JOINT STATEMENT
Timing of introduction of gluten into the infant diet

Background

1.   In 2010, the Department of Health and Food Standards Agency asked the Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to assess the evidence on timing of introduction of gluten into the infant diet and subsequent risk of developing coeliac disease or type 1 diabetes mellitus (T1DM). The request was made in response to the publication of a European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) Scientific Opinion on the appropriate age for the introduction of complementary food into infant diets in the EU; this included conclusions that were inconsistent with UK infant feeding advice.

European Food Safety Authority Scientific Opinion

2.   At the request of the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) has produced a Scientific Opinion on the appropriate age for the introduction of complementary food into infant diets in the EU (EFSA, 2009). This request arose because of an inconsistency within EU legislation and between EU legislation and the relevant Codex Standard for labelling of complementary food. The Opinion was adopted and published on the 22 December 2009.

3.   The Opinion discusses the available scientific evidence and draws a number of conclusions, most notably on the timing of introduction of gluten into the infant diet. The conclusions, as stated in the Summary and Overall Conclusions, are:

> *"On the basis of present knowledge, the Panel concludes that the introduction of complementary food into the diet of healthy term infants in the EU between the age of 4 and 6 months is safe and does not pose a risk for adverse health effects (both in the short-term, including infections and retarded or excessive weight gain, and possible long-term effects such as allergy and obesity)"*

> *"Exclusive breast-feeding provides adequate nutrition up to 6 months of age for the majority of infants, while some infants may need complementary foods before 6 months (but not before 4 months) in addition to breast-feeding in order to support optimal growth and development"*

"Based on the available evidence on autoimmune diseases the Panel notes that the early (<4 months) introduction of gluten might increase the risk of coeliac disease and type 1 diabetes mellitus, whilst the introduction of gluten between 4-6 months whilst still breastfeeding might decrease the risk of coeliac disease and type 1 diabetes mellitus"

"Presently available data on the risk of coeliac disease and type 1 diabetes mellitus support the timing of the introduction of gluten containing food (preferably while still breast-feeding) not later than 6 months of age"

EU legislation on the labelling of gluten and the composition of weaning foods and infant and follow-on formula

4.   EFSA's opinion is consistent with current EC labelling legislation on complementary food for infants, which requires manufacturers to label commercially prepared weaning foods with the appropriate age for use, which shall not be less than 4 months. Foods currently marketed in the EU as suitable for babies aged 4-6 months do not generally contain gluten. EU regulations stipulate, however, that for weaning foods meeting the compositional requirements of Regulation 2006/125/EC, the presence or absence of gluten must be stated on the label if the indicated age from which the product may be used is below 6 months.

5.   In addition, as stated in Directive 2006/141/EC on infant and follow-on formulae, infant formulae must be made from ingredients that naturally do not contain gluten.

Current UK Advice

6.   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.

7.   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 (Department of Health, 1994). See Annex 1 for an update on the status of scientific evidence on timing of introduction of solids and risk of sensitisation/allergy to foods.

8.   In the UK, mothers who introduce solids before 6 months of age are advised to avoid giving foods containing gluten until the infant is 6 months of age. This is based on advice regarding prevention of coeliac disease from the Committee on Medical Aspects of Food Policy (COMA) set out in their 1994 report *Weaning and*

the Weaning Diet (Department of Health, 1994). The advice was reconsidered by SACN in 2003 and it reaffirmed COMA's recommendation that foods containing gluten should not be given to infants below the age of 6 months; this advice applies to both formula- and breastfed infants[1].

9.   EFSA's conclusion that *"introduction of complementary food into the diet of healthy term infants in the EU between the age of 4 and 6 months is safe and does not pose a risk for adverse health effects",* is inconsistent with the current UK recommendations to breastfeed exclusively for around the first 6 months of life, and to avoid introduction of foods containing gluten (as well as other common allergenic foods and foods thought to increase the risk of food poisoning) before 6 months of age. It is also inconsistent with WHO advice to breastfeed exclusively for 6 months (WHO, 2001).

10.   SACN and COT were therefore asked by the Department of Health and the Food Standards Agency to review the evidence on the timing of introduction of gluten into the infant diet and subsequent risk of developing coeliac disease and T1DM (please see Annex 2 for detailed background information on coeliac disease and T1DM). SACN and COT were provided with a copy of the EFSA Scientific Opinion on the appropriate age for the introduction of complementary food into infant diets in the EU, alongside copies of the scientific studies EFSA had cited in its assessment of the evidence on timing of introduction of gluten and risk of coeliac disease and T1DM. In addition, a paediatric gastroenterologist attended Committee discussions to provide further expertise on coeliac disease. Minutes of relevant discussions can be found at:

http://www.sacn.gov.uk/meetings/sub_groups/maternal_child_nutrition/08092010.html
http://www.sacn.gov.uk/meetings/sub_groups/maternal_child_nutrition/19012011.html
http://www.sacn.gov.uk/meetings/committee/main_sacn_meetings/14022011.html
http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeet2010/cotmeet4may2010/cotmins4may2010
http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeet2010/cotmeet14dec2010/cotmins14dec2010

11.   The following sections provide a brief background on coeliac disease and T1DM, a description of the characteristics and findings of the studies cited by EFSA, SACN/COT's critique of those studies and finally the joint conclusions reached by SACN and COT.

Coeliac disease

12.   Coeliac disease is an autoimmune disorder precipitated by gluten in the diet of genetically predisposed individuals, with approximately 95% of those affected expressing the HLA-DQ2 haplotype and the remainder expressing HLA-DQ8 (Myleus *et al.,* 2009). Research studies investigating the epidemiology of coeliac disease therefore often identify at risk individuals through HLA genotyping, though individuals in the general population who are at risk of coeliac disease will not necessarily be aware of their genetic predisposition.

---

[1] http://www.sacn.gov.uk/meetings/sub_groups/maternal_child_nutrition/22012003.html

13. Approximately 30-40% of the general population are positive for either one or both of the HLA-DQ2 or HLA-DQ8 haplotypes (Wolters and Wijmenga., 2008), but only around 4% of these genetically susceptible individuals will develop coeliac disease (Silano *et al.*, 2010) despite the widespread consumption of gluten-containing foods. This suggests that additional factors play a role in pathogenesis (Norris *et al.,* 2005). The highly specific enzyme tissue transglutaminase (tTG) has been identified as the major autoantigen involved in the disease process (Dieterich *et al.*, 1997). Annex 2 provides further background on coeliac disease.

Type 1 diabetes mellitus

14. Type 1 diabetes mellitus is an autoimmune disorder resulting from destruction of the insulin-producing islet cells of the pancreas. The prevalence of T1DM in the general UK population (aged 10-79 years) increased from 0.33% in 1996 to 0.41% in 2005 (Gonzalez *et al.*, 2009). There is a predisposition to the disease associated with the HLA-DR3 and HLA-DR4 alleles, but also additional susceptibility associated with HLA-DQ alleles (Atkinson and Eisenbarth, 2001). HLA-DQ alleles also confer increased risk of coeliac disease. Thus, individuals with T1DM and their first-degree relatives have increased risk of coeliac disease (Collin *et al.*, 2002). Annex 2 provides further background on T1DM.

Summary of key studies reviewed by EFSA

Gluten and risk of coeliac disease

15. There is evidence from a systematic review of six retrospective case-control studies by Akobeng *et al.,* (2006) of an association between longer duration of breastfeeding and a lower risk of developing coeliac disease (it was not clear whether the studies had measured partial or exclusive breastfeeding). Breastfeeding at the time gluten was introduced into the diet was also associated with reduced risk. A meta-analysis of four of the case-control studies included in this systematic review found a pooled odds ratio (OR) of 0.48 (95% CI 0.40-0.59) for infants who were breastfed when gluten was introduced as compared with those who were not breastfed at that time. The ages and levels of exposure to gluten in these studies were not reported in the paper. The meta-analysis included a study by Ivarsson *et al.* (2002) which was cited separately by EFSA.

16. A small number of Swedish studies not included in Akobeng's systematic review, have also investigated the relationship between infant feeding patterns and coeliac disease. Ivarsson *et al.,* (2000) observed an increase in the incidence of coeliac disease in Swedish children between 1985 and 1987, following a national recommendation in 1982 to postpone the introduction of gluten into the diet from 4 months to 6 months of age. The authors also reported that daily consumption of wheat, rye and barley from a type of gruel given in a bottle to infants during weaning[2]

---

[2] Note that the gruel described here is referred to in the study by Ivarsson *et al.*, (2000) as "follow-on formula". However, after investigating this issue it is clear that this is not follow-on formula as defined in EU Regulation 2006/141/EC, but rather is a type of gruel comprising a mixture of cows' milk proteins and cereals (including gluten), given to infants in a bottle during the early phases of weaning

doubled between 1981 and 1983. From 1985 to 1987, the annual incidence of coeliac disease increased four-fold in children below 2 years of age, followed by a sharp decline in 1995 to previous levels.

17.   Swedish infant feeding recommendations changed again in 1996 to include guidance to introduce gluten into infants' diets slowly whilst still breastfeeding, and for introduction to start from 4 months of age instead of from 6 months of age (as previously advised from 1982). Carlsson *et al.,* (2006) compared the prevalence of coeliac disease in children aged 2.5 years who had been born in 1996/1997 (after this revised recommendation was introduced) to the prevalence among children of the same age born in 1992/1993. The prevalence of symptomatic coeliac disease declined post-1996 (0.3% among infants born in 1996/7 versus 0.7% among infants born in 1992/3, p=0.0134). This study did not provide any information on infant feeding patterns or knowledge/awareness of infant feeding recommendations. According to Ivarsson *et al.,* (2000) daily consumption of wheat, rye and barley from the type of gruel[2] given to infants during weaning also declined by a third after 1995.

18.   Norris *et al.,* (2005) conducted a prospective observational study [the Diabetes Autoimmunity Study In the Young (DAISY) study] in the USA from 1994-2004. They recruited 1560 children with increased risk of coeliac disease and type 1 diabetes [either positive for HLA-DR3 alleles (associated with HLA-DQ2 haplotype) or HLA-DR4 alleles (associated with HLA-DQ8 haplotype) or having a first-degree relative with T1DM]. The mean age at final follow-up was 4.8 years and the main outcome measure for coeliac disease was positive tissue transglutaminase (tTG) autoantibody on two consecutive follow-up visits or positive tTG and a positive small bowel biopsy. Infants' dietary histories were taken from parents at 3, 6, 9, 12 and 15 months after birth. The authors investigated the relationship between timing of introduction of gluten into the infant diet and risk of coeliac disease. After adjustment for HLA-DR3 status, children exposed to wheat, barley or rye in the first 3 months of life had a 5-fold increased risk [hazard ratio (HR) 5.17, 95% CI 1.44-18.57] of coeliac disease autoimmunity (CDA) compared to the reference group first exposed at 4-6 months of age. This association, although statistically significant, was based on only three cases with exposure before age 3 months. Children not exposed to wheat, barley or rye until after 6 months of age were also at increased risk of CDA compared to the 4-6 months reference group but the association did not quite attain statistical significance (HR 1.87, 95% CI 0.97-3.60). These findings were independent of timing of first exposure to rice and oats. When only cases defined by a positive biopsy were included in the analyses (n=25), the associations with introduction of gluten at 1-3 months and >6 months strengthened and were both statistically significant (HRs of 22.97, 95% CI 4.55-115.93 and 3.98, 95% CI 1.18-13.46 respectively).

19.   Ziegler *et al.,* (2003) explored determinants of coeliac disease in the German BABYDIAB cohort study, using tTG autoantibodies as a marker for risk of the disease. In this study, 1610 newborn children of parents with T1DM were followed up to age 11 years. No statistically significant differences in later prevalence of tTG autoantibodies were observed according to whether gluten was first introduced into

---

(personal communication Prof. Hernell, Department of Clinical Sciences at Umeå University, Sweden).

the diet at ≤3 months or >6 months of age (adjusted HRs were 2.9, 95% CI 0.4-24.1 and 0.7, 95% CI 0.3-1.8 respectively) compared to gluten introduction at 3.1-6 months of age. Furthermore, no trends in risk of tTG positivity were observed for duration of total or exclusive breastfeeding. Increases in risk were not statistically significant when infants who received gluten-containing (adjusted HR 3.8, 95% CI 0.5-30.6) or non-gluten containing food supplements (adjusted HR 2.7, 95% CI 0.6-12.7) before age 3 months were compared to infants who received only breast milk before age 3 months.

Gluten and risk of type 1 diabetes

20.   Although EFSA cited seven studies in its discussion of the evidence on introduction of gluten and risk of T1DM, only three studies are summarised here. The other four investigated the relationship between duration of breastfeeding and T1DM, and did not include analyses on the timing of introduction of gluten.

21.   Norris *et al.,* (2003) used data from the DAISY study, in which subjects were at increased risk of T1DM, to investigate whether the timing of introduction of gluten-containing cereals is related to T1DM risk. Islet autoimmunity[3] cases were defined by the presence of T1DM autoantibodies at consecutive follow-up visits, or a diagnosis of frank diabetes at the most recent visit. Infants' dietary histories were taken from parents at 3, 6, 9, 12 and 15 months after birth. The researchers observed that islet autoimmunity was found in a significantly higher proportion of children if cereals (rice, oats, wheat, barley and rye) were introduced in the first 3 months or after 6 months compared to a reference group who first received cereals at 4-6 months of age (HR 4.32, 95% CI 2.0-9.35 and HR 5.36, 95% CI 2.08-13.8 respectively). These results were adjusted for HLA genotype, family history of T1DM, ethnicity and maternal age. The authors also applied another statistical model that separated out exposure to gluten-containing cereals and exposure to rice. Under that model, the hazard ratios for risk of islet autoimmunity in infants who received gluten in the first 3 months and infants in whom gluten-containing cereals were introduced after 6 months were 2.65 (95% CI 0.76-9.33) and 1.70 (95% CI 0.79-3.66) respectively, relative to infants in whom gluten-containing cereals (not rice) were introduced at 4-6 months of age. These differences were not statistically significant. When cereals were introduced while the infant was still being breastfed the risk of islet autoimmunity was statistically significantly reduced (HR 0.50, 95% CI 0.25-0.99), compared to infants who were not being breastfed when cereals were introduced into their diets. Age of introduction of gluten when breastfed was not reported.

22.   The relationship between age of introduction of gluten and T1DM risk has also been investigated in the population-based All Babies in Southeast Sweden cohort (Wahlberg *et al.,* 2006). Babies born between October 1997 and October 1999 were followed up from birth to age 2.5 years. Tyrosine phosphatase-related antigen-2 autoantibodies (IA-2A) and glutamic acid decarboxylase autoantibodies (GADA) were used as indicators of T1DM[4]. The late introduction of porridge containing

---

[3] Defined as possession of autoantibodies to the insulin producing cells (islet cells) of the pancreas.
[4] Autoantibodies to the islet cells can be present for many years before the diagnosis of T1DM (Gorsuch *et al.*, 1981), and have been used as markers for T1DM in some studies. See annex 2 for more information about type 1 diabetes.

gluten[5] (over 6 months versus any other age) was related to the emergence of GADA (OR 1.6, 95% CI 1.2-2.3) and at least one autoantibody (GADA and/or IA-2A) (OR 1.4, 95% CI 1.1-1.8), but not both GADA and IA-2A, or IA-2A alone. Introduction of porridge before 3 months of age was not related to emergence of these autoantibodies at age 2.5 years, but only three infants were exposed to porridge before 3 months of age (OR and CIs not reported). The consumption of other gluten-containing foods (e.g. pasta) was not associated with GADA and/or IA-2A positivity at age 2.5 years. When cases were defined as infants who remained positive for GADA and/or 1A-2A at both 1 and 2.5 years of age (n=37), introduction of porridge containing gluten after 6 months was not significantly associated with beta-cell autoimmunity (OR 1.3, 95% CI 0.4-3.6). In the same cohort, short duration of breastfeeding was reported as a risk factor for beta-cell autoimmunity.

23.   The German BABYDIAB cohort study followed newborn children of parents with T1DM to age 11 years. From this study, Ziegler *et al.,* (2003) reported on early infant feeding and risk of T1DM, using the presence of insulin autoantibodies (IA), GADA and tyrosine phosphatase-related antigen-2 autoantibodies (IA-2A) as outcome measures at 5 years of age. The adjusted hazard ratio for risk of developing islet autoantibody positivity by 5 years of age with introduction of gluten-containing food supplements before 3 months of age compared to no food supplementation before 3 months was 4.0 (95% CI 1.4-11.5). The adjusted hazard ratio for positive islet autoantibodies was 5.2 (95% CI 1.7-15.5) for dietary introduction of gluten at or below 3 months of age as compared with introduction between 3.1 and 6 months. However, relative to the same comparison group, there was no statistically significant elevation of risk with introduction after 6 months of age (HR 1.2, 95% CI 0.7-2.0). No significant differences in islet autoantibody risk were observed with respect to duration of total or exclusive breastfeeding.

SACN/COT's critique of the evidence

Amount and quality of evidence

24.   Few studies were identified that relate the timing of introduction of gluten into the infant diet to subsequent risk of coeliac disease or T1DM. All were observational in design, and those available neither precisely nor accurately timed introduction of gluten into the infant diet[6] creating a lack of clarity about exposure around the 3 and 6 month of age thresholds applied in these studies. SACN and COT considered that the lack of published intervention studies on gluten introduction and subsequent risk of coeliac disease and T1DM is a major limitation of the evidence base.

Critique of the evidence on coeliac disease

---

[5] The Wahlberg paper refers to 'porridge containing gluten' but the amount of gluten in the porridge and type of cereal used to make the porridge are not stated.
[6] Ideally, studies examining the timing of introduction of gluten into the infant diet should have used a resolution of timing in weeks in order to prevent confusion. See paragraph 33 for a description of the limitations associated with measuring timing of introduction of gluten in the study by Norris *et al.,* (2005).

25.   The systematic review of six observational studies by Akobeng *et al.,* (2006), was considered to be of good quality. It reported an association between longer duration of breastfeeding and a reduced risk of developing coeliac disease, and that infants who were breastfed at the time gluten was introduced were at lower risk of coeliac disease.

26.   A strength of Akobeng's systematic review was that it included only studies based on histologically confirmed coeliac disease cases. However, it was not clear from the primary study reports whether investigators had assessed partial or exclusive breastfeeding, and there was heterogeneity in the methods by which duration of breastfeeding had been ascertained. In addition, the exact timing and amount of gluten consumed was not stated in the original study reports, and this precluded any conclusions about the effect of timing of introduction of gluten, or the level of exposure, on risk of coeliac disease. In addition, there were too few data to examine the effect of ever *versus* never breastfeeding on risk of developing coeliac disease. The studies included were all of case-control design, and may have been subject to differential recall bias and participation bias.

27.   Members noted that the reduced risk of coeliac disease associated with breastfeeding at the time when dietary gluten was introduced (Akobeng *et al.,* 2006) might have been a product of unidentified confounders (for example, factors associated with longer duration of breastfeeding). In the UK, the quinquennial infant feeding surveys have consistently shown that solids are introduced earlier to babies not being breastfed.

28.   Several possible mechanisms might plausibly explain Akobeng *et al.*'s observation that risk of coeliac disease was higher in children who were not breastfed at the time when dietary gluten was introduced:
   a) Breastfeeding reduces the risk of gastrointestinal infection and may in consequence decrease the permeability of the gut to gluten.
   b) Initial exposures to gluten may have been smaller in infants who are breastfed at the time the gluten is introduced.
   c) Not breastfeeding alters immunological processes in a way that predisposes to autoimmunity.

However, currently there is no direct experimental evidence to implicate these mechanisms in the pathogenesis of coeliac disease and they can only be regarded as speculative.

29.   The authors of two studies of time trends in coeliac disease among Swedish children (Carlsson *et al,.* 2006, and Ivarsson *et al.*, 2000) found significant changes in the incidence of coeliac disease from 1985 and suggested that these were temporally related to changes in national recommendations about the timing of introduction of gluten into the infant diet. They reported a sharp rise in incidence following recommendations to postpone introduction of gluten from 4 to 6 months of age, and then a sharp decline in incidence after recommendations reverted to advise introduction of gluten from 4 months of age alongside breastfeeding.

30.   At first sight, these observations appear to support the hypothesis that delaying the introduction of gluten into the infant diet increases the risk of developing

coeliac disease. However, SACN and COT observed that the sharp decline in coeliac disease incidence appeared to precede the second change in feeding recommendations, suggesting that some other factor was responsible. The quantity and form of gluten consumed over the periods studied was not measured directly and so there is some uncertainty about the extent to which gluten was given during the process of introducing solids in Sweden[7]. In addition, the reported reduction in risk of coeliac disease incidence appeared to be associated with an increase in duration of breastfeeding (more mothers exclusively or partially breastfeeding at 6 months) which could have had a confounding effect. Neither of the reports provides information derived from direct observation of the timing of infants' first exposure to gluten; instead, both base their conclusions merely on changes in recommendations.

31.   SACN and COT considered that the most informative studies on timing of gluten introduction and risk of coeliac disease were those by Norris *et al.,* (2005) and Ziegler *et al.,* (2003). Both focussed on high-risk populations identified through HLA genotyping or having a first-degree relative with T1DM (Norris *et al.*, 2005), or through having a parent with T1DM (Ziegler *et al.,* 2003), respectively. The quantitative estimates of risk associated with exposures would not apply to the general population, but as an indication of the existence and direction of association with infant feeding practices, the studies are valid.

32.   The study by Norris *et al.,* (2005) (DAISY study) provided the most detailed information on timing of introduction of gluten into the diet and risk of coeliac disease. Norris *et al.,* (2005) reported an association between introduction of gluten at >6 months of age and risk of coeliac disease defined by positive biopsy, which was statistically significant (n=25).

33.   The dietary assessment method and the reporting of dietary assessment in the Norris *et al.,* (2005) study have some limitations. There is some uncertainty about the precise time at which gluten was introduced since the authors provided data only on the number of infants newly exposed to gluten within each 3-month window. Also it was suggested that subject interviews used to ascertain dietary information may not all have occurred exactly at the 3 and 6 month time points used to distinguish exposure groups, leading to some insecurity around the classification of exposures, and particularly around the lower bound for the '≥ 7 months of age' threshold. The first author was therefore contacted to seek clarification. She confirmed that the phrase "1-3 months of age" used in the Norris *et al.,* (2005) paper, refers to infants during the period from birth up to 3 completed months (or 13 completed weeks) of age. Similarly, the phrase '≥ 7 months of age' was used to mean '> 6 completed months of age' (or >26 completed weeks).

34.   Furthermore, it was noted that the number of infants exposed to gluten in the first 3 months of life was very small (n=43) and only 3% of the total cohort. In comparison, the number of infants first exposed to gluten at >6 months was 931, which was 60% of the cohort.

---

[7] This is because the "follow-on formula" referred to in the Ivarsson et al., (2000) study is not as defined in EU Regulation 2006/141/EC, but rather is a type of gruel comprising a mixture of cows' milk proteins and cereals (including gluten), given to infants in a bottle during the early phases of weaning (personal communication Prof. Hernell, Department of Clinical Sciences at Umeå University, Sweden).

35.   SACN and COT considered the study reported by Ziegler *et al.,* (2003), which was based on a cohort established primarily to investigate T1DM, to be weaker overall than that carried out by Norris *et al.,* (2005). This was due largely to more robust measures of coeliac disease used in the latter study (based on both tTG autoantibodies and biopsy-confirmation). However, some limitations of the Norris *et al.,* (2005) study (particularly the small number of cases with gluten exposure below 3 months) and the inconsistencies between the findings of the two investigations relating to first exposure to gluten at > 6 months limit the conclusions that can be drawn.

Critique of evidence on type 1 diabetes mellitus

36.   Norris *et al.,* (2003) used T1DM autoantibodies as an outcome measure in the DAISY study to investigate whether infant age at dietary introduction of cereals (foods containing rice, oats, wheat, barley and rye) was related to subsequent risk of T1DM. SACN and COT noted that reported associations were statistically significant only when exposure to all cereals was considered, and not statistically significant for exposure specifically to gluten-containing cereals. A limitation of the study was its lack of adjustment for mode of feeding, i.e. breast or formula feeding, at the time when gluten was introduced.

37.   SACN and COT noted that the study by Ziegler *et al.,* (2003) found no statistically significant association between risk of T1DM and introduction of gluten after 6 months of age.

38.   Again, both of these studies were in high-risk populations, and the outcome measures were principally markers of T1DM rather than firm demonstration of the disease. It was also noted that the number of cases was larger in the study by Ziegler *et al.,* (2003) compared to the study by Norris *et al.*, (2003).

39.   SACN and COT considered the study by Wahlberg *et al.,* (2006) to show mixed findings depending on which autoantibodies were used as outcome measures. All outcomes were based on markers of T1DM rather than clinical symptoms. Furthermore, the exposures studied ('porridge containing gluten' and 'other gluten-containing foods') were ill-defined.

40.   Overall, SACN and COT judged the evidence relating age at introduction of gluten to risk of T1DM to be weaker than that for coeliac disease, and inconsistent. It was therefore not possible to draw useful conclusions in relation to risk of T1DM.

SACN and COT joint conclusions

41.   SACN and COT agreed the following conclusions on the evidence-base concerning timing of introduction of gluten into the infant diet and risk of coeliac disease and T1DM:

I.   The studies cited in the EFSA Opinion provide few data on the later risk of coeliac disease or type 1 diabetes mellitus in relation to the timing of introduction of gluten into the infant diet. The only evidence currently available is from observational studies. This means that there is uncertainty in the conclusions that can be drawn, and the balance of evidence might change in the future as the results of randomised controlled trials become available.

II.   Timing of introduction of gluten into the infant diet and risk of coeliac disease.

•   EFSA identified no data directly relating age of introduction of gluten to an increase in the risk of coeliac disease in the general population[8]. However, studies of children with a genetic predisposition to coeliac disease or a family history of T1DM are available.

•   The currently available evidence provides an indication that dietary introduction of gluten-containing foods in the period up to and including the first 3 completed months of age is associated with an increased risk of coeliac disease. This is largely based on findings from a single observational study (Norris *et al.,* 2005).

•   Relevant evidence on delayed introduction of gluten into the infant diet beyond 6 completed months of age is limited to that provided by two cohort studies (Norris *et al.,* 2005 and Ziegler *et al.,* 2003), with inconsistent findings and limitations in study design. There is therefore insufficient evidence to support a conclusion that the introduction of gluten into the infant diet after 6 completed months of age is associated with an increased risk of coeliac disease.

•   A systematic review (Akobeng *et al.,* 2006) reported an association between longer duration of breastfeeding and reduced risk of developing coeliac disease. This systematic review included a meta-analysis of four case-control studies, which indicated that introduction of gluten into the infant diet whilst not breastfeeding is associated with an increased risk of subsequent coeliac disease. However, there is an absence of evidence to determine whether this relationship varies according to the age at which gluten is introduced.

III.   Timing of introduction of gluten into the infant diet and risk of T1DM.

•   Currently available evidence on the timing of introduction of gluten into the infant diet and risk of T1DM is weak and does not allow specific conclusions to be drawn.

---

[8] Since publication of the EFSA Scientific Opinion, a population-based Swedish cohort study has been published which measured timing of introduction of gluten precisely and breastfeeding (exclusive and partial) duration. The study did not identify any statistically significant association between timing of introduction of gluten into infants' diets or duration of breastfeeding and risk of biopsy-confirmed coeliac disease after age 1 year (see Annex 3 for further details of this study). The results of this study do not alter SACN/COT's conclusions.

42.	**Overall currently available evidence on the timing of introduction of gluten into the infant diet and subsequent risk of coeliac disease and T1DM 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 T1DM.**

43.	These conclusions will inform a review to be conducted by SACN on complementary and young child feeding, which will include a critical appraisal of existing recommendations[9] regarding the appropriate timing for introduction of solids. This review is on SACN's work programme and started in early 2011.

COT Statement 2011/01
March 2011

---

[9] See NHS Choices www.nhs.uk/startingsolids

References

Akobeng AK, Ramanan AV, Buchan I, *et al.,* 2006. Effect of breastfeeding on the risk of coeliac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child 91, 39-43.

Atkinson MA and Eisenbarth GS, 2001. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 358, 221-229.

Bingley P, Williams A, Norcross A, *et al*., 2004. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study . BMJ 328, 322-3.

Carlsson A, Agardh D, Borulf S, *et al*., 2006. Prevalence of celiac disease: Before and after a national change in feeding recommendations. Scand J Gastroenterol 41, 553-558.

Collin P, Kaukinen K, Valimaki M, *et al.,* 2002. Endocrinological disorders and celiac disease. Endocr Rev 23, 464-483.

Department of Health, 1994. Weaning and the Weaning Diet. 45. London, The Stationery Office. Report on Health and Social Subjects.

Dieterich W, Ehnis T, Bauer M *et al.* 1997. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 3, 797-801.

European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009. Scientific Opinion on the appropriate age for introduction of complementary feeding of infants. EFSA Journal 7(12), 1423 (19pp).

Ferenci DA, 1998. Celiac disease. In: Altschuler SM, Liacouras CA, eds. Clinical pediatric gastroenterology (143-50). Churchill Livingstone.

Goddard A, James M, McIntyre A, *et al*., 2005. Guidelines for the Management of Iron Deficiency Anaemia. British Society of Gastroenterology.

Gonzalez EL, Johansson S, Wallander M-A, *et al*., 2009. Trends in prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 63, 332-336.

Gorsuch AN, Spencer KM, Lister J, *et al*., 1981. Evidence for a long prediabetic period in type 1 (insulin-dependent) diabetes mellitus. Lancet 2(8260-61), 1363-1365.

Hoffenberg E, Bao F, Eisenbarth G, *et al.,* 2000. Transglutaminase antibodies in children with a genetic risk for celiac disease. J Pediatr 137, 356-360.

Ivarsson A, Persson LA, Nystrom L *et al*., 2000. Epidemic of celiac disease in Swedish children. Acta Paediatr 89, 165-171.

Ivarsson A, Hernell O, Stenlund H *et al.*, 2002. Breast-feeding protects against celiac disease. Am J Clin Nutr 75, 914-921

Knip M, Korhonen S, Kulmala P *et al.,* 2010. Prediction of Type 1 diabetes in the general population. Diabetes Care 33, 1206-1212.

Myleus A, Ivarsson A, Webb C *et al.,* 2009. Celiac disease revealed in 3% of Swedish 12 year old boys born during an epidemic. J Pediatric Gastroenterol Nutr 49, 170-6.

Norris *et al.,* Barriga K, Hoffenberg EJ, *et al.,* 2005. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. J.A.M.A. 293, 2343-2351.

Norris JM, Barriga K, Klingensmith G, *et al.,* 2003. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. JAMA 290, 1713- 1720.

Orban T, Sosenko JM, Cuthbertson D *et al.,* 2009. Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial- type 1. Diabetes Care 32(12), 2269-2274.

Schuppan D, Junker Y and Barisani D, 2009. Celiac disease: from pathogenesis to novel therapies. Gastroenterology 137, 1912-1933.

Silano M, Agostoni C, Guandalini S *et al.*, 2010. Effect of the timing of gluten introduction on the development of celiac disease. World J Gastroenterol 16(16), 1939-1942.

Siljander HTA, Simell A, Hekkala A, *et al.,* 2009. Predictive characteristics of diabetes-associated autoantibodies among children with HLA-conferred disease susceptibility in the general population. Diabetes 58 (12), 2835-42.

Strobel S, Mowat, A, 1998. Immune responses to dietary antigens: oral tolerance. Immunol Today 19, 173-181.

Thomas P, Forbes A, Green J, *et al.,* 2003. Guidelines for the investigation of chronic diarrhoea, 2nd edition. Gut 52 (Suppl 5), v1-v15

Thompson R, Miles L, Lunn J *et al.,* 2008. Systematic review of literature on early life patterns of exposure to and avoidance of food allergens and later development of sensitisation and clinical food allergy. Available at: http://www.foodbase.org.uk/results.php?f_report_id=439

Wahlberg J, Vaarala O, Ludvigsson J; ABIS-study group, 2006. Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 2 1/2 year-old Swedish children. Br J Nutr 95(3), 603-8.

Welander A, Tjernberg AR, Montgomery SM *et al.,* 2010. Infectious disease and risk of later celiac disease in childhood. Pediatrics 125, e530-e536.

West J, Logan R, Hill P, *et al.,* 2003. Seroprevalence, correlates and characteristics of undetected coeliac disease in England. Gut 52, 960-965.

Wolters VM, Wijmenga C, 2008. Genetic background of celiac disease and its clinical implications. Am J Gastroenterol 103, 190-195.

Ziegler A-G, Schmidt S, Huber D, *et al.,* 2003. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. JAMA 290, 1721-1728.

Annex 1: Timing of introduction of solid foods and risk of sensitisation/allergy to foods

The issue of timing of introduction of solid foods (including allergenic foods) into the infant diet, from the point of view of minimising the risk of development of allergies, is an area of significant scientific uncertainty at the current time due to a lack of data. The EFSA Opinion states in the detailed discussion of allergy evidence at the end of section 2.4.2 that "*The Panel considers that the available data do not permit a conclusion on the appropriate age for introduction of complementary feeding with respect to allergy prevention or reducing the risk of allergy*".

A recent review by the Committee on Toxicity (COT) of their previous recommendations on peanut avoidance and peanut allergy was informed by a systematic review of studies investigating the effects of exposure to/avoidance of allergenic foods in early life and later development of allergy. This systematic review reported no consistent evidence to show that duration of breastfeeding (follow-up to 2-11 years of age) or timing of introduction of solids (general or specific) (follow-up to 2-4 years of age) was associated with development of food sensitisation or food allergy (Thompson *et al.*, 2008).

A number of research studies (some funded by the Food Standards Agency) are currently underway to investigate the importance of route and timing of initial exposure to food allergens and the risk of later development of tolerance or food allergies. These are not due to report for several years.

Annex 2: Background information on coeliac disease and type 1 diabetes mellitus

Coeliac disease

Coeliac disease (CD) is defined as a permanent intolerance to gluten (a protein found in cereals such as wheat, rye and barley) associated with mucosal disease of the proximal bowel (Ferenci, 1998). The condition is triggered by the presence of gluten proteins but also requires the presence of HLA-DQ2 or HLA-DQ8 alleles and the generation of circulating autoantibodies to the enzyme tissue transglutaminase (Schuppan *et al.*, 2009). It is therefore considered an autoimmune disorder in which the presence of gluten in the diet is necessary for the development of clinical symptoms. Coeliac disease is the most prevalent small bowel disease in Western populations (Thomas *et al.*, 2003), affecting approximately one percent of the UK population (Bingley *et al.*, 2004; West *et al.*, 2003). In the UK, it is the most common cause of malabsorption of nutrients (Goddard *et al.*, 2005).

Coeliac disease occurs only in genetically predisposed individuals, with approximately 95% of those affected expressing the HLA-DQ2 haplotype and the remainder expressing HLA-DQ8 (Myleus *et al.*, 2009). The presence of one or other of these alleles is necessary for the development of coeliac disease. Approximately 30-40% of the general population are positive for either one or both of the HLA-DQ2 or HLA-DQ8 haplotypes (Wolters and Wijmenga, 2008), but only around 4% of these genetically susceptible individuals will develop the disorder (Silano *et al.*, 2010; Schuppan *et al.*, 2009). The fact that this applies despite the widespread consumption of gluten-containing foods suggests that additional factors play a role in determining who gets the disease (Norris *et al.*, 2005).

It is difficult to investigate risk of coeliac disease prospectively as it is a relatively rare condition; however, HLA genotype can be used to identify individuals with an increased risk of developing the disorder. Research studies investigating the epidemiology of coeliac disease and how it develops have often used autoantibodies as a predictive marker for the disease. The highly specific enzyme tissue transglutaminase (tTG) has been identified as the major autoantigen involved in the disease process (Dieterich *et al.*, 1997). Alternatively, or in addition, tissue biopsies can be used, which are more definitive but also more invasive. For asymptomatic children with a genetic predisposition to coeliac disease, tTG antibodies have been shown to a have positive predictive value of 70% to 83% for biopsy evidence of coeliac disease (Hoffenberg *et al.*, 2000).

The Committees were advised that clinical guidance on the diagnosis of coeliac disease is being developed by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). It is due to be published in the near future, and is expected to recommend that the presence of autoantibodies alone is not sufficient for a diagnosis of coeliac disease. A single gut biopsy demonstrating histological changes characteristic of coeliac disease is required, followed by a positive response to dietary exclusion of gluten. Overall, there is some uncertainty around the predictive value of autoantibodies for coeliac disease, especially in the general population (as opposed to high-risk sub- populations).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder resulting from destruction of the insulin-producing islet cells of the pancreas. The prevalence of T1DM in the general UK population (aged 10-79 years) increased from 0.33% in 1996 to 0.41% in 2005 (Gonzalez *et al.*, 2009). It is thought that both genetic and environmental factors play a role in the aetiology of T1DM (Meloni *et al.*, 1997). There is a well-known predisposition to the disease associated with the HLA-DR3 and HLA-DR4 alleles, but also additional susceptibility associated with HLA-DQ alleles (Atkinson and Eisenbarth, 2001). HLA-DQ alleles also confer increased risk of coeliac disease. Thus, individuals with T1DM and their first-degree relatives have increased risk of coeliac disease (Collin *et al.*, 2002).

Autoantibodies to the islet cells, or islet autoimmunity, can be present for several years before the diagnosis of T1DM (Gorsuch *et al.*, 1981), and have been used as markers for T1DM in some studies. Several autoantibodies have been used in this way, including insulin autoantibodies (IAs), autoantibodies to the intracellular portion of the tyrosine phosphatase-related islet antigen-2 molecule (IA-2As) and autoantibodies to glutamic acid decarboxylase (GADA). Predictive values of the autoantibodies for clinical T1DM up to 27 years later lie in the range of 40% to 90%, depending on the number and combination of autoantibodies measured, and the population studied (general population or a population at high risk of T1DM) (Knip *et al.,* 2010; Siljander *et al.*, 2009; Orban *et al.*, 2009). Knip *et al.,* (2010) also reported that a third of subjects initially positive for GADA tested negative for GADA six years later, suggesting that presence of these antibodies can be transient. Testing positive for multiple autoantibodies appears to be more predictive than positivity for just one (Siljander *et al.,* 2009).

The role of environmental factors in development of coeliac disease and T1DM

Environmental exposures, such as the feeding patterns of infants, might influence the development of both coeliac disease and T1DM. It is known that exposure to foods is a normal route for the acquisition of immunological tolerance to foods (Strobel *et al.,* 1998). It is hypothesised that the pattern of that exposure (e.g. dose, timing, frequency, type of food) might influence the immunologic process, resulting in the development of oral immunotolerance or immunointolerance to a particular component in food (Strobel *et al.,* 1998; Ivarsson *et al.,* 2002). Moreover, the response of the immune system to an ingested antigen might be modified by other factors, such as breastfeeding (Ivarsson *et al.,* 2002), immaturity of the host immune system, microflora of the intestinal lumen and factors associated with antigen uptake (Strobel *et al.*, 1998), as well as genetic predisposition.

Annex 3: Characteristics and findings of the Welander *et al.,* (2010) study

The study by Welander *et al.* (2010) is a population-based study from Sweden in which data on diet (including timing of introduction of gluten, breastfeeding duration) and episodes of infectious disease in the first year of life were collected prospectively. Breastfeeding practices and timing of introduction of gluten were measured by diaries and data were available for 9849 children at age 1 year. Biopsy-confirmed coeliac disease cases presenting after the age 1 year (n=44) were identified through a survey of participating paediatric departments conducted ten years later.

Analyses were restricted to individuals with prospective data on both breastfeeding duration and date of gluten introduction. Individuals with a coeliac disease diagnosis before 1 year were excluded. Complete data for analyses were therefore available for 9408 infants.

Gluten was most often introduced during months 5 and 6. The age at which gluten was introduced was not associated with risk of future development of coeliac disease. The unadjusted HRs for introduction of gluten during months 7-8 or months 3-4 compared to months 5 and 6 were 1.1 (95% CI 0.6-2.0) and 1.0 (95% CI 0.3-3.3) respectively. Over half the participating children were breastfed longer than 10 months. The duration of breastfeeding was not associated with risk of future development of coeliac disease. The authors commented that the study had low statistical power to address these associations.