



1st meeting of the Joint SACN-COT Working Group on the timing of introduction of allergenic foods into the infant diet

9th December 2016, Skipton House, London

FINAL MINUTES- CLOSED meeting

Chair

Professor Mike Kelly, Independent Chair

Members

Dr Anthony Williams, SMCN chair/ SACN member
Professor Peter Aggett, SMCN/SACN member
Dr Ken Ong, SMCN member
Professor Alan Boobis, COT Chair
Dr René Crevel, COT member
Dr Paul Turner, External expert

Secretariat

Dr Louis Levy (PHE)
Rachel Elsom (PHE)
Alastair McArthur (PHE)
Liz Kendall (FSA)
Frances Hill (FSA)

Chair's welcome and introduction

1. Professor Mike Kelly welcomed Members to the meeting.
2. Members were reminded that all conflicts of interest should have been declared to the Secretariat prior to the meeting. The group was informed that no conflicts of interest had been declared.

**Agenda Item 1: Background to the working group and purpose of meeting
(SACN:COT/Allergenic/16/01)**

3. The Chair invited Dr Louis Levy to introduce this item. Members were informed that consideration of the introduction of allergenic foods into the infant diet was planned for inclusion in SMCN's (SACN's Subgroup on Maternal and Child Nutrition) review of feeding infants under one year.

4. To support this, the Food Standards Agency (FSA) commissioned Imperial College London to conduct a series of comprehensive systematic reviews¹ of the published scientific literature on the risks arising from the infant diet and the development of atopic outcomes and autoimmune disease. Systematic Review B covered the timing of introduction of allergenic foods into the infant diet and findings from this review are particularly pertinent to the joint working group's discussions. Members were informed that the systematic reviews had 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; Ierodiakonou *et al*, 2016).
5. 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 Systematic Review B, the joint SACN:COT working group was convened to consider the risks and benefits of the timing of introduction of allergenic foods into the infant diet in order to ensure that government advice is based on sound science and takes into account all relevant aspects of infant and child health.
6. Members noted that the background paper should refer to maternal as well as child health outcomes. The Secretariat agreed to amend the wording to reflect this point.

Action: Secretariat

Agenda Item 2: Agreement of terms of reference, output from the group, and process (SACN:COT/Allergenic/16/02)

7. The Chair invited Dr Louis Levy to introduce this item.
8. Members questioned the focus on hen's egg and peanut given the number of allergens covered by the Imperial College London reviews (e.g. cows' milk, fish/seafood, tree nuts, soya, wheat and gluten). The Chair confirmed that following extensive discussions, it was agreed that due to the findings of Systematic Review B and the key areas of potential divergence, the joint working group's discussions should focus on the introduction of hen's egg and peanut. It was therefore agreed that the terms of reference should be amended to reflect these discussions and refer only to 'hen's egg' and 'peanut'.

Action: Secretariat

9. Members raised a number of concerns regarding the limitations and uncertainties in the evidence base on the risks associated with timing of introduction of allergenic foods into the infant diet. These included:
 - poor understanding of the mechanisms of action;
 - heterogeneity in the study populations;

¹ Review A: Duration of total and exclusive breastfeeding and timing of solid food introduction; Review B: Timing of introduction of allergenic foods into the infant diet; Review C (I): Use of hydrolysed infant formula; and Review C (II): Maternal and other infant dietary exposures

- Design and methodologies employed, for example, differences in the form in which egg was introduced (e.g. pasteurised, baked, etc), screening approaches and the use of general population advice versus specialist intervention advice.
10. Members agreed that a comment on the quality of the evidence would be included in their statement.
11. The planned outputs from the meeting and the process going forward were outlined to Members:
- Produce and agree a Joint SACN-COT draft statement.
 - Present draft statement to SMCN, SACN and COT at their respective meetings in Spring/Summer 2017.
 - Final joint statement to be presented to the UK Health Departments.
12. Members queried whether the committees would have the opportunity to amend the draft statement. Dr Louis Levy clarified that the primary purpose of presenting the draft statement to the committees was to seek agreement.

**Agenda Item 3: Current government advice on infant feeding, to cover exclusive breastfeeding to around six months and the timing of introduction of solid foods, including potentially allergenic foods, into the infant diet.
(SACN:COT/Allergenic/16/03)**

13. The Chair invited Dr Louis Levy to introduce the paper outlining current government advice.
14. Members stressed that breastfeeding should always be framed as the physiological norm against which all other feeding behaviours are compared.
15. Members noted the use of the terms 'early', 'delayed' and 'late' and stressed that these are relative terms which need to be defined clearly.
16. Members noted that paragraph 8 appeared to suggest that foods should be matured for six months before giving to infants, rather than infants needing to be six months of age before consuming the food. The Secretariat agreed to clarify this wording.

Action: Secretariat

17. Members noted that the available evidence is focussed on exclusive breastfeeding in the first six months of life and that the evidence base on the consequences of mixed feeding (i.e. breast and formula feeding) during the first six months is limited. Members commented on the limited available evidence on the effects of continued breastfeeding alongside the introduction of small amounts of solid foods, or infant formula.

18. Members discussed the current UK policy recommending exclusive breastfeeding to around six months and stressed the beneficial impact this had had on the timing of introduction of solid foods into the infant diet. Data from the Infant Feeding Survey 2010 show that following the change in policy there has been a shift to later introduction of solid foods, with a five-fold increase in the proportion of mothers introducing solids between 4-6 months compared with when the policy recommendation was 4-6 months exclusive breastfeeding, when a high percentage of mothers introduced solids before four months. By six months, levels of exclusive breastfeeding in the UK are one per cent.
19. Concerns were expressed that since the discontinuation of funding for the Infant Feeding Survey, information has been lacking on: breastfeeding duration, the timing of introduction of complementary foods, supplementary vitamins use and breastfeeding rates once solid foods have been introduced.
20. Members highlighted that when SACN endorsed the WHO's recommendation of exclusive breastfeeding for the first six months of an infant's life, the Committee also recommended that there should be some flexibility in the advice, but that any complementary feeding should not be introduced before the end of four months (17 weeks).
21. The Chair reminded Members that the purpose of the joint working group was to conduct a benefit-risk assessment of the evidence. Outputs from the group would be passed to policy makers for discussions on risk management.

**Agenda Item 4: BRAFO tiered approach for benefit-risk assessment of foods
(SACN:COT/Allergenic/16/04)**

22. The Chair invited Professor Alan Boobis to introduce the paper on the BRAFO tiered approach for benefit-risk assessment, who outlined the background and methodology to this approach.
23. Members discussed the BRAFO approach and agreed that it provided a useful framework for consideration of the evidence on the risks and benefits of the introduction of allergenic foods into the infant diet.

**Agenda Item 5: Evidence on the timing of introduction of egg into the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease.
(SACN:COT/Allergenic/16/05)**

24. The Chair invited Frances Hill to introduce the paper.
25. Members noted the ambiguity in the terminology used across the different studies (i.e. the meaning of 'early', delayed versus current practice, and 'late') and highlighted further the heterogeneity between the studies under consideration, for example, the uncertainty and lack of precision in the timing of introduction of solid (including allergenic) foods.

26. They flagged the use of 'healthy' infants and noted that this term was not appropriate for some infants given that they already had atopic disease making this a clinical issue and therefore outwith the remit of both SACN and COT. They further noted that some participants' pre-existing allergic status was not yet available in some of the studies.
27. Members stressed the importance of distinguishing between studies which provide data on *all* infants (i.e. relevant to policy) and those which relate to a subgroup of infants. Members were informed that in the Imperial College London meta-analysis, two thirds of infants were considered representative of the general UK population.
28. Members highlighted the important distinction between allergenic foods and other solid foods when considering the timing of introduction of solids into the infant diet. They also stressed the need to acknowledge the different rate of development between infants. Members noted that the majority of published literature has not provided detail on the specific time points at which foods were introduced within the 4-6 month window.
29. Members noted that the studies were primarily explanatory studies and extrapolating findings from these to the general population was difficult. They noted that EAT represented the best quality evidence to date, however, the study population was not representative of the general population.
30. Members noted that GRADE does not cover the quality of the evidence of the individual studies feeding into the systematic review, rather GRADE provides a measure of the quality of the evidence arising from the meta-analysis.
31. Members discussed the Natsume *et al* (2016) paper. They noted the missing data and the lack of clarity regarding whether the placebo group maintained an egg-free diet until 12 months of age. Members were informed that Imperial College London had conducted a meta-analysis in which the Natsume data were removed and the overall finding remained i.e. a decreased risk of egg allergy with introduction of egg before six months.
32. Members agreed that, for benefit-risk assessment, it was vital to establish the reference scenario (current practice) and stressed that current advice (i.e. recommendation to exclusively breastfeed for around the first six months of life) is not the same as current practice. They noted that the reference scenario and the alternative scenario do not necessarily equate to the intervention and the respective control group (e.g. the placebo group) in each of the studies being considered. Members also noted the need to consider the consequences of not recommending change.
33. Members discussed whether the reference scenario should be current policy or practice and agreed that the alternative scenario should be *"Cooked egg (not raw egg) is introduced into the diet of all non-egg allergic infants between 4-6 months of age but no other foods are introduced"*.

34. Members agreed it was important to expand consideration of the reference scenarios to cover both current policy (i.e. exclusive breastfeeding to around six months) and current practice (e.g. 70% infants in the UK are on solids by 5 months of age) for both peanut and egg.
35. The Secretariat agreed to populate the table and circulate it to Members for comment.

Action: Secretariat (FSA)

Agenda Item 6: Evidence on the timing of introduction of peanut into the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease. (SACN:COT/Allergenic/16/05)

36. The Chair invited Liz Kendall to introduce the paper.
37. Members discussed the reference and alternative scenarios that should be used for the assessment on the timing of introduction of peanut into the infant diet. They agreed that the reference scenario should be current policy (i.e. exclusive breastfeeding to around six months).
38. Members agreed the wording of alternative scenario as follows: *“Alternative scenario: Peanut is introduced into the diet of all non-peanut allergic infants between 4-6 months of age but no other foods are introduced.”*
39. Members considered a second alternative scenario, that of deliberate avoidance of peanut during the first 12 months. The COT statement² on delayed peanut introduction was also highlighted and Members flagged that the EAT study findings might indicate evidence for the harmful effect of delaying the introduction of peanut beyond age 12 months rather than providing support for ‘early’ introduction.
40. Members noted that very specific amounts of peanut protein had been given in the trials and queried how this would translate into advice to the general population. They stressed the importance of considering the quantity of peanut protein consumed and the duration and pattern of exposure required to produce the desired effect.
41. It was noted that a strong recommendation needs to be made regarding the importance of population data collection on infant feeding behaviour in the absence of the Infant Feeding Survey. Without such data the impact of any change to recommendations would not be measurable at population level.
42. Members agreed that on the basis of the available evidence, it is not possible to determine whether either reference or alternative scenario is clearly preferable (Tier 0).

² COT report on Peanut Allergy. Department of Health. (1998)
(<http://www.food.gov.uk/science/ouradvisors/toxicity/cotreports/cotwgreports/cotpeanutallergy>)

43. Members agreed that both BRAFO Tiers 1 and 2 should be considered.
44. Members noted that it would be useful to scrutinize the supplementary appendices for data on adverse effects. They further stressed the need to characterize the dose-response relationship.
45. Members discussed the findings from the EAT study, and in particular, the differences in per protocol (PP) versus intention to treat (ITT) analyses. Members were informed that around 10% children who are expected to tolerate the intervention (i.e. show no signs of sensitisation), go onto develop an allergy/react, suggesting they are already allergic. It was noted that PP analysis tends to skew data in favour of the intervention. Members stressed that the differences in findings between the PP and ITT analyses must be acknowledged.
46. Members went on to discuss the findings from the LEAP Study, and noted that from the data available in the primary manuscript (Du Toit *et al*, 2015), it was not possible to ascertain the number of participants who had been introduced to peanut between 4-6 months. It was agreed Robert Boyle should be approached to establish whether data are available for this time period and if so, what it shows. Members were informed that all data from the LEAP study are in the public domain and that this analysis should be possible.
47. Members suggested that the ancillary data available from EAT and LEAP should be interrogated to help address these questions.

Action: A Member to take this forward with Imperial College London and whether it would be possible to conduct a meta-analysis on LEAP and EAT data relating specifically to the 4-6 month age range.

48. The Secretariat agreed to populate the table and circulate it to Members for comment.

Action: Secretariat (FSA)

Agenda Item 7: Agreement on the conclusions for this group.

49. Members discussed over-arching issues and noted the need to consider: nutrition-related data from EAT and LEAP; the impact of the interventions on the duration of breastfeeding; evidence on the impact of introduction of allergenic foods on the introduction of other solids; and the impact of introduction of allergenic foods in addition to other solid foods, on health outcomes such as infection rates.
50. They highlighted further the need to consider how the egg and peanut protein are delivered i.e. are these immunological studies providing a certain amount of

allergenic protein per day or are the potentially allergenic foods being introduced as part of a gradually diversifying complementary feeding diet?

51. It was agreed that the Secretariat would populate tables for both tier 1 and tier 2 and circulate to members for comment prior to the next meeting.

Action: Secretariat (FSA)

Agenda Item 8: Next steps and timings.

52. Members agreed that a further meeting was needed. The Secretariat agreed to trawl for a suitable date for the next meeting early in 2017.

Action: Secretariat (PHE)