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

REVIEW OF ADVICE ON PEANUT AVOIDANCE

Introduction

1. The advice of the Committee is being sought on whether the dietary recommendations made by the COT in their 1998 report on peanut allergy, remain appropriate, taking into account developments in the scientific evidence base that may have become available since that time. This item is to be discussed under closed session because the results of the literature review that is being presented to the Committee have yet to be accepted for publication in a peer-reviewed journal. Annexes 1 and 2, contain the final report of the literature review that has not yet published and will therefore be withheld from publication on the Agency’s website at this time. Annex 4 also contains unpublished scientific data and will therefore also be withheld from publication at this time.

Background

2. Peanut allergy is a serious health problem among UK children, with recent estimates of prevalence suggesting that 1.7 – 1.8% of 3 to 5 year olds may be affected\(^1\text{,2}\). Unlike certain other food allergies, peanut allergy is commonly persistent and life-long, and the only means of managing the condition currently is avoidance of peanut. This is both difficult to achieve in practice and also presents a range of financial, social and quality of life impacts on those affected and on their families.

3. The role of early life experiences in the development of sensitisation and clinical allergy to peanuts (and to other food allergens) has been an area of considerable scientific uncertainty and debate in recent years. In view of the particular severity of allergic reactions to peanut and the possibility that the prevalence of this allergy was increasing, the COT convened a Working Group in 1996. 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/peanut products and the incidence of peanut allergy in later life. The conclusions of that previous review were that there was some support for the suggestion that peanut allergy in infants can result from exposure \textit{in utero} or during lactation, but that the available data were inconclusive. With regard to the


mechanism of sensitisation and allergy however, a link between peanut consumption by pregnant and lactating women and the incidence of peanut allergy in the child was considered possible. On this basis, it was decided that it would be unwise to discount the possibility of sensitisation of offspring resulting from exposure of the mother. Another major factor considered by the Working Group was that many children are reported to display reactions to peanut following their first known exposure.

4. On the basis of the available scientific information in 1998, and in view of the fact that peanut allergy can result in life-threatening reactions (anaphylaxis), the 1998 COT Working Group issued a number of dietary recommendations, on a precautionary basis. These were aimed at pregnant women and mothers of infants considered at higher risk (i.e. those from atopic backgrounds). The COT also made recommendations for further research in a number of areas in order to progress the state of scientific knowledge. The dietary recommendations from the 1998 COT report on peanut allergy\footnote{COT report on Peanut Allergy. Department of Health. 1998 (http://www.food.gov.uk/science/ouradvisors/toxicity/cotreports/cotwgreports/cotpeanutallergy)} 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. ”

5. Since 1998, there have been several studies published on the subject of sensitisation and allergy to foods in relation to early life dietary (and to a lesser extent non-dietary) exposures, some of these funded by the Food Standards Agency. In addition, results from some recent studies, which have yet to be published, but which have been presented at scientific conferences, have suggested that early life peanut consumption is associated with low incidence of peanut allergy. This has led to the emergence of a new hypothesis, as yet unproven, that early high dose oral exposure to peanut might result in tolerance rather than allergy.

6. There is now a need to re-assess the current state of scientific knowledge in this area and, based on the available evidence, to re-consider whether the 1998 COT advice remains appropriate. A recent House of Lords Science and Technology Select Committee on Allergy also highlighted the need to re-consider
the current advice, and recommended that in the meantime the advice should be withdrawn pending the outcome of a comprehensive review by the Food Standards Agency and the COT. The Committee also recommended that the role of early life exposure to allergens such as peanuts requires urgent research⁴. The Government response to this recommendation⁵ was that it would be inappropriate to withdraw the advice without having available alternative advice (if appropriate) to put in its place, and made reference to the present review being undertaken by the Food Standards Agency based on advice from the COT, and to new research studies which had recently been commissioned in this area (see para. 12).

Review of the published literature since 1998

7. To facilitate the COT evaluation, in September 2007 the Food Standards Agency commissioned a literature review of studies that have been published since 1998 on the 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. The literature review has been conducted by the British Nutrition Foundation (BNF) and was structured around the need to address evidence in three different areas and against eight different research questions, as detailed in Table 1.

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

<table>
<thead>
<tr>
<th>Nature of evidence to be reviewed</th>
<th>Research questions to be addressed:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence from studies in humans</strong></td>
<td><strong>Research question 1</strong>: 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?</td>
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<tr>
<td><strong>Research question 2</strong>: 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?</td>
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<tr>
<td><strong>Research question 3</strong>: 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?</td>
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<tr>
<td><strong>Research question 4</strong>: 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?</td>
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<tr>
<td><strong>Evidence from studies in animals</strong></td>
<td><strong>Research question 5</strong>: 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?</td>
</tr>
<tr>
<td><strong>Research question 6</strong>: 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?</td>
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</tr>
<tr>
<td><strong>Research question 7</strong>: 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?</td>
<td></td>
</tr>
<tr>
<td><strong>Evidence from studies utilising human cord blood</strong></td>
<td><strong>Research question 8</strong>: Does intrauterine immunological sensitisation occur and is it associated with subsequent atopic disease?</td>
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⁴ Report of the House of Lords Science and Technology Committee on Allergy. 6th report of Session 2006-07. 2007 (http://www.publications.parliament.uk/pa/ld200607/ldselect/ldsctech/166/166i.pdf)

8. The Committee was informed of this literature review at its meeting in February 2008, during which Members were given an opportunity to comment on the scope and format of the review. At that meeting Members recommended that the literature review should encompass not just relevant animal model studies utilising peanut allergen, but also those using a hens’ egg allergen (ovalbumin), as it was considered that little information would be available for peanut and inclusion of animal studies that had utilised ovalbumin may provide more data in this context. This has been done (see Table 1, research questions 5 & 6). It was also suggested that data on prevalence of peanut allergy from both before and after the 1998 COT advice should be collated and included in order to assess trends in prevalence. This has also been added to the review (see Table 1, research question 4).

9. The nature of the evidence to be reviewed (falling in to the three discrete areas identified in Table 1), was such that essentially three separate literature reviews were required. The first, was a systematic review of all relevant studies conducted in humans and published since 1998. The second and third were two non-systematic reviews of the literature in two distinct subject areas considered of relevance to this review but which, by their nature, did not lend themselves to a systematic review: Dr Rebecca Dearman, COT Member and an expert in immunotoxicology, has conducted an expert review of published studies conducted in animals that have examined the influence of maternal and/or early life dietary and dermal exposures to peanut or ovalbumin (egg allergen) on the development of allergic sensitisation, allergy or other immunologically relevant endpoints. Dr Graham Devereux from the University of Aberdeen, who is a respiratory physician and an expert in the early life origins of allergic disease, has conducted an expert review of published studies on cord blood mononuclear cell responses and allergy. Studies in this latter area formed part of the evidence base considered by the Committee in 1998 which led to the advice and therefore it was considered appropriate to review scientific progress in this area since that time.

10. The literature review has now been completed and the results are being presented to the Committee for discussion and formulation of a Statement.

Results of the literature review of published studies

11. The results of the literature review are presented in Annex 1 (Main report document) and Annex 2 (Tables of evidence: Human studies). The results of the three separate elements of the review can be found on pages 17-75 (human evidence), pages 77-97 (animal evidence) and pages 98-102 (cord blood studies) of Annex 1. The final conclusions of the literature review in its entirety are detailed on pages 103-108 of the Main Report (Annex 1), and are summarised in the executive summary to that document (Annex 1, p 6-10).

Unpublished and ongoing research

12. In addition to the published research that has emerged since 1998 and which is covered in the above mentioned literature review, the Food Standards Agency is aware of two ongoing studies and one completed but as yet unpublished study,
which are also relevant to this review. The Committee will wish to be aware of these studies in considering the current state of scientific knowledge and in reviewing the 1998 COT advice. Summary details of these three projects, which are all funded or part-funded by the Food Standards Agency, are provided in Annex 3. In addition, an executive summary from the completed but unpublished study, which includes details of the main findings of that study, is provided in Annex 4.

Questions on which the views of the Committee are sought

13. Members are invited to comment on the review and consider the following questions:

   i  Do members consider that the review provides evidence of a link between peanut consumption/avoidance during pregnancy and subsequent development of sensitisation, allergy or tolerance to peanut in the child?

   ii Do members consider that the review provides evidence of a link between peanut consumption/avoidance during breastfeeding and subsequent development of sensitisation, allergy or tolerance to peanut in the child?

   iii Do members consider that the review provides evidence of a link between post-natal infant exposures to peanut (dietary or other exposures) and a risk of development of sensitisation, allergy or tolerance to peanut?

   iv If Members consider that there is evidence to support a link in any of the above three cases, Members are asked to comment on whether this link applies to the general population, those at increased risk of developing food allergy (e.g. those with atopic backgrounds), or both.

   v  Do Members consider that the expert reviews of animal studies and of cord blood studies provide any evidence that informs this review?

   vi Based on all the available data (and with regard to the possible influence of non-dietary as well as dietary exposures), do the Committee wish to amend their previous advice (summarised in para 4. above) on peanut consumption?

   vii Do Members have any other comments on the literature review or wish to raise any other matters arising from it?

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Summary details of relevant unpublished and ongoing research studies.

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Unpublished (completed) studies:

Research Project T07043: Peanut allergy - routes of pre-natal and post-natal exposure

Study Duration: September 2004 to August 2005
Contractor: Imperial College London
Funding Body: Food Standards Agency

This completed, but as yet unpublished, research project was a retrospective case controlled study which aimed to quantify the environmental (household) exposure to peanut allergen during the first year of life in children who go on to develop peanut allergy, compared with those who do not. The study aimed to test the hypothesis that low dose environmental exposure to peanut is a route of sensitisation in young children. The executive summary of this project is attached as Annex 4.

Ongoing studies:

Learning Early about Peanut (LEAP) study

Study Duration: 2006 to 2012
Contractor: King’s College London
Funding Bodies: Clinical Trial - US NIH Immune Tolerance Network
Immunological studies using blood and serum samples - Food Standards Agency

This clinical intervention study aims to test the hypothesis that early introduction of peanut into the infant diet will induce oral tolerance and prevent the development of peanut allergy. 640 young children at high risk of developing peanut allergy (defined by presence of eczema, egg allergy or both), are being recruited and randomised to either eat peanut at high levels from 4 to 10 months of age until 5 years of age or to exclude peanut from their diet until 3 (current Government advice for those at high risk of developing food allergies). The researchers predict a significant reduction in peanut allergy by 5 years of age in the intervention arm. The Food Standards Agency is funding additional mechanistic studies using blood and serum samples collected from subjects in the LEAP study in order to explore longitudinally the immune mechanisms that underlie the development of sensitisation, clinical allergy and tolerance to peanut. Blood and serum samples taken at specific time points throughout the study will be analysed for immunological markers that may be associated with allergy or tolerance. This data will underpin the clinical aspects of the trial and should help us to understand the processes in the developing immune system that lead to the acquisition of oral tolerance to peanut, to peanut sensitisation and to peanut allergy.
Research Project T07051: Randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants

Study Duration: January 2008 to September 2014
Contractor: Kings College, London
Funding bodies: Food Standards Agency, MRC

The UK Government currently recommends that infants are exclusively breastfed until six months of age, and that certain foods that can cause allergic reactions in some babies (e.g. egg, wheat, peanuts, tree nuts, seeds, fish and shell fish) are best avoided until after 6 months. It is currently unclear whether this advice is optimum from the point of view of minimising risk of development of food allergies. This randomised controlled intervention study aims to explore the effect of early introduction of allergenic foods (from 3 months of age) on the later development of food allergy, in infants from the general population. The hypothesis that the researchers are testing is that the early introduction of allergenic foods from 3 months of age will induce regulatory mechanisms that result in a reduced level of food allergy by 3 years of age. The project is currently at a very early stage and the recruitment phase has not yet begun. The study plans to recruit 3000 mothers during pregnancy to participate in the study. Once babies are born, all mothers will be encouraged to breast feed exclusively until three months of age, but, after this time the infants will be randomly split into two arms of the study. One half will introduce egg, milk, soya, fish and peanut sequentially from 3 months of age and wheat from 4 months of age. The other half (the control arm) will be encouraged to follow the current Government weaning advice of exclusive breastfeeding until 6 months of age and avoidance of allergenic foods. Both arms will be encouraged to breast feed for at least six months and the study will follow the Department of Health Infant Feeding Recommendation that breast milk “should continue to be an important part of babies’ diet for the first year of life”. Participants will be followed up to 3 years of age when the impact of the intervention on food allergy and other secondary allergy endpoints will be assessed.

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Executive Summary from Final Technical Report of Food Standards Agency funded research project T07043: ‘Peanut allergy - routes of pre-natal and post-natal exposure’ written by the contractor. The work described in this executive summary has not yet been accepted for publication in a scientific journal and as such has not yet been peer-reviewed. Therefore, it will be discussed by the Committee in closed session and will be published on the COT website at a later date.

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