The lactic acid bacteria, the food chain, and their regulation

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Introduction

This paper deals with the regulatory status of micro-organisms used in foods. In anticipation of specific European Union (EU) legislation on these micro-organisms, the paper describes how other bodies have carried out such regulation, and it proposes ways that the EU might regulate them. While microbial cultures added to foods may be yeasts, filamentous fungi, or bacteria, this paper discusses primarily the lactic acid bacteria (LAB), which are used extensively in a variety of food applications. The main categories of these applications are presented in Box 1.

Currently, the EU focuses very intensely on food safety, and especially on both chemical and microbiological hazards. Microbiological hazards are not only pathogenic micro-organisms that coincidently find their way into the food chain, but also can be microbial cultures deliberately added during food production. Of all 25 EU member states, only Denmark and France have legislation that explicitly regulates the addition of microbial cultures to food, and the EU itself only regulates them in infant formulae and only as to the configuration of the lactic acid molecule (European Parliament and Council, 1995). In light of this weak regulation, the EU Commission and the European Food
**Box 1**

**Functions in foods and regulatory categories of LAB**

The function that a given LAB has in a food does not unambiguously imply which regulatory category the LAB should be allocated to. Each country and international body must itself determine which regulatory category is the most appropriate according to its legislative tradition. Below are listed the functions of the LAB in foods and then regulatory categories that could correspond to each function.

<table>
<thead>
<tr>
<th>Functional group</th>
<th>Function of LAB</th>
</tr>
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<tbody>
<tr>
<td>i</td>
<td>Fermentation starter cultures or preservatives. Foods prepared with and containing live LAB.</td>
</tr>
<tr>
<td>ii</td>
<td>Probiotic (i.e. health-promoting) function for the consumer of the food. Foods containing living or dead LAB.</td>
</tr>
<tr>
<td>iii</td>
<td>Function carried out by particular compound produced by LAB other than lactic acid. Such compounds might be aroma compounds, exopolysaccharides, or bacteriocins.</td>
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Safety Authority (EFSA) have perceived a need of an EU law on food cultures. When passed, such a law can be expected to be formed as a regulation, which thus will be immediately and directly applicable in all member states. Therefore, the final content of this law will have far-reaching effects for both the traditional and novel applications of the LAB and all other food cultures.

In the following, brief reviews are given of the taxonomy of the LAB, of safety issues in connection with the addition of these bacteria to foods, and a review of consumers' perception of these bacteria. Then, the paper focuses on existing regulatory frameworks in the USA and in the EU and on emerging legislation in the EU. Finally, the authors give their opinion on the principles on which the eventual EU legislation might be based.

**Taxonomy**

Taxonomically, the term LAB denotes a rather diverse group of bacteria sharing the following characteristics: Gram-positive, non-sporulating, catalase-negative, devoid of cytochromes but aerotolerant, fastidious, acid-tolerant and fermentative with lactic acid as the major end-product of sugar fermentation. The common LAB genera in food fermentations include: *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, and *Weisella* (Stiles & Holzapfel, 1997). Of these, *Lactobacillus*, *Leuconostoc*, *Pediococcus* and *Streptococcus* historically represent the 'core genera', as recognized since the 1940s. After the introduction of the new genera *Enterococcus* and *Lactococcus* in the mid 1980s, the only species in the genus *Streptococcus* that is associated with food fermentations is *S. thermophilus*.

The genus *Bifidobacterium* is often considered to belong to the LAB as it shares some of the typical features of the LAB, e.g. fermentative metabolism and lactic acid production. Bifidobacteria are, however, phylogenetically unrelated to the LAB and use a unique metabolic pathway for sugar metabolism.

**Safety aspects**

A regulation for reasons of safety should be proportional to perceived risks, risk being a function not only of severity but also of probability of the adverse effect taking place (World Health Organization, 1999). All microbes that have the ability to grow in the conditions prevailing in the human body can in extreme situations cause infections. This includes members of the genera *Lactobacillus* and *Bifidobacterium*. However, of all the genera of LAB in food or probiotic use, only the enterococci are frequently encountered in opportunistic infections, and a number of virulence determinants have been associated with pathogenic strains of this genus.

The genera *Lactobacillus* and *Bifidobacterium* are among the bacteria with the lowest risk at all to humans. The observed frequency of bacteraemias where lactobacilli are involved is only 0.1–0.24%, and in practically every case there has been a severe underlying disease, thus predisposing the individual to opportunistic infections. No cases of bacteraemia caused by dairy starters are known (Gasser, 1994; Saxelin et al., 1996).

In two cases, however, i.e. a liver abscess and an endocarditis, probiotic lactobacilli may have been involved in the aetiology of the actual disease (Mackay, Taylor, Kibbler, & Hamilton-Miller, 1999; Rautio et al., 1999). In the latter case, the bacteriological identification was relatively uncertain. Two recent papers have shown that the extensive use of probiotics in Finland has not had any impact on the frequency of *Lactobacillus*-associated bacteraemia (Salminen et al., 2002; Saxelin, Rautelin, Salminen, & Mäkelä, 1996). Among the bifidobacteria, only *B. dentium*, *B. denticolens* and *B. inopinatum* are of potential concern as they have been found to be associated with human dental caries (Crociani, Biavati, Alessandrini, Chiariini, & Scardovi, 1996).

Enterococci are normal inhabitants of the gastrointestinal tract and are commonly found in various foods, either as contaminants, components of the spontaneously developing fermentative microflora, or as deliberately used starters (Giraffa, 2002; Giraffa, Carminati, & Neviani, 1997). Some strains are also used as probiotics (Fris-Møller & Hey, 1983). However, in recent years enterococci, and especially *Enterococcus faecalis*, have been associated with endocarditis, bacteraemia, and intra-abdominal, urinary tract, and central nervous system infections in hospitals (Franz, Holzapfel, & Stiles, 1999; Moellering, 1992).
Multi-resistance to antibiotics is particularly prevalent among the enterococci (Giraffa, 2002), and some of these resistances are efficiently transmitted to other strains, other species, and to other genera. Vancomycin resistant enterococci have become a cause of special concern because of their direct threat to antibiotic therapy (Noble, Virani, & Cree, 1992).

Consumer perception of food safety and the LAB

In addition to actual identified risks, regulatory measures should also reflect the concerns of consumers. Consumers’ perception of risk can differ from that of experts. Experts evaluate risks scientifically and base their assessment on the severity of the hazard and its likelihood to occur. Consumers tend to think in an intuitive manner and react to food-related issues with affective responses (Epstein & Pacini, 1999; Lindeman, 1998). Several authors have indicated that for consumers, familiarity with food implies safety, while novelty of food implies a possible threat (Pliner & Hobden, 1992; Rozin & Royzman, 2001). Foods produced with the aid of the LAB are part of consumers’ everyday diet (e.g. cheese, butter, and sauerkraut), and some of the foods even have a positive health image (e.g. yoghurt or sourdough bread). Therefore, the use of LAB should not be a cause of major concern. However, consumers may be unfamiliar with the actual fact that bacteria are an essential part of the food production, and especially that they are exposed to enormous numbers of live bacteria when they are eating these foods. On the other hand, in media and public discussion, bacteria have mainly been portrayed as a threat because of spoilage and food poisoning. Therefore, any safety information on microorganisms should clarify whether a bacterium is intentionally used as a desirable ingredient of the food or whether it is a coincidental contaminant.

Withholding information in the public debate can be interpreted as intentional concealing of relevant facts. This would reduce consumer trust and the willingness to use LAB-containing foods even in cases with obvious consumer benefits. To maintain public confidence in the safety of foods produced with LAB, communication should emphasize the well-established history of safe use and the very few anecdotal infections. Nevertheless, consumers should also be informed about the possible risks of ingesting live bacteria for people with particular medical conditions. This way, consumers are able to make their own decisions and choices between the possible benefits and risks. Furthermore, having control over exposure to a risk decreases anxiety, while uncontrollable risks increase it (Frewer, Howard, Hedderly, & Shepherd, 1996; Slovic, 1987; Sparks & Shepherd, 1994).

Regulating the use of the LAB in foods

Internationally, the LAB for foods are regulated in very different ways. Different countries and international bodies put them into quite different regulatory categories and regulate them to very different degrees. The different regulatory strategies are illustrated in Box 1. Especially among EU member states, these differences result in very different demands being put on new LAB cultures and are particularly well exemplified by the traditional use of the LAB as food starters, i.e. category (i) in Box 1. For instance, if a starter culture is categorized as a processing aid, and not as an additive or ingredient, it is exempt from the EU-wide requirements put on additives, and consequently the food does not have to be labeled as containing the bacteria (European Parliament and Council, 1995). If, on the other hand, a starter culture is categorized as an ingredient, it must appear on the list of ingredients. Finally, if the starter culture is categorized as an additive, as in Denmark, the food authorities must first be notified of the new culture prior to its marketing, and the culture’s safety and efficacy must be documented. Then again, some countries have no legislation covering starter cultures at all, such as Sweden and Finland, and some countries, such as France, are in the process of preparing national guidelines for a new strain’s documentation. In the USA, there is a well-functioning regulatory framework for microbial cultures for food and feed. In the following sections, the US system and the present and the emerging regulatory situations in the EU are reviewed.

The USA

In the United States, a new strain of micro-organism for use in food can either be classified as an additive or as a GRAS substance (i.e. substance generally recognized as safe), and the choice is virtually up to the industry using the new strain. Additive and GRAS substances are defined below. The US has had the concept of GRAS since 1958, and in 1997, the US Government launched a new GRAS programme. The object of the new programme is both to simplify the GRAS concept itself and to simplify the FDA’s administration of substances that due to their relative safety do not merit an extensive review by experts. A GRAS substance is defined in the US Federal Food, Drug, and Cosmetic Act as:

> generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case as a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use (Section 201(s), US Food and Drug Administration, 1999)

A food additive in the US is defined extremely broadly to include virtually anything that might come into contact with food, as long as it is not specifically evaluated as GRAS.

The responsibility for regulating new strains of microorganisms for foods as GRAS rests with the Food and Drug Administration (FDA) and its Division of Biotechnology and GRAS Notice Review. About GRAS determinations of bacterial cultures in food, the Division expressly emphasizes two limitations on the GRAS concept:
1. The GRAS status is not determined by the FDA. This is done by qualified experts, and these experts may be a panel summoned by a food company.

2. The intended use of the bacteria culture is as integral a part of the GRAS evaluation as the properties of the strain(s) in question. For instance, a strain of *Lactobacillus* may be determined to be GRAS for use in a yogurt product, but the GRAS determination is not valid for the same strain in infant formulae.

When the FDA receives a GRAS determination from a food industry, it evaluates the documentation and then gives either of two simple responses; either it agrees or it disagrees with the GRAS determination. Disagreement is not prohibition; a food company can still use the bacterium as it wishes.

The difference between a food additive and a GRAS substance has very practical consequences for the FDA. A GRAS determination puts very little administrative burden on the FDA offices and keeps the legal responsibility completely with the food company that uses the bacterium. On the other hand, classification as an additive demands preparing an application for approval based on toxicological and efficacy data that must be evaluated by the FDA.

A food company can use a new strain of a bacterium, however, it wishes without any GRAS determination and without ever notifying the FDA. This is fully legal according to US law. However, in the event of a microbiological food safety incident, dialogue with the FDA would be much easier and controversy and legal liability less if a company first had submitted a GRAS determination. In that case, when the causes of the particular food safety incident were unravelled, it could be documented that the FDA and the company had agreed on the quality of the safety evaluation of the new bacterium.

The conclusions of all GRAS determinations since January 1, 1998, and most of the correspondence from the food industry, it evaluates the documentation and then gives either of two simple responses; either it agrees or it disagrees with the GRAS determination. Disagreement is not prohibition; a food company can still use the bacterium as it wishes.

The European union

Except for two specific cases, the European Union (EU) has as yet no single, harmonized legislation that regulates the use of LAB in foods per se, whether as traditional starter cultures, as food supplements or as probiotic cultures. Specific legislation does exist for genetically modified cultures and for cultures for infant and follow-on formulae. For probiotic cultures for animal feed, completely harmonized and very detailed EU legislation has existed since 1994.

Most future EU food laws can be expected to be regulations and not directives. Regulations are laws that are directly applicable in all member states and override any member state legislation that might cover the same area. Directives are framework laws that subsequently must be enacted by the parliament of each member state in a form that suits the member state best. Currently, there are seven EU laws that can have direct bearing on the use of new strains of LAB in foods:

1. contain or consist of genetically modified organisms (as defined in (ii));
2. are produced from, but do not contain, genetically modified organisms; and
3. consist of, or are isolated from, micro-organisms, fungi or algae.

If a given lactic acid bacterium has never been used in food in the European Union before May 15, 1997, then it should theoretically be subject to the Novel Food Regulation. However, the Regulation does not specify the level of novelty intended, whether it be genus, species, or strain. As of Autumn 2003, the approval process of the Regulation has not yet been applied to any strain of LAB. It is to be noted that the regulation explicitly applies to both living and dead micro-organisms as part of a food or food ingredient.

The Novel Food Regulation was introduced because of consumer concerns about food safety in relation to a number of technological developments. The assessment of the safety must proceed according to guidelines set out by the former Scientific Committee for Foods (European Commission, 1997). Because the science behind modern biotechnology and novel foods advances so rapidly, the new EU Scientific Panels have been obliged to soon re-consider the safety assessment guidelines (European Parliament and Council, 1997). In addition, the EU Commission and the Scientific Panels are currently developing a new structure for the Novel Food Regulation.

Instead of being considered a novel food ingredient, a traditional starter culture might also be considered a processing aid, for instance because it carries out the acidification of a food or the production of flavour compounds. In this case, the culture is explicitly exempted
from the Novel Food Regulation. Functions as processing aids fall within (iii) and (iv).

A new strain of the LAB might also be marketed in the EU as a food supplement, which is especially relevant for probiotic LAB. As yet, the directive on food supplements (v) only encompasses vitamins and minerals as food supplements. However, the directive can be amended to include LAB as long as they, too, are pre-packaged in dose form, such as tablets or capsules, and as long as the property of preventing, treating or curing disease is not attributed to them.

The EU does have a directive that specifically regulates LAB cultures for infant formulae and follow-on formulae for infants in good health, and cultures for food for infants and young children for special medical purposes. This directive (vi), which regulates food additives other than colours and sweeteners, specifies that non-pathogenic \( l^{(+)\text{-lactic acid}} \)-producing cultures may be used for the manufacture of acidified milks. It is to be noted that a reservation about the use of \( d^{(-)\text{-lactic acid}} \)-producing cultures dates from a 1976 Codex standard (Codex Alimentarius Commission, 1997), whereas the FAO/WHO expert consultation on probiotics from 2001 does not identify the molecule’s configuration as a risk factor (FAO/WHO, 2001).

Finally, the EU legislation on animal feed additives (vii) may affect coming legislation on cultures for food.

Animal feed additives in the EU

Products containing LAB for feedingstuffs are categorized in the EU as feed additives. For these additives, the EU has had completely harmonized and very detailed legislation since 1996. Although the legislation is contained in directives, in practice they are interpreted as EU regulations, being EU laws directly and literally applicable in all member states. There are two directives and a scientific opinion that specifically relate to the LAB as feed additives:

(i) Directive 96/51/EC (Council of the European Union, 1996), that defines this category of feed additive;
(ii) Directive 94/40/EC (European Commission, 1994), that presents guidelines for the assessment of this category of feed additive; and

The Opinion (iii) contains proposed changes to directive 94/40/EC (ii) that are specifically relevant for microorganisms as additives.

In the EU, an LAB-containing feed additive is subject to a full approval process. As of 2003 the dossier for approval is evaluated by the Standing Committee on Food Chain and Animal Health and by the Scientific Panel on Additives and Products or Substances Used in Animal Feed. It is to be noted that a commercial feed additive is a product that contains not only the micro-organisms in question but most often also cryoprotectants, excipients, bulking material, and some impurities such as residues from the fermentation broth. The firm wishing to market the product must submit a full dossier that documents the product’s identity, its efficacy as an additive and its safety. Safety is specifically construed as safety for the animal species consuming the feed, for the worker handling the additive and handling feed containing it (including the farmer), and for the consumer of the animal product. Documentation for safety relates both to the micro-organism and to the other materials in the product. With few exceptions, all documentation for the micro-organism relates to the actual strain in question and not just its species or genus. In the following, some specific aspects of the safety documentation will be described. Here, it is particularly noteworthy that no exemption in the depth of documentation is given even for a species or strain of micro-organism that has a well-established history of safe use in human food. On the other hand, for the assessment of safety for the environment, explicit exemption is given to any micro-organisms of gut or soil origin, as these are deemed to be environmentally neutral (European Commission, 2001a).

In the safety documentation for the micro-organism itself, special attention must be paid both to its potential for the production of toxins if it belongs to a taxonomic group that includes toxin-producers and to its potential to produce virulence factors. Especially the latter are relevant for the safety evaluation of enterococcal strains (Franz et al., 1999). The absence of transmissible antibiotic resistance genes must also be documented. To this end, the former EU Scientific Committee on Animal Nutrition (SCAN) has formulated a guidance on the criteria for assessing resistance to antibiotics, which was last revised in 2003 (European Commission, 2003b). This opinion defines the kinds of studies required and lists a number of antibiotics and their minimal inhibitory concentrations (MICs) that function as breakpoints between sensitivity and resistance; if the MIC is above the breakpoint, the genetic basis for resistance (transmissible or intrinsic) must be elucidated. The specific breakpoints are listed for three genera (Pediococcus, Lactobacillus, Bacillus) and two species (Enterococcus faecalis, E. faecium). Specifically for Lactobacillus, the opinion acknowledges that the available data to determine the MIC breakpoints as yet are limited.

To specifically document safety for the farm animal consuming the additive, a tolerance test is especially stipulated. Accordingly, a feeding study must be carried out using at least a 10-fold overdose of the additive for a duration specific to the target animal category and relevant to the intended use. During the feeding period, visual evidence of adverse effects, as well as performance characteristics, blood chemistry, and any other relevant parameters are recorded.

To document safety for workers handling the additive, safety studies include the additive’s possible irritancy, skin sensitization, and effects on the respiratory system. To ensure safety for the consumer, specific requirements are given for
Emerging EU legislation on LAB in foods

As of yet, the European Commission has not officially announced coming EU legislation that would specifically cover micro-organisms added to foods, such as the LAB. However, in anticipation of such an announcement, an ad hoc group has been established on the initiative of SCAN, now superseded by the Scientific Panel on Additives and Substances Used in Animal Feed. In its position paper of 2002 entitled ‘Safety Assessment and Regulatory Aspects of Micro-organisms in Feed and Food Applications’, SCAN proposed creation of a list of micro-organisms with a history of safe use (European Commission, 2002). This list would clarify and facilitate the present approval process of food and feed products that contain such micro-organisms. The list would be based on a qualified presumption of safety (QPS), presumption being defined as ‘a belief or assumption based on reasonable evidence’ and qualified to allow certain restrictions to apply (European Commission, 2002).

In 2003, this position paper was followed by a more detailed working paper on a QPS system, that was open for comment and entitled ‘On a generic approach to the safety assessment of micro-organisms used in feed/food and feed/food production’ (European Commission, 2003a). This document presents a decision-tree approach for the assessment of the suitability for QPS of micro-organisms, including some practical examples. Among the examples are the dairy lactobacilli, which ‘could be reasonably considered for QPS-status. The only qualification that might be attached is evidence of the absence of acquired antibiotic resistance’ (European Commission, 2003a). Since the mandate of SCAN expired in the spring of 2003, it is the task of the EFSA to conduct any further developments towards the establishment of the QPS concept as a part of an EU regulatory framework.

Conclusions

LAB have been used in food fermentations all over the world for millennia. Not only have there been no obvious harmful effects of this enormous exposure to the bacteria, but also the LAB are, in fact, an integral part of food safety, the keeping quality, and the nutritional quality of many perishable foodstuffs. Especially in the developing countries, these bacteria are of paramount importance for the safety of many foodstuffs (Cooke, Twiddy, & Reilly, 1987).

Currently, emerging EU food legislation reflects the increased awareness of food safety. However, while aiming at reducing the microbiological risks of pathogenic organisms in the food chain, this legislation may also inadvertently trap the LAB and other useful microbes that have been traditionally used in food processes with no safety concerns. Wisely, when the legislation is being formulated, an attempt is made to base it on the results of risk assessments. However, the precautionary principle is frequently applied, and most often all potential and conceivable hazards are identified. Even when a proper risk assessment is completed, the resulting data on frequency and severity of risks are ignored. This approach invariably leads to great over-regulation, and ironically microbes that are needed to ensure a safe food supply are excluded from use only because they themselves have not been subjected to exhaustive safety studies.

When modelling EU legislation to regulate bacteria to be added to the food supply, a template might be sought in already existing EU legislation. Such legislation does exist for probiotic LAB as additives to animal feed. However, copying feed legislation to foods would reflect a rather indiscriminate regulatory practice. For instance, oral toxicity and in vitro genotoxicity tests are among the safety studies that the animal feed guidelines prescribe. These tests could be warranted when implementing a completely new micro-organism in the food supply. However, for a bacterium with a well-established history of safe use and which has been consumed in enormous quantities by humans, use of oral toxicity and genotoxicity tests seems at best exaggerated. In fact, this depth of safety testing has resulted in the odd situation of an LAB already used in food for humans for years without any safety precautions now being subjected to rigorous safety evaluations when applied in animal feed. Indeed, the EU guidelines on feed additives essentially equate the LAB with chemical substances, which results in prescribing the same safety testing. In addition, specific microbiological hazards such as toxins and virulence factors listed in the feed additive guidelines do not apply to the LAB, with the notable exception of some enterococci. No toxic substances with either acute or chronic effects have ever been reported for the LAB. Even for the enterococci, there have been no reports of adverse health effects related to the strains deliberately added to foods.

The consequences of safety guidelines for feed components being applied to food components would be that thousands of bacterial strains would have to be tested for safety in this way. This would result in enormous quantities of safety testing resources being pulled away from genuine safety issues. In addition, the increased demand on laboratory animals would be contradictory to the official EU Commission policy of phasing out all unnecessary animal testing (European Commission, 2001b). As well, requiring this testing would invariably raise unwarranted consumer concerns and questions as to why extensive and expensive safety testing now is necessary for foods that were thought to be safe before. In Box 2, we present...
viewpoints that we consider as pertinent for a future legislation on microbial cultures for foods.

Box 2
Regulatory recommendations

There is a large discrepancy between the EU regulatory frameworks for LAB in feed and for LAB in food. To reconcile this discrepancy, legislative harmonization will be necessary. In light of this, the authors of this paper make the following recommendations for the eventual legislation to regulate the traditional cultures of lactic acid bacteria and other micro-organisms added to food.

1. For each regulatory measure introduced, there should be a clearly identified need.
2. The legislation should be flexible and recognize that the primary responsibility for the safety of these cultures rests with the manufacturer.
3. The legislation should be based on scientifically complete risk assessments. Such risk assessments are initiated on the basis of scientifically identified hazards, for example known virulence factors or transfer of antibiotic resistance.
4. Whenever possible, the regulation should use a system of generic approval, instead of approval one strain at a time or one use at a time. We recommend a system that uses inventories, or lists, of species or subspecies of micro-organisms that either have a history of safe use or experimentally have been shown to be safe. The QPS approach, when correctly applied, would serve this end (cf. European Commission, 2002, 2003a).
5. In cases where generic approaches are not applicable, the legislation should allow for evaluation of microbial strains according to their characteristics and intended use, instead of specifying a fixed list of studies to be done on all micro-organisms.
6. Bacterial strains used for special purposes may require specific approval or notification procedures. Examples might be foods containing probiotic micro-organisms intended for special consumer groups (e.g. infants, elderly, immuno-compromised, pregnant women and others). Also in these contexts, the legislation should allow a case-by-case approach.

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