**SUPPLEMENTARY MATERIAL**

**Table S1**. Declaration of potential conflicts of interest related to current document (within last 5 years; in alphabetical order).

**Table S2**. Summary of considerations for determining the strengths of the recommendations.

**Table S3.** Summary of voting on the statements and recommendations. List of experts who agreed to take part in the voting on the statements and recommendations (names shown only if consent was given).

**Table S4.** Amount of gluten and coeliac disease.

**Table S5.** The gluten intake based on the data for flour consumption (based on retrospective data presented in references Ivarsson 2000 and Ivarsson 2002; both refer to the average daily consumption for infants < 2 y).

**Table S6**. Gluten-containing foods most frequently consumed by infants. Data obtained from official food composition database representing different countries (http://www.fao.org/infoods/infoods/tables-and-databases/europe/en/).

## Table S1. Declaration of potential conflicts of interest related to current document (within last 5 years; in alphabetical order)

|  |  |
| --- | --- |
| Group member | Declaration |
| Castillejo G | Grant from the European Union Project PreventCD (FP6-2005-FOOD-4B36383.PreventCD). Consultancy from Dr. Schär Institute. |
| Catassi C | Grant from the Associazione Italiana Celiachia (AIC; the Italian Patients Society for Celiac disease). Consultancy for Dr. Schär Institute; Consultancy for Heinz Italy; Consultancy for Menarini Diagnostics |
| Domellof M | Has recieved speaker/writer honoraria from Wyeth and Mead Johnsson. Has received research funding from Semper/Hero, Nestlé and Baxter. |
| Fewtrell M | Honoraria for lectures/workshops from Mead Johnson, Nestle Nutrition Institute. |
| Husby S | Thermo-Fisher: speaker’s honorarium 2013, Arla Food Ingredients: non-restricted grant, 2013-4. Non-restricted grants from Novo Nordic Research Foundation, Lundbeck Research Foundation, The Danish Research Councils and the Region of Southern Denmark |
| Kolacek S |  |
| Koletzko S | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD), Nutricia foundation, ESPGHAN, Deutsche Zöliakie Gesellschaft, Dr. Schär, Nestle, Mead Johnson.Consultancy or speaker’s fee from Menarini, Thermo-Fischer, Euroimmune, Heinz, Hipp, Danone, Nestle, Hipp. |
| Korponay-Szabó I | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD) |
| Lionetti E | Associazione Italiana Celiachia (AIC;Italian Patients Society for Celiac disease). Consultancy for Heinz Italy. |
| Mearin ML | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD), and from the European Union’s Seventh Framework Programme, project EarlyNutrition under grant agreement No. 289346; Stichting Coeliakie Onderzoek Nederland, and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition.  Thermo-Fisher: speaker’s honorarium 2014, Nutricia-Danone speaker’s honorarium 2015. |
| Papadopoulou A | Speaker's honorarium from Danone (Nutricia) and Nestle. |
| Polanco I | Grant from the European Union Project PreventCD (FP6-2005-FOOD-4B36383.PreventCD). Grant from the Spanish Ministry of Health ( Instituto Carlos III ) |
| Ribes Koninckx C | Grant from the European Union Project PreventCD (FP6-2005-FOOD-4B36383.PreventCD). Grant from the Spanish Ministry of Health ( Instituto Carlos III ). Consultancy for Nutricia, Mead Johnson, Nestle |
| Shamir R | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD). Consultancy to BiolineRX |
| Szajewska H | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD), and from the European Union’s Seventh Framework Programme, project EarlyNutrition under grant agreement No. 289346, and from Komitet Nauki (Project NN407171534; contract 1715/B/P01/2008/34), and from Fundacja Nutricia (RG2/2012 – 1W44/FNUT3/2013). |
| Troncone R | Grant from the European Union project PreventCD (FP6-2005-FOOD-4B-36383-PreventCD). Consultancy to BiolineRX |
| Vandenplas Y | None declared. |

**Table S2. Summary of considerations for determining the strength of the recommendations**

|  |  |
| --- | --- |
| **Quality of evidence** | * Very low quality of evidence for any BF compared with no BF and the risk of CD. * Low quality of evidence for the effect of BF at the time of gluten introduction and the risk of CD. * Moderate to high quality of evidence for the timing of gluten introduction. * Very low quality of evidence for the introduction of gluten before 3-4 months of age. * Very low quality of evidence for the effect of large amounts of gluten compared with small or medium amounts of gluten at weaning and the risk of CD. * Very low quality of evidence for the type of gluten at introduction. |
| **Values and preferences** | * As CD is common and is a burden on the quality of life, health and economy, any intervention to reduce the burden of CD is valuable. |
| **Trade-off between benefits and harms** | * Short-term and long-term benefits of BF are known and there is no evidence that challenges the current recommendations. BF should be promoted for its well established health benefits. * No evidence of harm of current practices in infants/children. * Infant feeding practices (breastfeeding, time of gluten introduction) have no effect on the risk of developing CD during childhood (at least at specific timeframes evaluated in the included studies). * Earlier (4 mo vs 6 mo or 6 mo vs 12 mo) introduction of gluten in children from families with CD was associated with higher incidences of CDA and CD during the first 2 years of life, with no difference in the cumulative incidences at 5 years of age and older. * Abstention from gluten beyond infancy may have still unexplored societal and health care consequences. The *pros* (avoiding early symptomatic disease that will affect growth) and *cons* (possible subtle symptoms and lack of diagnosis if there is no screening) of gluten avoidance for longer than 1 year need to be taken into account. |
| **Costs and feasibility** | * Current recommendations can be in**t**egrated into existing infant feeding guidelines at every level (i.e. global, regional, national). |

**Table S3.** Summary of voting on the statements and recommendations. List of experts who agreed to take part in the voting on the statements and recommendations (names shown only if consent was given).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Agree | Disagree | Abstain |
| 1 | STATEMENT: Breastfeeding compared with no breastfeeding has not been shown to reduce the risk of developing CD during childhood. | 30 | 1 | 1 |
| 2 | RECOMMENDATION. Recommendations on breastfeeding should not be modified due to considerations regarding prevention of CD (conditional recommendation; low quality of evidence). | 31 | 1 | 0 |
| 3 | STATEMENT: Breastfeeding at the time of gluten introduction, as compared to gluten introduction after weaning (i.e., cessation of breastfeeding), has not been shown to reduce the risk of developing CD during childhood | 31 | 1 | 0 |
| 4 | RECOMMENDATION: Introducing gluten while the infant is being breastfed cannot be recommended as a means of reducing the risk of developing CD (conditional recommendation; low quality of evidence). | 32 | 0 | 0 |
| 5 | Timing of gluten introductionThe effects of various timings of gluten introduction on the risk of developing CD were studied. We summarise the evidence for various timings followed by a single recommendation on the timing of gluten introduction. STATEMENT: Gluten introduction at 4-6 mo compared with gluten introduction at >6 mo of age does not reduce the cumulative incidence of CDA or CD during childhood. | 32 | 0 | 0 |
| 6 | STATEMENT: Gluten introduction at 6 mo compared with gluten introduction at 12 mo of age does not reduce the cumulative incidence of CDA or CD, but it leads to an earlier manifestation of CD. | 31 | 0 | 1 |
| 7 | STATEMENT: It remains unclear whether gluten introduction at <3-4 mo compared with gluten introduction at 4-6 mo of age has an effect on the risk of developing CDA or CD. | 28 | 1 | 1 |
| 8 | STATEMENT: It remains unclear whether gluten introduction at <3-4 mo compared with gluten introduction at >6 mo of age has an effect on the risk of developing CDA or CD. | 29 | 1 | 2 |
| 9 | STATEMENT: It remains unclear whether gluten introduction at <6 mo compared with gluten introduction at >6 mo of age has an effect on the risk of developing CDA. | 28 | 3 | 1 |
| 10 | SUMMARY RECOMMENDATION. Gluten can be introduced into the infant’s diet between the ages of 4 and 12 completed months.\* This age range does not seem to influence the absolute risk of developing CDA or CD during childhood (conditional recommendation; depending on the age, quality of evidence varies from very low to high quality of evidence). \*4 completed months = 17 weeks of age. | 32 | 0 | 0 |
| 11 | STATEMENT: The type of gluten at introduction was not shown to modify the risk of developing CD. | 31 | 0 | 0 |
| 12 | RECOMMENDATION: No recommendation can be made regarding the type of gluten to be used at introduction (conditional recommendation; very low quality of evidence). | 31 | 0 | 0 |
| 13 | STATEMENT: Introduction of 200 mg of vital wheat gluten (equivalent to 100 mg of immunologically active gluten) per day at 4-6 mo of age compared to avoidance of gluten did not modify the risk of developing CDA or CD at 3 years of age. Data from observational studies indicate that consumption of large amounts of gluten at weaning and during the first 2 years of life may increase the risk of CD during childhood. | 27 | 3 | 2 |
| 14 | RECOMMENDATION: Neither the optimal amounts of gluten to be introduced at weaning, nor the effect of different wheat preparations on the risk of CD and CDA have been established. Despite the limited evidence regarding the exact amounts and with no RCTs to support it, ESPGHAN suggests that consumption of large amounts of gluten should be discouraged during the first months after gluten introduction (conditional recommendation; very low quality of evidence). | 28 | 1 | 3 |
| 15 | STATEMENT: The very early development of CDA and CD (below 3-5 years of age) seems to affect preferentially children carrying the very high risk of CD alleles (HLA-DQ2.5 homozygous), which are found in only 1-2% of the general population but in 10 –15% of children with first-degree relatives having CD. | 27 | 3 | 2 |
| 16 | RECOMMENDATION. No recommendation was made on gluten introduction in children from families with first-degree relatives with CD. | 25 | 3 | 2 |

List of experts who agreed to take part in the voting on the statements and recommendations (names shown only if consent was given).

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* Indrio F, Dept of Pediatric University of Bari Italy
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* Lapillonne A
* Lionetti E. Department of Pediatrics, University of Catania
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* Wilschanski M. Hadassah Hebrew University Medical Center Jerusalem Israel

**Table S4. Amount of gluten and coeliac disease**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ivarsson et al. 2002** | **Large amount** | **Small/medium amount** | The food-frequency component of the questionnaire, which contained semiquantitative  information on portion sizes (3 levels) was used on the basis of experience from an earlier study (22). The pattern of introduction  for each food item was assessed on the basis of the age (in mo) of the infant at the time when the first portion was given, on  the size of the first portion, and on the average portion size and frequency 2 wk later. Dietary intake at 7 mo of age was assessed  on the basis of the frequency of consumption and portion sizes of each food item. |
| During the first 2 wk of consumption | >7.0 g flour/day | <7.0 g flour/day |
| 2 wk after the first portion | >16 g flour day | <16 g flour/day |
| At 7 mo | >58 g flour day   * >39 g flour/day for solid foods * >17 g flour/day for FUF | <58 g flour/day   * <39 g flour/day for solid foods * <17 g flour/day for FUF |

|  |  |  |  |
| --- | --- | --- | --- |
| **Ivarsson et al. 2013 (ETICS Study)** | 1993 Birth Cohort (Epidemic) | 1997 Birth Cohort (Postepidemic) |  |
| Average daily flour consumption from milk- and cereal-based  follow-on formulas in children below 2 y of age | 38 g/child/day | 24 g/child/day |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PREVENTCD Study**  **NEJM 2014** | Mean daily gluten intake after 9 mo (after controlled dose escalation; N=596) was not related to CD (per increase in gram/day)  12 mo HR 0.98 (p=0.74);  18 mo HR 1.1 (p=0.44);  24 mo HR 1.1 (p=0.32);  36 mo HR 1.2 (p=0.09) | | |  |
| **CELIPREV Study NEJM 2014** | Age | Gluten inroduction at 6 mo | Gluten introduction at 12 mo | The daily intake of cereal containing  gluten (wheat, rye, and barley) was assessed by means of a 24-hour dietary-recall questionnaire, and daily gluten intake was calculated as the sum of grams of protein obtained from gluten-related grains multiplied by 0.8. |
|  | At 9 mo | 3.2 ± 1.5 | 0 |  |
|  | At 15 mo | 6.5 ± 2 | 6.8 ± 2 |  |

**Table S5. The gluten intake based on the data of flour consumption (based on retrospective data presented in references Ivarsson 2000 and Ivarsson 2002; both refer to the average daily consumption for infants < 2 y)**

**Years of the epidemic (mid years)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **YEAR** | **1990** | | | **1991** | | | **92** | | |
|  | g flour | g protein | g gluten | g flour | g protein | g gluten | g flour | g protein | g gluten |
| Wheat | 29,00 | 3,48 | 2,78 | 29,00 | 3,48 | 2,78 | 29,00 | 3,48 | 2,78 |
| Rye | 6,10 | 0,50 | 0,40 | 6,00 | 0,49 | 0,39 | 6,00 | 0,49 | 0,39 |
| Barley | 2,30 | 0,23 | 0,18 | 2,20 | 0,22 | 0,18 | 2,20 | 0,22 | 0,18 |
| Oats | 9,80 | 1,47 | 1,18 | 9,80 | 1,47 | 1,18 | 9,80 | 1,47 | 1,18 |
| Total | 47,20 | 5,68 | 4,54 | 47,00 | 5,66 | 4,53 | 47,00 | 5,66 | 4,53 |

**Pre-epidemic years**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **YEAR** | **81** | | | **82** | | | **83** | | |
|  | g flour | g protein | g gluten | g flour | g protein | g gluten | g flour | g protein | g gluten |
| Wheat | 11,00 | 1,32 | 1,06 | 16,00 | 1,92 | 1,54 | 26,00 | 3,12 | 2,50 |
| Rye | 6,30 | 0,52 | 0,41 | 7,50 | 0,62 | 0,49 | 6,70 | 0,54 | 0,44 |
| Barley | 0,20 | 0,02 | 0,02 | 2,00 | 0,20 | 0,16 | 1,80 | 0,18 | 0,14 |
| Oats | 10,00 | 1,50 | 1,20 | 6,00 | 0,90 | 0,72 | 4,70 | 0,70 | 0,57 |
| Total | 27,50 | 3,36 | 2,69 | 31,50 | 3,64 | 2,91 | 39,20 | 4,54 | 3,65 |

**Table S6. Gluten containing foods most frequently consumed by infants. Data obtained from official food composition database from different countries (http://www.fao.org/infoods/infoods/tables-and-databases/europe/en/)**

|  |  |  |
| --- | --- | --- |
| Product | Unit / Portion | Gluten (mg) |
| Plain Biscuits+ | 1 piece (5-6 g) | 400 |
| Fruit jar with biscuit or cereals | 1 jar (130 g) | 600 |
| Gluten containing baby cereals | 1 spoonful (4 g)\* | 160 - 220\*\* |
| Semolina | 1 spoonful | 350 |
| Pasta, small size pasta | 20 g | 1740 |
| Baguette/French type (white) Bread | 1 portion 40 g | 2980 |
| White Sandwich Bread | 1 slice 30 g- 40 g | 2170- 2740 |
| Whole grain bread ( wheat&) | 1 portion 30g- 40 g | 2040 - 2720 |
| Whole grain bread ( rye or barley &) | 1 portion 30-40 g | 800-1200 |
| Croissant, ordinary or butter | 30 g | 1660 |

+ Plain biscuit content is manly flour, water and sugar

\* 1 Powder milk spoon represents about 4 g of cereals

\*\* Different brands have different gluten content.

&  the gluten content was calculated multiplying the grams of gluten containing vegetable proteins of each product by 0.8 for wheat and by 0.4 for barley and rye1.2

**REFERENCES**

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2. http://www.fao.org/docrep/x2184e/x2184e04.htm