Background to the working group and purpose of the meeting

Introduction

1. As part of the government review on complementary feeding for infants, the Food Standards Agency (FSA) commissioned Imperial College London to conduct a comprehensive systematic review of the published scientific literature on the risks arising from the infant diet and the development of atopic outcomes and autoimmune disease. The overall review was separated into four systematic reviews:

    - Review A: Duration of total and exclusive breastfeeding and timing of solid food introduction.
    - Review B: Timing of introduction of allergenic food introduction
    - Review C (I): Use of hydrolysed infant formula[1]
    - Review C (II): Maternal and other infant dietary exposures

2. These reviews have been peer-reviewed by the COT and have been published, or will be published in the near future, in the peer-reviewed literature (Boyle *et al,* 2016). In light of the draft findings from the SACN review [which support current policy recommendations on exclusive breastfeeding to around 6 months] and COT's statement on the timing of allergenic food introduction, a thorough consideration of the risks and benefits is necessary to ensure that government advice is based on sound science and considers all relevant aspects of maternal, infant and child health. A brief summary of the conclusions from Reviews A, C(I) and C(II) can be found in Annex A at the end of this document.

Scope of risk benefit assessment

3. Members of the joint COT/SACN subgroup are asked to consider the risks and benefits of the timing of introduction of allergenic foods into the infant diet (outcomes from Review B) and the influence on atopic outcomes and autoimmune disease. As mentioned above, the evidence base on which this RBA focusses has been assessed in a systematic review and meta-analysis

[1] Link to final report: https://www.food.gov.uk/science/research/allergy-research/fs305005hf
Link to the COT statement: https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statement-on-hydrolysed-cows-milk-formulae

(Ierodiakonou *et al*, 2016). The COT has published its statement on this evidence base[2].

4. The significant findings from the review related to the timing of introduction of peanut (between 4-11 months) and risk of developing peanut allergy; timing of introduction of egg (between 4-6 months) and risk of developing egg allergy; timing of introduction of fish (between 6-12 months) and risk of developing allergic sensitisation and allergic rhinitis and finally the timing of introduction of gluten (between 4-6 months) was found to NOT increase the risk of developing coeliac disease. A full summary of the findings of the systematic review can be found in the COT statement.

5. Current advice on complementary feeding can be found in more detail on paper number SACN COT/Allergenic/16/03. However, in summary, exclusive breastfeeding is recommended to around 6 months of age after which foods should be introduced gradually. The findings from the systematic review that may have an impact on current government advice are those relating to peanut and egg consumption and peanut or egg allergy, respectively, and therefore these foods will be the focus of this risk/benefit analysis. Background information on the development of food allergy can be found at Annex B at the end of this document.

Purpose of the SACN/COT subgroup

6. The joint SACN/COT secretariat has identified two areas from the systematic reviews that will require a risk-benefit assessment in order to ensure that future policy is based on a sound scientific basis. These are the timing of introduction of peanut into the infant diet and the risk of developing peanut allergy, and the timing of introduction of egg into the infant diet and the risk of developing egg allergy.

7. In order to conduct this risk-benefit assessment, the joint SACN/COT secretariat proposes using the Benefit-Risk Analysis for Foods (BRAFO) methodology (more details can be found in SACN COT/Allergenic/16/04).

8. Further background on the two areas of interest along with possible health effects suggested by the secretariat can be found in their respective discussion papers: SACN COT/Allergenic/16/05 for egg and SACN COT/Allergenic/16/06 for peanut.

[2] Available at: https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2016/statement-on-the-timing-of-introduction-of-allergenic-foods-to-the-infant-diet-and-influence-on-the-risk-of-development-of-atopic-outcomes-and-autoimmune-disease

References

Boyle, R. J.; Ierodiakonou, D.; Khan, T.; Chivinge, J.; Robinson, Z.; Geoghegan, N.; Jarrold, K.; Afxentiou, T.; Reeves, T.; Cunha, S.; Trivella, M.; Garcia-Larsen, V.; Leonardi-Bee, J. (2016) BMJ 352:i974

Ierodiakonou D.; Garcia-Larsen V.; Logan A,; Groome A,; Cunha S,; Chivinge J, et al (2016). Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. Journal of the American Medical Association. 316(11:1181-1192)

Summary of findings from the other systematic reviews

Review A: Duration of total and exclusive breastfeeding and timing of solid food introduction.

1. The evidence was assessed as VERY LOW using the GRADE system to support an association with increased length of breastfeeding duration and reduced risk of wheeze at age 5-14.

2. The evidence was assessed as VERY LOW under the GRADE system to support an association between increased length of breastfeeding duration and increased risk of type 1 diabetes mellitus (TIDM).

3. The evidence was assessed as LOW under the GRADE system for increased exclusive breastfeeding duration and reduced risk of TIDM. No other significant findings were identified for other indicators of atopic disease.

Review C(I): Use of hydrolysed infant formula

4. In the systematic review of hydrolysed formula for reducing risk of allergic or autoimmune outcomes, there was no clear evidence for a protective effect with respect to any of the outcomes studied.

5. In general, relatively few included studies carried a low overall risk of bias and low risk of conflict of interest. In particular, the studies in relation to allergic outcomes commonly had unclear or high risk of overall bias, often due to post-randomisation exclusion of participants (attrition bias) and unclear or high risk of conflict of interest due to support of the study or investigators by manufacturers of hydrolysed formula.

6. Evidence was found for publication bias, at least in analysis of eczema and recurrent wheeze as outcome measures. This body of evidence should be viewed as pertaining to children at high risk of atopic outcomes or autoimmune disease, since these accounted for most studies and participants, and almost all analyses were dominated by the findings in high risk children. Thus the evidence base for use of hydrolysed formula in children at 'normal risk' of allergic or autoimmune outcomes is largely unexplored (Boyle et al, 2016).

Review C(II): Maternal and other infant dietary exposures

7. The systematic review found MODERATE evidence, assessed using the GRADE system, to support an association between the use of probiotics during pregnancy, lactation and infancy and a reduced risk of eczema in high risk infants as well as eczema associated with allergic sensitisation both at ≤4 years of age.

8. There was LOW quality evidence, assessed using the GRADE system, that the use of probiotics during pregnancy, lactation and infancy reduces the risk of allergic sensitisation to cows' milk. There was no relationship between the use of probiotics

and the risk of wheeze, eczema, allergic rhinitis, allergic sensitisation, or food allergy.

9. Using the GRADE system, the evidence was found to be MODERATE that supplementation with omega-3 fatty acids reduces the risk of allergic sensitisation to eggs in high risk infants. The available evidence did not suggest a relationship between omega-3 supplementation and risk of wheeze, eczema or allergic rhinitis.

10. Using the GRADE system the evidence was found to be LOW that the use of multifaceted interventions reduce the risk of wheeze or recurrent wheeze at age 5-14 years, and allergic rhinitis at age ≤4 years. The available data indicated no evidence that multifaceted interventions reduce risk of wheeze, recurrent wheeze or allergic rhinitis at other ages, and there was no evidence that multifaceted interventions reduce risk of food allergy, allergic sensitisation, allergic conjunctivitis or eczema.

11. The evidence that vitamin A supplementation during pregnancy increases measures of lung function was classified under the GRADE system as LOW. No relationship was found between vitamin or mineral intake or supplementation, or vitamin D blood level, during pregnancy or infancy and the risk of wheezing, other allergic outcomes or autoimmune outcomes.

12. There was no relationship between the use of maternal allergenic food avoidance, prebiotics, fruit and vegetable consumption or fats and fatty acids and the risk of any of the allergic outcomes or autoimmune disease studied.

Factors influencing the development of food allergy

1. There are three factors that influence whether an individual will become allergic to a particular food. The nature of the food protein is an important factor in development of food allergy. There are significant differences among food proteins with respect to their ability to cause sensitisation and allergy. Some are very potent (such as certain peanut proteins), whereas others are associated very rarely, or not at all, with allergy. There are a variety of factors that can affect the inherent allergenicity of proteins and these include their functional properties such as enzymatic activity or their resistance to digestion.

2. Those most at risk of developing food allergy are subjects with atopy; this being a predisposition to mount IgE antibody responses. Most forms of food allergy are caused by IgE antibody reactive with the protein allergen. Atopy is inherited, but can also be influenced by various environmental factors.

3. The extent of exposure to the allergen and when the allergen is first encountered can have a significant impact on whether or not sensitisation and allergy will develop. However, sensitisation to food proteins does not develop only by dietary exposure. Skin exposure in infants can induce sensitisation to foods.

4. Eczema in infants has been shown to be an important risk factor for food allergy indicating the importance of skin barrier function in the development of food allergy (Hill *et al*, 2008). Fox *et al* (2009) reported that the median weekly consumption of peanut products in the household during the first year of a child's life is significantly higher in children who subsequently develop peanut allergy. Evidence from animal models has revealed that allergic sensitisation to peanut can be induced by exposure to peanut protein (Strid *et al*, 2004). Peanut-responsive T lymphocytes in sensitised subjects are predominantly skin-homing memory cells; the implication being that sensitisation had been acquired through skin contact resulting in a cutaneous immune response (Chan *et al,* 2012*).*

References

Chan S, Turcanu V, Stephens A, Fox A, Grieve A, Lack G. (2012) Cutaneous lymphocyte antigen and α4β7 T-lymphocyte responses are associated with peanut allergy and tolerance in children. Allergy. 67: 336-342

Fox A, Sasieni P, du Doit G, Syed H, Lack G. (2009) Household peanut consumption as a risk factor for the development of peanut allergy. Journal of Allergy and Clinical Immunology. 123(2): 417-423

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