

**ALLIANCE FOR NATURAL HEALTH INTERNATIONAL  
SUBMISSION TO EFSA CONSULTATION:**



## **Public consultation on a draft EFSA guidance on the scientific requirements for health claims related to gut and immune function**

The discussion document on which comments are sought can be found at the following link:

<http://www.efsa.europa.eu/en/consultations/call/nda100928.htm>

The following comments for each relevant subsection of the EFSA guidance document were made by the Alliance for Natural Health International and submitted electronically on the EFSA website on 22<sup>nd</sup> October 2010.

### **COMMENTS ON: 3.1. Claims on bowel function**

Line 163: The draft guidance mentions constipation as a disorder of normal bowel function, but does not discuss loose stools. The latter should be included.

Line 164: Reduced faecal bulk is discussed as being associated with constipation. However, there is considerable overlap in terms of faecal bulk between normal subjects and those with constipation, as noted by Cummings et al., 2004/PASSCLAIM. This should be clarified in the draft guidance.

Line 164: Although the draft guidance mentions diverticular disease as a potential sequela of constipation, it is not the only one. An extremely important omission – which was noted by Cummings et al., 2004/PASSCLAIM – is colorectal cancer, the most common form of non-sexual cancer in both male and females in Europe, which should be included in the guidance document. It should be noted that both diverticular disease and colorectal cancer are posited as sequelae of low stool weight.

Line 165: It is somewhat misleading to state that “changes in bowel function within the normal range might be considered beneficial”, since certain beneficial effects are associated with changes that could be considered to lie outside the normal range. For example, for most EU populations, an increase in mean daily stool weight of 50% would be beneficial in terms of reduced colon cancer risk and changes that bring transit time within the normal range are also considered beneficial (Cummings et al., 2004/PASSCLAIM). This situation has implications for both Article 13 (health claims other than those relating to reduction of disease risk or children’s development/health) and Article 14 (health claims relating to reduction of disease risk or children’s development/health) health claims.

Line 167: Among the appropriate outcome measures should be included diary-recorded quality/appearance of stool (Cummings et al., 2004/PASSCLAIM).

Line 168: For the sake of clarity, the "generally accepted methods" mentioned here should be defined.

Line 181: The draft guidance recognition of IBS as a relevant study population to support claims aimed at the general population is commendable. However, there is no universally recognized definition of irritable bowel syndrome (IBS), which may present problems with regard to extrapolating study results in IBS patients to the general population.

Line 188: The draft guidance should consider that increasing the levels of bowel microorganisms from the lower end of their normal range toward the upper limit of normal might be a beneficial effect. This may be particularly true for disturbances in the bowel microbiota following antibiotic therapy.

Lines 189 and 192: Although they have they same meaning, use of the terms "toxicogenic" and "toxinogenic", should be made consistent to aid clarity of the guidance.

Line 200: For clarity, use of the term "generally" should be avoided in this case by defining the situations in which a decrease in pathogen by less than 1 log value is considered meaningful.

Line 204: The draft guidance should be amended to recognize the fact that, since vaccines have been approved for market based on studies that demonstrated reduced incidence/duration of infections, a similar level of evidence should apply to health claims made under Articles 13 and 14.

Lines 226–235: A focus of the draft guidance on human intervention studies risks unnecessarily excluding other forms of evidence, such as epidemiological studies. It is entirely possible that health claims could be supported by examining symptom severity or duration of infection in populations exposed to a nutrient and comparing them with populations that lack such exposure.

Line 250: Clarity of the document would be improved by clarifying or avoiding the term "generally" regarding absorption of non-haem iron in the human intestine.

Line 254: The draft guidance refers to "generally accepted methods" of measuring iron absorption, but it would be useful to list them in the interests of clarity.

### *Reference*

Cummings JH, Antoine J-M, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC, et al. PASSCLAIM: Gut health and immunity. *Eur J Nutr* 2004;43(Suppl. 2):I1/118–I1/173.

## **ADDITIONAL COMMENTS**

### **COMMENTS ON: 3.4. Claims on digestion/absorption of nutrients**

While the draft guidance makes specific reference to problems caused by the deficiency of one enzyme, namely lactase, many suffer deficiencies in protein, carbohydrate and fat digestion linked to inadequate endogenous or exogenous intake of other enzymes, including those that are grouped as protease, peptidase, amylase, lipase, invertase. Cellulase and others. Foods or food constituents that contribute to healthy levels of these and other digestive enzymes should be regarded as beneficial and should be amenable to function or disease risk reduction claims.

### **ADDITIONAL AREAS TO BE INCLUDED AFTER SECTION 3.4 AND BEFORE SECTION 4**

#### **Stomach acidity**

pH plays a crucial role in a normally functioning digestive tract. Hypochlorhydria is a widespread problem even in healthy people and especially in the elderly. It leads to malabsorption of proteins and other nutrients. Hypochlorhydria may also lead to bacteria overgrowth in the intestine. Supporting a healthy pH should be regarded as a beneficial physiological function.

#### References:

Christiansen PM. The incidence of achlorhydria and hypochlorhydria in healthy subjects and patients with gastrointestinal diseases. *Scand J Gastroenterol.* 1968; 3(5): 497-508.

Kassarjian Z, Russell RM. Hypochlorhydria: A Factor in Nutrition *Annual Review of Nutrition*; 9: 271-285.

Holt PR, Russell RM. *Chronic gastritis and hypochlorhydria in the elderly.* 1993. CRC Press.

#### **Bile quality and release**

Bile quality and its timely release into the duodenum is essential for healthy function of the GI tract and proper absorption of fats and other nutrients.

Fatty acids in the lumen of the duodenum stimulate endocrine cells to release the hormone cholecystokinin (CCK). CCK stimulates contractions in the smooth muscle of the gallbladder. As well, CCK causes relaxation of the sphincter of Oddi, allowing bile release into the duodenum.

Acidic chyme in the lumen of the duodenum stimulates other endocrine cells to release the hormone secretin. Secretin stimulates duct cells in the liver to release bicarbonate into the bile.

Accordingly CCK and secretin should be recognised as useful biomarkers for healthy bile function.

*References:*

Maton PN, Selden AC, Chadwick VS. Large and small forms of cholecystokinin in human plasma: measurement using high pressure liquid chromatography and radioimmunoassay. *Regul Pept* 1982;4:251-260.

Chang TM, Chey WY. Radioimmunoassay of cholecystokinin. *Dig Dis Sci* 1983;28:456-468.

Jansen JBMJ, Lamers CBHW. Radioimmunoassay of cholecystokinin in human tissue and plasma. *Clin Chim Acta* 1983;131:305-316.

Himeno S, Tarui S, Kanayama S, Kuroshima T, Shinomura Y, Hayashi C, et al. Plasma cholecystokinin responses after ingestion of liquid meal and intraduodenal infusion of fat, amino acids, or hydrochloric acid in man: analysis with region specific radioimmunoassay. *Am J Gastro* 1983;78:703-707.

Izzo RS, Brugge WR, Praissman M. Immunoreactive cholecystokinin in human and rat plasma: correlation of pancreatic secretion in response to CCK. *Regul Pept* 1984;9:21-34.

Becker HD, Werner M, Schafmayer A. Release of radioimmunologic cholecystokinin in human subjects. *Am J Surg* 1984;147:124-129.

Ohgo S, Takemura J, Oki Y, Nishizono F, Ishikawa E, Yoshimi T, et al. Radioimmunoassay of cholecystokinin in plasma. *Clin Chem* 1988;34:1579-1584.

Hocker M, Schmidt WE, Creutzfeldt W, et al. Determination of plasma cholecystokinin (CCK) concentrations by bioassay and radioimmunoassay in man. A critical evaluation. *Regul Pept* 1992;37:255-269.

Ballinger AB, Clark ML. L-Phenylalanine releases cholecystokinin (CCK) and is associated with reduced food intake in humans: evidence for a physiological role of CCK in control of eating. *Metabolism* 1994;43:735-738.

Paloheimo LI, Rehfeld JF. Quantitation of procholecystokinin and its products in plasma by processing-independent analysis. *Clin Chim Acta* 1995;238:21-33.

Koizumi F, Ishimori A, Koizumi M. Measurement of secretin in the mucosa of digestive tract by radioimmunoassay. *Tohoku J Exp Med.* 1980; 131(4): 339-46.

## COMMENTS ON SECTION 4.1

It is of great concern to us that the draft guidance suggests that immune system markers can only be used as supporting evidence for a claim, as proposed in lines 287-292.

This is inconsistent with the view, drawn from the controversial area of vaccination, that “stimulation of protective antibody titres” may be used to substantiate immune function (lines 285-6).

Assuming that a particular alteration in the expression or amount of an immune marker or signalling chemical can be associated with enhanced immune system function, such markers should be able to be used to support immune system claims. Any claim, on a case-by-case basis, could be qualified according to the degree of evidence available to support it. It would make sense, where possible, to divide these markers according to whether they relate to the innate or cell-mediated immune system.

Innate immune markers would therefore include antimicrobial peptides, lysozymes, non-specific leukocytes, macrophages, specific interleukins, NF-kB, T-cells, Th1/Th2 cytokine ratios, etc.

An increasing body of research is pointing to the vital role of the gut in immune modulation. There are a vast array of biomarkers associated with the gut microbiota that have not been included in the guidance. Included in the biomarker list should be toll-like receptors, such as TLR-2, TLR-4 and TLR-5.

See extensive references in a paper review paper published through Nature Reviews in September 2010:

Eberl G. A new vision of immunity: homeostasis of the superorganism. *Mucosal Immunol* 2010; 3(5): 450-60.