COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON THE REVIEW OF THE 1998 COT RECOMMENDATIONS ON PEANUT AVOIDANCE

1. The COT was asked by the Food Standards Agency (FSA) to evaluate the results of a literature review that the Agency had commissioned following a research call issued in June 2007. The aim of this review was to assess the scientific evidence available since 1998 concerning avoidance versus exposure to peanut during early life and possible influences on the development of sensitisation and clinical allergy to foods, with particular reference to peanut. In the light of this literature review, and taking account of any other relevant information, the COT was asked to consider whether the recommendations to pregnant mothers that were issued in the 1998 COT report on Peanut Allergy[1] should now be amended or remain in place.

2. The literature review had been conducted by the British Nutrition Foundation (BNF), with assistance, where necessary, on specific aspects of the evidence, from other scientific experts.

3. The COT was provided with the final technical report of the review of published literature[2], as well as summary information about unpublished and ongoing research. This information was supplemented, at the request of the COT, by several key review articles together with summary details and abstracts of relevant studies published since these reviews, on the evidence concerning early life dietary exposures and atopic diseases other than food allergy, such as allergic asthma and atopic eczema. This additional information was requested by the COT to enable the Committee to take into account any relevant information from the wider body of evidence relating to early life exposures and the development of allergic disease beyond food allergy specifically, that might inform the present review. This supplemental information was collated by the FSA.

4. The Committee was grateful for the advice of a number of external medical and scientific experts, which informed its discussion of the literature review conducted by the BNF and of the wider evidence base. These were: Prof. Stephen Holgate, MRC Clinical Professor of Immunopharmacology from the University of Southampton; Dr Andrew Clark, Consultant in Paediatric Allergy from Addenbrookes Hospital, University of Cambridge; Prof. Graham Devereux, Clinical Senior Lecturer at the University of Aberdeen and Respiratory Physician at Aberdeen Royal Infirmary; and Prof. Ian Kimber, Professor of Toxicology at the University of Manchester and Programme Advisor to the FSA Food Allergy & Intolerance Research Programme (T07).

Background

Peanut allergy

5. Allergy to peanuts is a serious health problem among UK children, with estimates of prevalence suggesting that between 0.2 and 1.8% of children may be affected (see Table 2 on page 12). Allergic reactions to peanut in both children and adults can be severe and can involve life-threatening symptoms (anaphylaxis). Fatal food allergic reactions are rare and are more common in teenagers and adults than in children, but peanuts are reported to be the commonest cause of such fatalities across all age groups[3]. Sensitivity varies significantly between individuals and the most sensitive can react to very small (mg or, in very rare cases, μg[4]) amounts of peanut protein.

6. Unlike certain other food allergies such as egg and milk allergy, which are common in young childhood but which tend to be outgrown, peanut allergy commonly persists throughout life[5]. In common with allergy to other foods, there are currently no established primary preventive strategies for peanut allergy. Moreover, the only means of managing the condition once it has developed is complete avoidance of peanut coupled with use of rescue medication (antihistamines and adrenaline) to treat the symptoms of a reaction once it has happened. Avoidance is both difficult to achieve in practice[6], and also has socioeconomic and quality-of-life consequences for affected individuals and their families[7].

7. Allergic reactions to foods can occur through several mechanisms but, in the great majority of instances, peanut sensitisation and peanut allergy are mediated via IgE antibody. In common with other forms of IgE mediated allergy, IgE mediated peanut allergy develops in two phases. In the first phase, sensitisation is acquired by a susceptible individual following exposure to peanut. Sensitisation is characterised by specific immunological priming involving the induction of a special type of immunoglobulin, IgE, that is in this case specific for peanut allergen. This IgE is distributed systemically throughout the vascularised tissue and binds to mast cells. If the now-sensitised individual is exposed to sufficient quantities of the same allergen, the IgE on the surface of mast cells can be cross-linked and degranulation may be triggered, which will cause the release of various inflammatory mediators, leading to the clinical manifestations (symptoms) of allergy. Once this second stage has been reached then an individual is said to have clinical (symptomatic) allergy. In the case of peanut allergy, the inflammatory response may occur within a few seconds or minutes after contact with the food, leading to serious systemic responses that include anaphylactic shock, asthma, hives (urticaria and angioedema) and gastrointestinal reactions such as vomiting and diarrhoea. Usually reactions follow dietary consumption of peanut, but they can also result from inhalation or skin contact with the peanut or peanut products. As defined here, the key difference between sensitisation and allergy to foods is that sensitisation, which is a priming of the immune response, is not necessarily associated with symptoms when the food is consumed. Sensitisation is defined operationally by the presence of allergen-specific IgE antibody directed to particular parts of an allergen molecule (usually a protein or glycoprotein) and/or positive skin prick tests (SPT) when a very small dose of allergen is introduced through the skin. Allergy is diagnosed using a combination of

patient history, the presence of allergen-specific IgE and/or skin prick test results, and, where there is any doubt, a controlled food challenge.

8. The factors that determine susceptibility to food allergy and control its development are of considerable scientific and clinical interest, and the subject of current research. A major predisposing factor in the acquisition of food allergy is inheritance of an atopic phenotype – characterised by the ability to mount vigorous IgE antibody responses to allergens commonly encountered in the environment, in food, the workplace, certain drugs and insect stings. There are also a number of other factors that have important influences on the development of food allergy and determine which foods lead to allergy in a particular individual. Of special importance are the route, timing, duration and extent of exposure.

9. Early life environmental and dietary experiences are of particular relevance in determining whether allergy will develop, or whether the subject will develop protective tolerance. In the latter case the individual will either fail to induce the class of immune response required for effective sensitisation or will develop other immunological mechanisms that serve to prevent or neutralise IgE-dependant allergic responses and, as a result, will be able to consume the particular foodstuff without triggering the allergic cascade. The possibility that sensitisation (priming) to peanuts might be acquired from exposure via the mother during pregnancy through the placenta or during lactation, is of particular relevance to peanut allergy since in many cases, peanut allergy becomes apparent in children when they display reactions following what is believed to be their first known dietary exposure to peanut products. This possible sequence of events was one of the important pieces of evidence considered by the COT Working Party on Peanut Allergy in 1998[8,9], and was influential in the development of the precautionary recommendations made by the COT at that time.

Previous COT recommendations

10. In 1996, as a result of the particular severity of allergic reactions to peanut and the possibility that the prevalence of this allergy was increasing especially in children, the COT convened a Working Group. The aim of this Working Group was to review the scientific evidence on peanut allergy and to advise on whether there was an association between early exposure to peanuts or peanut products and the occurrence of peanut allergy in later life. Two of the four scientific experts who assisted the COT with the present review, were also members of that previous COT Working Group: Prof Stephen Holgate and Prof Ian Kimber.

11. At the time the COT Working Group was established few published studies were available on this subject. However, what literature there was suggested that some food allergens contained in egg and milk could be transmitted intact to infants via breastmilk[10,11], possibly leading to sensitisation (priming) of the infant[12]. There was also evidence from immunological studies of human umbilical cord blood mononuclear cells (CBMC) taken at birth, showing proliferative and cytokine responses following culture *in vitro* with certain food allergens. This evidence was considered suggestive of *in utero* sensitisation and there were indications from the literature that such responses might be associated with the subsequent development of allergic disease[13]. Published reports available at that time describing children

reacting on their first known dietary exposure to peanut[8,9] were thus interpreted as suggesting peanut allergen transfer *in utero* or during lactation as a route of sensitisation.

12. In considering the available published evidence on intrauterine immunological sensitisation and on other possible routes of exposure to allergens, the COT concluded in 1998 that there was some support for the suggestion that peanut allergy in infants could result from exposure *in utero* or during lactation, but that the available data were inconclusive. However, with regard to the mechanism of sensitisation and allergy, a link between peanut consumption by pregnant and lactating women and the occurrence of peanut allergy in the child was considered possible. On this basis, the COT considered that it would be unwise to discount the possibility of sensitisation of offspring resulting from exposure of the mother, and issued a number of precautionary dietary recommendations.

13. The dietary recommendations from the 1998 COT report on peanut allergy[1] were that:

" *(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. "

14. The report also recommended that parents or those charged with the care of peanut allergic children or infants should:

" *(i) be vigilant in reading labels on all multi-ingredient foods and should avoid any for which doubt exists about the ingredients;*

(ii) be aware that even minute amounts of peanut allergens may result in severe reactions. They should therefore be alert to the possibility of accidental exposure and should ensure that cross-contamination of foodstuffs with peanut allergens does not occur;

(iii) be aware of the treatment for anaphylaxis should inadvertent exposure occur at, for example, school, or the homes of other children. "

Developments since 1998

15. The previous COT recommendations formed the basis of Government advice that has now been in place for 10 years. Since 1998, several studies (including some funded by the FSA), have been published on the subject of sensitisation and allergy to foods in relation to early life dietary (and to a lesser extent non-dietary) exposures which add to the evidence base that underpinned the 1998 COT recommendations. One significant development during the intervening period has been recognition that, in principle at least, sensitisation to peanut proteins could be acquired via routes of exposure other than dietary intake, notably through skin contact. Although the importance of skin exposure in driving sensitisation to peanuts (and possibly other food stuffs) is suspected, it has not been established with certainty. If it were confirmed, however, the implication would be that sensitisation in early life might not require passage of peanut allergen via the placenta or breastmilk. Since the COT recommendations were made, there have also been several studies published on the frequency of sensitisation and allergy to peanuts, which could inform understanding of whether the prevalence of this allergy is increasing. It was therefore considered timely to re-assess the current state of scientific knowledge in this area and, based on the evidence now available, to re-consider whether the 1998 COT dietary recommendations remain appropriate.

16. The COT was also informed that a recent House Of Lords Science and Technology Select Committee inquiry on allergy, published in September 2007 [14], included a recommendation to the UK Government, based on submitted evidence, to revoke the current advice regarding peanut consumption by pregnant women and infants. The Government response to this inquiry was that it was important to review carefully all the relevant evidence that related to the acquisition of peanut allergy in order to reassess whether or not the advice should be rescinded or revised. The response also noted that a literature review commissioned by the Food Standards Agency was already being undertaken.

Literature review of studies published since 1998

17. A literature review, carried out by the British Nutrition Foundation (BNF), sought to identify and review studies published since 1998 on the early life patterns of exposure to, and avoidance of, food allergens and the later development of sensitisation and clinical food allergy, with particular reference to peanut. To address this overarching aim, the researchers structured the literature review from three different types of evidence: 1) studies conducted in humans; 2) studies conducted in animals; and 3) *in vitro* immunological studies conducted on human umbilical cord blood. The reviewers specified several research questions against which to identify studies of relevance, as detailed in Table 1.

Table 1: List of the research questions around which the BNF literature review was structured

Nature of evidence to be reviewed	Research questions to be addressed
Evidence from studies in humans	**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?
Evidence from studies in animals	**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) 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) 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?
Evidence from studies utilising human cord blood	**Research question 8**: Does intrauterine immunological sensitisation occur and is it associated with subsequent atopic disease?

Methodology

18. The following is a summary of the methodology used for the three different elements of the literature review (human, animal and human umbilical cord blood studies). Full details of the methodologies, including lists of search terms and data extraction forms, can be found in the final technical report of the project [2].

19. The review of human studies was conducted according to standard systematic review procedures and searched MEDLINE, EMBASE, the Cochrane Library and CAB Abstract databases to identify relevant papers published between 1st January 1999 and 7th March 2008 inclusive. Inclusion and exclusion criteria were drawn up for each research question and used to develop appropriate search term lists. In general terms, inclusion criteria were based on including all study designs except case reports and therapeutic or treatment studies; exposures of interest included exposure to or avoidance of any of the 14 allergenic foods listed in current EU legislation[15] and also kiwi fruit; and outcome measures included allergic sensitisation to foods and clinical food allergy including that which is self-reported. Studies which reported only other allergy endpoints such as asthma, atopic eczema, rhinitis, atopic wheeze and other respiratory outcomes were excluded. Identified publications were assessed against the relevant inclusion/exclusion criteria and those of potential relevance were assessed independently by two reviewers to determine whether they

should be included. Data extraction was performed in duplicate using modified versions of the extraction forms produced by the Scottish Intercollegiate Guidelines Network (SIGN) [16].

20. Twenty four separate studies were identified by the review of the human studies, including 9 clinical trials, 9 cohort studies, 4 case-control studies, 2 cross-sectional studies of associations between dietary exposure measures and allergy outcomes, and 2 prevalence studies (some investigations used more than one design).

21. The review of animal studies was conducted as two separate expert literature reviews. One review evaluated published experimental studies in animals which had examined the influence of maternal and/or early life dietary and dermal exposures to peanut on the development of sensitisation, symptoms of allergy or other immunologically relevant endpoints. The second identified similar studies that had employed ovalbumin (hens' egg allergen). In both cases the literature was searched systematically, followed by expert review of the relevant scientific evidence. Both reviews were carried out by Dr Rebecca Dearman, an expert in immunotoxicology and currently a Member of the COT. Search terms were drawn up and conducted in Pub Med to identify relevant articles published since 1980. This earlier starting date was chosen in order to encompass the entire body of relevant evidence from published animal studies, since such studies had not previously been reviewed by the COT. In fact, only 2 studies published before 1998 were identified as being of relevance to the review; the remainder being published from 1998 onwards. The searches resulted in a total of 30 papers being included in the review of studies on peanut, and 25 for ovalbumin[*].

22. The review of studies on human umbilical cord blood was conducted as an expert review of research published since the 1998 COT report on human CBMC responses and sensitisation and allergy, which was set in the context of the state of scientific knowledge in this area in 1998 when the COT report was published. This review was written by Prof. Graham Devereux, an expert in the early life origins of allergic disease*.

Findings of the literature reviews

Evidence from studies conducted in humans

Maternal dietary intake

23. The BNF review identified seven studies meeting the inclusion criteria that had investigated an association between maternal dietary intake of allergenic foods during pregnancy or lactation and the development of sensitisation or clinical allergy to foods in the child. These comprised one non-randomised clustered trial[17], two cohort studies[18,19], and four case-control studies[20-23]. According to the SIGN criteria, these studies, which involved a heterogeneous range of dietary exposures, were not considered to be of high quality. In non-atopic women but not in atopic women, one

[*] These expert reviews, including the list of references that they encompassed, can be found in the final technical report of FSA funded research project T07052 (http://www.foodbase.gov.uk)

of the case-control studies (Calvani *et al.*, 2006[20]) did report a statistically significant decreased risk of sensitisation to fish with increased maternal consumption of fish during pregnancy (consumption once a week versus once a month or less (OR 0.22 (95% CI 0.08-0.55), consumption 2-3 times a week or more than once a month versus once a month or less OR 0.23 (95% CI 0.08-0.69)). However, whilst the results had been adjusted for various possible confounding factors, this did not include those associated with breastfeeding; and the retrospective assessment of maternal diet, up to 18 years previously, could have led to significant recall bias. The non-randomised trial[17] found a higher rate of sensitisation to peanut (when assessed by positive SPT but not by peanut-specific IgE) and soy (when assessed by IgE but not by SPT), in mothers in the comparison group who were not avoiding allergenic foods when compared with the mothers in the intervention group who were avoiding eggs, cows' milk and fish for 3 months after delivery (soy OR 6.01 (95% CI 1.09-43.33), peanut OR 10.67 (95% CI 1.24-239.1)). However, the mothers in the intervention group were not instructed to avoid peanut or soy, which complicates the interpretation of these findings. Of the two case-control studies, one compared maternal consumption of peanut (during pregnancy and lactation) in a group of children who were sensitised to peanut, with that in a control group of children who were sensitised to egg or milk (but not peanut)[21]. The other study compared maternal consumption of peanut (during pregnancy and lactation) in a group of peanut allergic children, a control group of atopic (but non-peanut allergic) children, and a further control group of non-atopic children[22]. In the former study (Frank *et al.*, 1999) unadjusted odds ratios of between 2 and 4 were reported, but these were not found to be statistically significant (consumption of peanut by mothers during pregnancy more than once a week compared with less than once a week: unadjusted OR (peanut sensitisation as measured by positive peanut-specific IgE) 3.97 (95% CI 0.73-24.0); consumption of peanut by mothers during lactation more than once a week compared with less than once a week: unadjusted OR (peanut sensitisation as measured by positive peanut-specific IgE) 2.19 (95% CI 0.39 – 13.47))[*]. In the latter study (Lack *et al*., 2003), no statistically significant associations between dietary consumption and peanut allergy in the child were found after adjustment for potential confounding factors.

24. One other report included in the literature review, of a study aimed primarily at assessing prevalence of peanut allergy in young children, made reference to maternal peanut consumption and peanut sensitisation (defined as a positive SPT to peanut), in infants[6]. This study found no association between reduction in maternal consumption, or avoidance, of peanuts in response to the 1998 Government advice and whether or not their children were sensitised to peanuts, although it is unclear from the published report whether this statement related to intake during pregnancy, lactation or both.

Infant dietary intake

25. The BNF review identified nineteen studies meeting the inclusion criteria that had investigated dietary consumption or avoidance of allergenic foods in early childhood, and the association with subsequent development of sensitisation or allergy to foods. These included eight randomised controlled trials[24-31], ten cohort

[*] adjusted odds ratios were not reported

studies[19,22,32-39] and one case-control study[21]. Again, there were heterogeneous exposures and many of the studies did not adjust results for potential confounding factors. Most of the studies identified had not been designed specifically to look at consumption of peanut, or other allergenic foods, and food allergic outcomes, but instead focussed primarily on the impact of breastfeeding versus formula feeding, duration of breastfeeding, and/or timing of introduction of solids/specific foods, on a range of health outcomes including food allergy/sensitisation.

26. One general population study reported a statistically significant decreased risk of parental report of doctor-diagnosed food allergy when comparing cows' milk formula with breastfeeding, but the results were not adjusted for paternal history of atopy, breastfeeding was poorly assessed, and food allergy diagnosis was not confirmed by any objective testing[32]. Eight of the studies examined duration of breastfeeding and none found a statistically significant association between breastfeeding beyond 6 months and lower food allergy risk. In fact, results of the studies identified in this area, where statistically significant, tended to be in the opposite direction, i.e. increased duration of breastfeeding beyond six months was associated with increased rate of food allergy. Two studies[6,36] reported that breastfeeding compared with never breastfeeding was associated with an increased risk of food/peanut allergy in general populations, but these analyses did not adjust for possible confounding factors. One study[37] reported that children with a family history of allergy had an increased risk of food allergy, at both 5 and 11 years of age, with duration of exclusive breastfeeding of 9 months or longer compared with less than 9 months, (OR 5.3 (95% CI 1.2-24.1) for parental report of food allergy at 5 years of age, OR 7.9 (95% CI 1.4-50.0) for parental report of food allergy at 11 years of age). No such association was found for children without a family history of allergy. A study by Lack *et al.*, (2003)[22] reported an association between breastfeeding beyond 6 months and peanut allergy (based on positive peanut challenge), although this was not statistically significant after adjustment for potential confounding factors (maternal atopy, maternal diet during pregnancy, infant diet).

27. Of those studies that examined the timing of introduction of solids or specific foods into the weaning diet, one, conducted in a high risk population, reported a statistically significant increased risk of wheat allergy associated with a delayed introduction (beyond 7 months of age compared with before 6 months of age) of cereals into the diet[38] (OR 3.8 (95% CI 1.18-12.28) for parental report of wheat allergy at 4 years of age). Another study, conducted in an unselected general population, reported a statistically significant increased risk of parental reports of doctor-diagnosed food allergy in children who had milk or egg introduced later then 6 months of age, but in adjusted analyses there was no statistically significant association between introduction of any foods later than 6 months of age compared with before 5 months and food sensitisation (OR 0.83 (95% CI 0.49-1.41) for parental reports of doctor-diagnosed food allergy at 2 years of age)[39]. A further general population-based study[35] reported a statistically significant association between consumption of fish during the first year of life and decreased risk of food sensitisation after adjustment for other factors (consumption more than once a week versus never OR 0.47 (95% CI 0.33-0.69)). Clinical food allergy was not assessed in this study. One case-control study (Frank *et al.*, 1999)[21] reported earlier introduction of peanuts/peanut butter in children who went on to become peanut sensitised (mean age of introduction 12.5 (SD 6.4) versus 17.3 months (SD 5.5), p = 0.03), but the

study did not account for inadvertent exposure to peanut in the child's diet provided by caregivers outside the immediate household, or exposure outside the home.

28. Three of the trials identified investigated multi-faceted interventions[29-31], combining dietary avoidance measures (such as avoidance of specified allergenic foods during pregnancy and/or in infant diet) with non-dietary avoidance measures (e.g. house dust mite avoidance, avoidance of environmental tobacco smoke, no pets) in high risk populations. These studies reported some statistically significant associations between interventions and food sensitisation and/or food allergy outcomes. However, the multi-faceted nature of the interventions means it is not possible to attribute the observed associations to the dietary part of the intervention, or to any specific food within the dietary intervention.

Non-dietary maternal/infant exposure

29. The BNF review identified only two studies meeting the inclusion criteria that had investigated the possible influence of non-dietary exposure to peanut in childhood, for instance via the skin or respiratory tract, on subsequent development of sensitisation or allergy to foods. One was a cohort study[40] and the other was a case-control analysis[22].

30. The case-control study by Lack *et al.* (2003)[22], found a statistically significant increased prevalence of exposure to topical skin preparations containing peanut oil, in peanut allergic children (cases, n=23) compared with atopic (n=70) and non-allergic (n=140) control children. This result was still significant after adjustment for potential confounders (use versus no use of creams containing peanut oil and positive peanut challenge OR 8.34 (95% CI 1.05-66.1)), but the risk estimate may have been inflated by maternal recall bias due to the retrospective study design. No increased risk of peanut allergy in children was found for maternal use of such skin creams. The mean number of peanut oil preparations to which infants were exposed was also significantly higher for peanut allergic children (1.91) compared with atopic (0.93) and non-atopic controls (0.81) ($p<0.001$). The other study, in which peanut oil was used to deliver a vitamin supplement, conversely reported an increased risk of parental reported food hypersensitivity (cows' milk, egg, fish, soy, peanut and wheat allergy combined) for vitamins in water compared with vitamins in peanut oil in the first year of life (OR 1.87 (95% CI 1.32-1.65))[40].

Impact of the COT recommendations on dietary consumption of peanut and on sensitisation and allergy rates to peanut

31. The BNF review identified two general population studies that had specifically investigated the impact of the 1998 COT recommendations on maternal consumption/avoidance behaviour during pregnancy and that had measured rates of sensitisation and allergy to peanut in children[6,41]. These were prospective cohort studies (one carried out in Southampton and Manchester, and the other on the Isle of Wight) which assessed dietary consumption during pregnancy and breastfeeding, and subsequent rates of sensitisation and clinical allergy to peanut in children under 5 years old born after the COT recommendations were issued. In addition, the BNF review identified a number of other published studies reporting the prevalence of peanut sensitisation and/or peanut allergy in children of different ages, some born

before the 1998 COT recommendations and some born after. Many of these additional studies were based on cohorts of children recruited from the Isle of Wight, but they also included cohorts from elsewhere in the UK as well as some cross-sectional surveys conducted in the US and in Canada.

32. The two cohort studies conducted on mothers and their children born after the COT recommendations were issued, reported levels of recall of the COT recommendations at 40 – 60% (42% of mothers recalled the recommendations in Dean *et al.*, 2007[41], 61% in Hourihane *et al.*, 2007[6]). However, the percentage of mothers changing their diet as a result of the recommendations was lower. In the study by Dean *et al.*, 21% of mothers changed their diet during pregnancy (reduced or avoided peanut consumption), as a consequence of the recommendations, and Hourihane *et al.* reported that 37% of mothers who recalled the recommendations changed their diet, although only 10% of the latter reported eliminating peanuts totally during pregnancy (i.e. only 3.8% of the whole group of mothers). Further, both studies reported no indication that the target group of women whose children had a family history of allergy were more likely to take up the COT recommendations than the general population of mothers. Hourihane *et al.* also examined the mean age of introduction of peanuts into the diet of children and reported this as being 32 months of age for peanut-sensitised children and 29 months for those not sensitised. There was no significant difference between these values ($p = 0.42$). The BNF review noted that an earlier study by Frank *et al.* [21], which had been conducted before the 1998 COT recommendations were issued, but published in 1999, reported an earlier age of introduction of peanuts in those who became sensitised (mean 12.5 months, SD 6.4) compared with the more recent study conducted by Hourihane *et al.* (2007).

33. The BNF literature review compared the available data from studies that were identified on the prevalence of sensitisation and/or allergy to peanuts in UK children born before and after the 1998 COT recommendations were issued. A summary of these data is presented in Table 2.

34. Data from studies conducted in the US and Canada are comparable with those presented in Table 2. Bock (1987)[49] reported the prevalence of peanut allergy confirmed by double blind placebo controlled food challenge (DBPCFC) at 3 years of age as 0.6% (3/480), and data collected from a random dial telephone survey, in which no objective testing was performed, indicated a peanut allergy prevalence of 0.4% in 1997 and 0.8% in 2002 for children under 18 years of age[50]. In Canada peanut allergy prevalence was estimated at 1.5% in 1999-2000 in children of average age 7 years[51].

Table 2: Summary details of data on prevalence of sensitisation and clinical allergy to peanuts from published UK studies identified by the BNF literature review

Study	Region	Year of birth of study population	Age of study population (yrs)	Diagnostic method(s) used (s= sensitisation, a = allergy)	Prevalence of peanut sensitisation (%)	Prevalence of peanut allergy (%)
Children born before 1997						
Pereira *et al.* 2005[42]	Isle of Wight	1987-1988	15	SPT	2.6% (17/649)	nd
Emmett *et al.* 1999[43]	Great Britain	1981-1985	10-14	Interviews	nd	0.9% males (9/989) 0.6% females (6/952)
Pereira *et al.* 2005[42]	Isle of Wight	1991-1992	11	SPT	3.7% (26/699)	nd
Emmett *et al.* 1999[43]	Great Britain	1986-1990	5-9	Interviews	nd	0.8% males (7/909) 0.6% females (5/909)
Tariq *et al.* 1996[44]	Isle of Wight	1989-1990	4-5	(s) SPT (a) SPT + clinical history	1.1% (13/1218)	0.5% (6/1218)
Grundy *et al.* 2002[45]	Isle of Wight	1994-1996	3-4	(s) SPT for sensitisation (a) SPT and OFC or known peanut allergy	3.3% (41/1246)	1.5% (18/1246)
Lack *et al.* 2003[22]	Avon	1991-1992	2-3	DBPCFC	nd	0.2%
Emmett *et al.* 1999[43]	Great Britain	1991-1995	0-4	Interviews	nd	0.5% males(5/1063) 0.3% females (3/882)
Children born 1997-1998						
Venter *et al.* 2006[46]	Isle of Wight	1997-1998	6	(s) SPT (a) SPT, OFC and known peanut allergy	2.6% (18/700)	0.6% (5/798)
Children born after 1998						
Hourihane *et al.* 2007[6]	Southampton & Manchester	1999-2000	4-5	(s) SPT and IgE (a) SPT, DBPCFC and symptoms	2.8% (30/1072)	1.8% (20/1072)
Dean *et al.* 2007[41]	Isle of Wight	2001-2002	3	SPT	1.3% (7/543)	nd
Venter *et al.* 2008[47]	Isle of Wight	2001-2002	3	(s) SPT (a) SPT, OFC	2.0 (13/642)	1.2%* (11/891)
Dean *et al.* 2007[41]	Isle of Wight	2001-2002	2	SPT	2.0% (13/658)	nd
Venter *et al.* 2006[48]	Isle of Wight	2001-2002	1	SPT	0.4% (3/763)	nd

SPT = Skin Prick Test
DBPCFC = Double Blind Placebo Controlled Food Challenge
OFC = Open food challenge
IgE= Immunoglobulin E
nd = not determined/not reported
* prevalence calculated based on using the total cohort size as the denominator. (As a result of new information provided by the researchers to the FSA, this figure has been adjusted from the figure of 1.7% given in the technical report of the literature review conducted by the BNF, which was calculated using the number of children who had a SPT as the denominator).

Evidence from studies conducted in animals

Maternal intake

35. The expert reviews of studies conducted in experimental animals did not identify any relevant studies on maternal dietary intake of peanut allergen during pregnancy or lactation and sensitisation outcomes in the offspring. In relation to ovalbumin, two studies were identified that demonstrated suppression of specific IgE responses following intraperitoneal/subcutaneous immunisation with ovalbumin in the offspring of rats fed high oral doses of ovalbumin (200mg/day via the drinking water[52] or 21.5% of the animal's diet[53] respectively), during pregnancy or lactation. A more recent study was identified as demonstrating that intranasal or intragastric exposure of lactating mice to ovalbumin also resulted in reduced IgE antibody and reduced respiratory hypersensitivity responses in offspring on subsequent inhalation challenge[54].

Direct oral exposure during early life

36. The literature review identified a larger number of studies in animals that had investigated the direct impact (i.e. not via the mother) of oral exposure to peanut/ovalbumin on subsequent development of sensitisation. In relation to oral exposure to peanut, the review identified studies conducted in mice demonstrating that relatively low doses (0.02 to 0.2 mg) of peanut extract administered orally (either by gavage or in the diet), subsequently enhanced peanut-specific IgE responses to subcutaneous immunisation with peanut extract and adjuvant[55,56], whilst higher doses (100 mg) of peanut extract resulted in oral tolerance and inhibition of specific IgE responses following subcutaneous challenge[55]. In relation to ovalbumin, the review identified studies, conducted in mice and in dogs, that also found that low doses of oral exposure resulted in sensitisation responses, whereas high doses resulted in inhibition of sensitisation responses and reduced symptoms in response to subsequent challenge with the same allergen. The response pattern for ovalbumin was different from that for peanut, in that considerably lower doses (20 mg and above) of ovalbumin were found to result in tolerance[55,57]. In the case of ovalbumin it was also observed that mice of different strains exhibited varying degrees of tolerance to high doses of the allergen given orally[58].

37. Further studies were identified that confirmed that under some circumstances, oral exposure to either peanut extract or ovalbumin can lead to sensitisation rather than tolerance. For example in Brown Norway rats, repeated low dose oral exposure to ovalbumin induced anti-ovalbumin IgE responses in 50% of animals[59]. In relation to peanut allergen, repeated low dose oral exposure to peanut protein in BALB/c strain mice in the absence of adjuvant led to production of specific IgE over a 42 day period[60]. Finally, there were many studies demonstrating that oral (intragastric) administration of peanut extracts with adjuvant to various strains of mice induced the production of specific IgE antibody[61,62]. However, it was noted that the main aim of these latter studies was to induce vigorous IgE responses for further study, and not to replicate conditions of sensitisation in a human population. The nature of their experimental design, which included use of adjuvants to boost the immune response, complicates their extrapolation to oral exposure of the human population in which such adjuvants would not be present.

Non-dietary exposure

38. The literature review identified a number of studies which indicated that topical (dermal) exposure to protein allergens, including peanut and ovalbumin, may induce IgE-mediated immune responses. For example, topical exposure to low doses of peanut extract (0.1mg) through depilated intact skin of BALB/c strain mice augmented subsequent specific IgE responses to oral challenge with peanut and adjuvant[61]. Similarly for ovalbumin, mice exposed to 0.01 to 0.1 mg of ovalbumin via an occlusive patch on shaved skin, developed more vigorous specific IgE responses than did mice immunised by intraperitoneal injection of the same antigen in the presence of adjuvant[63]. Other investigators have confirmed these findings using similar exposure regimens (i.e. administration of antigen via an occlusive patch on shaved skin)[64-67]. Nedle *et al.* (2001) also demonstrated anaphylactic reactions upon oral challenge with ovalbumin following topical exposure to the same allergen[67]. Furthermore, studies with peanut extract have revealed that prior exposure to peanut through abraded skin prevented the tolerogenic effects of high dose oral exposure in BALB/c strain mice[56]. The subcutaneous route of exposure has also been shown to be effective for sensitisation of dogs to peanut extract[68,69], although the immunisation protocol used in these studies was vigorous, involving repeat injections in the presence of adjuvant (to boost the immune response) over a period of some months. The direct relevance of these data (deriving from experiments in which adjuvant has been incorporated) to humans is unclear.

Evidence from studies of human cord blood

39. The expert review of studies on human cord blood identified 16 relevant publications between 1999 and 2007. The review discussed the results and significance of these studies in relation to three key areas of continued scientific uncertainty since 1998 :

- whether the fetus is exposed to maternally derived allergen
- whether allergen responsive cord blood mononuclear cells (CBMC) have been exposed to allergen *in utero*
- whether allergen responsive cord blood mononuclear cells have been primed by allergen *in utero*

40. The literature review identified several studies that collectively demonstrate that the fetus is exposed to tiny amounts of ubiquitous nutrient allergens derived from the mother's diet. However, the placental transfer of aeroallergens appears to be less efficient and much less frequent[70-73]. Few data were available on the association between maternal consumption of food allergens (especially peanuts) and immune responses to the allergens in the offspring. However, the review identified studies based predominantly on aeroallergens which indicated that maternal allergen exposure during pregnancy does not have a major influence on subsequent CBMC responses. A single study reported a weak association between maternal exposure to aeroallergen and CBMC responses in the offspring[74], but this association was derived from multiple comparisons during the analysis of the study. The vast majority of studies on maternal allergen exposure during pregnancy and CBMC responses failed to find an association[75,76]. A further study demonstrated that maternal allergen exposure during pregnancy only partly explains corresponding

CBMC responses to that allergen. It was reported that only half of CBMC samples responding to the pollen allergen Bet v1 allergen came from pregnancies exposed to birch pollen, indicating that CBMC samples were responding in the absence of previous exposure[77]. Conversely, a high proportion of CBMC samples not responding to this allergen came from pregnancies exposed to birch pollen, suggesting that CBMC responses after stimulation with aeroallergens do not reflect *in utero* exposure to the allergen. Finally, the review identified two recent studies which comprised detailed investigations of CBMC responses and the timing of allergen sensitisation, and reported that neonatal T cell responses to allergens differ markedly from those occurring later in life[78,79]. Thornton *et al.* (2004)[78], demonstrated that neonatal T-cells responding to allergens express CD45RA and CD38 and the majority undergo apoptosis (cell death) after stimulation. These authors concluded that responding neonatal T-cells are naive immature thymic emigrants with modified antigen receptors that interact non-specifically with protein antigens, providing short-lived cellular immunity that does not generate conventional T-cell memory. More recent work by the same group has indicated 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[79]. However, this latter finding has yet to be confirmed by other studies.

Other evidence considered by the committee

Recently published research

41. A paper describing a cross-sectional study of peanut allergy prevalence and infant weaning practices among Jewish children resident in the UK compared with Jewish children resident in Israel, was published in October 2008, during the course of the Committee's current review of the evidence[80].

42. This paper described a comparison between over 5,000 Israeli children (aged 4 to 18 years) and a comparable number of Jewish schoolchildren of similar age range living in the UK. The study was prompted by the observation that in Israel, peanut-based products are widely used as weaning foods, resulting in very high levels of dietary exposure during infancy. This is very different from practice in the UK where dietary exposure to peanut products during infancy is substantially lower. Using a validated food allergy questionnaire, the researchers compared the prevalence among these two groups of children, of allergy to each of 5 foodstuffs (peanut, sesame, tree-nuts, hens' egg and cows' milk). Although the prevalence of allergies to egg and milk in the two groups was similar, a significant difference in peanut allergy was observed (UK 1.85% versus Israel 0.17%), and the authors reported an adjusted risk ratio for peanut allergy between these two populations of 9.8 (95% CI 3.1-30.5). The authors speculated that these findings may reflect a direct relationship between the early introduction of peanut products into the diet and a lower rate of peanut allergy among the children, concluding that they raised the question of whether early and frequent ingestion of high-dose peanut protein during infancy might prevent the development of peanut allergy through the induction of oral tolerance to peanuts. However, it is notable that differences between the UK and Israel cohorts were also observed with regard to the prevalence of tree-nut allergy, which were not correlated with differences in the dietary consumption of tree-nuts by infants. For this reason the findings reported by DuToit *et al*[80] cannot be regarded as

conclusive. Nor should the reported prevalence of peanut allergy among this selective UK population (at 1.85%) be regarded as representative of UK schoolchildren more generally.

Unpublished and ongoing research

43. The Committee also considered technical summaries of two relevant unpublished studies, together with a technical summary of a relevant published study whose published outputs had reported only selective aspects of the study and, therefore, had fallen outside the scope of the main literature review. All three studies had been funded by the FSA, under project codes T07043, T07028 and T07005. Final reports of these studies are available from the Agency's library[81-83].

44. The first (project T07043)[81] was a retrospective case-control study that compared environmental exposure to peanut during the first year of life in children with peanut allergy and two groups of referents – children with egg allergy who had been referred to the same food-allergy clinic and children attending general paediatric clinics with non-allergic complaints. Environmental exposure to peanut was defined in terms of total consumption of peanuts and peanut-containing foods by all household members, and was assessed using a previously validated food frequency questionnaire[84] that included questions about portion size as well as frequency of consumption. Information was also collected on maternal consumption of peanut during pregnancy and whilst breastfeeding, and on other possible risk factors such as use of peanut-containing creams during infancy. To counter possible recall bias, potential cases and egg-allergic controls were recruited on first attendance at a food-allergy clinic from children whose parents at that time did not identify peanut as a suspected cause of their symptoms. Their exposures were then assessed before the specific nature of their allergy was established. The study found that median weekly household peanut consumption during the first year of life was 78.9 g for the cases as compared with 29.1 g for the non-allergic controls, and only 7.8 g for the controls with egg-allergy. These figures are equivalent to 18.8 g, 6.9 g and 1.9 g respectively of peanut protein. These differences were statistically significant ($p < 0.0001$), and could not be explained by differences in maternal consumption of peanut during pregnancy or lactation. The researchers hypothesised that they occurred because environmental exposure to peanut, occurring through cutaneous or inhalation routes, led to sensitisation in the absence of significant oral exposure.

45. The second and third studies (projects T07028[82] and T07005[83]) were both based on a randomised intervention trial of the effect of maternal dietary avoidance of egg during pregnancy and lactation, on food and aero-allergen sensitisation and on allergy outcomes up to 18 months of age, in a high risk population (where the mother or father had a history of allergy). Project T07005 evaluated the effects of maternal egg avoidance on allergy outcomes and project T07028 used the maternal dietary data collected from the trial together with that obtained from a retrospectively administered dietary questionnaire, to investigate associations between peanut consumption/avoidance during pregnancy and the development of peanut allergy in the infant by 18 months of age.

46. Project T07028[82] found no consistent relationship between estimated peanut intake during pregnancy and the subsequent development of peanut allergy in children at 6, 12 or 18 months of age. Levels of peanut-specific IgG and IgE in maternal blood and breastmilk, measured during pregnancy and breastfeeding, also did not appear to be related to peanut allergy in children at any of these time points[82]. However, the statistical power of this study was limited (maternal diet diaries were available for 227 women, dietary questionnaires were available for 165 women, and the number of children who were sensitised to peanut ranged between 7 (at 6 months of age) and 10 (at 18 months of age)).

47. Project T07005[83] found that despite intense dietetic input and support, only 16% of the mothers in the egg avoidance group managed to remain completely egg-free from recruitment to delivery. Overall there was no association between the maternal egg avoidance diet and prevention of either egg sensitisation or any other associated allergy and allergic disease by 18 months of age. However, there was a significant positive relationship between total egg intake from recruitment to delivery and atopy at 18 months of age, (p=0.041) (where atopy was taken as being skin prick test positive to any allergen and/or the presence of eczema). A moderate weekly egg intake (range 65-149 g, roughly the equivalent of 2 to 4 eggs) was significantly linked with development of atopy compared to a low weekly intake (range 0-78 g, roughly equivalent to between 0 and 2 eggs). When these results were analysed together with the atopic status of the parents, it was reported that whilst a moderate egg intake by atopic women, when compared with a low intake, was associated with development of atopy in the infant (although not statistically significantly); when the mother was not atopic but the father was, a very low intake compared with a moderate intake was associated with atopy in the infant (p= 0.006). A very low total egg intake compared with a moderate intake by non-atopic mothers was also associated with sensitisation to egg in the child at 1 year (p=0.019). Overall egg intake in the study (even among the control arm mothers who were not avoiding egg) was relatively low when compared with national averages. Therefore, it was not possible to evaluate the effect of high egg intake on allergic outcomes in this trial. Egg proteins were detected in breast milk and umbilical cord blood in a number of cases, sometimes in association with other antibodies and sometimes free. Free levels occurred more frequently where the mothers were attempting to avoid egg and this was associated with more allergy in the babies. The researchers concluded that egg avoidance diets are very difficult to sustain and that there was no overall association between avoidance and atopic outcomes, although there were complex interactions between dietary intake, maternal atopic phenotype and allergy outcomes in the baby.

48. The Committee was also provided with brief summaries and study protocols of two major ongoing clinical intervention trials* that were testing the hypothesis that early introduction of allergenic foods into the diet of children, promotes the acquisition of oral tolerance as opposed to clinical allergy, and therefore results in a reduced rate of allergy to the food(s). One of these studies was focussing on peanut and was

*Summary details about these two randomised intervention trials can be found at http://www.leapstudy.co.uk/ and at http://www.food.gov.uk/science/research/researchinfo/foodcomponentsresearch/allergyresearch/t07programme/t07projectlist/t07051/

using a high risk infant population. The other was focussing on early introduction of six allergenic foods in the general infant population.

49. Finally, the Committee was also informed about a major EU Framework 6 funded research project that is currently investigating the prevalence of food allergies (including peanut allergy) in infants, children and adults across Europe. The project is called EuroPrevall[*]. The birth cohort part of the project, which includes a UK sample of ~1200 infants, has the potential to deliver robust data on the cumulative prevalence of individual food allergies in the first 2 years of life in a combined cohort size of more than 10,000 infants. It is expected that these data will become available in the next 2 years.

Evidence relating to asthma and atopic eczema

50. To supplement the human data relating to food allergy outcomes, the Committee was provided with three recent review articles plus one editorial that had evaluated the published evidence on dietary exposure to/avoidance of allergenic foods and the development of allergic disease more generally than just food allergy[85-88]. Collectively, these publications covered studies published up to March 2006. Relevant papers published since that time were identified via a literature search conducted by the British Medical Association (BMA) on behalf of the FSA, and through consultation with the four medical and scientific experts who were assisting the COT in this review and who had expert knowledge of the literature in this area.

51. The literature search conducted by the BMA was conducted in OVID MEDLINE, using search terms similar to those used by the BNF, but including allergy, asthma, atopy, eczema/atopic dermatitis and wheeze as additional outcome measures. This search identified a further 1001 papers, which were assessed at title and then abstract stage against eligibility criteria for inclusion/exclusion. This reduced the selection to 49 published papers, 25 of which were subsequently excluded on the basis that they focussed on breastfeeding (duration/exclusivity/comparison with formula(s)) and allergy outcomes, rather than on exposure/avoidance of allergenic foods specifically. A further 12 papers were excluded as not being of interest to the review on other grounds, for example studies that looked at associations between overall dietary pattern, or nutritional content, and allergy outcomes. A written summary[**] covering the remaining 12 papers identified as relevant[89-100], plus three additional papers published since March 2006 and identified via consultation with the four experts as of potential relevance[101-103], were provided to the Committee for its consideration.

[*] Further details about this project can be found on the project website www.europrevall.org/

[**] This written summary formed part of the papers for the 14th October 2008 COT meeting, and can be found on the COT website at: http://cot.food.gov.uk/pdfs/tox200833annex2.pdf

Committee Discussion

The literature review of human, animal and cord blood studies

52. The Committee considered that the literature review of human, animal and cord blood studies had been a significant and complex undertaking given the breadth of the subject areas to be covered. The review was considered to be of high scientific quality and rigour. It was noted that none of the studies identified in the review of human studies had been assigned high scores against the SIGN criteria used by the BNF, although the Committee had reservations about SIGN grading as an index of quality for observational data. Also, the overall evidence base was limited. Much of the relevant evidence was from studies not designed to investigate the influence of peanut in the diet and few data came from prospective studies.

53. Aspects of the design and scope of the human studies part of the literature review, could have limited the breadth of potentially relevant evidence that was captured and evaluated. The application of strict inclusion and exclusion criteria had resulted in a large number of studies being excluded, and it was possible that some of these studies contained information of indirect relevance to the review. In particular, it was considered that the exclusion of studies that had investigated exposure to or avoidance of allergenic foods and their possible influence on the development of allergic diseases other than food allergy, such as allergic asthma and atopic eczema, was a potential limitation of the BNF review. The Committee noted that the supplementary ascertainment of evidence in these latter areas was not fully systematic, but was able to consider recent review articles together with relevant papers published subsequently, in order to inform its discussions on the principal outcome of peanut allergy.

Evidence from human studies

54. The Committee noted that the BNF review did not identify any high quality studies published since 1998 that had directly examined the effect of consumption versus avoidance of peanut or other allergenic foods during pregnancy or lactation on the development of sensitisation or food allergy in the child. No published randomised controlled trials were identified by this part of the review. It was also noted that the two case-control studies identified that had looked for associations between peanut consumption and peanut sensitisation or allergy[21,22], did not report any statistically significant associations after adjustment for confounders, although the variables accounted for in the analysis by Lack *et al.* were not specified in the published paper[22]. Frank *et al.*, reported odds ratios of 2-4 for peanut consumption more than once a week during pregnancy/lactation compared with less than once a week, but the associated confidence intervals were wide[21]. The lack of high quality studies carried out in humans coupled with the heterogeneous range of exposures that these studies compared (e.g. low versus high peanut consumption/ none versus any peanut consumption), and the small number of studies that had focussed on peanut consumption, precludes definitive conclusions as to whether maternal consumption or avoidance of allergenic foods during pregnancy or lactation, has any impact on the subsequent development of sensitisation or allergy to peanut in the child. The two unpublished studies reported to the Committee by the FSA (projects T07005 and T07028), do not provide any evidence that alters this conclusion.

55. The available evidence from studies in humans on the effects of consumption versus avoidance of dietary allergens during infancy/early childhood and the development of sensitisation or food allergy, is also very limited. A greater number of studies were identified in this area of the BNF literature review, including some randomised controlled trials. However, none of these was designed to investigate the effects of dietary consumption or avoidance of peanuts specifically, on food allergic outcomes. The majority were designed to compare breastfeeding with formula feeding, or to investigate the effect of duration of breastfeeding and/or timing of introduction of solids on allergic outcomes, and few looked at exposure to peanut. Therefore, the relevance of these studies to the present review is limited.

56. In the published literature that is currently available, there is limited evidence from one randomised controlled trial (RCT)[37] that, in children with (but not without) a family history of food allergy, breastfeeding for 9 months or longer is associated with increased risk of food allergy. The Committee noted that out of eight studies identified by the BNF review as assessing the effect of duration of breastfeeding, none found that breastfeeding beyond 6 months was associated with lower risk of food allergy. The Committee considers that the single case-control study that reported an earlier age of introduction of peanut into the diet in subjects who became peanut sensitised compared with those who did not[21], does not by itself provide sufficient evidence on which to base firm conclusions. The Committee also noted that two out of 3 multifaceted intervention trials identified by the BNF review, reported a statistically significant association between combined allergen avoidance and a reduced risk of sensitisation to foods (which included peanut), in the child. However, the individual factors responsible for the observed effects in these cases could not be disentangled and there was no suggestion that such protective effects, if real, translated into a lower risk of clinical food allergy. Further, the third of these trials did not find a statistically significant protective effect of avoidance measures on sensitisation or allergy outcomes. Overall, the Committee considers that the available human data on whether dietary consumption or avoidance of allergenic foods in childhood has an impact on the development of allergy or sensitisation to allergenic foods are inconsistent. The two ongoing clinical intervention trials that are seeking to test the effect of early dietary introduction of high doses of peanuts, either alone, or in combination with other allergenic foods, on later allergic outcomes, have the potential to provide more conclusive data from humans on whether early high dose oral exposure to peanut and/or other allergenic foods leads to a reduction in sensitisation and food allergy. Results from these studies, will not, however, be available until 2013 at the earliest.

57. Currently, the available evidence from human studies regarding the possible importance of non-dietary routes of exposure is extremely limited. However, the findings of the two studies conducted by the research group led by Prof. Lack[22, 81], only one of which has yet been published in a peer-reviewed journal[22], together provide some indications that non-oral routes of exposure to peanut, such as through the skin, may be important in the development of sensitisation and peanut allergy during early childhood. Whether such a route of exposure might also be a risk factor for sensitisation in humans to other food allergens is unknown. The suggestion from the study by Lack *et al.* (2003)[22] that the use of infant skin creams containing peanut oil to treat inflamed skin is a risk factor for developing peanut allergy is of concern.

However, the Committee understands that following the publication of the findings of that study, which were reviewed in 2002 by the Committee on Safety of Medicines (CSM), actions were taken by the then Medicines Control Agency to ensure clear labelling of peanut (arachis) oil whenever present in creams used for treating inflamed skin. The CSM also issued advice at that time that patients known to be allergic to peanut should not take/use medicines containing arachis oil (peanut oil) and such advice was also included in updated product labels and information leaflets issued from that time onwards. A general decline in the number of infant skin creams containing peanut oils has subsequently been observed.

58. The Committee also noted that the study by Lack *et al.* published in 2003, found that peanut allergy in the cohort of children studied was independently associated with intake of soya milk or soya formula in the first two years of age (OR 2.6, 95% CI 1.3-5.2). The authors suggested that this association could have arisen from cross-sensitisation between peanut and soya through shared immunoreactive epitopes, and concluded that consumption of soya formula in early life may be an additional risk factor for subsequent development of peanut allergy. However, *in vivo* cross reactivity between peanut and soya is relatively uncommon[104] and a confounding factor in the observed association could be a family history of milk allergy. A recent randomised controlled trial found that, during the first 2 years of life, use of a soya formula compared with an extensively hydrolysed formula did not increase the risk of developing peanut-specific IgE antibodies or of clinical peanut allergy, in infants with cows' milk allergy[105]. In addition, a recent cohort study of babies with a family history of allergic disease found that whilst children whose parents introduced soya formula or soya milk into their child's diet were more likely to be sensitised to peanuts, this relationship was explained by family or child history of milk allergy (OR after adjustment for family/child history of milk allergy = 1.34, 95% CI 0.64-2.79, p = 0.4)[106].

Evidence from studies conducted in animals

59. The available data from animal studies suggests that maternal oral or mucosal exposure to hens' egg ovalbumin 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. However, at this time, there are no comparable data for peanut. Experimental studies in rodents can provide valuable insights into the mechanisms of immune responses to food proteins. However, because of significant interspecies differences, it is difficult to replicate all aspects of human allergic disease in a single animal model. Therefore, caution should be used when attempting to extrapolate from animal models to the human situation. However, the findings do suggest that well designed, adequately powered, studies are warranted in humans to investigate the influence of high versus low doses of food allergen consumption during pregnancy/lactation on food allergy outcomes.

60. The available data from animal studies that have investigated the effect of dietary exposure to food allergens on immunological responses in the same animal indicate that oral exposure to either ovalbumin or peanut extract in low doses may induce sensitisation (measured as IgE antibody and immediate type hypersensitivity reactions). Conversely, higher doses of the allergens may result in oral tolerance and/or inhibition of sensitisation to subsequent immunisation with the same allergen.

However, there are significant inter-strain differences in susceptibility to allergen, and the dose response relationships for the two allergens are different in that higher doses are required to generate tolerance to peanut compared with ovalbumin. Although not investigated in a systematic way, it is also probable 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[107]. For these reasons and those stated previously (para. 59), caution is required regarding extrapolation of these data to the human situation. However, they do suggest that dose, and possibly the time at which food allergens are first encountered orally, might be critical in determining the immunological outcome.

61. Potentially important evidence from studies in animals has emerged since the previous COT review relating to the skin as a possible route of sensitisation to food allergens. The available data in this area (all of which have been reported since 1998), provide evidence that relatively small amounts of peanut extract or ovalbumin when applied to skin that has been damaged to replicate eczematous skin, can induce strong IgE-mediated immune responses. These findings have been replicated in more than one animal species and in more than one study. Based on these investigations, the skin may be an important route of sensitisation to allergenic foods during early life. There is also limited evidence from these studies that where sensitisation is acquired via exposure to the skin, this may prevent the subsequent induction of tolerance that would normally be expected following oral exposure to the same antigen. In these studies, peanut protein was applied to damaged rather than intact skin, which may be an important factor. However, it is known that apparently healthy human skin often contains minor abrasions, and that barrier function in skin from atopic individuals is often compromised[108]. It remains to be confirmed whether abrasion, occlusion or impaired barrier function are necessary for the induction of allergic responses to proteins encountered at skin surfaces. Again, some caution is required in the extrapolation of these data from animal studies to the human situation, but there are already some parallels between the animal data and the associations between household (environmental) exposure to peanut and/or use of peanut oil-containing creams and peanut allergy in children, that have been reported from the few human studies available (see paragraphs 30, 44, and 57). More evidence from studies in humans is needed to confirm whether or not the skin is an important route of sensitisation to peanut and other food allergens, and if so, to define the relevant immunological mechanisms involved.

Evidence from studies of human cord blood

62. The evidence base relating to whether intrauterine immunological sensitisation to allergens can occur and whether this is associated with subsequent allergic disease has also changed since the 1998 COT review. At that time, the view among the scientific community was that umbilical CBMC proliferative and cytokine responses reflected *in utero* exposure to, and sensitisation by, allergens. However, the data that have become available since then (discussed in para. 39-40), indicate that the associations between antenatal allergen exposure and CBMC responses are more complex than previously thought, and cast doubt on the assertion that observed CBMC responses to allergen are necessarily a consequence of maternal exposure to that allergen either during pregnancy or lactation. On the basis of the evidence base that is now available, the Committee consider that it is highly probable that the fetus

is exposed to small (but variable) amounts of food proteins derived from the mother's diet and transported across the placenta, but it is unclear whether such fetal exposure results in *in utero* sensitisation of the fetal immune system. Furthermore, it is not possible to conclude that the *in vitro* CBMC responses observed after stimulation by food proteins necessarily reflect *in utero* exposure and/or sensitisation. Finally, the Committee consider that even if it could be established that *in utero* priming of fetal T-cells by maternal dietary proteins takes place, it would not necessarily follow that such priming results in clinical allergy in the infant.

Evidence relating to atopic asthma and atopic eczema

63. The Committee considers that the currently available evidence on dietary exposure to allergenic foods in early life and the risk of development of forms of atopic disease other than food allergy, such as allergic asthma and atopic eczema, is inconsistent and does not provide robust evidence of either harmful or beneficial effects associated with dietary exposure or avoidance. Most of the available literature in this area has not focused on the effects of exposure to peanut, but rather on exposure to other foods or on other possible dietary influences on these health outcomes, such as duration of breastfeeding, timing of introduction of solids, and use of infant formula. A single published study, based on a Dutch cohort of pregnant women and their babies, has reported a positive association between consumption of nut products during pregnancy and the asthma-related health outcomes of childhood wheeze, dyspnoea and 'asthma symptoms' (daily versus rare consumption of nut products OR (childhood wheeze) 1.42 (95% CI 1.06-1.89), OR (dyspnoea) 1.58 (95% CI 1.16 – 2.15), OR ('asthma symptoms') 1.47 (95% CI 1.08-1.99))[103]. However, whilst the sample size was large (n = 2832), there was no association of these endpoints with consumption of nuts as opposed to nut products, and there was also no association between nut or nut product consumption and any of the food allergy related endpoints that the researchers evaluated (skin prick test reactivity to milk, egg or inhalant allergens at 8 years of age and reported food allergy)[103]. In addition, the comparison was carried out in a context of multiple statistical analyses, and the finding has not been replicated by other studies. A similar dietary assessment analysis of pregnant mothers in the UK, which was carried out prior to this study, found no associations with either nuts or nut products[90].

Evidence relating to prevalence of peanut sensitisation and allergy

64. Estimates from population-based surveys of the prevalence of peanut sensitisation and allergy are heterogeneous, both across different age ranges, and within similarly aged children from different studies. This variation precludes confident derivation of a single summary estimate of the prevalence of peanut allergy in UK children. However the available data suggest that the current prevalence of peanut allergy in UK children lies between 0.2% and 1.8%.

65. There are several limitations of the current evidence base that complicate the evaluation of temporal trends in UK prevalence of peanut sensitisation and peanut allergy in children. These include the use of different methodologies for the determination of clinical allergy and, to a lesser extent, sensitisation, with few studies having used the gold standard methodology for determining food allergy, the Double Blind Placebo Controlled Food Challenge (DBPCFC); low response rates in some

studies with a potential for resultant bias; and (with the exception of the study by Lack *et al.* (2003)[22]), low statistical power to determine the prevalence of relatively rare health outcomes. Evaluation of trends is further complicated because studies have been conducted in different places and not always on children of the same ages.

66. Overall, the available data in the UK provide no clear evidence that age-specific prevalence rates of peanut sensitisation and peanut allergy among children have changed significantly during the past 20 years. If the data from the Isle of Wight studies of children aged 3 to 5 years are considered on their own[44,45,47], there is a suggestion that the rates of both peanut sensitisation and peanut allergy may have increased in that area between the late 1980's and the mid 1990's (before the 1998 COT recommendations were issued), but it is unclear whether this trend can be extrapolated to the wider UK population and there is no suggestion of a further increase since that time. Data on hospital admissions for food-related anaphylaxis, which are not specific for peanut[109] reveal a marked increase in England during the period 1990-2000, with a levelling off thereafter. However, it should be noted that this occurred in all age groups more or less in parallel, and even if driven by allergy to peanut (which is not known), appears to be a "period effect" and not a "cohort effect" of the type that would be expected if it reflected changes in exposure to peanut *in utero* or in infancy.

67. The Committee also noted the findings of the two published studies by Dean *et al.* (2007)[41], and Hourihane *et al.* (2007)[6], which examined the impact of the COT recommendations on children born after they were issued, and which were not able to discern any impact of the recommendations, either positive or negative, on the prevalence of peanut allergy in 3-5 year old children. The findings of those two studies on the low percentage take-up of the recommendations by mothers, coupled with evidence that the recommendations were taken up similarly by non-atopic as well as atopic women (the target group), are notable. They suggest that the recommendations have not been disseminated effectively, and/or that they have not been implemented by mothers as intended.

Conclusions and recommendations

68. From the evidence that was reviewed, the Committee has drawn the following conclusions:

i. It is unclear whether prevalence rates of peanut sensitisation and allergy in the UK have changed since the previous COT recommendations were issued in 1998.

ii. The new evidence that has become available since 1998 reduces the suspicion that maternal consumption of peanut or peanut products during pregnancy might predispose infants to the development of peanut sensitisation and allergy. In particular, it now appears that *in vitro* responses to allergens by umbilical cord blood mononuclear cells do not necessarily reflect maternal exposure to the allergens concerned. In addition, there is now limited human evidence, consistent with a larger body of animal data,

suggesting that non-oral routes of exposure to peanut, such as via the skin, may be relevant to the development of peanut sensitisation and allergy during early childhood. This casts doubt on the previous assertion that reactions to peanut on first known dietary exposure are necessarily indicative of sensitisation *in utero* or and/or during lactation. Data from animal studies indicate that exposure of damaged skin to egg (ovalbumin) or peanut allergens can result in the induction of IgE-mediated systemic allergic responses.

iii. Animal studies that have been reported since 1998 suggest that maternal oral exposure to the hens' egg allergen, ovalbumin, during gestation and/or lactation, particularly at high doses, may protect offspring from developing allergic responses to this allergen. There are no comparable data for peanut proteins in animals, or for humans, but the finding raises the possibility that maternal dietary consumption of peanut might in some circumstances reduce the risk of peanut allergy in offspring.

iv. Overall, the evidence now available does not indicate whether maternal dietary consumption of peanut during pregnancy or lactation is more likely to increase or decrease the risk of sensitisation and allergy to peanut in the child. An effect in either direction is possible, and it is possible that the direction of effect could differ according to the level of intake. Alternatively, there could be no effect at all.

v. Human data relating dietary consumption or avoidance of peanut or other allergenic foods in childhood to the development of sensitisation or allergy or tolerance to peanut, are limited and inconsistent. Data from animal studies suggest that, for peanut proteins and ovalbumin, the nature of the immune response may depend on dose, with high exposures tending to induce tolerance and low exposures sensitisation. However, there are no comparable published data for humans at this time.

69. The shift in the balance of evidence since 1998 is such that the Committee believes that the previous precautionary advice to avoid peanut consumption during pregnancy, breast feeding and infancy, where there is atopy or atopic disease in family members, is no longer appropriate.

70. However, the Committee considers that the basis of the more general recommendations made in 1998 is still justified and, therefore, recommends that:

(i) In common with the advice given for all children, infants with a parent or sibling with an atopic disease should be breast-fed exclusively for around 6 months;

and,

(ii) Infants and children who are allergic to peanuts or peanut products, should not consume them or foods that contain them;

and also recommends that:

(iii) those who are allergic to peanut should seek advice from medical professionals about avoidance strategies.

71. However, it should be recognised that there remains scientific uncertainty about the determinants of peanut sensitisation and allergy. Thus, further changes to this advice may be warranted in the future, as and when new data become available. In particular, studies are currently underway to investigate the impact on allergic outcomes of early dietary introduction of peanut and/or other allergenic foods into the infant diet, and these studies have the potential to provide more definitive data in the next 5 to 7 years.

72. In addition, the Committee recommends that further studies are needed in humans:

    a. to determine whether and to what extent the skin and respiratory tract are important routes of sensitisation to peanut and other food allergens, and if they are, to determine the importance of timing and dose, and the underlying mechanisms; and

    b. to investigate whether and how oral dose levels influence the development of sensitisation, allergy or tolerance to peanut and other allergenic foods.

73. The Committee also noted the need for clearer information on temporal trends in peanut consumption and the prevalence of peanut allergy in UK infants and children, as well as on infant weaning practices in the UK.

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December 2008

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APPENDIX 1

Glossary of Terms and Abbreviations.

This list defines the terms and abbreviations that appear in the Statement, as they have been used by the COT.

Adjuvant	A substance that non-specifically enhances immune responses
Allergen	Substance capable of inducing an allergic immune response
Allergy	Adverse health effects resulting from stimulation of a specific immune response
Anaphylaxis	Acute and severe allergic reaction characterised by urticaria, shortness of breath, rapid fall in blood pressure and swelling of the throat and lips. Without immediate treatment, anaphylaxis can be fatal
Antibody	Immunoglobulin which is specific for an antigen or allergen
Asthma	Chronic inflammatory disease of the airways which renders them prone to narrow too much. The symptoms include paroxysmal coughing, wheezing, chest tightness and breathlessness. The inflammation is commonly, but not always, associated with allergy and, therefore, occurs in individuals who are genetically predisposed to produce IgE antibodies
Atopic dermatitis	An allergic skin disorder, characterised by severe itching, a distinctive distribution of eczematous skin lesions, and, often, a personal or family history of atopic diseases.
Atopic disease	Asthma, eczema/atopic dermatitis or hayfever
Atopy	A predisposition to mount 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.
CBMC	Cord Blood Mononuclear Cell. CBMC is the mononuclear fraction of umbilical cord blood and comprises monocytes and lymphocytes and is usually considered to be indicative of T-cell responses to antigens.
CI	Confidence Interval
Cytokine	Soluble mediators that influence immune, inflammatory and other biological responses. Produced and secreted by T and

	B lymphocytes, macrophages and by a wide variety of other cells
DBPCFC	Double Blind Placebo Controlled Food Challenge. An *in vivo* test in which the patient and doctor do not know which food is being tested until after the tests and the recording of responses have been completed. Often regarded as the "gold standard" of food allergy testing but infrequently used in peanut allergy due to the severity of reactions that can be associated with this allergy.
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 atopic dermatitis)
EMBASE	An abstract and indexing biomedical database, which contains records from 1974 to present
Epitope	A discrete antigenic determinant within a protein that is recognized by antibody or lymphocytes
Food allergen	Substance found in food capable of inducing an allergic sensitisation and allergic disease
Food allergy	Adverse reaction to a food or food component that is mediated via immunological mechanisms
Food hypersensitivity	Heightened responsiveness induced by allergic sensitisation to food.
Gavage	Feeding via oral tube directly into the stomach.
IgE antibody	One of five classes of human immunoglobulin. IgE is involved in allergy and anaphylaxis as well as protecting against parasitic infection
Immunisation	The deliberate induction of an immune response by administration of foreign protein, often in the presence of adjuvant
Immunoglobulins	A family of proteins from which antibodies are derived. There are five main classes of immunoglobulin in humans known as IgM, IgA, IgD, IgE and IgG
Intragastric	Within the stomach
Intranasal	Within the nose
Intraperitoneal	Within the membrane that lines the abdominal cavity

In utero	Within the uterus
In vitro	In an artificial environment, rather than inside a living organism (*in vivo*) – usually implies in laboratory culture
MEDLINE	The US National Library of Medicine's bibliographic database that contains references to journal articles in the life sciences. It hold citations from 1950 to present
Occlusive patch	A patch that covers an application site on the skin and which enhances dermal absorption
OFC	Open Food Challenge. Challenging the patient with the food suspected to cause the adverse reaction, without any attempt to hide the nature of the challenge from the observer or patient
OR	Odds Ratio
Peanut (*Arachis hypogea)*	Also known as the groundnut or monkey nut. Comes from the legume family. Related botanically to peas and beans. Not related to tree nuts such as brazil, hazel or almond. Used in a number of foodstuffs and also used to produce peanut oil
Peanut oil	Also known as arachis oil.
Phenotype	The physical constitution of an organism as determined by the interaction of its genetic constitution and the environment
Prevalence	The proportion of a specified population with an attribute (e.g. having a disease) at a stated point in time, or during a stated period
PubMed	PubMed is a service of the US National Library of Medicine that includes over 18 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s
Rhinitis	Literally, inflammation of the nasal passages. Symptoms of nasal irritation, sneezing, rhinorrhea (running nose) and nasal blockage
Sensitisation	Immunological priming to an allergen such that the sensitised subject may exhibit an adverse reaction following subsequent encounter with the same allergen
SD	Standard deviation of the mean
SIGN	Scottish Intercollegiate Guidelines Network

SPT	Skin Prick Test. A test of allergenicity commonly used in allergy clinics
Th2 cells	T helper (CD4+) lymphocytes of the type 2 subgroup which produce cytokines that promote IgE antibody production and allergic responses
T helper cells	In general, T cells (CD4+) which help B lymphocytes to produce antibodies. Two principal subtypes exist. Th1 cells produce IFN-γ amongst other cytokines and antagonise IgE responses. Th2-type cells produce interleukins that promote IgE production and allergic sensitisation
T lymphocytes	Thymus-dependent lymphocytes which, amongst other functions, help B lymphocytes during immunological responses and provide protection from intracellular microbial infection. Distinct sub-populations have been characterised - see T helper cells above
Tolerance	Specific immunological unresponsiveness or hyporesponsiveness resulting from exposure to antigen
Tolerogenic	Producing immunologic tolerance - see tolerance above
Wheeze	A high-pitched whistling sound during breathing. It occurs when air flows through narrowed breathing tubes