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

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

Background

1. Atopic conditions, including asthma, eczema, rhinitis and food allergy, appear to have increased in prevalence in recent decades in many countries, and are some of the commonest causes of chronic illness in children and young adults living in the UK (Gupta *et al*, 2004; 2007; Venter *et al*, 2010; De Silva *et al*, 2014; Nwaru *et al*, 2014). This apparent increase in disease prevalence, combined with data from migration studies, suggests that early-life environmental factors may be important modulators of allergic sensitisation and atopic disease risk. Similarly, the autoimmune diseases type I diabetes mellitus (TIDM) and Crohn's disease also appear to have increased in prevalence in some countries (Burisch & Munkholm, 2015; Patterson *et al*, 2012).

2. The relationship between maternal and infant dietary exposures and a child's risk of developing any of the common atopic and/or autoimmune diseases has been an area of considerable scientific uncertainty and debate in recent years. In 2008 the COT assessed 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[1]. The COT concluded that:

> "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.
>
> "However, the Committee considers that the basis for 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*

[1] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200807peanut

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."

3. In 2011, COT and the Scientific Advisory Committee on Nutrition (SACN) published a joint statement on the evidence relating to the introduction of gluten into the infant diet and risk of developing coeliac disease and type I diabetes mellitus[2]. The committees concluded that:

"Overall currently available evidence on the timing of introduction of gluten into the infant diet and subsequent risk of coeliac disease and TIDM is insufficient to support recommendations about the appropriate timing of introduction of gluten into the infant diet beyond 3 completed months of age, for either the general population or high-risk sub-populations. SACN and COT do not consider the evidence sufficient to support EFSA's conclusion on the introduction of gluten into the infant diet not later than 6 completed months of age with the aim of reducing the risk of subsequent development of coeliac disease and TIDM."

4. More recently, there have been several studies published on the subject of sensitisation and allergy to foods in relation to early life dietary exposures, and some of these were funded by the Food Standards Agency (FSA) (Fox et al, 2009; Perkin et al, 2016)

5. The UK health departments currently advise that breast milk provides all the nutrients a baby needs up to six months of age, and recommend exclusive breastfeeding for around the first six months of an infant's life. 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. Currently in the UK, there is also advice to avoid the introduction before 6 months of age of commonly allergenic foods such as peanuts, nuts, seeds, egg, cows' milk, soya, wheat (and other cereals that contain gluten such as rye and barley), fish and shellfish[3].

[2] http://cot.food.gov.uk/sites/default/files/cot/cotsacnstatementgluten201101.pdf

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

7. 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 current UK Government advice remains appropriate.

8. The 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 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 allergenic food introduction
- Review C (I): Use of hydrolysed infant formula
- Review C (II): Maternal and infant dietary exposures

9. This statement focusses on Review B. To date, a COT statement has been published on the systematic review of use of hydrolysed infant formula[4]. A further COT statement will be published to cover Review A and Review C (II). The COT was asked for their opinion on the systematic review, which will be used to help guide the government's assessment and development of UK infant feeding advice.

10. The COT enlisted the help of two external experts to assist them in their considerations: Professor Ian Kimber, Chair of Toxicology at the University of Manchester and Programme Advisor to the FSA Food Allergy and Intolerance Research Programme and Dr Paul Turner, an expert in paediatric allergy and immunology from Imperial College London.

11. A glossary of terms is provided as Appendix 1 to this statement.

Methodology of the systematic review

12. The systematic review aimed to answer the question: Does the timing of introduction of specific allergenic foods (cows' milk, hen egg, peanut, tree nuts, fish/seafood, wheat, soya), into the infant diet during the first year of life, influence the future risk in children of atopic disease, allergic sensitisation or autoimmune disease? The review also aimed to identify whether any effects vary according to duration of exclusive/predominant or any breastfeeding.

13. Databases searched were The Cochrane Library; EMBASE; LILACS; MEDLINE and Web of Science, with the original searches run in July 2013 and

[4] https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statement-on-hydrolysed-cows-milk-formulae

updated in March 2016. PROSPERO was also searched for relevant systematic reviews.

14. Original research papers were included from any date up to 8th March 2016. Original studies included randomised controlled trials (RCTs), quasi-RCTs, controlled clinical trials, prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case-control studies and cross-sectional surveys. Both intervention and observational studies were included in the review.

15. Studies of infants between birth and 12 months of age were included in the review. Studies were excluded where participation was limited to infants with a specific disease state, premature infants <32 weeks gestation, or very low birth weight infants. Studies of infants at high risk of relevant outcomes on the basis of family or personal history or genotype were included.

16. The review described intervention studies of two types:

- 'Standard' intervention trials where comparisons have been made between giving no advice about introduction of allergenic foods (intervention), with advice to deliberately delay introduction of allergenic foods (control).
- 'Early' intervention trials in which comparisons have been made between deliberate early introduction of allergenic food(s) (intervention), with either no advice about introduction, or advice to delay introduction of allergenic foods (control).

17. In the review, the early or unrestricted (i.e. non-delayed) introduction of allergenic foods is considered as being the 'intervention', and the delayed or standard introduction of allergenic foods as being the 'control'. The reason for this is so that, where appropriate, both types of study can be incorporated into the same meta-analysis. This means that there is not a single definition of what month(s) represent 'early' introduction as the age at which allergenic foods were introduced varied amongst the studies. The earliest was the introduction of allergenic food (cows' milk) in the first 3-4 days of life versus later, and the latest was the introduction of allergenic food in the first 12 months versus later. Where evidence of an effect has been found, the months at which allergenic foods were introduced into the infant diet have been included in this statement. It should also be noted that the use of the term "early" does not refer specifically to the current UK infant feeding guidelines which advise introduction of solid foods at around six months of age.

18. During the analysis of intervention studies, *intention to treat* data were used in preference to *per-protocol* where possible, as is generally recommended for assessments of clinical effectiveness.

19. Outcomes of interest were chosen for their prevalence in children and young adults, with a minimum inclusion criterion of 1 in 1000 prevalence in the general population. Atopic outcomes comprised: asthma / wheeze; atopic eczema; allergic rhinitis[5]; food allergy; allergic sensitisation. Autoimmune outcomes comprised type 1 diabetes mellitus (TIDM); coeliac disease; inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); autoimmune thyroid disease (such as Grave's disease or Hashimoto's thyroiditis); juvenile rheumatoid arthritis; vitiligo and psoriasis. Outcome data were analysed and presented within the age groups 0-4 years, 5-14 years and ≥15 years. Although analysis of studies of vitiligo and psoriasis were planned, no eligible studies were identified.

20. Studies were quality assessed using the Cochrane Risk of Bias tool for intervention trials, and the NICE methodological quality checklists for cohort and case control studies; with an additional assessment of risk of conflict of interest (Cochrane, 2009).

21. The assessment of the evidence using the GRADE system[6] involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (which included assessment of conflict of interest). Risk of publication bias was assessed for meta-analyses that included at least 10 studies.

22. Where evidence of effect was suggested by the studies identified, and for key negative findings, the quality of evidence was rated as one of four categories: HIGH, MODERATE, LOW or VERY LOW depending on the strength of evidence using the GRADE system (Balsham *et al*, 2011) . The interpretation of GRADE evidence assessments is that where the quality of the evidence is rated as HIGH, there is considerable confidence that the true effect lies close to that of the estimate of the effect ; when rated as MODERATE, there is moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; when rated as LOW, confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Where the quality of evidence is rated as VERY LOW, there is very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

23. Meta-analyses were undertaken, if appropriate, where 2 or more studies reported the same outcome for a given exposure. Where meta-analysis was

[5] In many studies, the definition of allergic rhinitis included "itchy, watery eyes" or allergic conjunctivitis.
[6] http://www.gradeworkinggroup.org/

deemed inappropriate due to differences in population, exposure/intervention or outcome; or where meta-analysis was not possible due to the nature of the data reported, individual study results were summarised within each report. Sub-group analyses were carried out according to risk of bias, disease risk and study design, for meta-analyses including more than 5 studies. Separate analyses were undertaken for each disease outcome, and for each intervention and comparator. The approach taken for the meta-analysis was inclusive, with data pooled for maximum statistical power, but examined for important sources of statistical or clinical heterogeneity.

24. Published systematic reviews were included within the search strategy for the review. Two systematic reviews that were considered to be high quality using revised AMSTAR[7] criteria were included in the systematic review report.

25. *Post hoc* trial sequential analysis (TSA) was used to quantify statistical reliability of findings of moderate or high evidence. TSA quantifies statistical reliability of data in a cumulative meta-analysis in a similar way to an interim analysis in a single randomized clinical trial. TSA was used to estimate the information (sample) size needed to identify relative risk reductions of 10, 20 and 30% using 2-sided 5% significance, 80% power and control event rates from included studies, where indicated. TSA analyses were undertaken both with and without adjustment for heterogeneity present in the relevant primary meta-analyses.

Summary of findings

26. Original article titles were screened (16,289), from which data were extracted from the 204 relevant original studies. Data on allergic outcomes were available from 24 intervention trials and 69 observational studies in over 13,000 and 140,000 participants, respectively. Data on autoimmune diseases were available from 5 intervention trials and 48 observational studies in over 5,000 and 60,000 participants respectively.

27. Risk of bias was low in 4/24 (17%) of intervention trials and 29/69 (42%) of observational studies for allergic outcomes. One out of five (20%) intervention trials and 10/48 (21%) observational studies for autoimmune diseases were also considered to be at low risk of bias.

28. For those outcomes where possible evidence of an association was identified, the relevant forest plots and the GRADE score for the quality of evidence have been provided. A summary table of key findings is included as Appendix 2.

[7] Further information about AMSTAR can be found at: http://amstar.ca/ and in Kung et al, 2010.

Wheeze

29. In the 16 intervention studies and 30 observational studies available, there was no evidence for any association between timing of allergenic food introduction and the risk of wheezing or altered lung function.

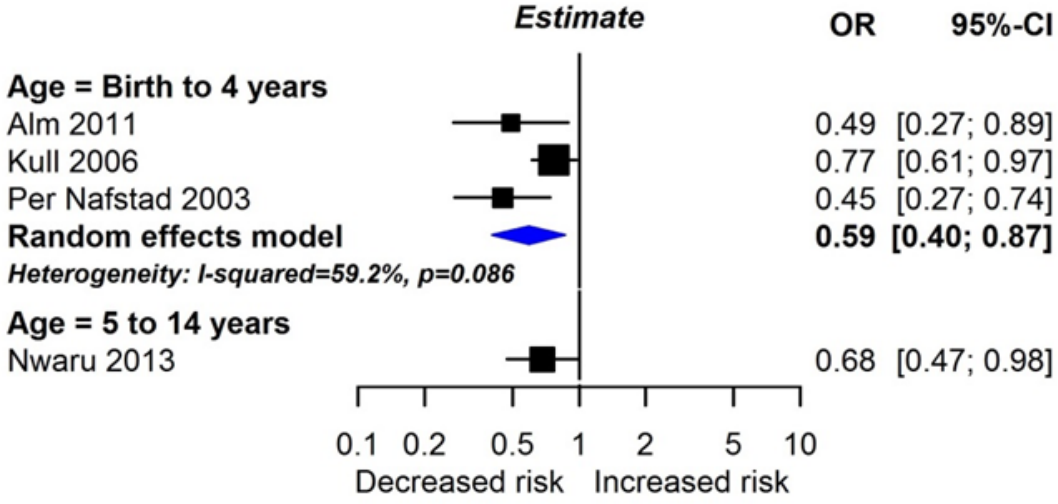
Eczema

30. From 17 intervention studies and 37 observational studies, no consistent evidence was found for any association between timing of introduction of allergenic foods and eczema.

Allergic rhinitis

31. In the four observational studies available, there was evidence to suggest that introduction of fish before 6-12 months may be associated with reduced risk of allergic rhinitis at age ≤ 4 or 5-14 years, the quality of the evidence being rated as LOW using the GRADE system (Figure 1). No such association was apparent in the three available multifaceted intervention trials, which included advice regarding timing of fish introduction, although the data in these studies were sparse and indirect. Regarding the introduction of other allergenic foods, there was no evidence for any association with allergic rhinitis in the 13 intervention studies and 12 observational studies available.

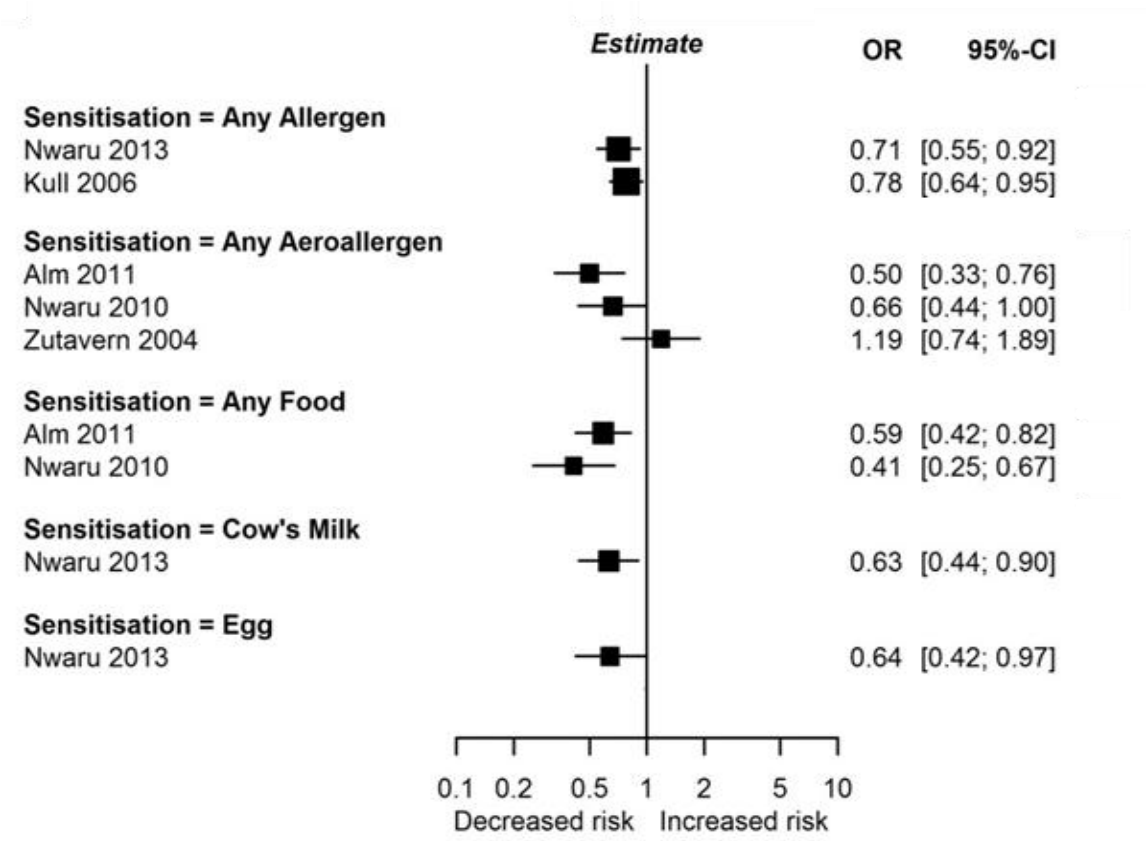
Figure 1: Forest plot of observational studies of introduction of fish at 6-12 months and risk of allergic rhinitis



Allergic sensitisation

32. In three observational studies, including over 13,000 participants (Kull 2006, Nwaru *et al*, 2010; 2013 and Alm *et al,* 2011), there was evidence suggesting a relationship between the introduction of fish before 6-9 months and reduced allergic sensitisation to various allergens (Figure 2). In two other studies, including over 700 participants (Zutavern *et al,* 2004 and Hesselmar *et al,* 2010) – the latter of which did not report numerical data), there was no evidence for any relationship between timing of fish introduction and allergic sensitisation. The quality of the evidence that fish introduction before 6-9 months is associated with reduced allergic sensitisation was rated as VERY LOW using the GRADE system, which means that there is very little confidence in the effect estimate. In the seven available intervention trials, which included advice regarding timing of fish introduction – in all cases as part of a multi-allergen or multifaceted intervention trial, there was no evidence for any such association. In the 17 intervention studies and 20 observational studies identified, there was no evidence for any effect on allergic sensitisation and the introduction of other allergenic foods. Due to heterogeneity in the age at which interventions were introduced and in the outcomes assessed, these 17 studies were not suitable for meta-analysis.

Figure 2: Forest plot of observational studies of introduction of fish before 6-9 months and risk of allergic sensitisation



Food allergy

33. A total of 15 intervention studies and 18 observational studies were identified in which food allergy was reported as an outcome. There was evidence that introduction of egg at 4-6 months of age (from 6 studies, 5 of which had data suitable for meta-analysis) reduces the risk of egg allergy compared with later egg introduction (Figure 3). Using the GRADE system, the quality of this evidence was rated as MODERATE.

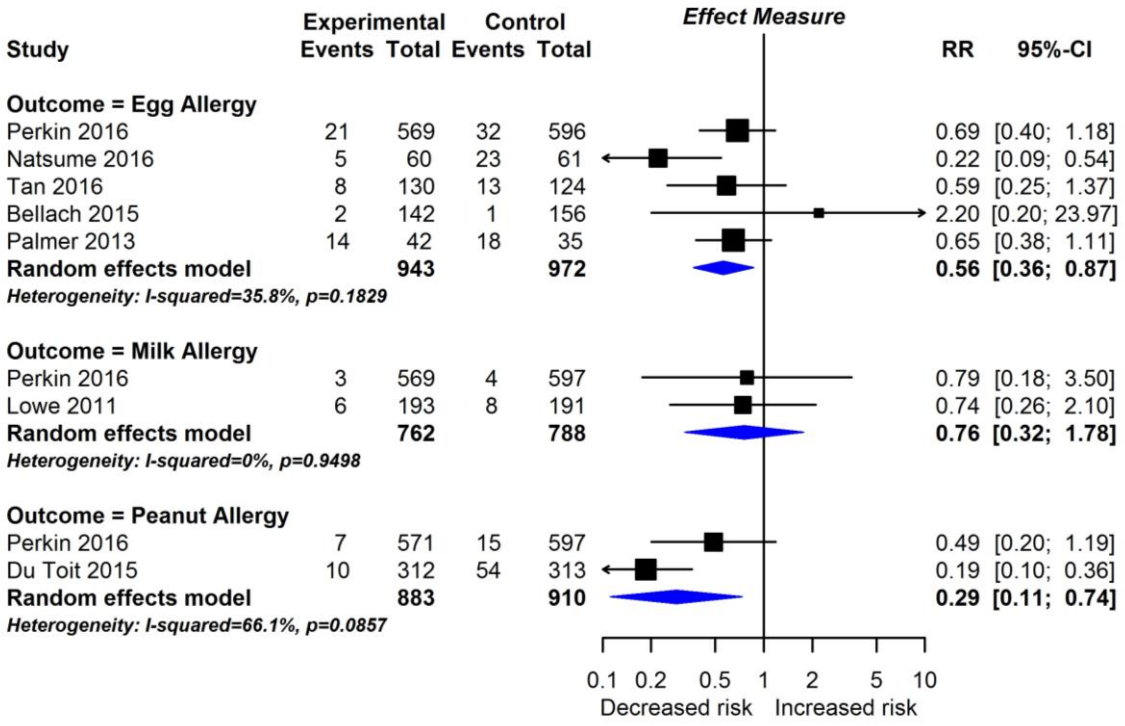
34. There was evidence that introduction of peanut at 4-11 months of age (from 2 studies) reduces the risk of peanut allergy, compared with later peanut introduction (Figure 3). Food allergy outcomes were followed-up in subjects at 6 years of age or younger. The quality of this evidence was rated as MODERATE using the GRADE system.

35. From the available studies, there was no evidence for any relationship between timing of introduction of cows' milk, fish or wheat and risk of food allergy.

36. A post-hoc trial sequential analysis (TSA) is presented at appendix 3. TSA was not possible for peanut introduction and peanut allergy because there were insufficient data. TSA was not possible for egg introduction and egg allergy for a 10% or 20% relative risk reduction, but was possible for a 30% risk reduction. Unpublished data from the recent STEP trial (Starting Time for Egg Protein)[8] were included in the TSA of egg introduction and egg allergy. This analysis showed that, on the basis of the available data, it is not possible to conclude with confidence that early egg introduction reduces egg allergy by at least 30% and further trials would be needed to confirm a treatment effect of this magnitude.

[8] https://www.sahmri.com/our-research/themes/healthy-mothers-babies-children/research/list/step

Figure 3: Forest plot of intervention trials of timing of egg, milk or peanut introduction and risk of egg, milk or peanut allergy.



Type 1 diabetes mellitus

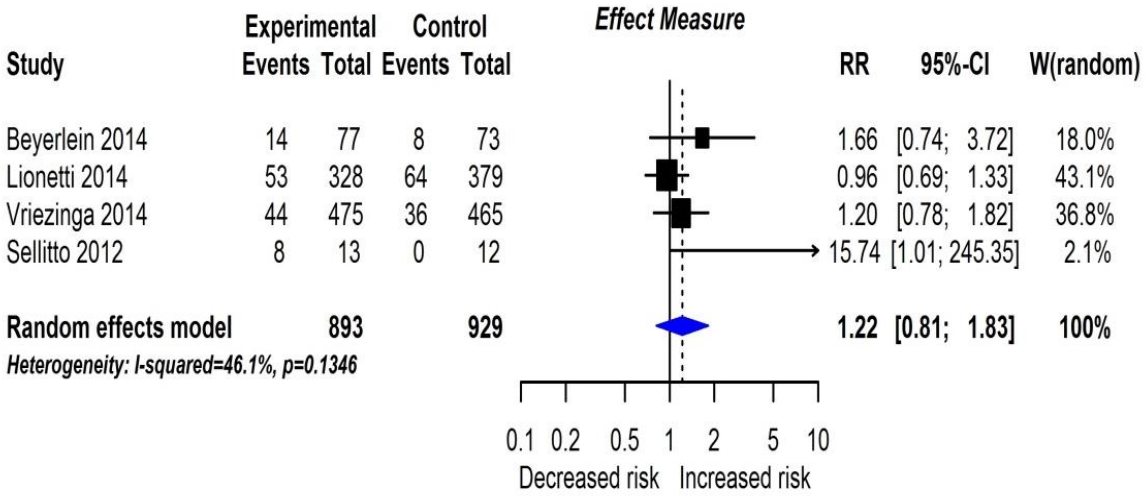
37. From the 2 intervention studies and 35 observational studies available, there was no consistent evidence that timing of allergenic food introduction influences the risk of TIDM.

Other autoimmune diseases

38. From the 4 intervention studies and 14 observational studies available, together with the 2 existing systematic reviews, there was no consistent evidence that introduction of cows' milk in the first 4 days of life, or before 3-4 months age, or introduction of gluten at 4-6 months, influences the risk of autoimmune disease, compared with later introduction. The available studies showed no evidence for any relationship between breastfeeding status at the time of gluten introduction and the risk of autoimmune disease, or between the introduction of cows' milk before 12 months and the risk of juvenile idiopathic arthritis. Overall, the evidence from the available studies indicated that the timing of allergenic food introduction has no influence on the risk of autoimmune disease. However, the evidence was limited to a small number of allergenic foods and autoimmune outcomes. The strongest evidence was found in relation to coeliac disease, where the quality of evidence was rated as HIGH (assessed according to GRADE), from four intervention trials in which there was no evidence of any relationship between timing of gluten introduction to the infant diet and risk of

coeliac disease (Figure 4). There was some evidence from the available studies that gluten introduction at 4-6 months leads to earlier manifestation of coeliac disease in predisposed individuals, without increasing longer term risk of coeliac disease.

Figure 4: Forest plot of intervention studies of introduction of gluten at 4-6 months of age and risk of coeliac disease



COT conclusions

39. Members were impressed with the scope and rigorous methodology used in preparing this systematic review 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.

40. From the available studies, there was no evidence that early introduction of allergenic foods increases risk of allergic or autoimmune disease.

41. The meta-analyses performed indicate that for egg and peanut allergy, early introduction (at 4-6 months for egg and 4-11 months for peanut) of allergenic food reduces subsequent development of an allergy to that food, based on six studies for 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.

42. To date, there is insufficient evidence for conclusions to be drawn on the effect of timing of introduction of common allergenic foods other than peanut and egg in relation to developing an allergy to that food.

43. Evidence from four intervention trials suggested that early gluten (4-6 months) exposure does not lead to increased risk of coeliac disease. The quality of the evidence for this was assessed as HIGH using the GRADE system, meaning that there is considerable confidence that the true effect lies close to that of the estimate of the effect.

44. *Post hoc* TSA analysis of early introduction of egg in reducing risk of egg allergy by 30% suggest that further research relating to these findings may increase the confidence in these conclusions. There were insufficient data to perform trial sequential analysis at lower levels of risk reduction.

45. The review also found an association with intake of fish before 6-12 months of age and reduced allergic rhinitis and allergic sensitisation, with the quality of evidence rated as LOW/VERY LOW respectively, using the GRADE system. LOW quality evidence means that confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. VERY LOW quality evidence means that there is very little confidence in the effect estimate: the true effect is likely to be substantially different from the any estimate of effect.

46. There was no evidence to suggest any association between the timing of introduction of other allergenic foods and the risk of other allergic and autoimmune outcomes that were included within the review.

47. The evidence base covers both the general population and high risk populations, and both breastfed and mixed/formula fed infants. Therefore, the findings can be considered to apply widely across the population.

48. The review also aimed to identify whether any effects vary according to duration of exclusive/predominant or any breastfeeding. Data on the influence of duration of breastfeeding alongside allergenic food introduction on the risk of development of atopic outcomes and autoimmune disease are sparse, and no conclusions can be reached regarding this question.

49. The committee therefore concludes 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. The committee noted that introduction of allergenic food into an infant's diet might elicit allergic symptoms in children who are already sensitised. It was considered that this does not represent an increased risk of food allergic reactions, but rather would cause an earlier presentation of food allergy in infancy as a consequence of earlier exposure. It was also considered that there would be no increase in the severity of such reactions. For coeliac disease, the earlier introduction of gluten was associated with earlier manifestation of the disease, but not with an increase

in prevalence. Possible adverse effects of early allergenic food introduction were not assessed beyond any effects on atopic manifestations or autoimmune disease development

50. In light of these findings the COT will work with SACN to review the previous recommendations as outlined in paragraph 2 alongside the SACN's review of complementary feeding. The outcome of this further work will be published in due course.

51. The review has been published in the peer reviewed literature and has the following citation: Ierodiakonou 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.

52. The full final report for this project can be found on the Food Standards Agency website using the following link: http://www.food.gov.uk/science/research/allergy-research/fs305005b

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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.

Allergen	A substance capable of inducing an allergic immune response
Allergic rhinitis	Inflammation of membranes in the nose caused by an allergic response and resulting in symptoms similar to the common cold.
Allergic sensitisation	Typically associated with the production of specific IgE antibodies directed against harmless environmental antigens such as pollens, mites, milk, egg or peanut. There may also be an increase in the serum level of total IgE immunoglobulin. . Allergic sensitisation is strongly associated with atopic disease.
Allergy	Adverse health effects resulting from stimulation of a specific immune response
AMSTAR	Tool for assessing the methodological quality of systematic reviews
Atopic dermatitis	An allergic skin disorder, characterised by itching, eczematous skin lesions, and, often, a personal or family history of atopic diseases
Atopy/atopic	A genetic predisposition toward mounting IgE antibody responses. Atopy is associated with IgE-mediated allergic disease and, in practice, atopic individuals are commonly defined as those who exhibit sensitisation to two or more allergens
Autoimmune disease	A disease in which the immune system attacks healthy cells or tissues in the body leading to chronic disease.
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
Food allergy	An adverse reaction to a food or food component that is mediated via immunological mechanisms
GRADE	A systematic approach to making judgements about quality of evidence and strength of recommendations
IgE antibody	One of five classes of human immunoglobulin. IgE is involved in allergy and anaphylaxis as well as

	protecting against parasitic infection
Intention to treat analysis	Analysis in which all subjects who were enrolled and randomly allocated to study groups (control or intervention) are included in the analysis and are analysed in the groups to which they were randomized.
LILACS	A comprehensive index of scientific and technical literature of Latin America and the Caribbean
MEDLINE	The US National Library of Medicine's bibliographic database that contains references to journal articles in the life sciences. It holds citations from 1950 to present
Per protocol analysis	A comparison of the study groups which includes only those subjects who completed the protocol originally allocated (control or intervention).
PROSPERO	International prospective register of systematic reviews
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
Sensitisation	Immunological priming to an allergen such that the sensitised subject may exhibit an adverse reaction following subsequent encounter with the same allergen
Skin prick test (SPT)	A test to determine whether an individual has an IgE mediated immune response to a specific inhalant or food allergen.
Type I Diabetes Mellitus	An autoimmune disease where the immune system attacks pancreatic cells which produce insulin
Wheeze	A high-pitched whistling sound during breathing. It occurs when air flows through narrowed breathing tubes. Asthma is commonly defined as recurrent wheeze.

APPENDIX 2 Summary table of key findings with GRADE of evidence assessment.

GRADE of evidence assessment								Summary of findings		Absolute Risk Reduction	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other consider ations**	**Estimate**	**GRADE of evidence**	**Control Risk: Cases per 1000 population**	**Risk Difference: Cases per 1000 population**
Outcome: Allergic Rhinitis **Intervention vs. comparator: Early introduction of fish versus later introduction of fish**											
4 observational studies	4 PC	Not serious 1 study at high risk of bias; all studies with low risk of conflict of interest	Not Serious I^2=59% (P=0.086), study estimates varying from 0.45 to 0.77 but all 4 studies statistically significant, and heterogeneity was reduced when early onset eczema cases were excluded from analysis due to potential reverse causation	Not serious Studies all undertaken in Scandinavia. 3 studies were in representative birth cohorts, 1 in a birth cohort selected for high risk of TIDM	Not serious 95% CI are wide, but not close to 1, and together the 4 studies include over 12,000 participants	Insufficient studies to undertake formal testing of publication bias.		**AR ≤4years** **OR = 0.59** **(0.40 to 0.87)** **AR 5-14 years** **HR = 0.68** **(0.47 to 0.98)**	⊗⊗○○ **Low**	**AR ≤4years** **50 (normal risk)** **100 (high risk)** **AR 5-14years** **100 (normal risk)** **200 (high risk)**	**18 cases less** **(6 to 30)** **38 cases less** **(12 to 57)** **32 cases less** **(2 to 53)** **64 cases less** **(4 to 106)**
Outcome: Allergic Sensitization to any allergen, any food **Intervention vs. comparator: Early introduction of fish versus later introduction of fish**											
5 observational studies	5 PC	Not serious 2 studies ~700 participants high risk of bias; 3 studies (~ 13,000) low risk of bias; no conflict of interest	Not serious Extreme heterogeneity for meta-analysis of inhalant sensitization; consistent findings for other sensitizations	Serious Allergic sensitization is an indirect measure of disease	Not serious 3 studies at low risk of bias were consistent - OR/HR from 0.41 to 0.78, and included over 13,000 participants	Insufficient studies to undertake formal testing of publication bias.		**AS any allergen** **OR = 0.75** **(0.64 to 0.88)** **AS any food** **OR = 0.52** **(0.37 to 0.73)**	⊗○○○ **Very Low**	**AS any allergen** **200 (normal risk)** **400 (high risk)** **AS any food** **100 (normal risk)** **200 (high risk)**	**42 cases less** **(20 to 62)** **67 cases less** **(30 to 101)** **45 cases less** **(25 to 61)** **85 cases less** **(46 to 115)**
Outcome: Egg allergy **Intervention vs. comparator: Early introduction of egg versus later introduction of egg**											
6 intervention studies (5 of which provided data	6 RCT	Not Serious 1 study at high risk of	Not serious I^2=36% (P=0.18). Study estimates vary from 0.22	Serious 3 studies only recruited infants	Not serious 95% CI for RR is wide. Trial	Insufficient studies to undertake formal testing		**RR = 0.56** **(0.36 to 0.87)**	⊗⊗⊗○ **Moderate**	**54** **(normal risk)**	**24 cases less** **(7 to 35)**

GRADE of evidence assessment								Summary of findings		Absolute Risk Reduction	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other consider ations**	**Estimate**	**GRADE of evidence**	**Control Risk: Cases per 1000 population**	**Risk Difference: Cases per 1000 population**
for meta-analysis)		bias, no studies at high risk of conflict of interest	to 0.69 for the studies at low risk of bias	without egg sensitization; 1 study only infants with eczema; 1 study used multiple allergenic foods	sequential analysis suggests that optimum information size has not yet been reached	of publication bias				**100 (high risk)** **500 (very high risk)**	**44 cases less (13 to 64)** **220 cases less (65 to 320)**
Outcome: Nut allergy **Intervention vs. comparator: Early introduction of nut versus later introduction of nut**											
2 intervention studies	2 RCTs	No Neither study had a high risk of bias or conflict of interest	Not Serious I^2=66% (P=0.09), study estimates vary from 0.49 to 0.19 but heterogeneity is likely to be explained by differences in participant adherence to the intervention	Serious 1 study only recruited infants with egg allergy or eczema, and without high-level peanut sensitization; 1 study used multiple allergenic foods	Serious 95% CI for RR is wide	Insufficient studies to undertake formal testing of publication bias	GRADE of evidence increased due to the strong effect size	**RR = 0.29 (0.11 to 0.74)**	⊗⊗⊗○ **Moderate**	**25 (normal risk)** **170(high risk)**	**18 cases less (6 to 22)** **121 cases less (44 to 151)**
Outcome: Type I Diabetes Mellitus **Intervention vs. comparator: Early introduction of cows' milk versus later introduction of cows' milk**											
33 observational studies	7 PC 1 NCC 25 CC	Not Serious 12 studies with high overall risk of bias; all studies with low risk of conflict of interest	Serious High or extreme statistical heterogeneity in several analyses. In some meta-analyses significant associations were seen for retrospective, but not for prospective studies	Not Serious All but one prospective reported islet autoimmunity as a surrogate for TIDM. Retrospective studies used clinical diagnosis	Not Serious Studies included over 40,000 participants. 95% CI for meta-analyses of prospective studies were wide	No Funnel plots and Egger's test do not indicate evidence of publication bias		**Prospective Studies** **CM ≤ 0-2m** **OR = 1.20 (0.53 to 2.71)** **CM ≤ 3-4m** **OR = 0.92 (0.75 to 1.13)** **CM ≤ 5-7m** **OR = 1.88 (1.05 to 3.39)**	⊗○○○ **Very Low**	**CM ≤0-2m** **1 (normal risk)** **10 (high risk)** **CM ≤3-4m** **1 (normal risk)** **10 (high risk)** **CM ≤5-7m** **1 (normal risk)** **10 (high risk)**	**0.2 cases more (0.5 less to 1.7 more)** **2 cases more (4.7 less to 16.6 more)** **0.1 cases less (0.2 less to 0.1 more)** **0.8 cases less (2.5 less to 1.3 more)** **0.9 cases more (0.0 to 2.4)** **8.6 cases more (0.5 to 23.1)**

GRADE of evidence assessment								Summary of findings		Absolute Risk Reduction	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Estimate**	**GRADE of evidence**	**Control Risk: Cases per 1000 population**	**Risk Difference: Cases per 1000 population**
Outcome: Coeliac disease **Intervention vs. comparator: Early introduction of gluten versus later introduction of gluten**											
4 intervention studies	4 RCT	Not serious 1 study with high risk of bias; all studies with low or unclear risk of conflict of interest	Not Serious I^2=46% (P=0.13), due to 1 small study with high risk of bias; other estimates from 0.96 to 1.66	Not Serious Two studies used only serology, but this surrogate is highly correlated with clinical disease	Not Serious significant benefit unlikely – lower bound RR 0.81, or 0.85 with high risk of bias study excluded	Insufficient studies to undertake formal testing of publication bias.	All studies included high risk patients based on family history and/or genotype	**RR = 1.22 (0.81 to 1.83)**	⊗⊗⊗⊗ **High**	**10 (normal risk)** **100 (high risk)**	**2.2 cases more (1.9 less to 8.3 more)** **22 cases more (19 less to 83 more)**

RCT, Randomized Controlled Trial; qRCT, quasi-Randomised Controlled Trial; CCT, Controlled Clinical Trial; PC Prospective Cohort study; NCC, Nested Case-Control Study; CC, Case-Control study; OR, Odds Ratio; RR, Risk Ratio; HR, Hazard Ratio; AR, Allergic Rhinitis; CM, Cows' Milk; AS, Allergic Sensitization

APPENDIX 3 Post-hoc trial sequential analysis of intervention trials for egg introduction and egg allergy.

Vertical red line is the optimal information size, horizontal brown lines are z scores of +1.96, equal to two-sided P=0.05. The cumulative Z-statistic (blue line) does not cross the trial sequential monitoring boundary (curved red line), or reach the optimal information size, indicating no reliable evidence for ≥30% relative risk reduction.

Figure 3A: Trial sequential analysis of intervention trials evaluating the effect of early dietary introduction of egg on risk of egg allergy – heterogeneity adjusted.

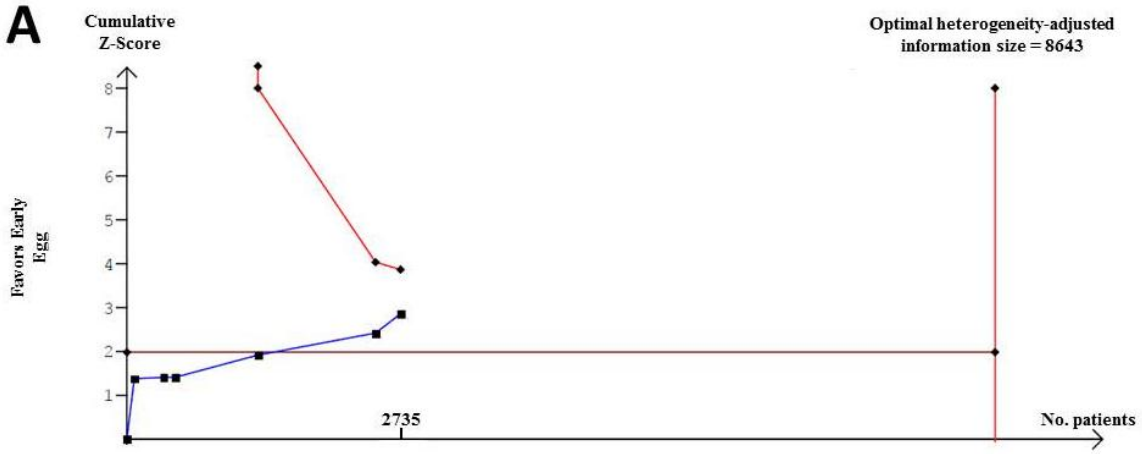

Figure 3B: Trial sequential analysis of intervention trials evaluating the effect of early dietary introduction of egg on risk of egg allergy – non-adjusted.