Assessing the health benefits and risks of the introduction of peanut and hen's egg into the infant diet before six months of age in the UK

A Joint Statement from the Scientific Advisory Committee on Nutrition and the Committee on Toxicity of Chemicals in food, Consumer products and the Environment

Executive Summary

Introduction

A comprehensive risk assessment of infant and young child feeding in the UK was last considered by the Committee on Medical Aspects of Food Policy (COMA) in its report 'Weaning and The Weaning Diet', published in 1994.

The Scientific Advisory Committee on Nutrition (SACN) therefore requested its Subgroup on Maternal and Child Nutrition (SMCN) to review recent developments in this area. To complement this work, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) conducted a review of the risks of toxicity from chemicals in the infant diet, and examined the evidence relating to the influence of infant diet on development of food allergy, and atopic and auto-immune disease. A joint SACN-COT working group (hereafter termed 'working group') was established to undertake a benefit-risk assessment on the timing of introduction of allergenic foods into the infant diet. The COT statement identified significant findings related to the timing of introduction of foods containing peanut and hen's egg into the infant diet and the risk of developing peanut and hen's egg allergy respectively. The working group therefore restricted its assessment to these foods.

This paper summarises the findings of the working group and provides consensus advice to government.

Background

The UK health departments currently recommend exclusive breastfeeding for around the first six months of an infant's life. It is recommended that solid foods are introduced from around six months of age, and that breastfeeding continues until at least 12 months of age, along with appropriate types and amounts of solid foods. Infant formula should be used when mothers do not breastfeed or choose to supplement breastfeeding in the first 12 months of life. It is also recommended that commonly allergenic foods, including peanuts, nuts, seeds, hen's egg, cows' milk, soya, wheat (and other cereals that contain gluten such as rye and barley), fish and shellfish[1], are not introduced before six months of age.

This joint SACN-COT statement details an assessment of the benefits and risks of introducing peanut and hen's egg into the infant diet before six months of age, with the aim of providing advice to government. The statement is based primarily on:

- the COT assessment of the evidence outlined in its Statement *'Timing of introduction of allergenic foods to the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease'* (2016); and
- consideration of the health outcomes associated with exclusive breastfeeding for around six months.

[1] http://www.nhs.uk/conditions/pregnancy-and-baby/pages/solid-foods-weaning.aspx

Approach

The findings from a systematic review and the accompanying COT Statement, which may impact on current government infant feeding advice, are those relating to the timing of introduction of foods containing peanut and hen's egg into the infant diet, and risk of developing peanut and hen's egg allergy respectively. The working group therefore restricted its assessment to these foods.

The Benefit- Risk Analysis for Foods (BRAFO) methodology (Hoekstra et al, 2012), a tiered approach for the assessment of the risks and benefits associated with foods, was used to evaluate the available evidence on the timing of introduction of peanut (two randomised controlled trials (RCT) and hen's egg (seven RCTs) into the infant diet, in the context of the current policy recommendation on exclusive breastfeeding to around six months of age. The BRAFO approach starts with a pre-assessment problem formulation stage to establish the scope of the assessment and requires two scenarios, the reference and an alternative, to be defined. The working group defined the two scenarios as follows:

Reference scenario (the same for both peanut and hen's egg):

Infants should be exclusively breastfed until around six months of age. Complementary foods should be introduced into the infant's diet from around six months of age alongside continued breastfeeding (and/or breastmilk substitutes, if used). Common allergenic foods should be avoided until after six months of age.

Alternative scenarios:

Peanut is introduced into the infant diet between the ages of four and six months.

Cooked (not raw) hen's egg is introduced into the infant diet between the ages of four and six months.

The nature of the data under consideration made it difficult to apply the BRAFO methodology rigorously. However, the BRAFO approach provided a useful framework to explore issues related to the introduction of peanut and hen's egg before six months of age and this process, together with the existing evaluations of the relevant evidence by SACN and COT, allowed clear conclusions for both peanut and hen's egg to be reached.

Conclusions

The benefit-risk assessment indicated that there were insufficient data to support the existence of a "window of opportunity" for the introduction of peanut before six months of age. Evidence that the introduction of hen's egg before six months might be beneficial was limited and derived from RCTs where participants were not representative of the general population.

The benefit-risk assessment indicated that there were insufficient data to demonstrate that the introduction of peanut or hen's egg into the infant diet between four and six months of age reduced the risk of developing food allergy to any greater extent than introduction from around six months.

Reasonable data exist to demonstrate that the deliberate exclusion or delayed introduction of peanut or hen's egg beyond six to twelve months of age may increase the risk of allergy to the same foods.

Recommendations for government

The government should continue to recommend exclusive breastfeeding for around the first six months of life. Advice on complementary feeding should state that foods containing peanut and hen's egg need not be differentiated from other complementary foods. Complementary foods should be introduced in an age-appropriate form[2] from around six months of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child.

The deliberate exclusion of peanut or hen's egg beyond six to twelve months of age may increase the risk of allergy to the same foods. Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and family. If initial exposure is not continued as part of the infant's usual diet, then this may increase the risk of sensitisation and subsequent food allergy.

Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

[2] Infants and young children should never be left alone while they are eating. Children under five years old must not be given whole nuts, as they can choke on them. Currently, it is advised that infants and young children should not eat raw eggs, eggs with runny yolks or any food that contains raw eggs and is uncooked or only lightly cooked. These can cause food poisoning and serious illness although this advice is currently under review as a result of the ACMSF recommendations (ACMSF, 2016). Eggs from other birds such as duck, goose and quail eggs should always be cooked thoroughly and this will not change following the current review.

Assessing the health benefits and risks of the introduction of allergenic foods (peanut and hen's egg) into the infant diet before six months of age in the UK

Introduction

1. Since the Committee on Medical Aspects of Food Policy (COMA) published its report 'Weaning and The Weaning Diet' in 1994 (DH, 1994), there has been no comprehensive risk assessment of infant and young child feeding in the UK.

2. The Scientific Advisory Committee on Nutrition (SACN) requested its Subgroup on Maternal and Child Nutrition (SMCN) to review recent developments in this area. To complement this work, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked by the Department of Health to conduct a review of the risks of toxicity from chemicals in the infant diet, and examine the evidence relating to the influence of infant diet on development of food allergy, and atopic and auto-immune disease (COT, 2016).

3. A joint SACN-COT working group (hereafter termed 'working group') was established to undertake a benefit-risk assessment on the timing of introduction of allergenic foods into the infant diet. This paper summarises the findings of the working group and provides consensus advice to government.

Current UK policy and practice for infant feeding

4. Since 2001, WHO has recommended that mothers worldwide exclusively breastfeed infants for the first six months to achieve optimal growth, development and health (WHO, 2001). Thereafter, they should be given nutritious complementary foods from around six months as breastfeeding continues up to the age of two years or beyond. This recommendation was endorsed by SACN (2001) and adopted by the UK government[3] in 2003 as the basis of its infant feeding policy:

"Breastmilk is the best form of nutrition for infants. Exclusive breastfeeding is recommended for the first six months (26 weeks) of an infant's life, as it provides all the nutrients a baby needs[4]. Breastfeeding and/or breastmilk substitutes, if used should continue beyond the first six months along with appropriate types and amounts of solid foods. Mothers who are unable to, or

[3] The recommendation on breastfeeding was announced by the then Minister for Public Health, Hazel Blears, on the 12 May 2003.

[4] In 2016, SACN published its report 'Vitamin D and Health' and recommended that a 'Safe Intake' of vitamin D in the range 8.5-10 µg/d (340-400 IU/d) for ages 0-12 months (including exclusively breast fed and partially breast fed infants, from birth). As a precaution, government recommends that all babies under 1 year should have a daily 8.5 to 10 microgram vitamin D supplement to ensure they get enough. Infants who have more than 500 ml of infant formula a day do not need any additional vitamin D as formula is already fortified.

choose not to follow these recommendations should be supported to optimise their infants' nutrition."

5. 'Exclusive breastfeeding' indicates that the infant has received only breastmilk. No other liquid or solid foods have been given, though drops and syrups containing medicines, mineral supplements or vitamins, and oral rehydration solutions may be given. It is recommended that solid foods are introduced at about six months of age, and that breastfeeding continues beyond this time, along with appropriate types and amounts of solid foods. Infant formula should be used when mothers do not breastfeed or choose to supplement breastfeeding.

6. It is currently advised that commonly allergenic foods are not introduced before six months of age. This includes peanuts, nuts, seeds, hen's egg, cows' milk, soya, wheat (and other cereals that contain gluten such as rye and barley), fish and shellfish.

7. Surveys indicate that infant feeding practice in the UK differs significantly from current advice with only 1% of mothers exclusively breastfeeding from birth to six months (26 weeks) and a significant percentage of mothers starting to introduce solid foods from four months (30% at four months, 57% at five months, 99% by six months) (McAndrew et al, 2012). However, despite the relatively early introduction of solid foods, consumption of peanut and hen's egg during infancy is not common practice. Data from the Infant Feeding Survey (2010) indicate that significant proportions of mothers provide egg or nuts less than once a week or never by eight to ten months of age[5]. Data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) indicate that only a minority of infants are consuming peanut or egg at or before six months of age[6] (Lennox et al, 2013)

8. The prevalence of both peanut and hen's egg allergy has been described in the literature. It has been estimated that approximately 1-2% of children in the UK have a peanut allergy [7] (Venter et al, 2016, Venter et al, 2010). For hen's egg allergy, the British Society of Allergy and Clinical Immunology report that confirmed hen's egg allergy has a prevalence of approximately 2% in children and 0.1% in adults (Clark et al, 2010).

[5] 73% of infants were consuming eggs less than once a week or never and 98% for nuts. Only 8% of infants had been introduced to peanut by eight to ten months of (McAndrew et al, 2012).

[6] Egg and egg dishes were consumed by 2 out 116 infants (unweighted) at six months, for peanut 1 out of 116 infants (unweighted) were exposed to peanut before six months of age. (Lennox et al, 2013)

[7] Prevalence of peanut allergy has been reported in different cohorts: 0.62-1.2% at 3-4 years, 0.58-1.5% at 10-11 years (Venter et al, 2016). Prevalence of peanut allergy has been reported as 0.5%, 1.4% and 1.2 % at 3-4 years in different cohorts in the same geographical location in the UK (Venter et al, 2009).

The COT review of atopic outcomes and autoimmune disease

9. To inform the COT review of the evidence relating to the influence of infant diet on development of food allergy, and atopic and auto-immune disease, the Food Standards Agency (FSA) contracted Imperial College London to conduct a comprehensive systematic review of the published scientific literature on the risks arising from the maternal and infant diet and the development of atopic outcomes and autoimmune disease. The overall review comprised four separate systematic reviews:

    - Review A: Duration of total and exclusive breastfeeding and timing of solid food introduction.
    - Review B: Timing of introduction of allergenic food
    - Review C (I): Use of hydrolysed infant formula
    - Review C (II): Maternal and other infant dietary exposures

10. These reviews have been evaluated by the COT and two have so far been published in the peer-reviewed literature (C (I): Boyle et al, 2016; B: Ierodiakonou et al, 2016). Systematic Review B considered many of the major food allergens (milk, hen's egg, fish, shellfish, tree nuts, wheat, peanuts, soya). However the significant findings related to: the timing of introduction of peanut (between four to eleven months) and risk of developing peanut allergy; timing of introduction of hen's egg (between four-six months) and risk of developing hen's egg allergy; timing of introduction of fish (between six and twelve months) and risk of developing allergic sensitisation and allergic rhinitis. The timing of introduction of gluten (between four to six months) was found to NOT increase the risk of developing coeliac disease.

11. A full summary of the findings of the systematic review on the timing of the introduction of allergenic food into the infant diet (referred to below as the systematic review) can be found in the COT statement (COT, 2016). Following consideration of the evidence, COT concluded that:

'*The meta-analyses performed indicate that for hen's egg and peanut allergy early introduction (at 4-6 months for hen's egg and 4-11 months for peanut) of allergenic food reduces subsequent development of an allergy to that food, based on six studies for hen's egg and two studies for peanut. The quality of evidence for this was assessed as MODERATE using the GRADE system, meaning that there is moderate confidence in the estimate of effect: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. To date, there is insufficient evidence for conclusions to be drawn on the effect of timing of introduction of common allergic foods other than peanut and hen's egg in relation to developing an allergy to that food.*'

12. COT further concluded that there was no evidence to suggest that delaying the introduction of common allergenic foods represented an effective prevention strategy for avoiding food allergy and indeed may have negative consequences:

"from the evidence available, early introduction of allergenic foods does not increase the risk of allergy or autoimmune disease. Indeed, the deliberate exclusion or delayed introduction of specific allergenic foods may increase the risk of allergy to the same foods."

Approach of the joint SACN-COT working group

13. A working group comprising SACN and COT members was convened to undertake a formal benefit-risk assessment of the evidence relating to the timing of introduction of allergenic foods into the infant diet in the UK.

14. The findings from the systematic review and the accompanying COT Statement which may impact on current government infant feeding advice are those relating to the timing of introduction of peanut and hen's egg into the infant diet, and risk of developing peanut and hen's egg allergy respectively. The working group therefore restricted its assessment to these foods**.**

15. The Benefit-Risk Analysis for Foods (BRAFO) methodology (Hoekstra et al, 2012), a tiered approach for the assessment of risks and benefits associated with foods, was used to evaluate the evidence. The benefits and risks associated with the timing of introduction of peanut and hen's egg into the infant diet were assessed independently, with the aim of answering the question:

What is the overall balance of health benefits and risks for the UK population of introducing peanut and hen's *egg into the infant diet before six months of age?*

Reference and alternative scenarios

16. The reference and alternative scenario for assessing the benefits and risks using BRAFO were as follows:

Reference scenario (the same for peanut and hen's *egg):*

Infants should be exclusively breastfed for around six months of age. Complementary foods should be introduced into the infant's diet from around six months of age alongside continued breastfeeding (and/or breastmilk substitutes, if used). Common allergenic foods should be avoided until after six months of age.

Alternative scenario:

Peanut is introduced into the infant diet between the ages of four and six months.

Cooked (not raw) hen's egg is introduced into the infant diet between the ages of four and six months.

17. While the BRAFO approach provided a useful framework to explore issues related to the introduction of peanut and hen's egg before six months of age, the nature of the data made further application of the methodology difficult. As a result, the BRAFO approach was applied, but without progressing to detailed tier one and two assessments.

Pre-assessment problem formulation

18. A pre-assessment problem formulation was conducted to define the scope of the assessment. This process involved using the defined reference scenario and comparing the impact of changing from this to one or more 'alternative' scenarios. A number of health effects were identified. These are outlined below, and detailed in Annex A.

19. Based on evidence considered by Ierodiakonou et al, 2016 and as assessed by COT (2016), the possible benefits associated with the introduction of peanut or hen's egg into the infant diet before six months of age were identified as:

    - Decreased incidence of peanut or hen's egg allergy

20. Based on evidence considered by SACN's Subgroup on Maternal and Child Nutrition (SMCN) in its draft review 'Feeding in the First Year of Life', and possible microbiological, toxicological and other safety considerations, the possible health risks associated with the introduction of peanut or hen's egg, and therefore commencing complementary feeding before six months were identified as:

    - For infants, a possible reduction in the duration of breastfeeding resulting in:

        - Reduced intakes of immunoprotective factors in breast milk leading to:
            - Increase in lower respiratory tract infections
            - Increase in acute otitis media (middle ear infection)
            - Increase in gastrointestinal infections

    - For mothers, a possible reduction in the duration of breastfeeding resulting in:

        - Reduced postpartum weight loss
        - Increase in breast cancer risk

    - Possible microbiological, toxicological and other safety considerations associated with earlier introduction of peanut or hen's egg into the infant diet, such as:

- Increased risk of choking hazard
- Increased risk of *Salmonella* infection from possible exposure to uncooked hen's eggs at an earlier age

21. Annex A considers further the evidence relating to the possible benefits and risks enumerated in paragraphs 19 and 20.

Conclusions on peanut

22. There is insufficient evidence to support the existence of a "window of opportunity" for the introduction of peanut between four and six months of age.

23. There is evidence that supports the introduction of peanut into the infant diet from around six months of age, alongside other complementary foods as part of the normal complementary feeding process, to reduce the likelihood of developing peanut allergy. As with other complementary foods, introduction should be at a time and in a manner to suit both the family and individual child.

24. The deliberate exclusion of peanut between six and twelve months of age does not reduce the likelihood of developing peanut allergy, and may increase the risk.

25. Importantly, once introduced, peanut should continue to be consumed as part of the infant's usual diet, in order to minimise the risk of peanut allergy developing after initial introduction.

26. Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing peanut.

Conclusions on hen's egg

27. There is insufficient evidence to support the existence of a "window of opportunity" for the introduction of hen's egg between four and six months of age.

28. There is evidence that supports the introduction of hen's egg into the infant diet from around six months of age, alongside other complementary foods as part of the normal complementary feeding process, to reduce the likelihood of developing an allergy to hen's egg. As with other complementary foods, introduction should be at a time and in a manner to suit both the family and individual child.

29. The deliberate exclusion of hen's egg between six and twelve months of age does not reduce the likelihood of developing an allergy, and may increase the risk.

30. Importantly, once introduced, hen's egg should continue to be consumed as part of the infant's usual diet in order to minimise the risk of hen's egg allergy developing after initial exposure.

31. Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing hen's egg.

Overall conclusions

32. The benefit-risk assessment indicated that there was insufficient evidence to support the existence of a "window of opportunity" for the introduction of peanut before six months of age. Evidence that the introduction of hen's egg before six months might be beneficial was limited and derived from randomised control trials (RCTs) where participants were not representative of the general population.

33. The benefit-risk assessment indicated that there were insufficient data to demonstrate that the introduction of peanut or hen's egg into the infant diet before six months of age reduced the risk of developing food allergy to any greater extent than introduction from around six months.

34. There was reasonable evidence to demonstrate that the deliberate exclusion or delayed introduction of peanut or hen's egg beyond six to twelve months of age may increase the risk of allergy to the same foods. Importantly, once introduced, these foods should continue to be consumed as part of the infant's usual diet, in order to minimise the risk of allergy to peanut or hen's egg developing after initial exposure. Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

35. There are differences in the evidence base for peanut and hen's egg: there are more RCTs investigating earlier introduction of hen's egg in a number of geographically-diverse areas; earlier age at presentation of clinical allergy (which might be related to hen's egg being introduced earlier during complementary feeding); greater heterogeneity in the food matrix in which the hen's egg is consumed. Despite differences in the available evidence, there is a need to maintain simple and consistent public health advice: at the present time peanut and hen's egg should be treated in the same way. Recommendations for health care professionals may need to take into account different clinical scenarios, and that targeted advice may be appropriate for individuals at a higher risk of developing a food allergy.

Recommendations for government

36. The government should continue to recommend exclusive breastfeeding for around the first six months of life.

37. Advice on complementary feeding should state that foods containing peanut and hen's egg need not be differentiated from other complementary foods.

Complementary foods should be introduced in age-appropriate[8] form from around six months of age, alongside continued breastfeeding, at a time and in a manner to suit both the family and individual child.

38. The deliberate exclusion of peanut or hen's egg beyond six to twelve months of age may increase the risk of allergy to the same foods. Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and family. If initial exposure is not continued as part of the infant's usual diet, then this may increase the risk of sensitisation and subsequent food allergy.

39. Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

40. These recommendations build on the conclusions from the COT statement that: 'from the evidence available, early introduction of allergenic foods does not increase the risk of allergy or autoimmune disease. Indeed, the deliberate exclusion or delayed introduction of specific allergenic foods may increase the risk of allergy to the same foods.

[8]Infants and young children should never be left alone while they are eating. Children under five years old must not be given whole nuts, as they can choke on them. Currently it is advised that infants and young children should not eat raw eggs, eggs with runny yolks or any food that contains raw eggs and is uncooked or only lightly cooked. These can cause food poisoning and serious illness although this advice is currently under review as a result of the ACMSF recommendations (ACMSF, 2016). Eggs from other birds such as duck, goose and quail eggs should always be cooked thoroughly and this will not change following the current review.

Annex A.

Risks

Possible reduction in breastfeeding and resultant risk for infant

41. Respiratory and gastrointestinal tract infections and acute otitis media (AOM; middle ear infection) are an important cause of morbidity in infancy (Yuan et al, 2001). Infants who are not breastfed are at greater risk of these infections in both resource rich and poorer settings, particularly in the first six months of life.

42. The U.S Department of Health and Human Service Office on Women's Health has compiled evidence from systematic reviews/meta-analyses, randomised and non-randomised comparative trials, prospective cohort, and case-control studies quantifying the effects of breastfeeding on short and long term infant and maternal health outcomes in developed countries. Infants not breastfed were 3.6 times more likely to be hospitalised compared with those exclusively breastfed for a minimum of four months. For every 26 infants exclusively breastfed for four months or more, one hospital episode secondary to respiratory disease could be prevented (Ip et al, 2007).

43. Not breastfeeding is associated with significant increased risk of AOM, non-specific gastrointestinal infection and hospitalisation from secondary to lower respiratory tract infections (LRTI) (Ip et al, 2007). Further UK data from the Millennium Cohort Study show that infants who consumed only breast milk had a significantly lower risk of hospitalisation for both diarrhoea and LRTI, compared with those not breastfed at all in the preceding month (Quigley et al., 2007; Quigley et al., 2009).

44. A systematic review by Kramer & Kakuma (2002, updated in 2012) assessed the effects of exclusive breastfeeding for six months compared with 3-4 months (followed by mixed feeding[9]). No significant differences were detected for any growth outcomes (length, weight, BMI) at 6.5 years of age, and infants who were exclusively breastfed for six months experienced less infectious morbidity than those who were exclusively breastfed for four months.

Possible reduction in breastfeeding and resultant risk for mother

45. There is some evidence to suggest that mothers who breastfed exclusively during the first six months have greater postpartum weight loss (Kramer and Kakuma, 2012). The impact of breastfeeding on British women's later Body Mass Index (BMI) has been investigated by the Million Women Study (Bobrow et al, 2013). After adjusting for confounding factors, post-menopausal BMI was significantly correlated with both parity and breastfeeding; at each level of parity mean BMI of women who had

[9] Mixed introduction of complementary liquids or solid foods with continued breastfeeding until at least six months of age.

breastfed was lower than that of women who had not. The effect size was 0.22 kg/m^2 (CI 0.21-0.22kg/m^2) for every six months of breastfeeding, approximating a one per cent reduction at population level.

46. There is evidence that mothers who do not breastfeed are at greater risk of developing breast cancer. A study of more than 147,000 women in 30 countries reported that women presenting with breast cancer had had fewer pregnancies than controls and were less likely to have breastfed (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Further evidence from the European Code against Cancer programme similarly estimated that there is a 2% reduction in breast cancer risk for every additional five months of breastfeeding during a mother's lifetime (Scoccianti et al, 2015).

47. The above risks were extrapolated from evidence relating to the consequences of reduced breast milk feeding, on the basis that complementary foods displace breast milk.

Possible increased exposure to aflatoxins and ochratoxin A from peanut

48. It has been proposed that earlier introduction of peanut into the infant diet might result in an increased exposure to aflatoxin and ochratoxin A. Animal studies and epidemiological studies from sub-Saharan Africa and South East Asia have consistently shown that higher aflatoxin exposures are associated with a higher incidence of hepatocellular carcinoma. EFSA have reviewed this evidence and concluded that small lifetime increase in duration of exposure to peanuts would be unlikely to increase overall risk posed by aflatoxins (EFSA, 2007). Evidence from animal studies indicates that ochratoxin A is a renal toxin and may cause kidney tumours through oxidative stress. EFSA has concluded however that peanuts are not a major source of ochratoxin A (EFSA, 2006).

Possible increased choking hazard from earlier exposure to peanut

49. The studies providing evidence on the timing of introduction of peanut into the infant diet did not use whole peanuts as the intervention. Whole peanuts are a known cause of choking, especially in children under two years (cases of choking, suffocation and strangling accounted for 2024 hospital admissions and 138 deaths from 2008-2013) (PHE, 2014). Two incidents of choking were reported by Perkin et al, 2016, both in the same individual, and were attributed to an IgE-mediated allergic reaction rather than consumption of whole peanut (Perkin et al, 2016).

Possible increased risk of Salmonella infection from possible exposure of uncooked hen's egg

50. It has been suggested that introducing complementary foods earlier than currently recommended might lead to an increased risk of *Salmonella* infection in infants due to the possible exposure to uncooked hen's eggs at an earlier age. In the past, UK hen's eggs have been found to contain *Salmonella* and consequently, it is currently recommended that children are only offered cooked hen's eggs. In 2016, the Advisory Committee on the Microbiological Safety of Foods (ACMSF) concluded that "Lion brand" hen's eggs or hen's eggs produced under demonstrably equivalent schemes carry a very low risk to all groups in society including vulnerable groups such as children. In practical terms this means that these types of hen's eggs can be eaten lightly cooked or runny by vulnerable groups too. This advice does not apply to non-"Lion" (or non-demonstrably equivalent) hen's eggs, non-UK hen's eggs and non-hen's eggs (ACMSF, 2016). Advice to consumers is currently under review. Eggs from other birds such as duck, goose and quail eggs should always be cooked thoroughly and this will not change following the current review.

Benefits

Timing of introduction of peanut: evidence from RCTs

51. Two randomised controlled trials (RCTs) have investigated the relationship between the timing of introduction of peanut into the infant diet and the risk of peanut allergy (Du Toit et al, 2015; Perkin et al, 2016) - see Table 1.

Table 1: Summary of peanut allergy interventions trials

Study (country)	**N**	**Intervention/Control**	**Population**
LEAP-DuToit et al, 2015 (UK)	N = 640 Of which *Intervention*: 319 *Control*:321 (530 of 640 infants in the intention-to-treat)	Infants at high risk of peanut allergy advised to either consume (intervention) or avoid (control) peanuts until 60 months of age. Infants in the intervention group were fed at least 6g of peanut protein per week, distributed in 3 or more meals per week until they reached 60 months of age.	Infants with severe eczema, egg allergy or both, at high risk of peanut allergy
EAT-Perkin et al, 2016 (UK)	N= 1303 of which early introduction group n = 652 and standard introduction group n = 651	Infants were randomly assigned to the introduction of six allergenic foods from three months of age (peanut, cows' milk, wheat, sesame, white fish and hen's egg) or to follow current UK infant feeding advice (i.e. exclusively breastfeed to around six months of age). Infants in the early introduction group consumed 2g of the protein, twice weekly after successful introduction.	All infants exclusively breastfeed to three months of age before randomisation in the general population of England and Wales.

52. The LEAP Study reported that introducing peanut into the infant diet between four to eleven months decreased significantly the frequency of the development of peanut allergy ($p<0.001$) (Du Toit et al, 2015). The control group avoided all peanut until five years of age. The mean and median age at screening in this study was 7.8 months of age. This study was not specifically designed to assess peanut introduction prior to six months of age, although a secondary analysis by Greenhawt et al, (2016) did assess outcome data for infants in the LEAP cohort who were introduced to peanut between four-six months of age.

53. The EAT Study did not show efficacy in an intention to treat analysis, however, a statistically significant reduction in peanut allergy was reported in the per protocol analysis ($p=0.003$) (Perkin et al, 2016). By six months of age, 96.8% children in the intervention (early introduction) arm of the EAT study had been introduced to peanut and 75% were regularly consuming at least 3g of peanut protein per week. Adherence rates for children regularly consuming peanut ranged from 39% children consuming at least 4g of peanut protein per week for more than six weeks to 85% children consuming more than 2g of peanut protein per week for more than four weeks.

54. These RCTs are included in the systematic review and meta-analysis conducted by Ierodiakonou et al, (2016), commissioned by the FSA to inform COT's consideration of the evidence and the resulting COT Statement. The systematic review concluded that there was MODERATE evidence that introduction of peanut at four to eleven months of age reduced the risk of peanut allergy, compared with the later introduction of peanut. COT agreed with the rating of the quality of this evidence as MODERATE using the GRADE system.

55. The joint SACN-COT working group (hereafter termed 'working group') agreed with the COT's conclusion but noted that the previous assessment had not considered the specific timing of the comparator - later introduction of peanut. The group concluded that there was insufficient evidence for a "window of opportunity" necessitating the introduction of peanut prior to six months of age.

Timing of introduction of hen's egg- evidence from RCTs

56. Seven RCTs have been published investigating the relationship between the timing of introduction of hen's egg (here after termed egg) into the infant diet and risk of egg allergy (Halpern et al, 1973; Palmer et al, 2013; Palmer et al, 2016, Bellach et al, 2016; Natsume et al, 2016; Perkin et al, 2016; Tan et al, 2016). These studies utilised different forms of egg for the intervention, in different doses, and administration to non-equivalent cohorts of differing risk profiles.

57. Five RCTs found no statistically significant effect of timing of introduction of egg into the infant diet on the risk of egg allergy from intention to treat

analyses (Bellach et al, 2016; Halpern et al, 1973; Palmer et al, 2013; Palmer et al, 2016, Tan et al, 2016). Although Perkin et al, (2016) did not show efficacy in an intention to treat analysis, a statistically significant reduction in egg allergy was reported in the per protocol analysis (p=0.003). Natsume et al, (2016) reported a statistically significant reduction in the risk of egg allergy with introduction of egg (as pulverised boiled egg) alongside management of eczema from six months of age (p=0.013). Table 2 provides a summary of these studies.

Table 2: Summary of egg allergy interventions trials

Study (country)	**N Int/Ctrl**	**Intervention/control**	**Population**
Halpern et al, 1973 (USA)	~875/ 875	Egg yolk given before 3 weeks, versus after 6 months.	Caucasian infants seen at birth by one of 11 private paediatricians in Dallas.
STAR Study Palmer et al, 2013 (Australia)	49/ 37	1 teaspoon (900mg whole egg protein) per day of pasteurized raw whole egg powder, versus rice flour powder, given daily from 4 to 8 months age.	Singleton term infants with moderate-to-severe eczema.
EAT Study Perkin et al, 2016 (UK)	652/ 651	Sequential introduction of 6 allergenic foods – including egg, target 2g protein for each food, twice weekly from age 3 months. 78% consuming 2+gram by 6 months. Control group was avoidance to ≥6 months, followed by std weaning.	Children born 37+/40, exclusively breastfed at 3 month.
HEAP Study Bellach et al, 2016 (Germany)	184/ 199	Pasteurised egg white powder (~2.5g protein, equivalent to 5g whole egg protein) versus rice powder 3 times per week from 4-6 (median 4.7months) to 12 months	Infants aged 4-6 months with specific IgE to egg <0.35 kU/L
PETIT study Natsume et al, 2016 (Japan)	60/ 61	Pulverised boiled egg (50mg daily from 6-9 months; 250mg daily from 9-12 months) versus placebo from 6 to 12 months. Eczema management.	Infants with eczema by 4-5 months.
STEP Study Palmer et al, 2016 (Australia)	407/ 413	900mg whole egg powder (0.4g egg protein) per day, versus rice powder/vegetable flour, given daily from randomization at 4-6 months (median 5.8 months) until age 10 months.	Singleton term infants without any atopic disease
BEAT Study Tan et al, 2016 (Australia)	165/ 154	Pasteurised whole egg powder (350mg whole egg protein) daily versus rice powder from the time of solid food introduction (median 4 months) until 8 months.	Infants with a first degree relative with allergic disease, and egg SPT <2mm at age 4 months.

58. These RCTs were included in the systematic review and meta-analysis conducted by Ierodiakonou et al, (2016) (commissioned by the FSA to inform COT's consideration of the evidence and the resulting COT Statement), with the exception of Halpern et al, (1973) and Palmer et al,

(2016) (where data were not available). The systematic review concluded that there was evidence that introduction of egg between four to six months of age reduced the risk of egg allergy, compared with the later introduction of egg and COT agreed with the rating of the quality of this evidence as MODERATE using the GRADE system.

The authors of the meta-analysis concluded that: *'the evidence base for a relationship between early allergy food introduction and food allergy to the same food was limited to a relatively small number of studies and events and was statistically significant for egg. Heterogeneity-adjusted trial sequential analysis (TSA) of early introduction of egg allergy suggests that further trials are warranted to confirm the findings and quantify the magnitude of the treatment effect'* (Ierodiakonou et al, 2016).

59. The working group agreed with the COT's conclusion but noted that the previous assessment had not considered the specific timing of the comparator – later introduction of egg. The working group considered the evidence for the introduction of egg before six months of age versus after six months. They noted that the data presented in Halpern et al, (1973) and Natsume et al, (2016) did not address this, and were therefore excluded. The working group concluded that there was limited evidence to support a health benefit of earlier egg introduction (between four to six months) versus later egg introduction (after six months), but the evidence for a "window of opportunity" necessitating the introduction of egg prior to six months of age was insufficient.

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