</td>
<td>29.49</td>
</tr>
</tbody>
</table>

NC – No consumers
* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.

You may notice that 0.1% of respondents ate peanuts in chocolate or cereal bars. This appears to be low, but we have double checked this statistic.
Table 2: Peanut Consumption rates – NDNS Survey 2000/01 Adults (ages 19-64) n=1724

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day for those eating peanut products (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>5.65</td>
<td>0.55</td>
<td>9.69</td>
<td>36.86</td>
<td>49.73</td>
<td>218</td>
<td>53.81</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>1.92</td>
<td>0.13</td>
<td>7.00</td>
<td>36.56</td>
<td>44.72</td>
<td>144</td>
<td>33.11</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>4.6</td>
<td>0.30</td>
<td>6.5</td>
<td>27.1</td>
<td>25.85</td>
<td>172.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>2.2</td>
<td>0.16</td>
<td>6.30</td>
<td>22.88</td>
<td>33.3</td>
<td>125</td>
<td>33.8</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>5.09</td>
<td>0.25</td>
<td>1.95</td>
<td>6.35</td>
<td>11.30</td>
<td>24.6</td>
<td>11.61</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>8.35</td>
<td>0.13</td>
<td>1.58</td>
<td>4.82</td>
<td>6.28</td>
<td>62.1</td>
<td>6.35</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>25.21</strong></td>
<td><strong>1.58</strong></td>
<td><strong>6.28</strong></td>
<td><strong>31.76</strong></td>
<td><strong>26.93</strong></td>
<td><strong>218</strong></td>
<td><strong>29.03</strong></td>
</tr>
</tbody>
</table>

NC – No consumers

* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
Table 3: Peanut Consumption Rates – Sub sample of NDNS 1986/87 Adults (females, ages 19-40) n=541

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>12.4</td>
<td>0.96</td>
<td>7.77</td>
<td>29.15</td>
<td>43.42</td>
<td>108</td>
<td>44.43</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>2.8</td>
<td>0.05</td>
<td>1.96</td>
<td>n/a</td>
<td>10.64</td>
<td>37.8</td>
<td>10.99</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>3.9</td>
<td>.30</td>
<td>7.74</td>
<td>21.17</td>
<td>26.41</td>
<td>93</td>
<td>28.85</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>0.4</td>
<td>0.01</td>
<td>1.51</td>
<td>n/a</td>
<td>10.54</td>
<td>20</td>
<td>10.54</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>12.2</td>
<td>0.13</td>
<td>1.10</td>
<td>7.29</td>
<td>5.84</td>
<td>53.01</td>
<td>5.91</td>
</tr>
<tr>
<td>TOTAL*</td>
<td>28.47</td>
<td>1.5</td>
<td>5.27</td>
<td>24.94</td>
<td>25.58</td>
<td>122.31</td>
<td>26.79</td>
</tr>
</tbody>
</table>

NC – No consumers

* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
Table 4: Peanut Consumption Rates – Sub sample of NDNS 2000/01 Adults (females, ages 19-40) n=468

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>4.9</td>
<td>0.38</td>
<td>7.79</td>
<td>29.43</td>
<td>42.03</td>
<td>206</td>
<td>54.42</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>1.1</td>
<td>0.06</td>
<td>5.3</td>
<td>n/a**</td>
<td>17.85</td>
<td>46.4</td>
<td>20.85</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>2.8</td>
<td>0.13</td>
<td>4.74</td>
<td>n/a**</td>
<td>21.46</td>
<td>56.7</td>
<td>21.46</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>2.8</td>
<td>0.13</td>
<td>4.71</td>
<td>n/a**</td>
<td>21.55</td>
<td>62.5</td>
<td>21.73</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>3.6</td>
<td>0.10</td>
<td>2.70</td>
<td>6.41</td>
<td>11.66</td>
<td>24.60</td>
<td>12.90</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>8.4</td>
<td>0.10</td>
<td>1.20</td>
<td>4.79</td>
<td>5.54</td>
<td>35.10</td>
<td>5.61</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>22.1</strong></td>
<td><strong>1.01</strong></td>
<td><strong>4.57</strong></td>
<td><strong>24.88</strong></td>
<td><strong>21.02</strong></td>
<td><strong>206</strong></td>
<td><strong>24.29</strong></td>
</tr>
</tbody>
</table>

NC – No consumers
* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
** These are non-applicable as there are not enough consumers for the calculation of the statistic
### Table 5: Peanut Consumption rates – NDNS Survey 1997/98 Young Persons (ages 4-18) n=1701

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>2.7</td>
<td>0.19</td>
<td>7.00</td>
<td>27.4</td>
<td>38.71</td>
<td>150</td>
<td>40.63</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>0.65</td>
<td>0.01</td>
<td>1.37</td>
<td>n/a**</td>
<td>9.60</td>
<td>33.5</td>
<td>9.60</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>9.4</td>
<td>0.64</td>
<td>6.75</td>
<td>26.6</td>
<td>22.47</td>
<td>142.5</td>
<td>23.77</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>2.1</td>
<td>0.09</td>
<td>4.04</td>
<td>10.3</td>
<td>23.42</td>
<td>73.5</td>
<td>24.98</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>8.82</td>
<td>0.19</td>
<td>2.20</td>
<td>7.48</td>
<td>10.39</td>
<td>25.6</td>
<td>10.96</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>12.2</td>
<td>0.15</td>
<td>1.24</td>
<td>5.57</td>
<td>4.68</td>
<td>36.45</td>
<td>4.96</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>31.5</strong></td>
<td><strong>1.38</strong></td>
<td><strong>4.39</strong></td>
<td><strong>21.57</strong></td>
<td><strong>16.56</strong></td>
<td><strong>150</strong></td>
<td><strong>17.63</strong></td>
</tr>
</tbody>
</table>

NC – No consumers

* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.

** These are non-applicable as there are not enough consumers for the calculation of the statistic

163
Table 6: Peanut Consumption Rates – Sub sample of NDNS Survey 1997/98 Young Person’s (ages 4-6) n=355

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>3.59</td>
<td>0.16</td>
<td>4.46</td>
<td>n/a**</td>
<td>27.06</td>
<td>69</td>
<td>25.80</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>0.24</td>
<td>0.002</td>
<td>0.96</td>
<td>n/a **</td>
<td>n/a**</td>
<td>6.7</td>
<td>n/a**</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>12.1</td>
<td>0.61</td>
<td>5.00</td>
<td>18.0</td>
<td>19.01</td>
<td>142.5</td>
<td>14.50</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>0.86</td>
<td>0.01</td>
<td>1.63</td>
<td>n/a**</td>
<td>11.44</td>
<td>15</td>
<td>11.44</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>3.5</td>
<td>0.04</td>
<td>1.15</td>
<td>n/a**</td>
<td>7.53</td>
<td>12.8</td>
<td>7.53</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>13.6</td>
<td>0.10</td>
<td>0.76</td>
<td>2.87</td>
<td>3.30</td>
<td>12.96</td>
<td>3.39</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>31.5</strong></td>
<td><strong>0.95</strong></td>
<td><strong>3.02</strong></td>
<td><strong>16.77</strong></td>
<td><strong>12.71</strong></td>
<td><strong>142.50</strong></td>
<td><strong>13.12</strong></td>
</tr>
</tbody>
</table>

NC – No consumers
* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
** These are non-applicable as there are not enough consumers for the calculation of the statistic
Table 7: Peanut Consumption Rates – Sub sample of NDNS Survey 1997/98 Young Person’s (ages 7-11) n=613

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>3.2</td>
<td>0.22</td>
<td>6.88</td>
<td>21.3</td>
<td>43.83</td>
<td>150</td>
<td>43.83</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>0.7</td>
<td>0.01</td>
<td>2.06</td>
<td>n/a**</td>
<td>14.42</td>
<td>33.5</td>
<td>14.4</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>11.9</td>
<td>0.81</td>
<td>6.79</td>
<td>26.36</td>
<td>22.56</td>
<td>80.91</td>
<td>23.92</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>3.2</td>
<td>0.12</td>
<td>3.81</td>
<td>10.1</td>
<td>21.80</td>
<td>62.5</td>
<td>23.36</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>7.4</td>
<td>0.17</td>
<td>2.32</td>
<td>7.50</td>
<td>10.27</td>
<td>24.4</td>
<td>10.92</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>11.9</td>
<td>0.15</td>
<td>1.28</td>
<td>7.15</td>
<td>4.59</td>
<td>19.44</td>
<td>4.85</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>32.9</strong></td>
<td><strong>1.56</strong></td>
<td><strong>4.75</strong></td>
<td><strong>21.5</strong></td>
<td><strong>17.92</strong></td>
<td><strong>150</strong></td>
<td><strong>18.89</strong></td>
</tr>
</tbody>
</table>

NC – No consumers
* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
** These are non-applicable as there are not enough consumers for the calculation of the statistic
Table 8: Peanut Consumption Rates – Sub sample of NDNS Survey 1997/98 Young Person’s (ages 12-18) n=731

<table>
<thead>
<tr>
<th>FOOD</th>
<th>% of survey consuming products</th>
<th>Average consumption over whole population (g/person/d)</th>
<th>Average consumption for those eating peanuts or peanut products (g/person/d)</th>
<th>Consumption at 97.5 percentile (g/person/d)</th>
<th>Average of max amount of peanuts consumed on one occasion (g/person/occasion)</th>
<th>Highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
<th>Average highest amount recorded for consumption of peanuts in one day (g/person/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole peanuts</td>
<td>1.9</td>
<td>0.18</td>
<td>9.30</td>
<td>n/a**</td>
<td>42.01</td>
<td>100</td>
<td>48.17</td>
</tr>
<tr>
<td>Peanuts in mixes</td>
<td>0.82</td>
<td>0.01</td>
<td>0.97</td>
<td>n/a**</td>
<td>6.82</td>
<td>10.1</td>
<td>6.82</td>
</tr>
<tr>
<td>Peanut butter and spreads</td>
<td>6.3</td>
<td>0.52</td>
<td>8.3</td>
<td>51.0</td>
<td>25.44</td>
<td>110.1</td>
<td>26.99</td>
</tr>
<tr>
<td>Coated peanuts</td>
<td>1.9</td>
<td>0.09</td>
<td>4.86</td>
<td>n/a**</td>
<td>28.14</td>
<td>73.5</td>
<td>30.04</td>
</tr>
<tr>
<td>Peanuts in chocolate or cereal bars</td>
<td>12.4</td>
<td>0.28</td>
<td>2.28</td>
<td>7.28</td>
<td>10.83</td>
<td>25.6</td>
<td>11.43</td>
</tr>
<tr>
<td>Peanuts in dishes</td>
<td>11.69</td>
<td>0.17</td>
<td>1.46</td>
<td>5.61</td>
<td>5.51</td>
<td>36.5</td>
<td>5.91</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>30.4</td>
<td>1.44</td>
<td>4.74</td>
<td>25.40</td>
<td>17.2</td>
<td>138</td>
<td>18.69</td>
</tr>
</tbody>
</table>

NC – No consumers
* These totals are not the sum of the groups. The total statistics are from the distribution of all peanuts and all products and recipes including peanuts.
** These are non-applicable as there are not enough consumers for the calculation of the statistic
**Food items**

The following are the food items that make up each food set along with their ID codes.

**Whole peanuts**

PEANUTS FRESH KERNEL ONLY - 2191  
PEANUTS FRESH WEIGHED WITH SHELLS - 2192  
PEANUTS SALTED - 2193  
PEANUTS, ROASTED UNSALTED - 2323  
ROASTED UNSALTED - 94028

**Mixed Peanuts**

BOMBAY MIX - 80763  
BOMBAY MIX / CHEVDA - 2605  
KP NUTS - TOBAGO & CHILLI - 81736  
MIXED NUTS AND RAISINS UNSALTED - 2629  
MIXED NUTS UNROASTED UNSALTED - 2188  
TESCO HONEY ROAST CASHEWS & PEANUTS – 81744

**Coated peanuts**

CHOCOLATE AND CANDY COVERED NUTS - 7956  
CHOCOLATE COVERED NUTS AND RAISINS - 8372  
YOGHURT COATED PEANUTS/RAISINS - 7885

**Peanut Butter**

PEANUT BUTTER AND CHOCOLATE SPREAD PURCHASED - 8542  
PEANUT BUTTER CRUNCHY - 90436  
PEANUT BUTTER CRUNCHY NOT WHOLENU - 2196  
PEANUT BUTTER SMOOTH - 90437  
PEANUT BUTTER SMOOTH NOT WHOLENU - 2195  
PEANUT BUTTER WHOLEGRAIN WHOLENU NO A DDED SUGAR - 8047  
PEANUT BUTTER, REDUCED FAT - 3160

**Bars**

CADBURY’S STAR – 80409  
CADBURY'S PICNIC TWIN DESSERT - 5133  
FRUIT & NUT BAR - 94682  
LEAF 'LOW' PEANUT - 82383  
MR. TOM PEANUT BAR - 80677  
NATURES HARVEST SESAME STICKS - 82255  
PREWETTS FRUIT BAR - 9066  
SHEPHERD BOY GINGER FRUIT & NUT BAR - 81354  
SHEPHERDBOY FRUIT & NUT - 94334  
SLIM FAST PEANUT BUTTER CRUNCH - 81177  
SLIMFAST BAR - 80092  
TOPIC/MARATHON (SNICKERS) - 7964  
TRACKER BAR CHOCOLATE CHIP - 7967

**Dishes**
APPLAUSE - 7971
ASDA CELERY NUT AND SULTANA SALAD - 80171
BEEF CHICKEN AND PORK SATAY - 8596
BHE POORI - 80543
BROWN RICE AND NUT SALAD - 81296
CHICKEN SATAY - 5494
CHICKEN SATAY WITH CHINESE STYLE RICE (EG JS) - 9902
CHICKEN WITH SATAY SAUCE - 94151
CHINESE CHICKEN - 6014
CHOCOLATE AND NUT CAKE (GERMAN) - 93297
CHOCOLATE FLAVOURED SPECIAL FLAPJACK CAKE - 81442
CHUNKY NUT CHEX - 9823
COCONUT AND NUT CAKE - 93597
CRUNCHY NUT CHEX - 5161
CRUNCHY NUT CORNFLAKES - 93675
CRUNCHY NUT CORNFLAKES KELLOGGS & OWN BRAND - 232
CUISINE VERT THREE VEGETABLE SATAY - 80174
DALEPAK SPICY BEAN BURGER - 80715
DATE AND RAISIN CAKE (NO SUGAR) HOMEMADE - 9744
DIWANA BUFFET LUNCH BHE POORI FOOD - 80141
FANCY FLAPJACK-STRAWBERRY FLAVOUR CHOCOLATE ICING - 81617
FARMHOUSE BRAN WITH HONEY AND NUT - 209
FARMHOUSE BRAN WITH HONEY AND NUT - 94004
FEAST - 732
FLORENTINES - 330
FRUIT CAKE WITH SEMOLINA, NO FAT - 3339
FRUIT PUDDING BOILED - 9669
FRUIT PUDDING FRIED IN OIL - 93728
FRUIT SALAD WITH NUTS - 93532
GRANOSE VEGETARIAN PEANUT BASED NUT LOAF-NUTTOLENE - 81427
H/M GRANOLA - 93849
HEALTHFOOD SHOP GRANOSE FOODS NUTLOAF - 80721
HOMEMADE PEANUT BUTTER COOKIES - 8969
HONEY & NUT BRAN FLAKES OWN BRAND E.G. SAFEWAY, SAINSBURY - 3008
HONEY NUT CHEERIOS - 9275
HONEY NUT SHREDDED WHEAT, NESTLE - 6824
ICE CREAM NON-DAIRY WITH CHOC/NUT/TOFFEE/BISCUIT - 8009
KELLOGGS COMMON SENSE OAT BRAN FLAKES + RAISINS & APPLE - 7648
KELLOGGS NUT FEAST - 8958
LA LOMA NUT MEAT - 80722
LENTIL AND PEANUT BAKE - 81299
M & S PEANUT CRISPY - 82184
M+S CELERY +NUT SALAD - 94067
M+S RICE +WHOLEFOOD SALAD - 94301
NUT BALLS - 94618
NUT CROQUETTES - 81984
NUT LOAF IN SPICY TOMATO SAUCE - 9595
NUT ROAST CODE 81562 - 81562
NUT ROAST CODE 82009 - 82009
NUT ROAST FRIED IN SUNFLOWER OIL - 80075
NUTBURGER FRIED IN VEG OIL RETAIL - 6027
NUTTY FINGERS WITH CORNFLAKES - 94077
NUTTY TUNA - 81564
ORANGE AND LEMON ROULADE WITH PEANUTS - 2993
PEANUT BUTTER RISOTTO WITH LEEK,COURGETTE,PEPPER,TOMATO AND POTATOES - 3277
PEANUT COOKIES - 80277
PORK SATAY - 6908
PORK SATE WITH PEANUT SAUCE - 94550
POTATO AND NUT RISOTTO - 80206
POTATO CURRY MADE WITH PEANUT BUTTER - 8734
RED PEPPER DISH - 81341
SAFEWAY YOGHURT HONEY SURPRISES- RICE AND WHEAT CRUNCHY CEREAL - 8037
SAINSBURYS HOT OAT CEREAL WITH BRAN - 94158
SARAH LEE VANILLA DANISH BAR - 5959
SATAY VEGETABLE DISH - 80536
SAVOURY RISSOTTO WITH NUTS AND SEEDS - 93411
SAVOURY SPICED CAKE - 80612
SAVOY CABBAGE WITH APPLES AND PEANUTS - 80573
SHEPHERDS PIE WITH PEANUTS - 9059
STEAMED CABBAGE PARCELS - 80361
STIR FRY CODE 80627 - 80627
STUFFED CABBAGE - 94884
STUFFED COURGETTE WITH NUTS - 80495
SWEET PLAIN BUN - 81394
TESCO BEANBURGERS - 80350
TESCO NUT LOAF - 80398
TOAD IN THE HOLE USING SAUSOLATAS - 81690
TRIFFIN CAKE - 93186
TRIFLE - 94213
TRIFLE CODE 3730 - 93730
TRIFLE HOMEMADE - 573
TRIFLE HOMEMADE WITH ARTIFICIAL CREAM - 581
TRIFLE, PURCHASED, FROZEN WITH DAIRY CREAM - 575
VEGETABLE PATTIES - 82100
VEGETABLE STEW WITH CABBAGE, SWEET POTATOES, TOMATOES, OKRA AND PEANUTS - 3509
VEGETARIAN HAGGIS - 9361
VEGI MIX BALLS IN PEANUT BUTTER SAUCE - 82197
WEETABIX CRUNCH NUT CHEX - 81021
WHITWORTHS BREAKFAST BOOSTER - 93749
WHOLE EARTH NUT CLUSTER WITH CARAMEL TOPPING - 82007
YOGHURT & CRUMBLE PEACH & APRICOT - 81582
YOGHURT LOW FAT WITH MUESLI OR NUTS - 706
YOGHURT TOPPED STRAWBERRY OAT BAR – 81609
Glossary

**Allergen** - Any substance to which a person is allergic (for example, pollen, house dust mite droppings, animal dander, peanuts).

**Allergic foods**
- Foods that may trigger allergies or cause allergic sensitisation.

**Anaphylaxis**
- An immediate (IgE mediated) reaction to a foreign substance, which in severe cases can be generalised and life-threatening.

**Antibodies**
- Proteins that are produced by our immune system in order to protect our body from ‘intruders’ such as bacteria and viruses. Immunoglobulin E is the antibody involved in allergic reactions.

**Antigen**
- Substance recognised by the immune system.

**Asthma**
- A disease in which the airways (the breathing tubes taking air in and out of the lungs) become inflamed and swollen, making breathing difficult. In many cases it is caused by an allergy.

**Blinding**
- Blinding is not telling someone what treatment a person has received, or in some cases, what their outcome has been, to avoid them being influenced by this knowledge. The person who is 'blinded' could be either the person who is being treated or the researcher assessing the effect of the treatment (single blind), or both of these people (double blind).

**Case-control study**
- Case-control studies are epidemiological studies which are often used to identify risk factors for a medical condition. This type of study compares a group of patients who have that condition with a group of patients that do not and looks back in time to see how the characteristics of the two groups differ.

**Cohort study**
- This is a study which identifies a group of people and follows them over a period of time to see how their exposures affect their outcomes. This type of study is normally used to look at the effect of suspected risk factors that cannot be controlled experimentally on outcomes.

**Confounding factor/Confounder**
- This is something that can distort the true relationship between two (or more) characteristics. When it is not taken into account, false conclusions can be drawn about associations.

**Cross sectional study**
- These are epidemiological studies which describe characteristics of populations. They are ‘cross sectional’ because data is collected at one point in time and then the relationships between characteristics are considered. Importantly, because such a study doesn’t look at time trends, it can’t establish what causes what.

**Crude oil**
- Unrefined edible oil that may contain sufficient quantities of protein to induce an allergic reaction.

**Dermatitis**
- Another name for eczema which includes Atopic Dermatitis and Contact Dermatitis.

**Double-blind Placebo-controlled food challenge (DPBPFC)**
Test in which neither the physician nor the patient knows whether a placebo (dummy) is being administered or specific food is being administered.

**Eczema**
A group of skin conditions characterised by dry, red, flaky, itchy skin. The most common form of eczema is allergic or Atopic Eczema (also called Infantile Eczema or Atopic Dermatitis).

**Emollients**
Special moisturisers – available as bath oils, creams and ointments – that are used to help prevent eczema and hydrate the skin. Usually contain Liquid Paraffin, Cetomacrogol and Emulsifying Wax.

**Food Challenge**
Test carried out in hospital to identify suspected food allergens by giving traces of food concealed in capsules or broth. Open Food Challenge is when the food is not concealed.

**Hay fever**
An allergy caused by breathing in pollen and by pollen getting into the eyes. Affects the delicate lining of the nose and eyes. Also known as seasonal allergic rhinitis.

**House dust mite**
A tiny 0.5mm long spider-like insect that inhabits carpets, bedding and soft furnishings. It eats human skin flakes and thrives in humid environments. Their droppings cause allergies such as Asthma, Eczema and Rhinitis.

**IgE**
E-class immunoglobulin (antibody). The type of immunoglobulin that triggers release of Histamine from Mast Cells and sets off an acute allergic reaction.

**Immunoglobulin**
A type of immune antibody that may be involved in ‘policing’ the body for foreign bacteria and allergens. Examples are IgE, IgA, IgG an IgM.

**Incidence rate**
A measure of morbidity based on the number of new episodes of illness arising in a population over an estimated period. It can be expressed in terms of sick persons or episodes per 1000 individuals at risk.

**Non-randomised study**
In the context of study design, this means that participants were not allocated randomly to receiving an intervention or not.

**Peanut**
Nut from a herbaceous plant. It is also known as the groundnut or monkey nut, botanical name *Arachis hypogaea*. It is a member of the Leguminosae family and thus related botanically to peas and beans, rather than tree nuts such as brazil, hazel or almond.

**Peanut oil**
Also known as arachis oil. Used in foods and other products such as skin creams.

**Prevalence rate**
A measure of morbidity based on current sickness in a population, estimated either at a particular time (point prevalence) or over a stated period (period prevalence). It can be expressed either in terms of sick people (persons) or episodes of sickness per 1000 individuals at risk.

**Randomised controlled trial (RCT)**
This is a study where people are allocated randomly to receiving a particular intervention or not (this could be two different treatments or one treatment and a
placebo). This is the best type of study design to determine whether a treatment is effective.

**Radio AllergoSorbent Test (RAST)**
Radio AllergoSorbent Test — a blood test to diagnose what causes a particular allergy. It measures the amount of IgEs in the blood, produced in response to certain allergens. The CAP-RAST is a newer version RAST with over 400 different allergen tests available.

**Refined oil**
Oils containing no detectable protein.

**Skin prick test**
An allergy test that involves putting a small amount of a known allergen on to a scratch in the skin, to see if the body reacts. Used to diagnose allergy to various foods, pollens, house dust mite droppings and pet dander.

**Wheal**
A raised bump on the skin that indicates an allergy in a skin prick test.