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Risk assessment on use of *Lactobacillus rhamnosus* (LGG) as an ingredient in infant formula and baby foods

The Norwegian Scientific Committee for Food Safety
Panel on Nutrition, Dietetic products, Novel food and Allergy

Contents

I- Summary

Lactobacillus rhamnosus GG (LGG) is one of the most studied probiotics strains. Due to production of lactic acid by LGG, the faecal pH decreases which inhibits colonization by potentially pathogenic bacteria. Short-term effects of LGG in infants and young children with infectious diarrhoea have been reported in a number of studies; however there are no published data supporting long-term clinical benefits of using infant formula supplemented with LGG. Possible long-term effects on intestinal colonization and its effects on long-term gastrointestinal and immune functions are unknown. LGG as an ingredient in infant formula and baby foods is intended for daily or regular use and not for short-term specific treatment. Furthermore, the targeted consumer group includes, and is partly even primarily intended to be, children under the age of one year. These two aspects demand particular consideration with regard to the unknown possible effects of long-term treatment with large doses of live bacteria on the ecology of the microflora, and on the immune system, particularly since these systems have not yet fully matured in infants and small children. There is no documented prophylactic effect of LGG on any diseases in children. Following careful review, The Norwegian Scientific Committee for Food Safety finds that the data available are insufficient to support the safety of LGG in infant formula and baby foods neither for healthy infants (0-12 months), for inclusion in infant formula classified as food for special medical purposes for infants and children up to 12 months nor for children above 1 year when intended for use several times a day.

Key words; Probiotics, *Lactobacillus rhamnosus* GG (LGG), infant formula, baby foods, intestinal microflora, immune system, diarrhoea, eczema

II- Background

The term probiotic is derived from the Greek, meaning “for life”. Probiotics were defined by a group of experts of the Food and Agriculture Organization (FAO) of the United Nations and World Health Organization (WHO) as “live microorganisms which, when administered in adequate doses, confer a health benefit on the host” (Food and Agriculture Organization of the United Nations and World Health Organization 2001).

The Scientific Committee on Food (SCF) of the European Commission recommended that infant formulas with probiotic microorganisms should be marketed only if their benefit and safety had been evaluated according to the principles outlined by the same Committee. SCF did not object to the addition of probiotic bacteria to follow-on formulas. The Committee emphasized that only bacterial strains with defined identity and genetic stability, as demonstrated by cultural and molecular methods, should be used. Furthermore, the identity of the probiotic strain should be described by molecular methods in a dossier and be available to food control authorities (Scientific Committee on Food.European Commission.Health and Consumer Protection Directorate-General. 2004). SCF recommended that for safety reasons, based on current knowledge, probiotics should not be given to immunocompromised or premature infants.

The European Society of Pediatric Gastroenterology and Hepatology (ESPGHAN) Committee on Nutrition has recently reviewed the available information on the effects of adding probiotic bacteria to infant formula, follow-on-formula, and special medical foods (Agostoni *et al.* 2004). ESPGHAN recognizes that there is evidence that some probiotic preparations have benefits on health and well-being; for instance there are some data supporting a short-term benefit of some probiotic strains in infants and young children with infectious diarrhoea. However, ESPGHAN found that the available clinical trials contain only limited data on the safety and clinical effects of probiotic preparations added to infant formula, follow-on-formula, and special medical food. ESPGHAN mentioned the lack of data regarding long-term clinical benefits of infant formula supplemented with probiotic bacteria, and long-term effects on intestinal colonization and its effects on long-term gastrointestinal (GI) and immune functions.

Probiotics comprise an increasing group of microorganisms. The microorganisms commonly used as probiotics for humans belong to the Lactic Acid Bacteria (LAB), which have the ability to metabolise carbohydrates to lactic acid, thereby lowering the micro-environmental pH. The lactic acid bacteria group comprises 16 genera including *Streptococcus*, *Lactobacillus*, *Leuconostoc*, and *Pediococcus*. Bifidobacteria are not part of the LAB group, but are members of the commensal gut flora. Historically, *Lactobacillus* and *Bifidobacterium* associated with food have been considered safe (Adams and Marteau 1995). Both genera of bacteria are considered as part of the mammalian commensal flora. Recently, *Lactobacillus rhamnosus* (LGG) has been identified as a probiotic for use in certain paediatric nutrition products, by Mead Johnson (USA).

The Norwegian Food Safety Authority (Mattilsynet) has been asked by Nutri Konsult Täby (Finland) to permit the marketing of infant-formula and baby foods that have been supplemented with *Lactobacillus rhamnosus* (LGG) at a concentration of 10^8 CFU/g formula. The intention is to ensure a concentration of at least 10^6 CFU/g powder formula throughout the shelf-life of the product. The Norwegian Food Safety Authority (Mattilsynet) is not aware of any infant-formula or baby food containing LGG that is on the Norwegian market (Nutramigen is intended for infants and children > 4 months).

In March 2004 The Norwegian Food Safety Authority (Mattilsynet) asked the Norwegian Scientific Committee for Food Safety to address this issue (00/1956/touse and 2000/1956/gyomj). In response, an *ad hoc* Working Group of experts was appointed with the mandate to draft a risk assessment regarding the use of LGG in infant-formula and baby foods.

III- Terms of reference

The Norwegian Scientific Committee for Food Safety (Vitenskapskomitéen for mattrygghet) has been asked by the Norwegian Food Safety Authority (Mattilsynet) for a risk assessment regarding the use of LGG in infant-formula and baby foods.

Questions to the Norwegian Scientific Committee for Food Safety[*]:

1. Is LGG, based on generally recognized data, suitable for inclusion in ordinary infant formula?
2. Is LGG, based on generally recognized data, suitable for inclusion in infant formula classified as food for special medical purposes for infants 0-4 months old with the diagnosis " cow's milk protein and soy allergy"
3. Is LGG, based on generally recognized data, suitable for inclusion in infant formula classified as food for special medical purposes for infants and children > 4 months?
4. Is LGG, based on generally recognized data, suitable for inclusion in baby foods intended for use in healthy infants and children between 4 months and 3 years?

IV- Methodology

Data sources: We searched the MEDLINE database, 1966-2004 and Word Wide Web (WWW), using the various search terms, for example; probiotics, *Lactobacillus*, *Lactobacillus* GG, *Lactobacillus rhamnosus*. Furthermore, documentation had been provided from Mead Johnson (Finland) to the Norwegian Food Control Authority (Mattilsynet).
Data extraction: English-language articles were selected that provided information on the use of probiotics and *Lactobacillus* GG as probiotic bacteria.

V- Exposure assessment

Industrially, some *Lactobacillus* species are used for the production of foods that require lactic acid fermentation like yoghurt and cheese, fermented vegetables (olives and pickles), fermented meats (salami) and sourdough bread. Lactobacilli are part of the normal flora of animals. During the last 10 years, strains of lactobacilli, including LGG, have been included in a number of probiotic products (Jay 2004).

VI- *Lactobacillus* spp.

Lactobacillus is a broad genus characterized by formation of lactic acid as a sole or main end product of carbohydrate metabolism. The production of lactic acid by *Lactobacillus* makes the environment acidic and this may inhibit the growth of some harmful bacteria. *Lactobacillus* is

[*] *Spørsmål til Vitenskapskomittéen for mattrygghet*
Er LGG basert på generelt anerkjente data, egnet til å inngå i vanlige morsmelkerstatninger?
Er LGG basert på generelt anerkjente data, egnet til å inngå i morsmelkerstatninger som er klassifisert som medisinske næringsmidler til spedbarn fra 0-4 mnd med diagnosen kumelkproteinallergi og soyaallergi?
Er LGG basert på generelt anerkjente data, egnet til å inngå i morsmelkerstatninger som er klassifisert som medisinske næringsmidler til spedbarn og barn >4 mnd?
Er LGG basert på generelt anerkjente data, egnet til å inngå i barnemat beregnet til friske sped- og småbarn mellom 4 mnd. og 3 år?

a genus of Gram-positive microaerophilic, non-spore-forming rods or coccobacilli. Eighty species of *Lactobacillus* are recognised at present (Satokari *et al.* 2003). They are common, and usually benign, inhabitants of the bodies of humans and animals; they are, for example, present in the GI and the vagina (Hammes and Vogel 1995).

VI-A- Lactobacillus rhamnosus GG (LGG) characteristics

Lactobacillus rhamnosus GG (ATCC 53103) is a probiotic strain that has been isolated from healthy human intestinal flora. It is one of the most extensively studied probiotic lactic acid bacterial strains (Agarwal *et al.* 2003;Armuzzi *et al.* 2001;Baharav *et al.* 2004;Biller *et al.* 1995;Goldin *et al.* 1992;Gorbach *et al.* 1987;Guandalini 2002). Valio Finnish Cooperative Dairies Association, Helsinki, Finland is a large dairy/food company that was granted exclusive license for LGG in 1987.
In the human digestive system, LGG has been shown to:
1- Tolerate intestinal conditions (i.e. stomach acidity and bile salts) and survive the passage through the GI tract to effectively, but temporarily, colonize the digestive tract (Goldin *et al.* 1992).
2- Adhere to the mucosa of the human intestine and colonize the human GI tract (Ahrne *et al.* 1998). The colonization is believed to be transient, but long-term during continued administration.
3- Produce antimicrobial substances with activity against potential pathogens such as *Escherichia coli*, streptococci, *Clostridium* spp., *Salmonella* spp. and *Clostridium difficile*(Gorbach *et al.* 1987;Silva *et al.* 1987)

Using colon biopsies, the attachment of LGG to human intestinal mucosa and the persistence of the attachment after discontinuation of LGG administration was studied (Alander *et al.* 1999;Vilpponen-Salmela *et al.* 2000). LGG was shown to persist in the colonic mucosa for 2 weeks following the end of administration, although the LGG counts in the faeces were already below the detection level. The authors concluded that the study of faecal samples alone might underestimate the extent of colonization.

VII- Survival kinetics

The effectiveness of probiotics is related to their ability to survive passage through the acidic stomach environment and the alkaline conditions in the duodenum, as well as their ability to adhere to the intestinal mucosa of the colon and to colonize the colon. *Lactobacillus* GG is more prone to colonize the colon than other probiotic lactobacilli. After passage through the stomach and the small intestine, those probiotics that survive are transiently established in the colon.

VIII- The intestine in infancy

At birth the basic architecture of the intestine is organised, but undergoes major development in the first months and years of life. There is substantial immaturity of the intestine at birth and early nutrition may programme the enteric nervous system by stimulating release of gut-tropic hormones. The gut has a number of important functions:
The onward passage of the ingested food bolus;
To mix and grind the ingested food bolus;
Digestion of ingested food;
Absorption of the digested nutrients into the blood and lymph vessels;

A major immunological function;
A regulatory role in protein metabolism;
Secretion of hormones;
Absorption of water;
Bacterial colonization and fermentation.

The small intestine is a major immunological organ and the total number of lymphocytes within the intestine is equivalent to the number in the spleen. There is a rich representation of the innate immune system with cells like macrophages, eosinophils and mast cells.
The body's defence against potentially harmful substances and organisms is brought about by a combination of innate and acquired cellular and humoral immunity. Microbial colonization of the intestine plays a fundamental role in the priming and maturation of the mucosal immune system and may also affect enterocyte function in more subtle ways. The intestine is a complex organ and in infancy is still under development. There are many factors involved in the development of a healthy intestinal flora, normal immune responses to antigen and oral tolerance. This is an area for further research, at present we do not know the final consequences of changing one single factor in the complex environment of the intestine.

IX- Intestinal microflora

Studies in germ-free animal models have indicated that colonization of the GI-tract plays an important role in the development of the gut immune system (Umesaki and Setoyama 2000). The intestinal microflora provides essential stimuli for the diversification of the antibody repertoire after birth. Studies on germ-free animals indicate that a successful colonization of the intestine is a prerequisite for the development of a normal immune response system (Sudo *et al.* 1997)
The human intestinal microflora is frequently discussed as if it were a defined entity. However, the intestinal microflora comprises a dynamic mixture of microorganisms. It has been observed that the predominant bacterial community attached to the colonic mucosa is equally distributed along the colon, but is significantly different from the faecal community. Host-related factors have a major impact on the bacterial composition in the human GI tract. Thus, every individual has a unique microflora; even homozygotic twins differ in the composition of their microflora (Zoetendal E.G. 2001). The intestinal microflora develops over time, determined by an interaction between genetic factors, contact with the environment, diet and disease.
In utero the intestine is sterile, but at birth the baby acquires bacteria such as *Lactobacillus, Bacteroides, Peptostreptococcus,* and *Peptococcus* from the maternal birth canal (Larsen and Monif 2001). Subsequently, the child will be exposed to microbes from the environment. The first microorganisms to colonize are the facultative anaerobes, although strict anaerobes can also be detected from the first day after birth (Benno and Mitsuoka 1986). Genera and species of bacteria isolated from infant faeces include (Benno and Mitsuoka 1986;Beritzoglou 1997):
1- Facultative anaerobes: *Escherichia*, *Staphylococcus*, *Streptococcus*, *Enterobacter*, *Klebsiella*, *Proteus*, *Citrobacter*, *Pseudomonas,* and *Bifidobacterium*.
2- Strict anaerobes: *Clostridium*, *Bacteriodes*, *Eubacterium*, *Veillonella*, *Peptococcus, and Peptostreptococcus,* and
3- Microaerophilic/facultative anaerobes like *Lactobacillus*; *L. acidophilus, L. fermentum, L. brevis, L. salivarius, L. plantarum*.

Two to three days after birth, anaerobic bacteria are the main microorganisms found in the faeces of infants. The reason may be that facultative anaerobes reduce the redox potential in

the gut and render the environment suitable for obligate anaerobes. Thus, establishment of the gut microflora is considered a step-wise process with facultative anaerobes such as the enterobacteria, coliforms and lactobacilli colonizing the intestine first, rapidly succeeded by bifidobacteria and other lactic acid bacteria. The critical stages of gut colonization are in the days after birth and during weaning, as illustrated in Figure 1.

The colonic population of breast-fed babies is dominated by bifidobacteria and other lactic acid bacteria, with very few *Bacteroides*, *Clostridium*, and coliforms. In contrast, more variation occurs in the microflora of formula-fed babies, which tend to contain larger numbers of *Bacteroides*, *Clostridium*, and enteric bacteria. The mechanisms responsible for the differences in the microflora of infants fed human milk and modern formula are numerous and difficult to reproduce. Immunological factors such as secretory IgA (sIgA) and lysozyme in human milk prevent the growth of some bacteria. The faecal pH of breast-fed infants may promote bacteria like *Lactobacillus* and *Bifidobacterium*, which are more acid-tolerant.

The intestinal microflora constitutes a highly interconnected ecosystem where factors that modulate one aspect may have many consequences downstream of the initial events. The ability of the bacteria to modulate immune function, metabolise carcinogenic agents and provide a direct barrier to invasion of the gut by pathogenic microorganisms are examples of the diverse functionality conferred by the microflora. Many of these interactions and functionalities are still unknown or are poorly understood. It is difficult to manipulate the human microflora; one problem being that the composition of the intestinal microflora is quite different from one human to another, which is an obstacle to manipulation. In particular, the consequences of LGG transfer to the intestine of infants and children by using LGG in infant-formula and baby foods are unknown. Despite this fact, there are a number of manufacturers interested in establishing probiotic therapies for humans. This raises the question as to whether an artificial microflora could be designed to benefit babies who do not consume breast milk.

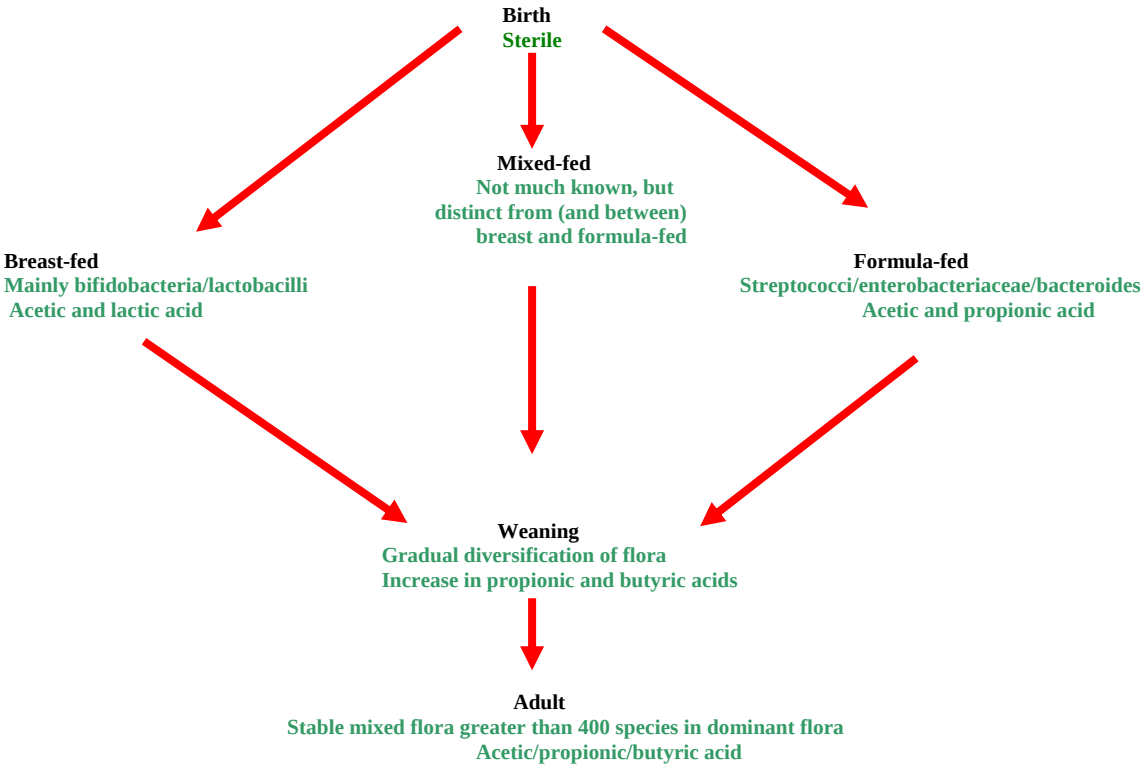

FIG. 1. A scheme of the development of the intestinal microflora in humans (Edwards and Parrett 2002)

X- Risk and safety aspects

In healthy adult individuals, lactobacilli are natural inhabitants of the oral cavity, the ileum and the colon and they are the predominant microorganisms in the vagina (Shortt 2002). Historically, lactobacilli naturally associated with food have been considered safe with no pathogenic potential. However, probiotics may theoretically be responsible for some potential side effects like systemic infections, altered intestinal metabolism, infections, gene transfer and immunomodulation and adjuvant effects (Davidson and Butler 2000).

X-A- Systemic infections

The possible effects of the increased probiotic use of LGG on the occurrence of bacteraemia due to lactobacilli were studied in Finland between 1990-2000 (Salminen *et al.* 2004). Eleven LGG isolates were found in blood cultures from patients, without any temporary increasing trend that would suggest an association with the increase in the probiotic use. Most of the cases of infection with lactobacilli occur in patients with underlying conditions that are predominantly severe(Husni *et al.* 1997;Saxelin *et al.* 1996). To date, there are two cases of infections which have been reported and are assumed to be associated, although not necessarily proven, with the consumption of commercial products containing *L. rhamnosus* (Mackay *et al.* 1999;Rautio *et al.* 1999).
The European Society of Pediatric Gastroenterology and Hepatology (ESPGHAN) (Agostoni *et al.* 2004) and the Scientific Committee on Food of the European Commission (Scientific Committee on Food.European Commission.Health and Consumer Protection Directorate-General. 2004) have concluded that, based on current knowledge, probiotics should not be given to immunocompromised patients or premature infants.

X-B- Altered metabolic activity

There is currently limited knowledge of the enzymatic functions of microbes intended for probiotic use. The intestinal microflora is considered to have a metabolic capacity equalling the liver. In newborns the detoxification capacity of the liver is low and the margins may be small. It is thus essential to gain knowledge of the enzymatic properties of probiotic microbes, especially when they are intended for use in infants. The intestinal microflora is involved in the synthesis of vitamins, the conversion of cholesterol, bile acids, and the formation and elimination of toxic and procarcinogenic products. Microbially-derived enzymes often participate in reversing the detoxification processes that have taken place in the liver (Hawksworth *et al.* 1971). This may have negative consequences, especially in newborns and infants, in whom the detoxification capacity of the liver is limited.

X-C- Gene transfer

Horizontal transfer of resistance/virulence genes between bacteria may occur by different mechanisms: 1) the acquisition of exogenous DNA containing resistance/virulence genes by transformation; 2) the acquisition of resistance/virulence genes by transduction mediated by bacteriophages; and 3) the acquisition/virulence of resistance genes on mobile genetic elements such as plasmids or transposons by conjugation. There are no reports concerning virulence factors in LGG. Bacteria belonging to genus *Lactobacillus* are intrinsically resistant to vancomycin, which means that vancomycin-susceptible strains of these species do not exist (Tynkkynen *et al.* 1998). The intrinsically vancomycin-resistant lactobacilli species, including LGG have not been shown to contain *van* genes, which encode for resistance against

vancomycin in enterococci and vancomycin-resistant staphylococci. It is not clear whether intrinsic vancomycin resistance in *Lactobacillus* is associated with any resistance genes. In clinical microbiology, the emergence of vancomycin-resistant enterococcal strains has caused a serious therapeutic problem, since enterococci may contain several other antibiotic-resistance genes, vancomycin is often the only effective antibiotic for treatment. Furthermore, many concerns have been expressed about the possible transfer of *van* genes to staphylococci. There is no indication that intrinsically vancomycin-resistant lactobacilli can transfer vancomycin-resistance genes to other species.

X-D- Immunomodulation and adjuvant effects

Probiotics have, in common with other microbes and microbial products, the potential to modulate immune responses. They interact with so called Toll-like receptors present on cells belonging to the immune system. Toll-like receptors are a family of receptors involved in the recognition of a wide range of microbial molecules, e.g. lipopolysaccharide (LPS) for Gram-negative bacteria and peptidoglycan for Gram-positive bacteria. Different microbes, or combinations of different microbes or microbial products, act through different types of Toll-like and other receptors resulting in different end-effect signals. In accordance with such a model it has been reported that LGG causes different effects on the cytokine pattern, depending on whether it has been given alone or in combination with other probiotics (Pohjavuori *et al.* 2004).

Different species within a genus may also cause opposite effects on cytokines. This is illustrated by studies on species within the Bifidobacterium genus (He *et al.* 2002). Knowledge of the signals by which microbes and microbial products exhibit their effects is relatively recent and incomplete. The mechanisms that lie behind the clinical improvement claimed in some conditions such as eczema is unknown. Neither the total effect of any given probiotic on the immune system, nor the potential negative effects such as immunomodulation that might result in allergy or autoimmunity, are known. In particular, inappropriate immune stimulation may theoretically lead to autoimmune diseases.

XI- LGG for healthy infants and children

Beneficial intestinal microflora has been shown to stimulate the normal mucosa and defence systems, and to inhibit pathogenic microorganisms (Dai and Walker 1999). Thus, the idea of controlling the process in newborn intestinal colonization is intriguing. Studies on the neonatal intestinal flora and the differences in colonization patterns have influenced feeding practices, and more recently formula development. We have provided a summary of results and evaluated various clinical studies, including studies referred to by Mead Johnson, involving consumption of LGG by healthy and compromised infants and children.

XI-A- LGG and intestinal colonization

The ability of LGG to colonize the intestine of healthy newborns (1-week to 1-month old) and the influence of its administration on normal microflora establishment has been studied (Sepp *et al.* 1993). According to the authors, 14 days of administration of LGG, which started right after birth, increased intestinal lactobacilli concentrations and did not impair the establishment of a normal faecal bacterial microflora. The authors concluded that the faecal microorganisms' predominance pattern did not differ in 1-week and 1-month old newborns of

the LGG group. However, the concentrations of both lactobacilli and coliform bacteria were higher in 3-4 and 5-7 day old newborns of the LGG group than in the control group. The authors studied only the major bacterial species in the infant faeces and the possible presence of anaerobic bacteria was overlooked. Finally, the duration of the study was too short to draw any conclusions with regard to long-term effects. Therefore, the conclusion that LGG did not impair the establishment of a normal faecal bacterial microflora cannot be made. In a study performed by (Marini *et al.* 1997) significant decreases in the aerobic/anaerobic ratio was observed in LGG-treated children as compared to untreated pre-term children.
The ability of the LGG to colonize the immature bowel of premature infants has been studied (Millar *et al.* 1993). The authors demonstrated that orally administrated LGG was well tolerated and colonized the bowel of premature infants. However, colonization with LGG did not reduce the faecal reservoir of potential pathogens, and there was no evidence that colonization gave any clinical benefit for this particular group of infants.

XI-B- LGG for prevention and treatment of diarrhoea

One of the primary areas of probiotic use in children has been in the treatment and prevention of diarrhoea. The positive effect of LGG in the treatment of paediatric antibiotic-associated diarrhoea, which is caused by *Clostridium difficile,* has been reported.
Prevention
In a Peruvian study (Oberhelman *et al.* 1999), 204 undernourished children, aged between 6 and 24-months old at the study start, were given a once-daily intake of LGG, 6 days a week, for 15 months. The results showed a reduction in the frequency of acute diarrhoea in non-breast-fed infants aged 18-24 months. There were, however, no detectable effects in younger or older children or in breast-fed infants.
Nosocomial diarrhoea is a major problem in paediatric hospitals worldwide and is commonly caused by enteric viral pathogens, especially rotavirus. The effect of orally administrated LGG in conjunction with live oral rotavirus vaccine was tested in 2-5 month-old infants (Isolauri *et al.* 1995). Infants who received LGG showed an increased response with regard to rotavirus-specific IgM secreting cells, measured with an ELISPOT technique, on day 8 after vaccination. Both IgM and IgA seroconversion were higher in infants receiving LGG as compared to the placebo group. However, the authors did not study the duration of protection against rotavirus, and the IgM and IgA seroconversion against serogroups of rotavirus other than those used in the study were not measured. Measurements of the concentration of IgA and IgM in intestinal mucus layer and studies on cellular immunity were not performed.
In a study performed in Poland (Szajewska *et al.* 2001), the efficacy of orally administered LGG in the prevention of nosocomial diarrhoea in hospitalised infants aged 1-36 months was studied. The study showed that prophylactic use of LGG significantly reduced the risk of nosocomial diarrhoea in infants, particularly nosocomial rotavirus gastroenteritis. The study did not give information regarding the effect in relation to age distribution or breast-fed versus formula-fed infants.
Different lactic acid bacteria were compared for their effect on the immune response to rotavirus in children with acute rotavirus gastroenteritis (Majamaa *et al.* 1995). Among the lactic-acid bacteria, LGG therapy was associated with an enhancement of IgA specific antibody-secreting cells to rotavirus and serum IgA antibody level at convalescent stage. The mean duration of diarrhoea was lowest in children who received LGG as compared to those receiving lactic acid bacteria other than LGG. Protection against different serogroups of rotavirus and the concentration of IgA in intestinal mucus membranes was not investigated in this study.

Treatment

In a double-blind, placebo-controlled study, 301 children between 1 month to 3 years of age with acute-onset diarrhoea were investigated (Guandalini *et al.* 2000). Patients were randomised to group A (144 patients) receiving oral rehydration solution plus placebo, or group B (147 patients), receiving the same preparation but with a live preparation of LGG (at least 10^{10} CFU/250 ml). After rehydration for the first 4 to 6 hours, patients were offered their usual feeding plus free access to the same solution until diarrhoea ceased. Duration of diarrhoea was 71.9±35.8 h in group A as compared to 58.3±27.6 h in group B. In rotavirus-positive children, diarrhoea lasted 76.6±41.6 h in group A as compared to 56.2±16.9 h in group B. Diarrhoea lasted longer than 7 days in 10.7% of group A as compared to 2.7% of group B. Hospital stays were significantly shorter for group B than for group A. Unfortunately, the effect of LGG in different age groups of the infants and children was not analysed.

XI-C- LGG for treatment and prevention of atopic eczema

Treatment

The treatment of atopic eczema with probiotics has been investigated in four studies. A significant improvement in atopic eczema after 2 months treatment as assessed by SCORAD (European Task Force on Atopic Dermatitis 1993) was observed in infants who were given probiotic supplemented hydrolysed formula (Isolauri *et al.* 2000b). LGG and *Bifidobacterium lactis* Bb-12 were equally effective. These studies were flawed by the small number of children in each group. Their findings were not replicated in two subsequent larger studies carried out by other research groups. They studied the effect of LGG alone or in a mix (Viljanen et al., 2005 Allergy, in press) and a combination of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 122460 (Rosenfeldt *et al.* 2003), respectively. No overall improvement in eczema as assessed by SCORAD was noted in these two studies. However, in a subgroup of children with IgE sensitization, there was a significant improvement, although the effect was moderate. (Viljanen et al., 2005 Allergy, in press; (Rosenfeldt *et al.* 2003). In another study, the treatment of atopic eczema with probiotics was examined in infants who developed eczema whilst being exclusively breast-fed (Isolauri *et al.* 2000a). The infants were weaned to probiotic supplemented hydrolysed formula. After 2 months of treatment, SCORAD was significantly decreased in the infants who received *Bifidobacterium lactis* Bb-12 or LGG supplemented formula as compared with infants who received unsupplemented hydrolysed formula.

Prevention

The effect of LGG in the prevention of early atopic disease in high risk children, (i.e. with a family history of atopy) was investigated (Kalliomaki *et al.* 2001). LGG was given daily in capsules to mothers for 2-4 weeks before expected delivery, and after delivery to the breast-feeding mothers and directly to the infants (capsule content mixed with the water and given with spoon) for 6 months. In this prospective study from birth, atopic eczema was diagnosed at two years of age in 46 of 132 (35%) children. The frequency of atopic eczema was half that of the placebo group (15/64; 23%, vs 31/68; 46%). The mechanisms of LGG treatment in the treatment of atopic eczema were, however, not clarified in this study. No differences in sensitisation were observed between the placebo and probiotic group as the results of skin prick tests, and total and specific IgE were similar. The study did not include results with regard to cell-mediated immunity. The study group was also evaluated at 4 years of age. Atopic eczema was diagnosed on the basis of questionnaire and a clinical examination. Fourteen of 53 children who had received LGG had clinical symptoms of atopic eczema as

compared to 25 of 54 children in the placebo group (Kalliomaki *et al.* 2003). There was a non-significant tendency for an increase in asthma and pollen allergy among the children of the treated group (Niers *et al.* 2003). Furthermore, the incidence of diagnosed cow milk allergy was doubled in the probiotic group (Kalliomaki *et al.* 2003), although these differences were no longer apparent at the age of 4 years. Evidently there is a need for further studies that may clarify whether these were chance findings, or if the risk of other atopic diseases increases in parallel with a decrease in atopic eczema.

In conclusion, there is no convincingly documented effect of LGG with regard to the prevention of any condition. With regard to treatment, short-term effects are demonstrated with regard to shortening the duration of acute viral diarrhoea. Conclusive evidence is presently lacking with regard to bacterially caused diarrhoea or diarrhoea induced by antibiotics. None of the published studies have reported side effects related to the use of LGG, other than suggestions of increased allergic sensitisation, but the studies generally focused on detecting positive effects rather than on safety. All the studies lack information regarding long-term effects and possible changes in the infant intestinal microflora related to LGG consumption. When reviewing studies on the effects of LGG in infants and young children it is clear that such studies are difficult to verify, since the children are exposed to different microorganisms and compliance in using the LGG-containing formula will vary.

XII- LGG for immunocompromised infants and children

Since LGG has been implicated in systemic infections in severely ill patients, the use of LGG for the management of diarrhoea in immunocompromised children cannot be recommended and needs further evaluation. The European Society of Pediatric Gastroenterology and Hepatology (ESPGHAN) Committee on Nutrition has noted that the available data are not sufficient to support the safety of probiotics in newborns, nor in very young infants with immature defence systems, immunocompromised infants, premature infants, and infants with congenital heart disease (Agostoni *et al.* 2004).

XIII- Products containing probiotic bacteria, intended for consumption by infants and small children – dose considerations

If the concentration of a probiotic in a baby food product is 10^8 cfu/g powders, this would result in a dose of ~10^7cfu/g in the prepared food. At present there is no international consensus on the number of living probiotic cells that should be consumed per day. In the case of a probiotic infant-formula, this food would probably constitute the sole source of nutrition, and so the dose of probiotic bacteria per body weight or intestinal volume would be considerably higher than that in adults. It must be remembered that baby food containing probiotic bacteria would totally 'fill' the GI tract, as opposed to being only a portion of the total GI content. Ingestion of 1kg product during one day would give a daily dose of 10^{10} bacterial cells. A child of 10kg might have a GI content of 500g, which if the probiotic food were the only source of nutrition, would contain a concentration of 10^7 cfu probiotic strain/g,assuming neither growth nor death of the ingested cells. Information concerning possible proliferation of the probiotic bacteria during digestion is lacking, both for adults and infants. An adult has a GI content of >2000g. 150mL of yoghurt, containing 10^7cfu/mL, would give a probiotic cell density of ~$10^{5.8}$cfu/mL. In a dried product, such as a milk powder, freeze-dried bacteria would not proliferate but could die. After reconstitution, growth

of the strain would depend on the temperature, time and also on the available carbohydrate. Many products contain carbohydrates other than lactose and therefore the product would give a good nutritional source for growth of most probiotic strains.

XIV- Data gaps

The following data gaps listed below have been identified:
1. Long-term effects of consumption of LGG
2. Use of molecular methods for differentiation of *Lactobacillus* GG from other lactobacilli in samples from consumers
3. Information regarding colonization in the human intestine
4. Standardised methods for evaluating the concentration of LGG in infants formula and baby foods (i.e. the dose)
5. Standardised methods for assessing of colonization by LGG in intestine
6. Microbiological examination of the different parts of the intestinal tract in children receiving LGG. Microbiological examination has been performed in samples from faeces, representing the microflora in colon, but certainly not the flora in higher regions of the GI tract or bacteria adhering to the mucosa
7. Data regarding use of LGG in infant formula, classified as “food for special medical purposes” in infants (0-4 months) with cow’s milk protein and soy allergy
8. Data regarding use of LGG in infant formula, classified as “food for special medical purposes” in infants and children > 4 months
9. Data regarding use of LGG in baby foods intended for use in healthy infants and children between 4 months and 3 years
10. Independent scientific research

XV- Conclusions

LGG has been widely studied and characterized in short-term trials, but long-term trials in children are lacking.
LGG seems to have beneficial effects in treatment of viral infectious diarrhoea in infants and young children. Furthermore, LGG may have a moderate effect on atopic eczema in IgE-sensitised children, although this is not yet sufficiently documented and needs to be confirmed in further studies.
There is no consistent scientific evidence of prophylactic effects of LGG, whether for diarrhoea or for atopic diseases, or for any other diseases.
No immediate adverse effects of LGG have been observed in healthy individuals,
The long-term effects on the microflora of the intestine when LGG is given to small children are unknown.
The long-term effects on the immune function (immune defence, allergy, and autoimmunity) of the gut, and systemically, when LGG is given to small children is unknown
The long-term effect of a heavy, artificial, single-species bacterial load on the newborn infant intestine is unknown.

Since there is no documented prophylactic effect of LGG on any diseases in children, there is currently no medical indication for supplementing milk substitutes or children’s food with LGG.

The products assessed in this paper are products intended for daily use (cow's milk substitutes intended for daily use for children who do not tolerate cow's milk) or regular use (children's food) and not for short-term specific treatment. Furthermore, the targeted consumer group includes, and the products are in part even primarily intended for, children below the age of one year. These two aspects demand particular consideration with regard to the unknown effects of long-term treatment with live bacteria on the ecology of the microflora and on the immune system, particularly since both these systems have not yet fully matured in infants and small children. Thus if future studies were to document any prophylactic effects of LGG with regard to any disease, the unknown, long-term possible adverse effects on the immune system and on the microbial ecology would still need to be considered in the age group below 4 years, and especially below the age of one (theoretically, the younger the child, the larger the potential for long-term effects due to immaturity).

These conclusions apply to probiotic products intended for use in infants and small children, and they do not necessarily apply to probiotic products intended for older children and adults (age groups in whom the digestive and immunological systems are considered mature). Neither do these conclusions apply to products intended for short-term treatment of a disease in which a documented effect has been shown (e.g. acute diarrhoea). However, the products that the group has been asked to evaluate do not fall into the two above-mentioned categories.

XVI- Recommendations*

1. LGG is, based on generally recognized data, not suitable for use in infant formula intended for daily use.
2. LGG is, based on generally recognized data, not suitable for use in infant formula classified as food for special medical purposes for infants 0-4 months old with the diagnosis " cow's milk protein and soy allergy".
3. LGG is, based on generally recognized data, not suitable for use in infant formula classified as food for special medical purposes for infants between 4 months and 1 year, nor for children >1 year if it is to be given several times per day.
4. LGG is, based on generally recognized data, not suitable for use in baby foods for healthy children >1 year if the food is intended for use several times per day.

* LGG er, basert på generelt anerkjente data, ikke egnet til å inngå i morsmelkerstatninger beregnet på daglig bruk til spedbarn.
LGG er, basert på generelt anerkjente data, ikke egnet til å inngå i morsmelkerstatninger klassifisert som medisinske næringsmidler til sped barn (0 – 4 måneder) med diagnosen kumelkallergi eller soyaallergi.
LGG er, basert på generelt anerkjente data, ikke egnet til å inngå i morsmelkerstatninger klassifisert som medisinske næringsmidler til spedbarn mellom 4 måneder og 1 år og heller ikke til barn > 1 år hvis det skal gis flere ganger daglig.
LGG er, basert på generelt anerkjente data, ikke egnet til å inngå i
barnemat beregnet på bruk til friske småbarn > 1 år hvis maten er beregnet til bruke flere ganger daglig.

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SCIENTIFIC PANEL MEMBERS

Panel on nutrition, dietetic products, novel food and allergy: Martinus Løvik (Chair), Lene Frost Andersen, Livar Frøyland, Ragnhild Halvorsen, Margaretha Haugen, Kåre Julshamn, Judith Narvhus, Helle Margrete Meltzer and Jan Erik Paulsen.

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Scientific coordinators from the Secretariat: Siamak Yazdankhah (Panel on Biological hazards) and Bente Mangschou (Panel on Nutrition, Dietetic products, Novel food and Allergy).

Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment on use of *Lactobacillus rhamnosus* (LGG) as an ingredient in infant formula and baby foods

Corrigendum
28.06.05

The Norwegian Scientific Committee for Food Safety
Panel on Nutrition, Dietetic products, Novel food and Allergy

XI- Page 13. In our opinion, a positive health effect of LGG with respect to atopic eczema is not documented and needs further investigation.
Since some studies have shown that the consumption of food containing LGG may significantly reduce the risk of nosocomial diarrhoea in hospitalized infants, particularly nosocomial rotavirus gastroenteritis, we have changed this phrase in our risk assessment:
"In conclusion, there is no convincing documented effect of LGG with regard to the prevention of any condition"

to the following:

"In conclusion, there is no convincing documented effect of LGG with regard to the prevention of atopic eczema. However, prophylactic LGG supplementation has been shown to reduce the risk of nosocomial diarrhoea in hospitalized infants".

XV Page 14. Since there is some evidence of prophylactic effect of LGG supplementation on nosocomial rotavirus gastroenteritis we have changed the phrase:
"Since there is no documented prophylactic effect of LGG on any diseases in children, there is currently no medical indication for supplementing milk substitutes or children's food with LGG",

to the following:

"There is some evidence for a prophylactic effect on diarrhoea in hospitalized children. However, apart from some at risk hospitalized children, there is currently no medical indication for supplementing milk substitutes or children's food with LGG, neither in order to prevent atopic eczema nor for daily use in healthy children or children who are intolerant to cow's milk or soy formula."