



## **Paper for Discussion: Timing of introduction of gluten into the infant diet**

### **Agenda Item: 2**

The European Food Safety Authority (EFSA) Scientific Opinion on the appropriate age for the introduction of complementary food to infants was published in December 2009. SMCN had an initial discussion on the conclusion made in the EFSA statement on the appropriate timing of introduction of gluten into the infant diet and the evidence used to support this, at its last meeting on 5th May 2010. The COT (Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment) also discussed the same evidence at their meeting on 4th May 2010 and a full report of their discussion is now available within the final COT meeting minutes. SMCN is now asked to have a fuller discussion of the evidence on the appropriate timing of introduction of gluten into the infant diet in relation to the risk of type 1 diabetes and coeliac disease, and taking account of the views of the COT, draw conclusions to be published in a statement.

Please see paper attached.

## **Timing of introduction of gluten into the infant diet**

### **Background**

1. On 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 to infants in the EU. This request arose because of an inconsistency within the EU legislation and between the EU legislation and the relevant Codex Standard with regard to labelling of complementary food. The Opinion, which was adopted and published on the 22 December 2009, can be found attached as Annex 1.
2. 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”

### *Current Advice*

3. Current UK advice indicates that breast milk provides all the nutrients a baby needs in the first half of infancy and recommends exclusive breastfeeding for around the first six months of an infant's life. It is recommended that introduction of solid foods occurs at around six months, and that breastfeeding should continue beyond the first six months along with appropriate types and amounts of solid foods. Infant formula may be used as an alternative when mothers do not breastfeed or choose to supplement breastfeeding.

4. In the UK, there is also further 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).

#### *Introduction of solids into the infant diet*

5. 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 the common allergenic foods before 6 months of age. It is also inconsistent with WHO advice to breastfeed exclusively for 6 months (WHO, 2001). 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. EU regulations however state that for weaning foods meeting the compositional requirements of Regulation 2006/125/EC the presence or absence of gluten must be given on the label if the indicated age from which the product may be used is below 6 months.

#### *Introduction of gluten into the infant diet*

6. In the UK, mothers who decide to introduce solids before 6 months of age are advised to avoid giving wheat-based foods and other foods containing gluten to infants who are under 6 months old. This is based on advice to prevent coeliac disease from the Committee on Medical Aspects of Food Policy (COMA) in their 1994 report *Weaning and the Weaning Diet* (Department of Health, 1994). This advice was reconsidered by SACN in 2003 and they restated COMA's advice that foods containing gluten should not be given to infants below the age of 6 months, and that this advice applied to both formula and breastfed infants<sup>1</sup>. Foods currently marketed as suitable for babies aged 4-6 months do not generally contain gluten. In addition as stated in Directive 2006/141/EC on infant and follow-on formulae, the use of ingredients containing gluten is prohibited in infant formulae.
7. The latest UK Infant Feeding Survey (Bolling *et al.*, 2007) showed that in the UK, 51% of mothers had introduced solids into their infants' diet by 4 months of age though information on the exact age at introduction of gluten was not available. The survey also showed that at 4-6 months of age (Stage 2), only 17% of mothers were exclusively breastfeeding, 68% were giving only infant formula, and 15% were mixed feeding (breast milk and infant formula). As a result, it is likely that a large proportion of infants

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<sup>1</sup> [http://www.sacn.gov.uk/meetings/sub\\_groups/maternal\\_child\\_nutrition/22012003.html](http://www.sacn.gov.uk/meetings/sub_groups/maternal_child_nutrition/22012003.html)

in the UK are not receiving breastmilk at a time when EFSA states that it would be beneficial to introduce gluten.

*Timing of introduction of solids and risk of sensitisation/allergy to foods*

8. The issue of timing of introduction of 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*”.
9. A recent review by the Committee on Toxicity (COT) of their previous recommendations on peanut avoidance and 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 2-11 years) or timing of introduction of solids (general or specific) (follow-up 2-4 years) is associated with development of food sensitisation or allergy (Thompson *et al.*, 2008).
10. 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 allergenic foods and the risk of later development of tolerance or food allergies. These are not due to report for several years.

**Coeliac disease**

11. Coeliac disease 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). It is thought to be an autoimmune condition in which the presence of clinical symptoms is entirely dependent on the presence of gluten in the diet. Coeliac disease is the most prevalent small bowel disease to affect Western populations (Thomas *et al.*, 2003); it affects approximately one percent of the UK population (Bingley *et al.*, 2004; West *et al.*, 2003) and is the most common cause of malabsorption of nutrients in the UK (Goddard *et al.*, 2005). Coeliac disease occurs 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). These alleles are necessary, but not sufficient for coeliac disease development; only 36-53% of individuals with these haplotypes develop coeliac disease. As a result, only a proportion of genetically susceptible individuals develop coeliac disease, despite the widespread consumption of gluten-containing

foods. This suggests that additional factors play a role in disease risk (Norris *et al.*, 2005). In addition to these alleles, the highly specific enzyme tissue transglutaminase (tTG) has been identified as the major autoantigen involved in the disease process (Dieterich *et al.*, 1997).

12. Research studies investigating the epidemiology of coeliac disease and how it develops have often used antibodies (tTG) as a predictive marker for the disease, rather than (or in addition to) tissue biopsies which are more definitive but also more invasive. For asymptomatic children with a genetic risk, tTG antibodies have been shown to have positive predictive value of 70% to 83% (Hoffenberg *et al.*, 2000).

### **Type 1 diabetes mellitus**

13. Type 1 diabetes mellitus (T1DM) is an autoimmune condition resulting from destruction of the insulin-producing islet cells of the pancreas. The prevalence of T1DM in the UK has 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). The most important genes are located in the HLA class II region, accounting for about 45% genetic susceptibility for T1DM. There is a well-known risk for disease associated with HLA-DR3 and HLA-DR4 alleles, but also an additional susceptibility associated with HLA-DQ alleles (Atkinson and Eisenbarth, 2001). As outlined in paragraph 11, HLA-DQ alleles also confer increased risk for coeliac disease; thus, individuals with T1DM and their first-degree relatives have increased risk of coeliac disease (Collin *et al.* 2002).
14. Autoantibodies to the islet cells, or islet autoimmunity, can be present for several years prior to the diagnosis of T1DM (Gorsuch *et al.*, 1981), and these have been used as predictive markers of T1DM in several studies. Several autoantibodies have been used in this way including insulin antibodies (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 for the autoantibodies lie in the range of 40% to 90%, depending on the number and combination of autoantibodies measured (Knip *et al.*, 2010, Siljander *et al.*, 2009, Orban *et al.*, 2009). For example, Knip *et al.* (2010) reported an initial positivity for GADAs and/or IA-2As to have a sensitivity of 61% (95% CI 36-83) for T1DM. However, 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 just one (Siljander *et al.*, 2009).

## **Environmental factors playing a role in coeliac disease and T1DM development.**

15. 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. doses, timing, frequency, type of food) might influence the immunologic process, resulting in the development of oral immunotolerance or alternatively immunointolerance to a particular component in food (Strobel *et al.*, 1998; Ivarsson *et al.*, 2002). The response of the immune system to an antigen could be further modified by another exposure, such as breastfeeding (Ivarsson *et al.*, 2002), or other factors including genetic background, host immaturity, digestive flora and antigen update (Strobel *et al.*, 1998)

## **Summary of key studies reviewed by EFSA**

### *Gluten and risk of coeliac disease (see Annex 2 for full papers)*

16. There is evidence from a systematic review of six retrospective case-control studies by Akobeng *et al.*, (2006) that the risk of coeliac disease is affected by breastfeeding. In this review, there was a reported association between increased breastfeeding duration and a decreased risk of developing coeliac disease (it was not clear whether the studies had measured partial or exclusive breastfeeding). Breastfeeding at the time of introduction of gluten was also shown to be an important factor associated with decreased risk. A meta-analysis of four case control studies included in this systematic review, showed that infants who were breastfed at the time of introduction of gluten had a reduced risk of coeliac disease compared to those who were not breastfed at that time; the pooled odds ratio reported was 0.48 (95% CI 0.40-0.59). The age and dose of exposure to gluten in these studies were not presented in the paper. This meta-analysis included the study by Ivarsson *et al.* (2002) which was reported separately by EFSA. The retrospective nature of the studies included in this systematic review means that they may be subject to recall bias.
17. A small number of Swedish studies have investigated the relationship between infant feeding patterns and coeliac disease. Ivarsson *et al.*, (2000) observed an increased 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 of age, to 6 months of age. The authors also reported that the daily consumption of wheat, rye and barley from follow-on formula doubled from 1981 to 1983. From 1985 to 1987 the annual incidence rate increased four-fold in children below 2 years of age, followed in 1995 by a sharp decline to previous levels.

18. Swedish infant feeding recommendations changed again in 1996 and these included recommendations to introduce gluten into infants' diet slowly, and for introduction to start from 4 months of age instead of (the previous advice from 1982) from 6 months of age. Carlsson *et al.*, (2006) compared the prevalence of coeliac disease in infants (aged 2.5 years) born in 1996/1997 (when this revised recommendation was introduced) to the prevalence among those born in 1992/1993. The prevalence of symptomatic coeliac disease declined post-1996 (0.3% in 1996/7 versus 0.7% 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 follow-on formula also declined by a third from 1995<sup>2</sup>.
19. At first sight, these observations appear to be consistent with the hypothesis that delaying the introduction of gluten into the infant diet increases the risk of developing coeliac disease. However, the potential effects of confounding factors such as fluctuation in the amount of gluten given in follow-on formula or other foods and breastfeeding alongside introduction of gluten to the infant's diet also need to be considered. These studies do not provide any information on the exact timing of infants' exposure to gluten.
20. It is difficult to investigate risk of coeliac disease prospectively as it is a rare condition; however, HLA genotype can be used to identify individuals with an increased risk of developing coeliac disease and markers such as antibodies [for example tissue transglutaminase (tTG) autoantibodies] can be used to screen for early asymptomatic disease. Norris *et al.*, (2005) conducted a prospective observational study (the 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 follow-up period was 4.8 years and the main outcome measure for coeliac disease used in this study was positive tissue transglutaminase (tTG) autoantibody on two consecutive visits or positive tTG and a positive small bowel biopsy for coeliac disease. Norris *et al.* (2005) investigated in this cohort the relationship between timing of introduction of gluten to the infant diet and risk of coeliac disease. Adjusting for HLA-DR3 status, children exposed to wheat, barley or rye in the first 3 months of life had a 5-fold increased hazard (HR=5.17, 95% CI 1.44-18.57) of coeliac disease autoimmunity (CDA) compared to the reference group exposed at 4-6 months. Children not exposed to wheat, barley or rye until their 7<sup>th</sup> month or later were at slightly increased risk of CDA compared to the 4-6 months reference group but this was not statistically significant (HR=1.87, 95% CI 0.97-3.60). These findings were independent of timing of first exposure to

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<sup>2</sup> The Secretariat is trying to ascertain whether gluten was permitted in infant/follow-on formula in Sweden at this time as they did not join the EU until 1995.

rice and oats. When these analyses were restricted to cases of infants with a positive biopsy result (n=25), the associations for introduction of gluten at 1-3 months and 7+ months strengthened and were statistically significant (HRs of 22.97, 95% CI 4.55-115.93 and 3.98, 95% CI 1.18-13.46 respectively). It should be noted that these results are from a population selected for increased risk of coeliac disease and may not be generalisable.

*Gluten and risk of type 1 diabetes (see Annex 3 for full papers)*

21. 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 remaining four investigated the relationship between duration of breastfeeding and T1DM, and did not include analyses on the timing of introduction of gluten.
22. Autoantibodies to islet cells can be found years prior to diagnosis of type 1 diabetes (T1DM). Norris *et al.*, (2003) used T1DM antibodies as an outcome measure in the DAISY study to investigate whether the timing of introduction of gluten-containing cereals is related to T1DM risk. Subjects were at increased risk of T1DM and islet autoimmunity outcomes were identified as children with consecutive positive results for autoantibodies or who tested positive for/had diabetes on their most recent visit. The researchers observed that T1DM antibodies appeared in a significantly higher proportion of children if cereals (rice, oats, wheat, barley and rye) were introduced in the first 3 months or at 7 months or older compared to the reference group who introduced cereals at 4-6 months (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 introduced gluten in the first 3 months and infants who introduced gluten-containing cereals after 7 months were 2.65 (95% CI 0.76-9.33) and 1.70 (95% CI 0.79-3.66) respectively, compared to infants who introduced gluten-containing cereals (not rice) at 4-6 months. However, these differences were not statistically significant. When cereals were introduced while the infant was still being breastfed the risk was slightly but statistically significantly reduced (HR: 0.50 95% CI 0.25-0.99).
23. 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. The autoantibodies tyrosine phosphatase autoantibodies (IA-2A) and glutamic acid decarboxylase autoantibodies (GADA) were used as outcome

measures of T1DM. The late introduction of porridge containing gluten<sup>3</sup> (over 6 months versus any other age) was related to the emergence of GADA (OR 1.6, 95% CI 1.2, 2.3) and GADA and/or IA-2A (OR 1.4, 95% CI 1.1, 1.8). The early introduction of porridge before 3 months of age was not related to emergence of these autoantibodies at age 2.5 years (only three infants were exposed to porridge before 3 months of age). The consumption of other gluten-containing foods (pasta, macaroni, and spaghetti) was not associated with GADA and/or IA-2A positivity. Among a small number of high-risk individuals at 2 ½ years (n=37) (infants who remained positive for both GADA and/or IA-2A during the follow up, consecutive samples taken at 1 and 2.5 years of age), introduction of porridge after 6 months was not significantly associated with beta-cell autoimmunity. In the same cohort, short duration of breastfeeding was reported as a risk factor for beta-cell autoimmunity.

24. The German BABYDIAB cohort study followed newborn children of parents with T1DM to age 11 years. In this study, Ziegler *et al.*, (2003) reported on early infant feeding and risk of T1DM using insulin antibodies (IA), GADA and insulinoma antigen-2 (IA-2) autoantibodies as outcome measures at 5 years of age. The adjusted hazard ratio for risk of developing islet autoantibody positivity with introduction of gluten-containing foods before 3 months of age was 4.0 by 5 years of age (95% CI 1.4-11.5). In terms of age of introduction of gluten-containing foods, the adjusted hazard ratio was 5.2 (95% CI 1.7-15.5) for introduction at or below 3 months compared to introduction between 3.1 and 6 months. However, there was no statistically significant effect of introduction over 6 months of age (HR 1.2, 95% CI 0.7-2.0). The risk of tTGCA (tissue transglutaminase A autoantibodies) was not associated with early or late introduction of gluten. No significant differences in islet autoantibody risk were observed with respect to duration of total or exclusive breastfeeding.

#### **Input from the Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment (COT)**

25. Following publication of the EFSA Opinion, the Committee on Toxicity of Chemicals in Foods, Consumer Products and the Environment (COT) was asked to consider the evidence discussed in the EFSA Opinion concerning timing of introduction of gluten into the infant diet and the risk of subsequently developing coeliac disease and type I diabetes. The COT held this discussion on 4<sup>th</sup> May 2010; the full minutes of this discussion are available in Annex 4. The COT was provided with the same paperwork that was given to SMCN at its meeting on 5<sup>th</sup> May 2010. The COT reached the following conclusions:
- Few data are available from the studies cited in the EFSA Opinion that directly address risks of coeliac disease or diabetes mellitus in relation to

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<sup>3</sup> The Wahlberg paper refers to 'porridge containing gluten' but the level of gluten in the porridge and particular cereal used to make the porridge is not stated.

the timing of introduction of gluten into the infant diet. This means that there is significant uncertainty in any conclusions that can be drawn.

- However, the balance of evidence currently available provides a strong indication that early (three months of age or earlier) introduction of gluten-containing foods into the diet is associated with an increased risk of coeliac disease.
- There is limited evidence suggesting that delaying the introduction of gluten into the infant diet beyond six months of age marginally increases the risk of coeliac disease.
- Currently available evidence on the timing of introduction of gluten into the infant diet and risk of type I diabetes is weak and does not allow specific conclusions to be drawn.
- There is limited evidence suggesting that the introduction of gluten into the infant diet whilst breastfeeding reduces the risk of coeliac disease, particularly if gluten is introduced between 4 and 6 months of age.

26. The COT noted that these conclusions relate to overall effects at a population level, and that there might be differences between individuals that could not be teased out from the currently available data.

27. Overall, the COT considered that the current balance of evidence on coeliac disease, while limited, broadly supported EFSA's conclusions regarding the introduction of gluten into the diets of healthy term infants at between four and six months of age. However, there were uncertainties in the underlying science because of the limited evidence base. This meant that the balance of evidence might change importantly in the future as the results of ongoing randomised controlled trials become available.

## **Discussion**

28. The SMCN is asked to consider the EFSA Scientific Opinion on the appropriate age for introduction of complementary feeding of infants. Taking account of the available evidence and views of the COT, SMCN are asked to comment on the conclusions of the Opinion relating to the timing of introduction of gluten into the infant diet and draw conclusions on the appropriate age at which gluten should be introduced into the infant diet, in relation to coeliac disease/T1DM risk.

29. The full review of the scientific evidence underlying EFSA's conclusions can be found in section 2 of the Opinion (Annex 1). The specific evidence on introduction of gluten into the infant diet in relation to coeliac disease and type I diabetes mellitus risks can be found at section 2.4.3 in Annex 1. Copies of the key scientific papers on gluten introduction and risk of coeliac disease/type 1 diabetes that are referenced in that section are attached in Annexes 2 and 3 for the Subgroup's information.

30. As a reminder of the Subgroup's initial discussion on the appropriate timing of introduction of gluten to the diet, it may be useful to refer to the minutes of the SMCN meeting held on 5<sup>th</sup> May 2010.

**31. The SMCN are asked to consider the following specific questions in relation to the risk of developing coeliac disease and/or T1DM:**

- **Whether the evidence set out in the EFSA Opinion and publications appended support the introduction of gluten to all infants between 4 and 6 months of age?**
- **Whether the evidence set out in the EFSA Opinion and publications appended support the introduction of gluten to those infants with a family history of coeliac disease and/or T1DM between 4 and 6 months of age?**
- **Whether there are any risks associated with delaying introduction of gluten to infants' diets beyond 6 months of age?**
- **Whether any health risks or benefits of introducing gluten between 4 and 6 months, are associated with the infant receiving breast milk and/or infant formula?**

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**Annex 1 – EFSA Opinion on the appropriate age for the introduction of complementary food to infants in the EU**

**Annex 2 - Key papers on gluten and risk of coeliac disease as referenced by EFSA**

Please see following papers attached:

- Akobeng *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
- Carlsson A, *et al.*, 2006. Prevalence of celiac disease: Before and after a national change in feeding recommendations. *Scand. J. Gastroenterol* 41, 553-558
- Ivarsson A, *et al.*, 2000. Epidemic of celiac disease in Swedish children. *Acta Paediatr.* 89, 165-171
- Norris *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

**Annex 3 - Key papers on gluten and risk of type 1 diabetes as referenced by EFSA**

Please see following papers attached:

- Norris JM, Barriga K, Klingensmith G, Hoffmann M, Eisenbarth GS, Erlich HA, Rewers M, 2003. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. J.A.M.A. 290, 1713- 1720.
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#### **Annex 4 – Minutes of COT discussion (04/05/2010) on the appropriate age for introduction of complementary feeding of infants**

##### **Item 7: Timing of introduction of gluten into the infant diet – TOX/2010/11**

Dr Tuthill declared a personal, specific interest, in that in a professional capacity he had advised companies making both infant formulas and weaning foods. He added that in his capacity as an allergy clinician he did not specifically advocate exclusive breastfeeding for the first 6 months of life. These interests were noted. However, Dr Tuthill was permitted to contribute to the discussions as his experience was particularly relevant to the topic.

Paper TOX/2010/11 explained the background to the issue for consideration. At the request of the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) had produced a Scientific Opinion on the appropriate age at which to introduce complementary food to infant diets in the EU. This request had arisen because of an inconsistency between EU legislation and the relevant CODEX Standard with regard to labelling of complementary foods and the ages at which they should be introduced. The Panel had adopted and published its opinion on the 22<sup>nd</sup> December 2009. The Opinion discussed the available scientific evidence and drew a number of conclusions, most notably on the timing of introduction of gluten into the infant diet. The conclusions, as stated in its Summary and Overall Conclusions, were:

- *“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 and 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 the age of 4 months) in addition to breastfeeding to support optimal growth and development”*
- *“... presently available data on the risk of celiac 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”*

Paper TOX/2010/11 also summarised the current UK advice, which is that breast milk provides all the nutrients a baby needs in the first 6 months of life, exclusive breastfeeding being recommended up to about six months of age. The advice further recommends that solid foods be introduced at around six months, and that breastfeeding should continue beyond the first six months in combination with appropriate types and amounts of solid foods. Infant formula may be used as an alternative when mothers choose not to breastfeed or wish to breastfeed partially. In addition, it is advised that commonly allergenic foods including peanuts, nuts, seeds, egg, cows' milk, soya, wheat (and other cereals that contain gluten such as rye and barley), fish and shellfish, should not be introduced before six months of age.

The Sub-group on Maternal and Child Nutrition (SMCN) of the Scientific Advisory Committee on Nutrition (SACN) would be considering the EFSA recommendations and the evidence that had been cited in support of them, and had requested comments from COT on the cited evidence concerning timing of introduction of gluten into the infant diet and the risks of subsequently developing coeliac disease and Type I diabetes. Paper TOX/2010/11 contained the paper that was to be discussed by the SMCN, together with the published reports of relevant studies.

Members considered the evidence on coeliac disease and diabetes separately.

### *Coeliac disease*

Members commented on each of the relevant studies. A systematic review conducted by Akobeng *et al.* (Arch. Dis. Child. 91, 39-43, 2006), which was considered to be of high quality, indicated a decreased risk of coeliac disease with increased duration of breastfeeding, although it was unclear whether the association was with partial or exclusive breastfeeding. However, risk had not been examined in relation to the time at which gluten was introduced into the infant diet. Nor was it clear from the studies included in the review whether longer breastfeeding was associated with a lower lifetime risk of coeliac disease or only with a delayed onset of the disease. Members noted that the findings were limited insofar as they were derived entirely from case-control studies, which may have been liable to bias in the retrospective recall of dietary exposures.

A study by Ivarsson *et al.* (Acta Paediatr. 89, 165-171, 2000) analysed changes in the incidence of coeliac disease in Swedish children in relation to national changes in infant feeding recommendations and practices. It indicated an increase in the frequency of the disease following a recommendation in 1982 to postpone the introduction of gluten into the diet from four to six months of age, and later a marked decline at about the time when advice was changed to recommend introduction of gluten in small amounts from four months of age, preferably while the child is still being breast-fed. However, this decline somewhat preceded the change in recommendations, and whilst it might be explained by changes in feeding practices prompted by media coverage in advance of the modified national recommendations, it is possible that some other factor was responsible.

A second Swedish study by Carlsson *et al.* (Scand. J. Gastroenterol 41, 553-558, 2006) compared the prevalence of coeliac disease in children born before and after the 1996 recommendation to introduce gluten in small amounts from four months of age. There was a lower prevalence of symptomatic coeliac disease among children born during 1996-97 (0.3%) than in those born during 1992-93 (0.7%).

Another Swedish study by Ivarsson *et al.* (Am. J. Clin. Nutr. 75, 914-921, 2002) found a reduced risk of coeliac disease before age two years in children who

were still being breast-fed when dietary gluten was introduced. This was a case control investigation in which dietary histories were ascertained retrospectively by questionnaire, and may therefore have been prone to error. However, unless such errors occurred differentially in cases as compared with controls, they would not be expected to generate spurious associations.

Members agreed that a prospective cohort study described by Norris *et al* (J.A.M.A. 290, 1713-1720, 2003) had a strong design. This was the only study that had directly explored the risk of coeliac disease according to the time at which gluten was introduced into the infant diet. It provided strong evidence that genetically predisposed infants exposed to foods containing wheat, barley or rye during the first three months of life were at higher risk of developing coeliac disease (as indicated by a positive biopsy and/or positive coeliac disease autoantibody responses) than those first exposed between four and six months of age. It also appeared that children first exposed to gluten at seven months of age or older had a marginally increased risk of developing coeliac disease in comparison the same reference group, although the elevation of risk was relatively small (hazard ratio 1.87 (95% CI 0.97-3.60), and was only statistically significant when the analysis was restricted to those cases with biopsy-confirmed coeliac disease. The protective effect of breastfeeding that had been reported in the other studies was not observed in this investigation. However, it was proposed that this may have been a consequence of differences in other aspects of infant diet. The Committee considered that the findings of this study were suggestive, but could not be regarded as conclusive in the absence of independent replication.

### *Type I Diabetes Mellitus*

The evidence base relating to the timing of introduction of gluten into the infant diet and risk of developing Type I diabetes mellitus was judged to be weaker than that for coeliac disease, the only two studies of note being by Norris *et al*. (J.A.M.A. 290, 1713-1720, 2003) and Ziegler *et al*. (J.A.M.A. 290, 1721-1728, 2003). Both of these investigations focused on infants at high risk of developing diabetes. The first suggested that there is a window of exposure when cereals should be introduced (between four and six months of age), outside of which there is an increased risk of a child developing islet autoimmunity<sup>1</sup>, while the second found that food supplementation with gluten-containing foods before age three months was associated with significantly increased risk.

Members noted that using islet autoantibodies as an endpoint rather than clinically manifest disease added some uncertainty to interpretation, and recommended that their predictive value for frank diabetes be checked.

### *Conclusions*

The Committee reached the following conclusions:

- Few data are available from the studies cited in the EFSA Opinion that directly address risks of coeliac disease or diabetes mellitus in relation to the timing of

introduction of gluten into the infant diet. This means that there is significant uncertainty in any conclusions that can be drawn.

- However, the balance of evidence currently available provides a strong indication that early (three months of age or earlier) introduction of gluten-containing foods into the diet is associated with an increased risk of coeliac disease.
- There is limited evidence suggesting that delaying the introduction of gluten into the infant diet beyond six months of age marginally increases the risk of coeliac disease.
- Currently available evidence on the timing of introduction of gluten into the infant diet and risk of Type I diabetes is weak and does not allow specific conclusions to be drawn.
- There is limited evidence suggesting that the introduction of gluten into the infant diet whilst breastfeeding reduces the risk of coeliac disease, particularly if gluten is introduced between four and six months of age.

The Committee noted that these conclusions relate to overall effects at a population level, and that there might be differences between individuals that could not be teased out from the currently available data.

Overall, the Committee considered that the current balance of evidence on coeliac disease, while limited, broadly supported EFSA's conclusions regarding the introduction of gluten into the diets of healthy term infants at between four and six months of age. However, there were uncertainties in the underlying science because of the limited evidence base. This meant that the balance of evidence might change importantly in the future as the results of ongoing randomised controlled trials become available.

<sup>1</sup> Subsequent to the meeting, the Committee Chair provided a supplementary critique of the Norris 2003 paper, in which he considered whether the reported increased risk of developing islet autoimmunity with early (before 3 months) or late (7 months or older) exposure to cereals was attributable to rice, gluten-containing cereals, or both. He noted that the paper described a correlation between age at first exposure to gluten-containing cereals and age at first exposure to rice ( $r = 0.26$ ). After adjustment for potential cofounders, analysis indicated significant independent effects of early (1-3 months) or late (> 7 months) age at first exposure to rice. For gluten-containing cereals, risks were also increased, although not to the point of statistical significance. While these findings suggested independent effects of both rice and gluten-containing cereals, he considered that they were only suggestive as the analysis was based on relatively few cases and the two exposures were somewhat correlated, which may have led to some instability in the statistical model.