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Celiac Disease and the Safety of Oats

Health Canada's Position on the Introduction of Oats to the Diet of Individuals Diagnosed with Celiac Disease (CD).

Canada

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Published by authority of the Minister of Health.

Celiac Disease and the Safety of Oats Health Canada's Position on the Introduction of Oats to the Diet of Individuals Diagnosed with Celiac Disease (CD) is available on Internet at the following address:

http://hc-sc.gc.ca/fn-an/securit/allerg/cel-coe/oats_cd-avoine_e.html

Également disponible en français sous le titre :

La maladie coeliaque et l'innocuité de l'avoine Position de Santé Canada sur l'introduction de l'avoine à l'alimentation des personnes ayant reçu un diagnostic de maladie coeliaque.

This publication can be made available on request on diskette, large print, audio-cassette and braille.

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Cat.: H164-51/2007E-PDF
ISBN: 978-0-662-46940-7

Celiac Disease and the Safety of Oats

Health Canada's Position on the Introduction of Oats to the Diet of Individuals Diagnosed with Celiac Disease (CD).

Executive Summary

Celiac disease (CD) is an immune mediated disease, triggered in genetically susceptible individuals by the ingestion of gluten. It is also known as celiac sprue or gluten-sensitive enteropathy. Gluten is a generic name given to storage proteins in wheat, barley, rye and other closely related cereal grains. It is the gluten in wheat flour that binds and gives structure to bread, baked goods, and other foods, making it widely used in the production of many processed and packaged foods. In those with CD, these proteins trigger an inflammatory injury in the absorptive surface of the small intestine resulting in malabsorption of protein, fat, carbohydrate, fat-soluble vitamins, folate and minerals, especially iron and calcium.

CD is a lifelong condition, and if it is not diagnosed early and treated with a strict gluten-free diet, it can be associated with serious complications, including osteoporosis, lymphoma and infertility in both men and women. In children can be associated with failure to grow and delayed puberty. A small intestinal biopsy is necessary to confirm the diagnosis.

The symptoms and associated conditions in CD vary greatly in number and severity resulting in frequent delays in diagnosis, and misdiagnoses such as irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia are common.

With the advent of new blood tests, the worldwide prevalence of the disease is now estimated to be between 1/100 to 1/200. Certain groups have markedly elevated risks of CD. First-degree relatives of individuals diagnosed with CD have a 10% to 20% risk of developing CD. A high prevalence is also found in those with Down syndrome. CD patients have an increased risk of association with other serious conditions such as Type I diabetes mellitus and other autoimmune disorders.

There is no cure for CD. A strict lifelong avoidance of gluten in the diet is the only effective management of this disease and for the prevention of complications.

Historically, the safety of oats in a gluten-free diet has been an issue of debate. Based on an extensive review of the scientific literature, Health Canada has concluded that the majority of people with CD can tolerate limited amounts of pure oats, uncontaminated with other cereal grains such as wheat, barley and rye. The literature also suggests that pure oats can be beneficial to those individuals with CD who tolerate it, and its palatability may help to increase compliance with a gluten-free diet. Pure oats are an important source of proteins and carbohydrates, especially fibre, and would permit a wider choice of foods for celiac individuals when selecting foods within the grains and cereals category.

Health Canada also recognizes that there are limitations in the available scientific literature regarding the safety of pure oats for individuals with CD, including: limited information on long-term consumption, small numbers of subjects

tested, limited information on reasons for patients dropping out from study protocols, reports that some individuals may be intolerant to even pure oats, and an indication from some in vitro studies of an immunological response in the absence of clinical manifestations. Despite these limitations, the possible benefit for a larger group of individuals with CD warranted that Health Canada assess the currently available scientific data. This review concurs with the position issued earlier by the Canadian Celiac Association (CCA) that the majority of people with CD can tolerate moderate amounts of pure oats. When introducing pure oats into their gluten-free diet, Health Canada recommends that individuals with CD have proper follow up by a health professional, including initial and long term assessments. The amounts of pure oats should be limited to 20–25 grams/day (65 ml – or ¼ cup dry rolled oats) for children and 50–70 grams/day (125 to 175 ml – or ½ to ¾ cup dry rolled oats) for adults, as recommended by the Canadian Celiac Association (www.celiac.ca)

In this document, Health Canada is sharing a summary of its review of the current scientific research related to the introduction of pure oats into the diet of individuals with CD, which supports the position it issued in January 2007 (link to info update: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_97_e.html).

Celiac Disease and the Safety of Oats

Summary of Health Canada's Review – February 2007

Celiac disease (CD) is a life-long, immune mediated disease, estimated to affect 1/100 to 1/200 of the general population (Fasano, 2003; National Institutes of Health, 2004). The symptoms are triggered by ingestion of gluten in genetically susceptible individuals. Gluten is a generic name given to storage proteins in wheat, barley, rye and other closely related cereal grains[1]. These proteins trigger an inflammatory response which damages intestinal villi, the fingerlike projections of the small intestine that increase surface area for optimal nutrient absorption, resulting in malabsorption in those susceptible individuals. The symptoms of CD vary greatly in number and severity, resulting in frequent delays in diagnosis. If it is not diagnosed early and treated with a life-long gluten-free diet, CD can be associated with serious complications including osteoporosis, cancer and reproductive problems in adults and failure to grow and delayed puberty in children (Ciclitira *et al.,* 2005; Green and Jabri, 2006; Helm, 2005; Koning 2005; Lee and Green, 2006; Lowichik and Book, 2003; McGough and Cummings, 2005; Rashid *et al.,* 2005). Although blood tests are available the gold standard for diagnosis is biopsy of the small bowel (Dickson *et al.,* 2006; Reddick *et al.,* 2006).

Presently, the treatment of CD is based on the life-long exclusion of wheat, rye, barley and other related cereal grains[1] from the diet (Case, 2006; Zarkadas, 2006). Whether or not those with CD can safely consume oats has been an issue of interest and investigation in the recent scientific literature.

In order to assess the recent literature relating to this issue, a computerized database search of scientific literature was conducted to include publications on oats and celiac disease from 1995 to January 2007. Documents including clinical trials on the safety of oats in CD patients, in vitro and other relevant studies and recent reviews were evaluated (Table 1, Appendix 1). Documents by the US Food and Drug Administration Threshold Working Group on "Approaches to Establish Thresholds for Major Food Allergens and for Gluten (March 2006) and Gluten-free labeling of foods (January 2007), and internal documents submitted by the Canadian Celiac Association (CCA) were also reviewed.

Janatuinen *et al.,* (1995) were the first to evaluate the possible toxicity of oats in a large controlled study. Since then, a number of studies (Table 1) have assessed the safety of oat consumption by individuals diagnosed with CD and dermatitis herpetiformis – the skin manifestation of CD. Most studies (Table 1) were conducted among adults, with a smaller number of studies performed with children. In addition to the clinical studies, other relevant publications included in vitro studies, retrospective analysis and recent reviews.

[1] Cereal grains that are known to trigger celiac disease/dermatitis herpetiformis reactions include the following: wheat (including durum wheat or "durum", spelt wheat or "spelt", kamut), barley, rye, triticale, atta, bulgur, einkorn, emmer and farro. Also of concern are: wheat bran, wheat farina, wheat flour, wheat germ, wheat-based semolina, wheat starch (imported foods labeled "gluten-free" made with wheat starch), graham flour. Commercial oats that may be contaminated with the foregoing grains are also of concern. Some individuals with celiac disease may not be able to tolerate even pure oats (Case, 2006; FDA, 2007).

Abbreviations: Antibodies (Abs) ; Celiac Disease (CD); Dermatitis Herpetiformis (DH); Diagnosis (Dx); Endomysial (EM) Antibodies; Gastro-intestinal (GI); Gluten-Free Diet (GFD); Intraepithelial Lymphocytes (IELs); Laboratory (Lab);Tissue Transglutaminase (tTG) Antibodies; reticulin (Ret); Immunohistochemistry (IH).

Table 1: Pivotal clinical studies of the effects of oats on patients with celiac disease and dermatitis herpetiformis

Reference Authors/ Year	Number of Subjects Tested	Study Length	Amount of Oats Added to a GFD	Purity Tested	Control	Clinical and Lab Tests	Intestinal Biopsy Findings After Challenge	Conclusion
Adults								
Srinivasan *et al.*, 1996, 1999, 2006	10	12 weeks	50 g/day	Yes	Self-control	Gliadin and EM Abs No detected after Oats challenge	Normal histology after Oats challenge No change IEL and Enterocyte height and immunohistochemical biomarkers Lactase +	Oats are not toxic to celiac patients
Micro-challenge with 500 mg of gluten/ day	2	6 weeks				Relapse after gluten	Relapse after gluten	
Hardman *et al.*, 1997	10 DH patients	12 weeks	62.5 g/day (mean)	Yes	Self-control	Gliadin Ret and EM Abs No detected after Oats challenge	Normal histology after Oats challenge. No change IEL and Enterocyte height No change in dermal IgA	Adults with DH tolerate moderate amounts of oats
Lundin *et al.*, 2003	19 18 completed the study 1 drop-out after two weeks due to GI symptoms	12 weeks	50 g/day	Yes	Self-control	Normal gliadin EM and tTG Abs	18 patients with normal histology 1 villous atrophy 5+ interferon γ (IFN-γ) mRNA	Most CD patients tolerate uncontaminated oats in the diet
Follow up	12 continued oats regularly	1.5 years	less 50 g/day			Normal serology	Normal histology 2+ IFN-γ) mRNA	
Reuanala *et al.*, 1998	23 DH 11 oats 1 oats drop-out due to rash	6 months	53.2 g/day (mean)	Yes	11 control and self-control	8 asymptomatic 2 oat and 3 control developed transient rash EM Abs normal in all subjects	Normal villous architecture, EIL and IH markers Skin biopsy no different than normal	Absence of oats toxicity in small bowel and no activation of DH

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Reference Authors/ Year	Number of Subjects Tested	Study Length	Amount of Oats Added to a GFD	Purity Tested	Control	Clinical and Lab Tests	Intestinal Biopsy Findings After Challenge	Conclusion
Adults								
Janatuinen *et al.*, 1995	52 in remission 26 oats/26 control 49 new Dx 19 oats/21 control 6 drop-out on oats 5 drop-out control	6 months 12 months	49.9 g/day 46.6 g/day	Yes	26 in remission 21 new Dx 5 drop-out	No serology	Normal villous architecture at 6 months and 12 months One out of 19 new Dx did not enter remission after 12 months/oats	Most subjects tolerated oats in the amounts of 50–70 g/day in an otherwise GFD
Janatuinen *et al.*, 2000	As above	As above	As above	Yes	As above	Gliadin Reticulin Abs no difference oats with controls	IEL no difference at 6 and 12 months oats with controls	Support above conclusion
Peräaho *et al.*, 2004 a	39/23 oats and 16 control 20 oats completed; 3 oats drop-outs due to GI symptoms	1 year	50 g/day	?	16 control	Yes EM and tTg Abs	Biopsy available from 18 treated and 13 control Others refused it Morphology no difference between groups IELs higher in oats vs. control	In this study is not clear if oats used were uncontaminated
Størsrud *et al.*, 2003a, b	20 in remission 15 remained for 2 yr on oats 5 drop-outs	2 years	93 g/day	Yes	Self-control	Yes Gliadin and EM Abs	11 patients normal at baseline and after oats 3 partial atrophy at baseline and after oats No difference after oats baseline	Adult patients in remission can tolerate 70–100 g/day of oats with nutritional and compliance benefits
Janatuinen *et al.*, 2002 (follow-up from previous study)	35 oats/28 control 23/35 remained on oats 12 drop-outs	5 years	34 g/day (mean)	Yes at 6–12 months, but not thereafter	28	Yes Gliadin, EM and Ret Abs	20/35 oats and 20/28 had biopsy All normal No difference oats with control group	Supports the view that oats in moderate amounts are tolerated by CD patients up to five years. Limitations: higher number of drop-outs; purity of oats not tested after long-term use
Kemppainen *et al.*, 2007 continuation of Janatuinen *et al.*, 2002	22 12 continued on oats 10 oats drop-out	5 years	As above	As above	20		Biopsy of 12 oats and 20 control IELs biomarkers No difference oats vs. controls	Long-term use of oats does not stimulate local immunologic response in the small bowel

Abbreviations: Antibodies (Abs) ; Celiac Disease (CD); Dermatitis Herpetiformis (DH); Diagnosis (Dx); Endomysial (EM) Antibodies; Gastro-intestinal (GI); Gluten-Free Diet (GFD); Intraepithelial Lymphocytes (IELs); Laboratory (Lab);Tissue Transglutaminase (tTG) Antibodies; reticulin (Ret); Immunohistochemistry (IH).

Table 1: Pivotal clinical studies of the effects of oats on patients with celiac disease and dermatitis herpetiformis

Reference Authors/ Year	Number of Subjects Tested	Study Length	Amount of Oats Added to a GFD	Purity Tested	Control	Clinical and Lab Tests	Intestinal Biopsy Findings After Challenge	Conclusion
Children								
Hoffenberg *et al.*, 2000	10 New Dx	6 month	24 g/day	Yes	Self-control	Yes tTG Abs	Villous architecture and IEL count improved after oats	Commercially available oats, tested for purity was tolerated by newly Dx celiac children in this study
Högberg *et al.*, 2004	116 new Dx 57 oats/ 59 control 42 oats completed this study 15 oats drop-outs	1 year	25-50 g/day	Yes	59 50 completed 7 drop-outs 2 lost to follow-up	Yes Gliadin and tTG Abs	Normal histology improved on oats no difference with control Two control did not improve on GFD	Addition of oats to GFD is tolerated by newly Dx CD children
Hollén *et al.*, 2006 continuation of Högberg *et al.*, 2004	38 New Dx included in this part of the study	As above	As above	As above	48	Yes Avenin Abs	Decrease avenin Abs titers no difference with control	Oats per se do not induce hormonal immune reaction
Holm *et al.*, 2006	36/32 consented 9 new Dx 23 in remission 13/23 challenged with oats and 10/23 challenged with gluten, after relapse with gluten 9/10 placed on GFD + oats	2 years	43 g/day (mean)	Yes	Self-control	Yes EM, gliadin and tTG Abs	Relapse after gluten but not oats challenge Recovery of all groups on GFD + oats as per histology IELs and biomarkers	Pure oats can be safely added to the GFD of children with CD No evidence of toxicity of immune reaction
	22 long-term clinical follow-up	7 years						

The available information is summarized in Appendix 1 and is organized according to:

A. Clinical trials which tested the safety of oats by introducing oats into an otherwise gluten-free diet are grouped by subject (Adults vs. Children) and are organized by the increasing duration of the trial. These pivotal studies are also summarized in Table 1.

B. Other relevant publications, including in vitro studies, a retrospective analysis and a systematic review of the responses of celiac patients to oats, are organized chronologically by publication date.

An overall assessment of the studies published since 1995 (Table 1) supports the view that the majority of adults and children who have CD or dermatitis herpetiformis, regardless of whether the condition is newly diagnosed or in remission, can tolerate moderate amounts of pure oats, uncontaminated with gluten from wheat, rye and barley. However the following issues should be taken into consideration when introducing oats into the gluten-free diet of individuals with CD:

- Comparisons of the various studies are complicated by the different study designs, the different conditions used in the testing and reporting of the purity of the oat products used in the clinical trials, and the different specifications for gluten-free products among different countries. All the studies reviewed had some limitations; however, regardless of these limitations most studies indicated that subjects could tolerate the inclusion of oats in a gluten-free diet.
- All publications of clinical challenge studies testing the safety of oats in adults and children with CD were evaluated (Table1). The majority of the study designs were short in duration (a year or less). There was one study in adults with a 5-year follow-up period (Janatuinen *et al.,* 2002) with a follow up analysis of the local immunological response of the small bowel (Kemppainen *et al.,* 2007), and one study in children with 7-year follow-up period (Holm *et al.,* 2006). Therefore the potential effects of a lifetime exposure to oats continue to need further investigation. Long-term compliance with a gluten-free diet is one of the major difficulties in the management of CD and the collection of long-term data related to consumption of oats is also challenging. Tin a long-term study is also difficult to obtain information on reasons for patient drop outs.
- The number of subjects included in each challenge study was limited, most likely due to the difficulty of recruiting enough subjects willing to comply with the long and laborious study protocols. More specifically, studies involving children, particularly those including very young children are further challenged by the possible reluctance of the children and/or their parents to participate, which may interfere with compliance and with the desire to continue in the study. Training the families of the children to maintain compliance to the study protocol is an additional essential requirement to ensure accurate results. Furthermore, CD patients willing to participate in challenge studies may face reactivation of the clinical symptoms or delay in their recovery. For ethical reasons, most studies that recruited newly diagnosed patients had exclusion criteria to eliminate patients with the most severe pathologies. It is important to recognize the limitations that are encountered in CD challenge clinical trials, as the information gleaned from these trials must be interpreted and evaluated with caution.
- The differences in the oat products used and the testing and reporting of the purity of oats further limited a comprehensive safety assessment. In the literature, it was not always clear from the study design as to the specifications of the "pure and uncontaminated" oats. Most recent studies (Table 1) indicated that the purity of the oats was tested and that the oats were free from contamination with other cereal grains such as wheat, barley and rye. However, many studies failed to indicate the levels of detection for the testing techniques or the cut-off values

used to determine whether the oat samples were considered to be free of gluten from other cereal grains. It was assumed that unless otherwise specified, the oat samples reported as free of contamination were negative as per the detection limit of the applied testing method(s). An emphasis has been placed on the purity of the oats because the contamination of oat products by gluten-containing wheat, barley and rye cereals has been reported as an intermittent problem and can potentially skew trial results (Hernando *et al.,* 2006; Kilmartin *et al.,* 2003; Thompson, 2004 and 2005). However gluten contamination from various sources can also be found in natural gluten-free products (i.e. maize, rice and buckwheat) (Ciclitira and Ellis, 1991; Collin *et al.,* 2004; Holm *et al.,* 2006). A standardization of the reporting of the purity of oats utilized within the studies would increase the accuracy of safety assessments and assist in the establishment of a threshold for the tolerance to wheat, barley and rye gluten. Cross validation, standardization and international agreement on the test methodologies to assess purity of oats will also need re-evaluation as further information becomes available. A worldwide definition for the term "gluten-free", and a threshold for the amount of gluten required to initiate or maintain an immunological reaction in CD individuals has not yet been fully established. Determination of such a threshold is complicated by variations in sensitivity to wheat, barley and rye gluten among affected individuals. Specific labeling regulations with regard to the gluten content of a product often vary considerably from one country to another (Case, 2006). It should be noted that there are limited clinical scientific data on safe gluten threshold levels and the current figures of 20 ppm (20 mg/kg) and 200 ppm (200 mg/kg) do not represent values that are supported by a consensus of scientific opinion (Case, 2006). The FDA March 2006 report entitled "Approaches to Establish Thresholds for Major Food Allergens and for Gluten defines three categories of gluten-free foods in the US. The Canadian standard for gluten-free simply states that "No person shall label, package, sell or advertise a food in a manner likely to create an impression that it is a "gluten-free" food unless the food does not contain wheat, including spelt and kamut, or oats, barley, rye, triticale or any part thereof" (Canada's Food and Drug Regulations B.24.018). For compliance purposes, Canada applies an action level for gluten of 20 ppm for products claiming to be gluten-free. This action level, which is historically based on the performance of available analytical methods, will be subject to periodic review as new data become available regarding emerging analytical techniques and a possible gluten threshold.

- Collin *et al.,* (2004) estimated a limit for residual gluten based on present scientific literature and the measurement of gluten in gluten-free products on the market. The gluten content of 59 natural gluten-free products and 24 wheat starch-based gluten free products was analyzed using enzyme-linked immunosorbent assays. The daily intake of gluten-free flours was also estimated from 76 adults and 16 children with CD consuming gluten-free diets, and the mucosal histology of these participants was examined. The results of this study indicated that a number of natural gluten-free and wheat starch-based products contained gluten ranging from 20 to 200 ppm (20-200 mg/kg). The median daily gluten-free flour consumption was estimated to be approximately 80 g/day and within these conditions the long-term mucosal recovery was considered good. The authors suggested that a threshold for gluten tolerance could be established at 100 ppm (100 mg/kg) and further indicated that even if the daily intake of gluten-free flour were 300g/day, at a threshold of 100 ppm, the intake would be equivalent to 30 mg gluten/day. In contrast, Hischenhuber *et al.,* (2006) conducted a comprehensive review and suggested a threshold range for the maximum tolerated daily intake of gluten could be greater than 10 mg/day but lower than 100 mg/day. Case (2006) noted that there are various gluten tolerance levels in people with

CD and that this tolerance level may be between 6–30 mg gluten/day. Recently (Catassi *et al.* 2007) published the results of a prospective, double blind, placebo-controlled trial, conducted to establish a safe gluten threshold of prolonged exposure to trace amounts of gluten (i.e., contaminating gluten) for patients with CD. The authors concluded that the ingestion of contaminating gluten should be kept lower than 50 mg/d in the treatment of CD. Evidently, further research is required to determine a tolerable gluten threshold level and the amount of gluten-free products that can be safely consumed by the CD population at large. The establishment of a gluten tolerance threshold, though difficult to achieve, would assist in unifying global labeling regulations and vastly improve the ability to comply with a gluten-free diet lifestyle.

Despite the noted challenges of conducting a comprehensive evaluation of the most recent clinical trials, the majority of the evidence indicated that most people with CD could tolerate the inclusion of a moderate amount (20–25 grams/day [65 ml – or ¼ cup] dry rolled oats) for children and 50 –70 grams/day (125 to 175 ml – or ½ to ¾ cup dry rolled oats) for adults of pure oats (uncontaminated with other cereal grains such as wheat, barley and rye) in a gluten-free diet (Table 1, Appendix 1). Based on some evidence that a possible sensitivity to pure oats exists, most investigators in the field recommend a clinical follow-up when introducing pure oats to the gluten-free diet. This includes initial and long term assessments (Rashid *et al.,* 2007; Haboubi *et al.,* 2006).

- With regard to the clinical trials evaluating the inclusion of oats within a gluten-free diet (Table 1, Appendix 1), Størsrud *et al.,* (2003a, b) tested 93 g/day of pure oats in a small number of adult subjects for 2 years and (Holm *et al.,* 2006) studied for 2 years children who ingested of a median of 43 g (up to 81 g/day) oats daily; neither study reported any adverse effects. These amounts of oats are higher than those recommended by the Canadian Celiac Association (CCA) for adults (50 to 70 g/rolled oats/day) and children (20 to 25 g of rolled oats/day). Although these studies did not specify the cut-off values used to determine whether the oat samples were considered gluten-free, Størsrud *et al.,* (2003a, b) reported a 20 ppm limit of detection and Holm *et al.,* (2006) reported that 29 out of 30 oat samples tested contained gliadin levels below 28 ppm.
- As reported in the clinical trials, some CD patients experienced gastrointestinal symptoms more often on an oat-containing diet than with a traditional gluten-free diet. However, in general, such symptoms have been reported as transient, mild, and are explained as the effect of an increased intake of fiber from oat products rather than the reoccurrence of clinical manifestations of CD. The appearance of mild gastro-intestinal symptoms was not considered adverse enough to exclude the introduction of oats from the gluten-free diet of CD patients. There were a couple of reports regarding a few highly sensitive adult CD patients who were intolerant to pure uncontaminated oats based on intestinal morphology and serological parameters (Hollén *et al.,* 2003, 2006a,b; Lundin *et al.,* 2003). However, with the exception of one patient in one study (Lundin *et al.,* 2003) there was no evidence to associate oats with the development of atrophy of the small bowel mucosa, the definitive histopathological criterion of CD. Furthermore, clinical studies conducted with newly diagnosed adult patients (Janatuinen *et al.,* 1995, 2000) reported healing of the bowel mucosa in patients on a gluten-free diet that included oats. Despite the limited information on drop outs, reports of 5 year follow up of adult CD patients including oats in their diet show evidence that exposure to oats does not alter the small bowel morphology and does not stimulate an immunological response locally in the mucosa of the small intestine (Janatuinen *et al.,* 2002; Kemppainen *et al.,* 2007).

- Similar to the findings in adult CD patients, a randomized double-blind study conducted with children who were newly diagnosed with CD showed that the consumption of an oat-containing gluten-free diet for 1 year did not interfere with clinical, serological or small bowel mucosal recovery. Despite these results, 26% of the children in the oat-containing gluten-free diet group withdrew from the study (Högberg *et al.,* 2004 and Hollén *et al.,* 2006a, b). It is not clear why they withdrew from the study protocol. On the other hand, Holm *et al.,* (2006) followed 22 CD children on gluten-free diet plus oats for 7 years without clinical or serological evidence of relapse.
- Arentz-Hansen *et al.,* (2004) indicated that their in vitro study demonstrated that even if oats seem to be well tolerated by many CD patients, there are patients who have an intestinal T cell response to oats. Other investigators who also conducted an in vitro study (Kilmartin. *et al.,* 2003, 2006) demonstrated that purified avenin, the oat prolamin, is not immunogenic to the bowel mucosa of CD patients. Furthermore, it has been suggested by other investigators that because avenin accounts for 5–15% of the total protein in oats, whereas in wheat, barley and rye, prolamins constitute 40–50% of the total protein (Kilmartin *et al.,* 2006), large amounts of oats still may be toxic to CD patients. Investigators believe that there are similarities between the protein structure of oats and some wheat-like sequences, but the putative toxic amino acid sequences are less frequent in avenin than in other prolamins, which could explain the less toxic nature of oats (Arentz-Hansen *et al.*,; Ellis and Ciclitira, 2001; McLachlan *et al.,* 2002; Shan *et al.,* 2002; Vader *et al.,* 2002, 2003; Valdes *et al.,* 2003).

In conclusion, the safety/benefit evaluation for the introduction of oats in the gluten-free diet of CD patients indicates that moderate amounts of pure oats are well tolerated by the majority of individuals with CD and dermatitis herpetiformis.The term "pure oats" is used to indicate oats uncontaminated with gluten from other closely related cereal grains, including wheat, barley and rye as detected using current test methods. Based on clinical trials in the published literature, the amount of pure oats considered within safe limits is 50 to 70 g/day for adults and 20 to 25 g/day for children. The benefits include: improved compliance with a gluten-free diet, increased palatability, increased source of fiber and greater variety of choices to an already highly restrictive gluten-free diet. However, the above-noted limitations call for some caution when introducing oats to the gluten-free diet. Although the majority of evidence supports the toleration of oats in a gluten-free diet, the fact that some people with CD cannot tolerate even pure oats requires further investigation and cautious progress. Currently, it is unclear what proportions of people with CD do not tolerate pure oats. Because of the limited long term data, the number of drop outs without specific knowledge of their reasons, the small number of subjects tested and the indication from some in vitro studies of an immunological response in the absence of clinical manifestations, most researchers suggest that until the prevalence of oats intolerance among people with CD is well established, a clinical follow-up of CD patients consuming oats in their diet is advisable. This includes initial and long term evaluations. In addition, the terminology for pure uncontaminated oats needs to be further defined, including sampling and testing methodologies. At present in Canada, pure uncontaminated oats are identified at the source. These oats shall meet or exceed the purity standards of Foundation #1 as defined by the Canada"s Seeds Act and shall be harvested, transported, stored, processed and manufactured under Good Manufacturing Practices to minimize the presence of wheat, including spelt and kamut, barley, rye or triticale or any part thereof. Those individuals and/or practitioners interested in introducing oats to people with CD or dermatitis herpetiformis are advised to consult physicians, dieticians and health practitioners. The Canadian Celiac Association web site is a recommended source for further information and guidance www.celiac.ca.

Appendix 1:

A. Pivotal in vivo clinical studies testing the safety of oats (Table 1).

a. Adults

1. Srinivasan *et al.,* (1996, 1999) studied the safety of oats in ten adult patients with CD in clinical and histological remission. Each patient consumed 50 g of oats (as porridge) daily for 12 weeks while maintaining a strict gluten-free diet. The oat cereal used in the study was tested for evidence of gluten contamination using reverse phase high performance liquid chromatography, enzyme linked immunoassay, and polymerase chain reaction techniques. The oats were determined to be entirely gluten-free. Details were not provided as to the levels of detection for these techniques or the cut-off values used to determine whether the oat samples were considered gluten-free. The patients were assessed clinically at 0, 1, 4, and 12 weeks. At each assessment the following laboratory investigations were performed: full hematological and biochemical profiles and serological tests for antibodies to gliadin and endomysium. Duodenal biopsies were obtained before the start of the oats challenge and after the12 week trial period. All patients complied fully with the study protocol. Throughout the oat challenge all patients remained asymptomatic with normal hematological and biochemical indices. Endomysial and gliadin antibody values were unaltered by the oats supplementation and no morphological damage was evident using a standard histological evaluation. Quantitative histological examinations showed no significant change in the intraepithelial lymphocyte count or enterocyte height. Subsequently, two patients were given a gluten "micro-challenge" consisting of 500 mg of gluten daily for six weeks: both developed histological evidence of relapse and one patient tested positive by antibody production tests. These investigators further assessed the toxicity of oats in celiac disease patients by immunohistochemically detecting the presence of lactase enzyme in the intestinal biopsy. This enzyme is lost in active celiac disease, but was unaffected by oats challenge (Srinivasan *et al.,* 1999).
2. Hardman *et al.,* (1997) studied seven men and three women (mean age: 58 years) with biopsy-confirmed dermatitis herpetiformis. The subjects had followed a strict gluten-free diet for a mean of 15.8 years and had controlled the rash and enteropathy. The subjects added oats to their diets for 12 weeks (mean [±SD] daily intake, 62.5±10.8 g). The purity of the oats was tested by enzyme linked immunosorbent assay and polymerase chain reaction. Details were not provided as to the levels of detection of these techniques or the cut-off values used to determine whether the oat samples were considered gluten-free. All patients underwent duodenal and skin biopsies at the beginning and end of the study. None of the patients reported any adverse effects. Serologic tests for antigliadin, antireticulin, and antiendomysial antibodies were negative both before and after the trial period. Villous architecture remained normal after the 12-week period: the mean (±SE) ratio of the height of villi to the depth of crypts was 3.59±0.11 before the diet and 3.71±0.09 afterward (normal, 3 to 5), and the mean enterocyte heights were 31.36±0.58 micron and 31.75±44 micron, respectively (normal range, 29 to 34). Duodenal intraepithelial lymphocyte counts all remained within normal limits (mean, 13.8±1.03 per 100 enterocytes before the diet and 14.2±1.2 per 100 enterocytes afterward; normal range, 10 to 30). Dermal IgA in skin biopsies showed no significant changes.
3. Srinivasan *et al.,* (2006) evaluated the response of the small intestine to oats by assessing

the activation of the gastrointestinal immune system. This study involved 10 adults who ingested 50 g of oats daily in conjunction with an otherwise gluten-free diet for a 12-week period. The oat cereal used in this study was reported to be entirely free of contamination as tested by various methodologies including, reverse phase HPLC, enzyme linked immunoassay and polymerase chain reaction. Patient compliance, clinical symptoms and serology (IgG antigliadin and IgA anti-endomysial antibodies) were monitored throughout the study period. Duodenal biopsies were obtained by endoscope at the beginning and end of the study. After the 12 week trial, four of the patients were challenged with 500 mg gluten/day and another two patients with 10 g gluten/day for a period of 6 weeks. Duodenal biopsies obtained before and after the inclusion of oats in the diet were stained with a series of antibodies directed against the following molecules: human leukocyte antigen D-related (HLA-DR), Ki-67, CD25, and CD54 [intercellular adhesion molecule 1 (ICAM-1)] and mast cell tryptase. These detailed immunohistological studies of the biopsies did not reveal evidence of immune activation or morphological damage following the consumption of oats. On the other hand, all patients challenged with gluten (500 mg or 10 g/day) showed evidence of reactivation of the disease with various degrees of gastro-intestinal symptoms, serological responses and evidence of morphological changes within the duodenal biopsy. The authors concluded that under these trial conditions, the ingestion of oats did not show evidence of immunogenic or toxic effects on the duodenal mucosa of celiac individuals and supported the viewpoint that oats is well tolerated by the majority of celiac patients.

4. Lundin *et al.,* (2003) conducted an oat challenge study in 19 adult CD patients who were in remission on gluten-free diets. The gluten-free diets were supplemented with 50 g/day of oats for 12 weeks. Oat samples were obtained from a single manufacturer who upheld strict practices to avoid contamination with wheat and other gluten related grains. Twenty-five oat samples from this manufacturer were analyzed in-house and a reference laboratory analyzed an additional 120 samples. No contamination was detected in any of these samples using ELISA and mass spectrometry (MS) with a limit of detection for gluten contamination reported as 20 ppm. Six oat samples were later analyzed by western blot, an ELISA test using a cocktail of antibodies and MALDI-TOF mass spectrometry with a limit of detection reported as 5 ppm. The level of gluten detected in five of these samples was estimated to be between <1.5 and 23 ppm and considered negative for gluten contamination. The sixth sample was considered contaminated (>400 ppm by western blot, ELISA, and MS). MS was unable to determine the source of the contamination due to the large amount of oat avenins in the sample and the fact that barley and oats are not distinguishable by MS. An additional sample was analyzed from the bottom of the same bag of contaminated oats and <1.5 ppm of gluten was detected. The authors assumed that a single or a few seeds of barley might have been present in the bag but determined that the oats used in the study were sufficiently pure and adhered to the limitations by the revised suggested Codex standard limit of 20 ppm for natural gluten-free products. All patients were evaluated by serological testing including IgA anti-gliadin, antiendomysium and antitransglutaminase antibodies. Gastroduodenoscopy was performed before and after the oat challenge. Biopsies were scored using Marsh score and levels of mRNA specific for interferon (IFN-) were determined by reverse transcription-polymerase chain reaction analysis. Interferon was tested as a marker for T cell activation. Oats were well tolerated by most patients but several reported transient abdominal discomfort and bloating at the beginning of the challenge. This could have resulted from increased fibre consumption in

patients unused to much fibre in their diets. One patient withdrew due to gastrointestinal symptoms and another patient developed partial villous atrophy and a rash during the first oats challenge. This patient subsequently improved on an oat free diet but developed subtotal villous atrophy and dramatic dermatitis during a second challenge with oats. There was no evidence of contamination in the oats consumed by the patient exhibiting intolerance. Five of the subjects had positive levels of interferon- mRNA but no corresponding histological abnormalities after the challenge. The significance of this finding is not fully understood but the authors suspect that T cell activation might not be directly responsible for the villous atrophy seen in CD. The major difference observed in this study is that one of the patients was intolerant to oats. The authors reported that after the completion of this challenge study they became aware of other patients identified as clinically intolerant to oats (dermatitis, abdominal pain, and general anaphylactoid-like reactions) but not further confirmed by endoscopy with a duodenal biopsy. However, none of the subjects were willing to ingest oats again. Therefore, the authors concluded that despite the ability of most patients to tolerate the incorporation of oats into their diets, some individuals might be intolerant to oats.

5. Reunala *et al.,* (1998) conducted an oat challenge study with eleven patients who had dermatitis herpetiformis (DH). Another 11 patients with DH were used as a control group. At diagnosis all patients had skin and duodenal biopsies. All patients were in remission on gluten-free diets for at least 5.5 years and free of a rash for 14 months. Test subjects consumed 50 g oats/day for six months within an otherwise gluten-free diet. The oats used in this challenge were free of gluten contamination as tested by enzyme linked immunosorbent assay and polymerase chain reaction. In this study, the specifications for the amount of gluten allowed to be consumed from wheat starch flours was up to 0.3 g protein equivalent to 50 mg of gluten per 100 g flour which is in accordance with Codex Alimentarius 118-1981. Clinical symptoms, serum, skin and small bowel biopsies were assessed before and after the oat challenge. Eight patients challenged with oats remained asymptomatic, two developed transient rashes, and one withdrew because of the appearance of a more persistent but mild rash. Three of the 11 controls also developed transient rashes. IgA endomysial antibodies remained negative in all patients and the small bowel villous architecture remained unaltered after the oat challenge. The densities of intraepithelial CD3 and $\alpha\beta$ and $\gamma\delta$ T cell receptor positive lymphocytes and crypt epithelial cell DR expression were assessed by immunohistochemistry. These biomarkers are considered to be sensitive indicators of immune response to gluten. Except for γ T cell receptor these biomarkers were not altered by oats challenge. The expression of $\gamma\delta$ T cell receptor showed a significant difference ($p<0.001$) when compared oats to controls. However, it should be noted that this biomarker was elevated at baseline and improved after the oats challenge.

6. Janatuinen *et al.,* (1995) were the first to evaluate the possible toxicity of oats in a large controlled study in adult celiac patients. In this randomized trial, which lasted up to 12 months, they compared the effects of gluten-free diets with and without oats. They studied two groups of patients: those with previously diagnosed celiac disease who were in remission and those with new diagnosis. The previously diagnosed group was selected based on records of the recovery of the duodenal mucosa while on a gluten-free diet for at least 12 months. For the new diagnosis, endoscopy with a duodenal biopsy was performed and the diagnosis of CD was based on the presence of the subtotal or total villous atrophy of the duodenal mucosa prior the introduction of a gluten-free diet.

Fifty-two adults with CD in remission were followed for 6 months and 40 adults with newly diagnosed CD for 12 months. Patients were randomly assigned according to sex to either the oats or the control group. The oats group included 26 patients in remission and 19 newly diagnosed. The control group included 26 patients in remission and 21 newly diagnosed. The controls received a gluten-free diet containing 0.74 mg of gluten/g of foodstuff. The oat groups supplemented the same basic gluten-free diet with 50 to 70 g/day of oats in the form of wheat-starch flour mixed with an equal amount of oats, muesli containing 60% oats, and rolled-oat breakfast cereal. The authors neglected to report whether the oats added to the gluten-free diets were tested for purity. The mean (± SD) oat intake in the oat group was 49.9 ± 14.7 g per day for 6 months among patients in remission and 46.6 ± 13.3 g per day for 12 months among patients with a new diagnosis. The oat and control groups did not differ significantly in nutritional status, symptoms, or laboratory measures. The authors reported that patients in remission, regardless of diet, did not have a worsening architecture of the duodenal villi nor increased mononuclear-cell infiltration. All the patients with a new diagnosis were in remission within one year, except for one subject in the control group. The rate of withdrawal was comparable: six patients in the oat group and five in the control group withdrew from the study. The investigators concluded that moderate amounts of oats could be included in a gluten-free diet for most adult patients with celiac disease without adverse effects. In this study, the basic gluten-free diet consumed by participants contained 0.74 mg of gluten/g of foodstuff, and the oats were not tested for purity. Nevertheless, there were no significant differences between the control and the test group in remission as per the duodenal biopsies and clinical findings.

7. Janatuinen *et al.,* (2000) conducted a randomized controlled intervention study over a 6–12 month period with 40 adults who were newly diagnosed with celiac disease and 52 adults who were in remission. Patients were randomized by sex into either the oat consuming or the control groups. The control groups received gluten-free cereal. The oat consuming groups received products supplemented with oats: two types of gluten-free wheat starch flour including 50% oats, muesli including 60% oats, and rolled oat breakfast cereal. Some of the oat products used in this study were commercially available. The daily intake of oats was 50–70 g. The purity of the oats was regularly monitored. Gluten was analyzed by a quantitative enzyme immunoassay using a specific monoclonal antibody to -gliadin. This antibody detects all prolamins in wheat and rye, only some of the prolamins in barley and none of the prolamins in oats. All oat samples were considered gluten-free but no specification was provided with regard to the limit of detection. All patients were evaluated using serum levels of gliadin and reticulin antibodies. In the intestinal biopsies, the number of intraepithelial lymphocytes (IELs) in the intestinal mucosa was examined before and after the intervention. The rate of disappearance of gliadin and reticulin antibodies did not differ between the diet groups of the patients with newly diagnosed celiac disease. Oats also had no effect on gliadin or reticulin antibody levels in the patients who were in remission. The number of IELs decreased similarly regardless of the diet of newly diagnosed patients and no increase in the number of IELs was found in the patients who were in remission and consuming diets with or without oats. In summary, there were no significant differences between the clinical symptoms, laboratory measures and histology of duodenal biopsies among the test groups who received oats or those who did not receive oats. The authors concluded that this study further strengthens

the view that adults with celiac disease can tolerate moderate amounts of oats.

8. Peräaho M. *et al.,* (2004a) studied 39 celiac disease patients who consumed gluten-free diets. Patients were randomized to a gluten-free diet with 50 g oats/day (23 patients) or without oats (16 patients) for 1 year. The purity of the oats used in this study was not specified in the report. The following parameters were evaluated: quality of life, gastrointestinal symptoms, small-bowel histopathology, and serum endomysial and tissue transglutaminase antibodies. The quality of life did not differ between the groups, but there were more gastrointestinal symptoms in the oats-consuming group. Patients consuming oats suffered significantly more often from diarrhea, but there was also a simultaneous trend towards more severe constipation symptoms. Three patients on the oats diet dropped out of the study due to gastrointestinal symptoms. The villous structure did not differ between the groups, but the density of intraepithelial lymphocytes was slightly significantly higher in the oat group. The severity of the gastrointestinal symptoms did not appear to be dependent on the degree of inflammation. Antibody levels did not increase during the study period. The authors concluded that the oat-containing gluten-free diet caused more intestinal symptoms than the traditional diet. Although the mucosal integrity was not disturbed, there was more inflammation evident in the oat group. However, the sources and purity of the oats used in this study are unknown so it is possible that the gastro-intestinal symptoms and the increased inflammation among the oat-consuming group were due to gluten-contamination from other cereal grains such as wheat, barley and rye. Despite the limitations of this study and of the effects observed in the oat group, the authors suggested that oats can provide an alternative within a gluten-free diet but that celiac patients should be aware of the possible effects on the gastro-intestinal system. Furthermore these investigators (Peräaho M. *et al.,* 2004b) also conducted an analysis on the effect of oats on symptoms and quality of life in 1,000 randomly selected members of their Celiac Society. Altogether, 710 patients responded: 423 (73%) with celiac disease and 70 (55%) with dermatitis herpetiformis were currently consuming oats. Patients appreciated the taste, the ease of use, and the low costs; 94% believed that oats diversified the gluten-free diet; 15% of celiac disease and 28% of dermatitis herpetiformis patients had stopped eating oats. The most common reasons for avoiding oats were fear of adverse effects or contamination. The authors suggest that there is a market demand for oats, and celiac societies and dietitians should make efforts to promote the development of products free of wheat contamination.

9. Størsrud *et al.,* (2003 a, b) studied the effects of adding uncontaminated rolled oats to the daily diets of 20 adult celiac patients who were in remission. Although there are two reports, they represent one main study. The core results are based on the 15 patients who completed the study. These subjects added oats to their gluten-free diet for 2 years. The median intake of oats was 93 g/day. The oats were free from wheat, rye and barley as tested by enzyme-linked immonosorbent assay that detects -gliadin. This method detects high molecular weight proteins in wheat, rye and barley, but not oats (avenin). The method is quantitative with a detection limit of 20 ppm. The examinations of the subjects were performed four times during the study period and included small bowel endoscopy with biopsies, blood samples (nutritional status, serological analysis), height and body weight, gastrointestinal symptoms and dietary records. Histopathology of duodenal biopsies was assessed at baseline (n=20), 6 month (n=17) and 2 years (n=14). One patient refused the biopsy. Villous architecture and inflammatory infiltrate were assessed. Evidence of partial atrophy and inflammation of the small bowel

was present at baseline in some patients at baseline and remained after oats exposure (n=3). None of the patients with normal histology deteriorated after exposure to oats (n=11). None of the parameters evaluated indicated any evidence of reactivation of the disease in response to the introduction of pure oats into the gluten-free diet after the 2-year trial period. Five patients withdrew from the study, 2 due to gastro-intestinal symptoms and the other 3 for non-medical reasons. Examinations of the patients after their withdrawal did not reveal any deterioration in small bowel histology, nutritional status or raised levels of antibodies. The other report that was based on the subjects who completed this 2-year trial study focused on the benefits and the nutritional status of the participants. The mean intakes of iron and dietary fiber increased ($P<0.001$) with the consumption of oats, as well as the intakes of thiamin and zinc ($P<0.02$). Temporary increased flatulence was also experienced during the first few weeks of consuming oats, as well as improved bowel function. All participants who completed the study period reported a desire to continue to eat oats after the study because they found that the addition of oats to the gluten-free diet gave more variety, better taste and satiety. The consumption of oats improved the nutritional value of the gluten-free diet, did not have negative effects on nutritional status and was appreciated by the subjects. The authors suggested that including oats could help people improve their compliance to a strict gluten-free diet.

10. Janatuinen *et al.,* (2002) assessed the safety of the long term ingestion of oats in the diet of celiac patients. In a previous study, the effects of a gluten-free diet and a gluten-free diet including oats were compared in a randomized trial involving 92 adult patients with celiac disease (45 in the oats group, 47 in the control group). Oat products were obtained from commercial sources. The mean amount of oats added to the gluten-free diet was 34 g/day. The purity of the oats and the gluten-free products were monitored during the 6–12 month intervention (Janatuinen et al 2000). After the initial phase of 6–12 months, patients in the oats group were encouraged to eat oats freely in conjunction with an otherwise gluten-free diet. However, there was no systematic monitoring of the purity of these oat supplements. A follow-up was conducted after a 5-year period; there were 23 patients still on an oats diet. Of the original oat-consuming group, 12 subjects dropped out for reasons including uncertainty about safety, flatulence and rash. In the control group 28 patients on a conventional gluten-free diet were examined. In addition to the clinical and nutritional assessment, the following parameters were evaluated: duodenal biopsies histopathology and histomorphometry, and measurement of antiendomysial, antireticulin, and antigliadin antibodies. There were no significant differences between controls and those patients consuming oats with respect to duodenal villous architecture, inflammatory cell infiltration of the duodenal mucosa, or antibody titers after the 5-year follow-up. The authors reported that in both groups histological and histomorphometric indexes improved equally over time. Despite the high withdrawal rate and the fact that neither the oats nor the gluten-free products were monitored for gluten, making it impossible to access the level of gluten contamination in the diets, 23 out of 35 patients remained in the study for five years and were without signs of disease relapse as evaluated by clinical symptoms, serology or histopathology.

11. Kemppainen *et al.,* (2007) presented additional data from their 5-year follow-up study on the safety of oats in CD patients (Janatuinen *et al.,* 2002). In the present study they assessed the local cellular immunological responses using immunohistochemical biomarkers. Forty-two CD patients took part in an earlier oats intervention study for 6–12 months. Twenty-two of these patients originally consumed oats

as part of their gluten-free diet. During the 5-year follow-up 10 patients had felt uncertain about the safety of long term consumption of oats and gave up this part of their diet. Finally, 12 of the 22 patients consumed oats for the whole 5-year period. The control group consisted of the remaining 20 CD patients using a strict, conventional, gluten-free diet without oats. Intraepithelial CD3, $\gamma\delta$ T cell receptors ($\gamma\delta$ IEL) and $\alpha\beta$T cell receptors ($\alpha\beta$ IEL) T cells were counted after specific staining of small intestinal biopsy specimens. There were no differences in the densities of CD3, $\alpha\beta$ IEL and $\gamma\delta$ IEL T cells between the oat and the control groups. This study provides additional evidence that long term use of oats included in the gluten-free diets of patients with CD does not stimulate an immunological response locally in the mucosa of the small intestine. The high number of drop outs demonstrates the difficulties of conducting long term studies in CD patients as the main reason for giving up was feeling of uncertainty about the long term safety of oats. Further studies on this regard will help to increase patient's compliance and confidence about the safety of oats.

b. Children

1. Hoffenberg *et al.,* (2000) conducted a self-controlled, open-label, 6-month trial of the consumption of a commercial oat breakfast cereal among children newly diagnosed with celiac disease. The children were placed on a gluten-free diet plus commercially available oats. Over 6.6 ± 0.7 months, they consumed 24 grams of oat cereal per day, or 1.2 ± 0.9 g/kg/d. The gliadin contamination of the oat cereal used in this study was tested by an enzyme-linked immunosorbent assay, which detects gliadin. This method was chosen because it detects high molecular weight proteins in wheat, rye and barley, but not oats avenin. The samples were considered negative at a level of <0.01% (100 ppm). The 10 children who completed the study were 6.8 ± 4.0 (mean ± SD) years of age and 5 were male. To be included in the study all children had at least one sign or symptom suggestive of CD at the entry into the study. Patients were evaluated clinically including, small bowel histology and anti-tissue transglutaminase IgA antibody titer. Compared with the start of the study, there was a significant decrease in biopsy score ($P < 0.01$), intra-epithelial lymphocyte count ($P < 0.005$), anti-tissue transglutaminase IgA antibody titer ($P < 0.01$), and number of symptoms ($P < 0.01$) at the completion of the study. This study was limited because the children were newly diagnosed and the families were still learning how to manage a gluten-free diet so hidden sources of gluten may still have been present in the diet. However, the overall results showed improvement with the test diet.

2. Högberg *et al.,* (2004) reported the results from a double blind multi-centre study, which included 116 children with newly diagnosed celiac disease. Children were randomized into two groups, 59 received a gluten-free diet and 57 received a gluten-free diet plus oats. The study period was one year. The oats used in the study were specially grown, milled, and packaged to avoid contamination with wheat, rye, or barley. The oat products were tested by an ELISA assay to ensure absence of gluten contamination. The daily oat intake was 25–50 g. Small bowel biopsies were performed at the beginning and end of the study. Serum IgA antigliadin, antiendomysium, and antitissue transglutaminase antibodies were monitored at 0, 3, 6, and 12 months. Ninety-three patients completed the study, 42 on gluten-free diet plus oats and 50 gluten-free diet controls. The remaining subjects withdrew from the study, 15 in the oats group and 7 in the standard gluten-free diet and a majority of these children were from the youngest age groups in the study. However, all patients were in clinical remission after the study period and there were no significant differences between control and test groups for all of the above

noted parameters. It should be noted that avenin antibodies were also tested in the same group of patients and were reported separately by Hollén *et al.,* (2003, 2006).

3. Hollén *et al.,* (2006) reported the results from the serology tests in the double blind study described above (Högberg *et al.,* 2004). The focus of the Hollén *et al.,* study was to evaluate the antibodies to oats prolamins (avenins). Sera were obtained from the study participants. IgA and IgG anti-avenin antibodies were monitored at 0, 3, 6 and 12 months. Nitric oxide metabolites were measured in 7 patients with deviating antibody results. There was a significant decrease in anti-avenin antibodies in both groups (standard gluten-free diet and gluten-free diet plus oats) at the end of the study as compared to the beginning of the study ($p<0.001$) but no difference was found between the two groups, suggesting that oats was not producing a humoral immune reaction. IgA titers declined after 3 months. IgG titers, although significantly decreased, remained high in the majority of patients in both groups. Nitric oxide levels were high in four of the analyzed samples. The authors indicated that this study does not exclude the possibility that some CD patients are susceptible to oats based on the sero-positive results and evidence of high levels of nitric oxide metabolites in some subjects.

4. Holm *et al.,* (2006) conducted a 2-year controlled clinical trial. A total of 36 children who were over 7 years of age and were either previously diagnosed or had newly detected CD were recruited for this study. Of these children, 32 consented and 4 refused because they found the protocol too laborious. In all patients, the diagnosis of CD was based on the presence of small bowel mucosal severe, partial or subtotal villous atrophy with crypt hyperplasia, and initially all had been serum endomysial antibody (EMA) positive. Twenty-three out of the 32 children were previously diagnosed CD patients and had been treated with a conventional (avoiding wheat, rye, barley and oats) strict gluten-free diet for at least 2 years before they were included in the study. All children exhibited disease remission. These 23 patients were randomized either to undergo an open oats challenge or a gluten challenge allowing the consumption of wheat, rye and barley in addition to oats. The intake of oats was 50 g/day and patients in the gluten-challenge group ate 20 g of gluten per day. The purity of the oats (gluten-free) was confirmed by enzyme-linked immunosorbent assay and polymerase chain reaction techniques (PCR). In addition to the patients in remission, 9 newly diagnosed CD children were included in the trial consuming a comparable gluten-free diet including oats. In all the patients the following parameters were assessed: small bowel mucosal morphology, intraepithelial lymphocytes (IELs), human leucocyte antigen (HLA) DR expression and celiac serology. During the first 2 years on an oat-containing diet, clinical, nutritional and serological assessments were carried out at 0, 1, 3, 6, 12, 18, 24 months. Small bowel mucosal biopsies were evaluated at baseline and after 6 and 24 months. If the small bowel mucosal biopsy confirmed a relapse among the gluten challenge group, the patients reverted to a gluten-free diet (avoiding wheat, rye and barley) including the consumption of oats. Follow-up examinations of the gluten challenge group were carried out similarly to the oats group until small bowel mucosal histological relapse was evident. After the relapse and commencement of an oat-containing gluten-free diet, examinations continued to be carried out in the same way as in the oats challenge group. After the 2-year trial, patients continued to supplement their diets with commercially available oat products. The purity of these products were previously

analyzed: 29 out of 30 tested samples had gliadin levels below 28 mg/kg (= 28 ppm) and only one was clearly wheat-contaminated in excess of 200 ppm gluten. Follow-up visits after the 2-year trial included nutritional and serological assessments once a year or every other year for 7 years. In the long term follow-up, small bowel mucosal biopsies were considered only if the patient's clinical condition or serology implied a relapse of the disease. The authors reported that oats had no detrimental effect on intestinal histology or serology of the CD children who were in remission, during the 2-year trial. In contrast, the gluten-challenge group relapsed after 3–12 months. Complete recovery from the disease was accomplished in all patients on gluten-free diet plus oats. After the 2-year trial, 86% of the children preferred to continue to consume oats and they all remained in remission for the duration of the 7-year follow-up. This study permitted higher levels of oat ingestion (median 43 g/day and up to 81 g/day) than other studies conducted in children (median 15 to 24 g/day) (see Table 1). The trial was conducted for two years and patients on the gluten-free diet plus oats were followed-up clinically for 7 years thereafter. The authors concluded that uncontaminated oats could be safely included in a gluten-free diet in the majority of children suffering from CD. In their view, oats diversifies the gluten-free diet and children preferred it in their diet.

B. Other relevant publications on the evaluation of the safety of oats.

1. Picarelli *et al.,* (2001) used an in vitro model to test whether oats induce endomysial antibody (EMA) production in the supernatant fluid of cultured duodenal mucosa specimens which were collected from 13 treated celiac disease patients. The biopsy specimens were cultured with and without a peptic-tryptic digest (PT) of gliadin and avenin (from oats) and in medium alone. Samples from 5 of the 13 patients were cultured with the C fraction of PT-avenin. Indirect immunofluorescence was used to detect EMAs. These antibodies were detected in specimens from all 13 patients after the challenge with gliadin but not after culture in medium alone or with PT-avenin or its C fraction. The authors concluded that PT-avenin and its C fraction did not induce EMAs in celiac patients.

2. Hollén *et al.,* (2003) conducted a study in order to assess the antibodies of oat prolamins (avenin) in children who had verified celiac disease in comparison with a reference group. They measured the antibodies to avenin in sera from 81 children. Of these children, 34 were verified to have celiac disease on the basis of intestinal biopsy. The children all exhibited villous atrophy at the first biopsy, normalized intestinal mucosa after gluten withdrawal and relapse upon a gluten challenge. The remaining 47 children in the primary investigation were used as a reference group. These children had symptoms that prompted the consultation but after investigation were classified as non-celiac. Serum samples were also obtained from 7 children on gluten-free diets and after a challenge with 30 g/day of oats. The total number of serum samples was 88. All children were tested for IgA and IgG antibodies to avenin and gliadin. Crude avenin was prepared by extraction with ethanol and salt solutions and was used as an antigen in a three-step ELISA. This methodology included a series of tests to rule out possible cross-reactions. The authors found that children with celiac disease on a normal gluten-containing diet (n=23) had significantly higher levels of antibodies to avenin, both IgG and IgA, than reference children (n=47) ($P < 0.001$). The levels of avenin antibodies correlated positively with gliadin antibodies, especially of the IgA-type

(r=0.798). Serum samples from CD children after consuming gluten-free diets (which did not include oats) showed significantly lower levels of anti- avenin antibodies as compared to levels at presentation. The absorption test did not indicate cross-reactivity between the prolamins of wheat and oats. The authors conclude that children with celiac disease have antibodies to oat proteins at significantly higher levels than reference children.

3. Kilmartin, C. *et al.,* (2003) investigated the immunogenicity of avenin using cytokines interferon gamma (IFN-gamma) and interleukin (IL)-2 as markers of immunological activity. In this study, duodenal biopsies from celiac patients were cultured with 5 mg/ml of peptic tryptic gliadin (n=9) or 5 mg/ml of peptic tryptic avenin (n=8) for 4 hours. These biopsies were compared against control biopsies cultured with the medium alone and biopsies from non-celiac patients cultured with peptic tryptic gliadin (n=8) or avenin (n=8). Cytokine mRNA was quantified by TaqMan polymerase chain reaction. Secreted cytokine protein was measured in the culture supernatant by enzyme linked immunosorbent assay. The authors found that after culture with peptic tryptic gliadin, an increase in IFN-gamma mRNA was observed in all nine patients with celiac disease. Increased IFN-gamma protein was also found in four of these patients and smaller increases in IL-2 mRNA were detected in six of the CD subjects with a corresponding increase of IL-2 protein found in two of these patients. In contrast, the biopsies of celiac patients cultured with peptic tryptic avenin did not show a significant response of IFN-gamma or IL-2. Similarly, the biopsies from normal controls did not respond to either gliadin or avenin stimulation. The authors suggest that the immunogenic sequences in gliadin are not present in avenin. This suggestion supports the results of in vivo studies that report that oats are safe for consumption by celiac patients.

4. Peräaho M. *et al.,* (2004b) did a retrospective evaluation beginning in 1997, on the use of oats within a gluten-free diet by celiac and dermatitis herpetiformis patients in Finland. The use of oats and the effect of oats on symptoms of the illness and quality of life were investigated in 1,000 randomly selected members of the Celiac Society. Altogether, 710 patients responded to the questionnaire: 423 (73%) with celiac disease and 70 (55%) with dermatitis herpetiformis were currently consuming oats in their diets. Patients reported appreciating the taste, the ease of use, and the low cost of oats. Of the respondents, 94% believed that oats diversified the gluten-free diet. However, 15% of celiac and 28% of dermatitis herpetiformis patients reported that they had stopped eating oats. The most common reasons for avoiding oats were fear of adverse effects or contamination.

5. Arentz-Hansen H. *et al.,* (2004) conducted an in vitro study using intestinal T cell lines. The study included 9 adults with celiac disease who had a history of oats exposure. The oats were derived from a quality control production line and were shown to be free of contamination from other cereals. The selection of the study participants was not random. Five of the patients had also participated in a clinical challenge study consisting of 19 adults with CD who ate 50 g of oats for 12 wk (Lundin *et al.,* 2003). Four of the patients had clinical symptoms on an oat-containing diet and 3 of these 4 patients had intestinal inflammation typical of celiac disease at the time of oats exposure. The investigators established oats-avenin-specific and -reactive intestinal T-cell lines from these 3 patients, as well as from 2 other patients who appeared to tolerate oats. The avenin-reactive T-cell lines recognized

avenin peptides in the context of HLA-DQ2. These peptides have sequences rich in proline and glutamine residues closely resembling wheat gluten epitopes. The authors concluded that some celiac disease patients have avenin-reactive mucosal T-cells that can cause mucosal inflammation. The authors point out that the T cell response to the avenin epitopes were found in T cell lines derived from intestinal biopsies of patients with CD that were stimulated with gliadin (Vader *et al.,* 2003). It is unknown whether any of the patients from whom these T cells were isolated had clinical symptoms or mucosal inflammation related to ingestion of oats. The authors suggest that it will only be possible to establish the frequency of intolerance and possible complications with extended clinical follow-up of CD patients consuming oats. The authors indicate that their observations demonstrate that even if oats seem to be well tolerated by many CD patients, there are patients who have intestinal T cell responses to oats. They suggest that until the prevalence of oats intolerance in CD patients is well-established, clinical follow-ups of celiac disease patients eating oats is advisable.

6. Kilmartin, C. *et al.,* (2006) conducted investigations on the etiological role of the wheat-related cereals, barley, rye, and oats, by examining the immune response of gliadin≈reactive mucosal T cell lines from celiac patients to fractions from all four cereals. The oats used in this study were free from wheat contamination. Cell stimulation was determined by measuring proliferation (employing 3H-thymidine incorporation) or cytokine (IL-2, IFN-γ) production. All five T cell lines demonstrated immunoreactivity to protein fractions from the four related cereals. In some cell lines, reactivity to wheat, barley, and rye was evident only when these cereal fractions had been pretreated with tissue transglutaminase. The authors concluded that this study confirms the similar T cell antigenic reactivity of these four related cereals, which has implications for their exclusion from gluten-free diets. However, they also indicated that despite oat stimulation of T cell lines, this cereal does not activate a mucosal lesion in most celiac patients. The authors indicate that in this study, even when 5 mg/ml of avenin was added to the biopsy culture, there was no evidence of cytokine production. An equivalent amount of gliadin activated the celiac mucosa. Because avenin accounts for only 5–15% of the total protein in oats (whereas wheat, barley and rye prolamins constitute 40-50%), it has been suggested by other investigators that large amounts of oats still may be toxic to CD patients. The authors argued against this and demonstrate that purified avenin is not immunogenic to the bowel mucosa of CD patients. The authors noted from their results that the immunogenic sequences of gliadin were not present in avenin, which further supports the conclusion that oats are safe for consumption by CD patients.

7. Reviews on the safety of oats in CD patients were used as background information (Dor *et al.,* 2002; Kumar and Farthing, 1995; Schmitz, 1997; Thompson, 1997, 2003). Haboubi et al (2006) conducted a systematic review of the literature related to the inclusion of oats in the gluten-free diet for patients with CD to assess whether oats can be recommended. This report was published in October 2006, but their cut off period excluded 2005/2006. They used specific search and selection criteria to identify 17 primary studies, 6 of which met their inclusion criteria. However, the purity of oats was not part of their selection criteria. They found that two of the six studies reported significant difference ($p<0.001$; $p=0.039$) in intraepithelial lymphocyte counts between the oats and control groups. However, the

purity of oats was not tested in one of the selected publications (Peräaho *et al.,* 2004 a). Reunala *et al.,* (1998) reports difference in the expression of $\gamma\delta$T cell receptor ($p<0.001$) when comparing oats to controls. However, this biomarker was elevated at baseline and improved after the oats challenge and other biomarkers assessed did not show difference between oats and controls. Kemppainen *et al.,* (2007) did not find evidence of local immune activation after oats challenge using similar immunohistochemical biomarkers. None of the six studies selected by Haboubi et al (2006) found any significant difference in the serology between the group consuming oats and controls. Haboubi et al (2006) excluded all studies where the same patient served as control. It is, however, well accepted that there is high variability in the susceptibility of CD patients to gluten. Hence, studies using same subjects as control provide valuable data. Based on their review Haboubi et al (2006) concluded that oats can be symptomatically tolerated by most patients with celiac disease. They advised that patients with CD wishing to consume a diet containing oats should receive regular medical follow-up, including small bowel biopsy at a specialist clinic for life as part of the follow up evaluation. It is clear that the long term use of oats in CD patients needs further evaluation and that the clinical management of these individuals needs continued re-assessments as new information is made available.

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