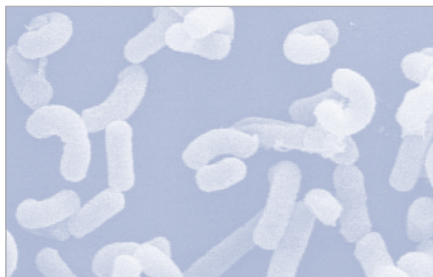


## Lactobacillus acidophilus La-14



### CHARACTERISTICS OF THE GENUS

*Lactobacillus acidophilus* is a Gram-positive, non-spore forming, homo-fermentative, catalase-negative rod. It is a common inhabitant of the human intestinal tract, the human mouth and vagina. It is also found in some traditional fermented milks (e.g. kefir) and is today widely used in probiotic foods and supplements. Numerous studies have demonstrated the diverse beneficial effects of different strains of *L. acidophilus* validating its use as a probiotic.



### SELECTION AND TAXONOMY

The group of organisms previously known as *L. acidophilus* was shown to be highly heterogeneous (1). The results of DNA-DNA hybridisation studies have suggested that the previous *L. acidophilus* species was composed of six different species (2), which were divided into different DNA homology groups. Homology group AI was designated as *L. acidophilus*.

These species are quite difficult and sometimes impossible to differentiate by phenotypic methods, so they are still considered the “*L. acidophilus* group”.

*L. acidophilus* La-14 has been confirmed as a type AI *L. acidophilus* using phenotypic and genotypic methods, including

16S rRNA gene sequencing and hybridisation to a species-specific probe.

*L. acidophilus* La-14 is of human origin and has been deposited in the American Type Culture Collection as SD5212.

### SAFE FOR CONSUMPTION

Lactic acid bacteria have long been considered safe and suitable for human consumption. Very few instances of infection have been associated with these bacteria and several published studies have addressed their safety (3-6). Moreover, no *L. acidophilus* bacteraemia were identified in a 10-year survey in Finland (7).

More specifically, *L. acidophilus* has been consumed in fermented milks and other food products for decades and is listed in the *Inventory of Microorganisms With Documented History of Use in Human Food* (8). The European Food Safety Authority has also added the species to the Qualified Presumption of Safety list (9).

In addition to a long history of safe human consumption of the species, no acquired antibiotic resistance was detected in *L. acidophilus* La-14 during screening by the EU-funded PROSAFE project.

### GASTROINTESTINAL PERFORMANCE

#### Resistance to acid and bile

According to the generally accepted definition of a probiotic, the probiotic microorganism should be viable at the time of ingestion to confer a health benefit. Although not explicitly stated, this definition implies that a probiotic should survive GI tract passage and, according to some, colonize the host epithelium.

A variety of traits are believed to be relevant for surviving GI tract passage, the most important of which is tolerance both to the highly acidic conditions present in the stomach and to concentrations of bile salts found in the small intestine.

*In vitro* studies have shown that *L. acidophilus* La-14 is very resistant to low pH conditions and survive the presence of bile at concentrations present in the duodenum.

#### Adhesion to intestinal mucosa

Interaction with the intestinal mucosa is considered important for a number of reasons. Binding to the intestinal mucosa may prolong the time a probiotic strain can reside in the intestine. This interaction with the mucosa brings

Acid tolerance	++++ (>90% survival in hydrochloric acid and pepsin (1%) at pH 3 for 1h at 37°C)
Bile salt tolerance	++++ (>90% survival in 0.3% bile salt containing medium)
Pepsin resistance	+++ (>60% in 0.3% pepsin containing medium at pH 2 for 1h)
Pancreatin resistance	+++ (>60% survival in 0.1% pancreatin containing medium at pH 8 for 2h)

Selected characteristics of *L. acidophilus* La-14 (internally generated data):  
++++ Excellent; +++ Very good; ++ Good; + Fair

the probiotic in close contact with the intestinal immune system, giving it a better opportunity to modulate the immune response. It may also protect against enteric pathogens by limiting their ability to colonize the intestine.

Currently, adherence is measured using two *in vitro* cell lines, Caco-2 and HT-29. While this is not a thorough test of the ability of probiotics to adhere to intestinal mucosa in the body, attachment to these cell lines is considered a good indicator of their potential to attach.

*L. acidophilus* La-14 has demonstrated excellent adherence to human epithelial cell lines (HT-29) applied in *in vitro* studies.

Adherence to human intestinal cells <i>in vitro</i>	HT-29: +++++ Caco-2: +++++
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Selected characteristics of *L. acidophilus* La-14 (internally generated data): +++++ Excellent; +++++ Very good; ++ Good; + Fair

### Inhibition of pathogens

The protective role of probiotic bacteria against gastrointestinal pathogens is highly important to therapeutic modulation of the enteric microbiota. Probiotics are able to inhibit, displace and compete with pathogens, although these abilities are strain-dependent.

The probiotic strains' putative mechanisms of action against pathogenic microorganisms include the production of inhibitory compounds, competition with pathogens for adhesion sites or nutritional sources, inhibition of the production or action of bacterial toxins, ability to coaggregate with pathogens, and the stimulation of immunoglobulin A.

*In vitro* inhibition is usually investigated using an agar inhibition assay, where soft agar containing the pathogen is laid over colonies of probiotic cultures, causing the development of inhibition zones around the colonies. This effect may be due to the production of acids, hydrogen peroxide, bacteriocins and other substances that act as antibiotic agents as well as

competition for nutrients. It should be pointed out, however, that extending of such results to the *in vivo* situation is not straightforward. The assessment in the table below is based on an *in vitro* assay.

*L. acidophilus* La-14 displayed *in vitro* inhibition of selected pathogens.

Pathogen inhibition <i>in vitro</i>	<i>Salmonella typhimurium</i> : +++++ <i>Staphylococcus aureus</i> : +++++ <i>Escherichia coli</i> : ++ <i>Listeria monocytogenes</i> : +
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Selected characteristics of *L. acidophilus* La-14 (internally generated data): +++++ Excellent; +++++ Very good; ++ Good; + Fair

### L/D- lactic acid production

Lactic acid is the most important metabolic end product of fermentation processes by lactic acid bacteria and other microorganisms.

Due to the molecular structure, lactic acid has two optical isomers. One is known as L(+)-lactic acid and the other, its mirror image, is D(-)-lactic acid. L(+)-lactic acid is the normal metabolic intermediary in mammalian tissues. D(-)-lactic acid is normally present in the blood of mammals at nanomolar concentrations.

In the past, D(-)-lactic acid was thought to be "non-physiological" and, due to the slower metabolism in the human body, the possible cause for lactate acidosis (10, 11). In 1967, this led to a recommendation from WHO/FAO for a maximum D(-)-lactic acid intake of 100mg per kg body weight. More recent studies using modern methods have shown that, in fact, the metabolism of D(-)-lactic acid in healthy humans is comparable with L-lactate. Due to the scientific evidence, WHO/FAO withdrew this intake recommendation in 1974, but still with the restriction not to use D(-)-lactic acid in food for infants (12).

Special attention has been paid to children below the age of 12 months, because their metabolism is premature. The CODEX Standard for Infant Formula for the age group below 12 months (STAN 72-1981 revision 2007) contains the

restriction under "Optional ingredients": "Only L(+)-lactic acid producing cultures may be used" as well as for the use as acidity regulator.

This recommendation is based on three studies (13, 14, 15) in which DL-lactic acid was added to infant formulas at concentrations of 0.35 to 0.5%. Some infants in the study could not tolerate lactic acid supplementation. The effects were reversed on withdrawing these high doses of lactic acid from the diet.

In another recent study (16), healthy infants fed a D(-)-lactic acid producing *Lactobacillus* sp. at 10<sup>9</sup> CFU/day from birth to 12 months demonstrated no change in serum D(-)-lactic acid levels compared to placebo-fed control, this study concluded that probiotics producing D(-)-lactic acid can be safely fed to infants.

Considering all these results, the use of D(-)-lactic acid in infant nutrition is still questioned today.

Anyhow, these concerns should not be applied directly to the use of probiotics as nutritional ingredients that do not produce lactic acid in the infant formula.

In conclusion, despite the fact that there is no real scientific consensus to suggest that healthy infants or any healthy human would be affected detrimentally by the addition of lactobacilli that produce D(-)-lactic acid, Danisco follows the CODEX recommendation not to use D(-)-lactic acid producing cultures in food for infants below the age of 12 months.

L/D-lactic acid production	<b>60/40</b>
Molar ratio	Boehringer Mannheim/ R-Biopharm D-lactic acid/ L-lactic acid UV-method

Internally generated data

### OXALATE-DEGRADING ACTIVITY

A study was undertaken to evaluate the oxalate-degrading activity of 60 *Lactobacillus* strains, including *L. acidophilus* La-14. In humans, an accumulation of oxalic acid can result in a number

of pathological conditions, including hyperoxaluria, kidney stones, renal failure, cardiomyopathy and cardiac conductance disorders.

The oxalate-degrading activity of *L. acidophilus* La-14 was found to be 100%, which was as high as the positive control *Oxalobacter formigenes* DSM 4420. The activity of other strains of *L. acidophilus* ranged from 35 – 100%. The use of probiotic strains with oxalate-degrading activity may offer the opportunity to provide this capacity to individuals suffering from oxalate associated disorders (17).

Another study, including *L. acidophilus* La-14 and *O. formigenes* DSM 4420 evaluated the kinetics of Oxalyl-coenzyme A decarboxylase (OXC), which is a key enzyme in the catabolism of the highly toxic oxalate. Steady state kinetic constants of OXC were estimated for both the bacteria. Although *L. acidophilus* La-14 provided a lower oxalate breakdown than *O. formigenes* DSM 4420, it could be a potentially useful probiotic in the prevention of diseases related to oxalate (18).

### **Animal studies**

A study has investigated the effects of the spent culture supernatant (SCS) of *L. acidophilus* La-14 on the intestinal flora of mice with antibiotic-associated diarrhoea (19).

The microbiota imbalance in this animal model was induced by intraperitoneal administration of ampicillin 2000mg/ (kg•d) for 3 days.

In the mice administered with ampicillin, there was an obvious change in the numbers of four main groups of the microbiota. Compared with those in the control group, the numbers of *Escherichia coli* and *Enterococcus* spp. were significantly increased.

After the mice were administered with SCS, living bacteria, and SCS plus living bacteria, the numbers (compared with those in the spontaneous recovery group) of *Lactobacillus* and

*Bifidobacterium* had increased remarkably while the numbers of *Escherichia coli* and *Enterococcus* were significantly reduced. These results indicate that both living bacteria and SCS of *L. acidophilus* La-14 can regulate the microbiota imbalance in mice with antibiotic-associated diarrhoea, and help to recover the numbers of *Lactobacillus* and *Bifidobacterium* in the intestinal tract (19).

### **IMMUNOMODULATION**

An immune system that functions optimally is an important safeguard against infectious and non-infectious diseases. The intestinal microbiota represent one of the key elements in the body's immune defence system. Probiotic bacteria with the ability to modulate certain immune functions may improve the response to oral vaccination, shorten the duration or reduce the risk of certain types of infection, or reduce the risk of or alleviate the symptoms of allergy and other immune-based conditions.

Modulation of the immune system is an area of intense study in relation to the Danisco probiotic range. The goal is to understand how each strain contributes to the maintenance and balance of optimal immune function. The immune system is controlled by compounds known as cytokines. Cytokines are hormone-like proteins made by cells that affect the behaviour of other cells and, thereby, play an important role in the regulation of immune system functions.

### **In vitro studies**

*In vitro* assays are widely used to define the cytokine expression profiles of probiotics and, thereby determine their immunological effects. By measuring the impact of probiotic bacteria during interaction with cytokine-expressing peripheral blood mononucleocytes (PBMCs), information is generated that can help determine the ability of each strain to contribute to balanced immune health.

*L. acidophilus* La-14 was investigated *in vitro* for its ability to induce the PBMC secretion of selected cytokines: interleukin (IL)-10, IL-12, tumour necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$ . The results were compared with a strain of *L. plantarum* (8826). *L. acidophilus* La-14 was found to induce IL-10, TNF- $\alpha$  and IFN- $\gamma$  to a lesser degree than *L. plantarum*. However, *L. acidophilus* La-14 induced significantly higher PBMC excretion of IL-12 (figure 1). This is known to shift the immune system towards a so-called Th1 type of response; which plays a key role in, for example, warding off tumours and viruses and the anti-allergy response. This is also in line with the moderate induction of TNF- $\alpha$  and IFN- $\gamma$  (results not published).

In another study including *L. acidophilus* La-14, it was investigated whether bacterial DNA is involved in the beneficial effects obtained by probiotic treatment. Peripheral blood mononuclear cells (PBMC) from healthy donors were incubated with pure DNA of probiotic strains before and after probiotic ingestion. Cytokine production was analysed in culture supernatants. It was shown that the DNA of *L. acidophilus* La-14 stimulated the secretion of IL-10 only to the same level as that induced by lipopolysaccharides (LPS) (20).

These results are in accordance with those obtained with living cells (see above). They also indicate the possible role of pure bacterial DNA in probiotic efficacy.

### **Animal studies**

Using the cytokine expression data as a predictive test, *L. acidophilus* La-14 would not be expected to be a strong inflammation reducer due to its relatively low induction of IL-10. This has been confirmed in a chemically-induced inflammation animal model. The graph below (figure 2) depicts an inflammation score (Wallace) in which *L. acidophilus* La-14 does not significantly reduce the intestinal inflammation in this model, compared to

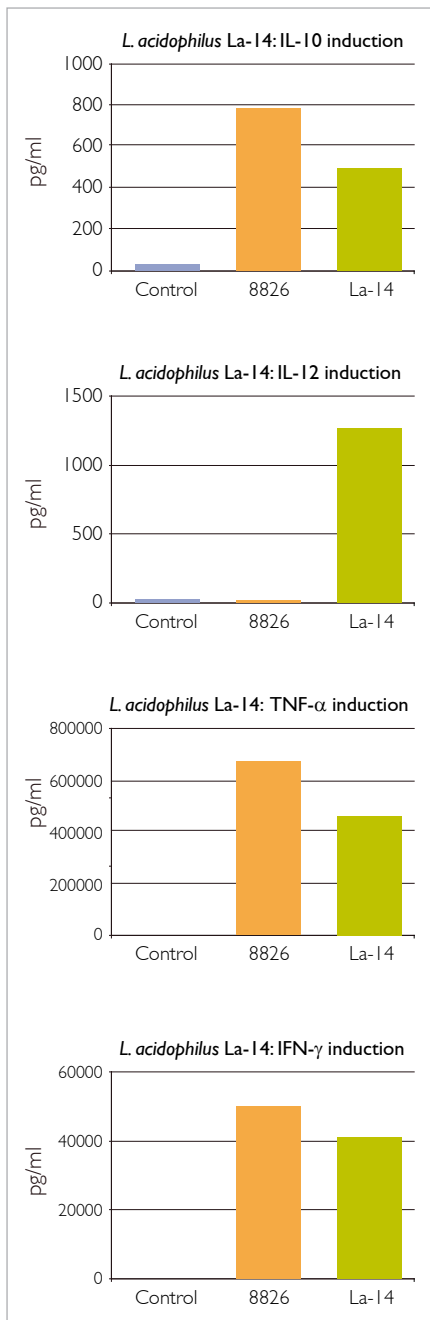


Figure 1. *In vitro* cytokine expression of *L. acidophilus* La-14 (internally generated data).

a control. Although *L. acidophilus* La-14 has been shown to modulate several immune response markers, according to Danisco's condition-specific approach to health benefits, the strain would not be recommended for conditions requiring downward modulation of an inflammation response. The strain is more suitable for an anti-infection and anti-allergy response (results not published).

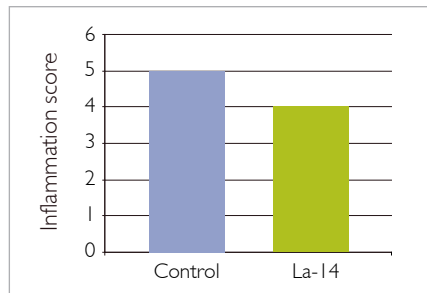


Figure 2. Influence of *L. acidophilus* La-14 on inflammation score (internally generated data).

### Human studies

The ability of *L. acidophilus* La-14 to stimulate specific immunity has been evaluated in a human study measuring primary immune reaction following vaccination.

Human volunteers were orally vaccinated (using cholera vaccine as the vaccination model) and then received either a placebo (maltodextrin, n=20) or *L. acidophilus* La-14 (n=9). Supplementation with *L. acidophilus* La-14 or the placebo started on day 0 and continued for 21 days. The subjects consumed two capsules a day with  $10^{10}$  CFU *L. acidophilus* La-14 or two capsules a day with maltodextrin (control). On day 7 and 14, the subjects received the oral vaccine. Blood samples were collected on day 0, 21 and 28, and antigen-specific antibodies (immunoglobulins, IgA, IgG, IgM) were determined. These immunoglobulins play different roles in the body's immune defence strategy.

Supplementation with *L. acidophilus* La-14 resulted in a faster and higher induction of specific IgA and IgG than in the control group. This indicates the stimulation of specific immunity by *L. acidophilus* La-14 (manuscript submitted, figure 3).

### ANTIBIOTIC RESISTANCE PATTERNS

Antibiotic susceptibility patterns are an important means of demonstrating the potential of an organism to be readily inactivated by the antibiotics used in human therapy.

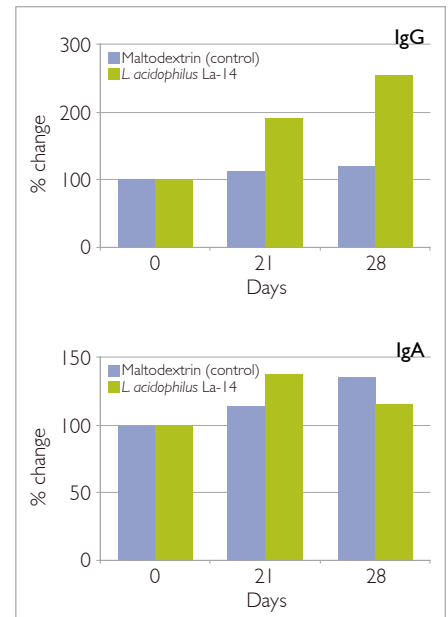


Figure 3. Relative change in specific IgG and IgA titre in orally vaccinated humans after supplementation with *L. acidophilus* La-14.

Antibiotic resistance is a natural property of microorganisms and existed before antibiotics became used by humans. In many cases, resistance is due to the absence of the specific antibiotic target or is a consequence of natural selection.

Antibiotic resistance can be defined as the ability of some bacteria to survive or even grow in the presence of certain substances that usually inhibit or kill other bacteria. This resistance may be:

**Inherent or intrinsic:** most, if not all, strains of a certain bacterial species are not normally susceptible to a certain antibiotic. The antibiotic has no effect on these cells, being unable to kill or inhibit the bacterium.

**Acquired:** most strains of a bacterial species are usually susceptible to a given antibiotic. However some strains may be resistant, having adapted to survive antibiotic exposure. Possible explanations for this include:

- A mutation in the gene coding for the antibiotic's target can make the antibiotic less efficient. This type of antibiotic resistance is usually not transferable.
- A resistance gene may have been acquired from a bacterium.

Of the acquired resistances, the latter is of most concern, as it may also be passed

on to other (potentially pathogenic) bacteria.

Much concern has arisen in recent years regarding vancomycin resistance, as vancomycin-resistant enterococci are a leading cause of hospital-acquired infections and are refractory to treatment. The transmissible nature of genetic elements that encode vancomycin resistance in these enterococci is an important mechanism of pathogenicity.

Resistance to vancomycin in certain lactobacilli, pediococci and leuconostoc is due to intrinsic factors related to the composition of their cell wall. It is not due to any transmissible elements (21).

As yet, no case of antibiotic resistance transfer has ever been identified and

reported for the lactic acid bacteria used in foods and feed.

*L. acidophilus* La-14 is vancomycin sensitive.

The antibiotic susceptibility patterns for *L. acidophilus* La-14 are summarised in table 1.

#### APPLICATIONS AND STABILITY

*L. acidophilus* La-14 is available as a high-count freeze-dried material with very good stability in powder formulations, taking advantage of Danisco's patented stabilisation technology, FloraFit® RT (22). *L. acidophilus* La-14 is suitable for food and dietary supplement applications.

#### BENEFIT SUMMARY

Extensive *in vitro* and *in vivo* studies support the health-enhancing, probiotic properties of *L. acidophilus* La-14. Following is a summary of these attributes:

- Long history of safe use
- Well-suited for intestinal survival
  - High tolerance to gastrointestinal conditions (acid, bile, pepsin and pancreatin)
  - Strong adhesion to intestinal cell lines
- Ability to inhibit common pathogens
- Beneficial modulation of immune functions
  - May improve specific immune response, as demonstrated in a human clinical study (manuscript submitted)
  - May influence immune regulation, as demonstrated by the induction of IL-12 and moderate induction of tumour necrosis factors *in vitro*

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<b>Lactobacillus acidophilus La-14 antibiogram</b>	
Amoxicillin	S
Ampicillin	S
Ceftazidime	I
Chloramphenicol	I
Ciprofloxacin	R
Clindamycin	I
Cloxacillin	S
Dicloxacillin	S
Erythromycin	S
Gentamicin	R
Imipenem	R
Kanamycin	R
Neomycin	R
Nitrofurantoin	R
Penicillin G	S
Polymixin B	R
Rifampicin	S
Streptomycin	R
Sulfamethoxazole	R
Tetracycline	R
Trimethoprim	R
Vancomycin	S

S = Susceptible (minimum inhibitory concentration ≤ 4µg/ml)  
 I = Intermediate (minimum inhibitory concentration = 8 to 32µg/ml)  
 R = Resistant (minimum inhibitory concentration ≥ 64µg/ml)

Table 1.

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First you add knowledge...