**UPDATE**

Safety assessment of “familiar” microorganisms used in food and agriculture

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**SUMMARY**

Bacteria and micro-fungi are currently used in the agro-food sector, both for human consumption and animal feeding. The evolution of technological processes, consumers’ habits and international trade has led to question the safety of microorganisms considered as “familiar” (i.e. traditionally used). Several criteria have been identified in order to define this notion. Furthermore, international standards have been proposed for their safety assessment. However, harmonization should be developed, taking particularly into account the lack of regulatory status.

**Key words**

microorganisms, agrofood sector, familiarity, safety, assessment.
A wide variety of bacteria and micro-fungi are currently used in the agro-food sector, both for human consumption and animal feeding.

Several food/feed categories are concerned:

1) Food containing living microorganisms that have been intentionally added. These are cultured products; in this case, addition is part of the technological process (cheese, fermented drinks, bread, etc.);

2) Supplemented food/feed, where addition is made for physiological or health purposes (probiotics in human consumption and animal feeding);

3) Food ingredients or processing aids produced by microorganisms (enzymes, amino acids, polysaccharides and oligosaccharides, natural flavours, vitamins, etc.);

4) Food or food supplement containing non-living microorganisms.

These uses have been known for several millennia. Evolution of food technology and international trade have contributed to change the use of microorganisms and/or consumers exposure. This evolution has led to distinguish microorganisms considered either as “familiar” (i.e. traditionally used) or “new”. However the notion of “familiarity” needs to be clarified, particularly in order to conduct harmonized risk assessments at national and international level. The French food safety agency is often questioned to assess the safety of microorganisms concerned by the categories listed above. In the absence of regulatory bases and of consensual recommendation, this paper gives general up-to-date information on the main criteria used to precise the notion of “familiarity” (=“tradition”) of microorganisms used in the food sector. It presents different standards for their safety assessment in Europe and the United States.

1 – NOTION OF FAMILIAR MICROORGANISMS

As far as microorganisms used in the agro-food sector are concerned, a specific attempt of definition has been recently proposed by a working group consisting of members of three European scientific committees: “familiarity includes practical experience of use of the organism(s) including its history of use for particular purposes and any body of literature on the biology of the taxonomic unit” (ANONYMOUS, 2003).

On a regulatory basis, the notion of familiarity may be opposed to the notion of “novelty”, defined by the European Novel Food/Novel Feed Regulation N°258/97. Food or ingredients covered by this regulation are those “which have not hitherto been used for human consumption to a significant degree within the Community”. On the contrary, the notion of familiarity referred mainly to the knowledge and experience available for conducting a risk safety assessment. Several scientific committees have developed this notion during the last ten years. Several criteria can be highlighted.
1.1 Identification of the organism

Taxonomic identification is a key element in microorganism characterization. It provides a common frame of references between microorganisms. Several methods are used for their characterization: phenotypic methods (study of morphology and biochemical features) and genotypic methods (comparison between known sequences). These methods allow to precisely identify strains of microorganisms.

From a risk assessment point of view, unequivocal identification is needed for microorganisms. However, taking into account the improvement of knowledge of bacterial taxonomy, inadequacies in older techniques have been highlighted and may have led to misclassified “traditional” bacteria in the past. Therefore, identification should be performed with up to date methods, including molecular methods.

Moreover, pertinent microbial identification are not always available for some “traditional” fermented food, resulting from a fermentation process by a mixture of species, generally referred to as a Symbiotic Culture Of Bacteria and Yeast (SCOBY): for examples, traditional kefir, a milk fermented by a natural microbiological mother-culture composed of specific symbiotic lactic acid bacteria and yeasts, and Kombucha, a traditional Asiatic drink fermented by another SCOBY.

These examples highlight that the recognition of the “traditional” aspect needs to take into account other criteria than taxonomy, mainly based on the knowledge resulting from its use.

1.2 Knowledge of historical use

If “tradition” explains how human has selected his food since prehistory until today, it cannot however be similar, in term of demonstration, to the data brought by an experimental study. Nevertheless, long-term use of microorganisms in food is considered to establish a panel of experiences, considered as references, in a field where experimental studies are rare and difficult to realize.

Even if the safety of these products is based on their long-term use in several parts of the world, mutual recognition between countries may not be systematically easy. Actually, differences in life styles, consumption habits... may make some comparisons difficult.

For example, taking into account the lack of scientific data concerning the identity of the microorganisms used in Kombucha and the lack of control and reproducibility of the process, the French Food Safety Agency had given a negative opinion for the sale of this product in France (AFSSA, 2000), even though this product is traditionally consumed in several parts of the world.

Furthermore, the notion of familiarity does not take into account:

– Environmental changes, which can lead to emergence of hazard related to modifications of the biological properties of the microorganisms (for example, emergence of antimicrobial resistance);

– Changes in the exposure of the consumer related to a potential increase of the dose ingested for a microorganism that was usually used in a food
with limited distribution and without obvious health risk. A limited distribution limits the risk;

– Consumer behaviour: the more people consume, the more people are at risk.

1.3 Reference to geographical or temporal standards

The above considerations highlight the usefulness of temporal and/or geographical criteria. Thus, the Canadian government has defined a “Canadian familiarity” in the biotechnology field as “the knowledge of the characteristics of a given organism and experience with the use of that organism in Canada”. In the United-States of America, a substance can be eligible for the GRAS (Generally Recognised As Safe) status if its history of use is known prior to 1958. In France, traditional food containing plants has been defined, in reference to the European directive 2004/24 (EC), with geographical and temporal criteria, by a French expert group as “a corpus of knowledge established from data stemming from the European tradition and dating 30 years at least, confirmed by experimental data”.

2 – DEFINITION OF STANDARDS FOR THE SAFETY ASSESSMENT OF FAMILIAR MICROORGANISMS

Food safety and the development of consumer’s interest is of increasing concern to the general public and it is necessary to ensure the consumers confidence. According to the regulation 178/2002, the Community has chosen a high level of health protection as appropriate in the development of food law. These measures governing food and feed should generally be based on risk assessment.

Nowadays, it should be underlined, however, that safety assessment of microorganisms used in the agro-food sector is heterogeneous depending on the use of the microorganisms, either in the feed or the food sector. Actually, although microorganisms used in animal feeds are subject to precise community regulation, those used in human food production are generally assumed to be as safe because of their “familiarity”, their long history of presumed safe use.

For those microorganisms, safety may be assessed taking into account several reference frames.

– Existence of “positive lists” of familiar microorganisms considered as safe.

Familiar microorganisms can be included in the list defined by the Food and Drug Administration (FDA) for additives and ingredients generally recognized as safe (GRAS status). A substance may be GRAS only if its general recognition of

safety is based on the views of experts qualified to evaluate the safety of the substance. This status may be based either on a history of safe use in food prior to 1958 or scientific procedures, which require the same quantity and quality of evidence as would be required to obtain an agreement for a food additive. For a “familiar” substance, commonly used in food in the United States prior to 1958, information documenting this use must be available. If this substance was only used outside the United States, then published documents, or other information (that shall be corroborated by information from a second independent source that confirms the history and conditions of use) must be readily available in the country in which the history of use occurred.

This list has no regulatory status. It has been established by a voluntary process and information essential to a GRAS affirmation must be available to the public in the open literature.

Nowadays, few microorganisms have been included in the American GRAS list (Strains of Bacillus subtilis, Bifidobacterium lactis, Streptococcus thermophilus, Saccharomyces cerevisiae...); however they all have been evaluated by the scientific approach and not recognized by their “familiar” status.

A list of specifically traditional microorganisms (starter cultures) has also been established by the International Dairy Federation (IDF), in collaboration with EFFCA (European Food and Feed Cultures Association) (MOGENSEN et al., 2002) These microorganisms (bacteria, fungi, and yeast) are considered as safe food ingredients, on the basis of a documented history of use in food, at an international level. The inventory takes into account taxonomic changes that have taken place over time and considers microorganisms used to a significant degree. This notion is defined quantitatively as “species or cultures sold for human consumption in quantities exceeding an equivalent of 10 kg of freeze dried culture. This amount of culture used for inoculation in amounts of 0,01% corresponds to a produced amount of approximately 100 tonnes of fermented products containing approximately $10^8$ microorganisms per gram of product”. This criterion however should be clarified by the scale of use, in fine exposure of the consumer.

The inventory is the result of a consensus among the 41 countries members of the IDF and 15 companies that adhere to EFFCA. However, the authors underline that this list does not cover all industrial uses all over the world and therefore must be considered only for information. Particularly, artisan starters cultures are not considered in this inventory.

– Generic approach to the safety assessment of microorganisms

In 2003, a working group consisting of members of three committees of the European Commission proposed an approach similar to the American GRAS definition, specifically for microorganisms used in the feed/food sector, and taking into account issues of importance for European countries. The approach, called “Qualified presumption of safety” (QPS) provides a system that would harmonise safety assessment throughout the food chain. The general scheme is presented as a decision tree, including several considerations: identification, the degree of “familiarity”, experimental data in the case of microorganisms without a long history of use, human and/or animal exposure, eventual clinical reports... This document underlines that safety assessment based on QPS scheme
should be conducted on a case-by-case basis. This status should be estab-
lished by risk assessors and should not be considered as a legal status.

This approach has now been proposed to be included in the European food
safety agency’s work programme. A debate at the European scale is planned, in
order to explore options how to develop the concept of QPS into a proposal for
the regulatory community that is based on scientific principles.

3 – CONCLUSION

The evolution of the use of microorganism in the food sector is continuous,
as regard human habits and technical evolutions. This paper points out the
unclear frontier between “familiar” uses and “new” ones. For this purpose, in
2002, the French Food Safety Agency1 defined recommendations in order to
gather data to conduct safety assessment related to new strains and/or new
uses of known strains. Thus, the whole of these recommendations should be
helpful for all stakeholders: applicants (responsible for the safety of their pro-
ducts) requesting authorisation to use micro-organisms and people requiring an
advance assessment (administrative admissibility), as well as the experts who
perform the assessment.

Moreover, the conclusions of this analysis highlight both the heterogeneity
of microbial safety assessment in the agro-food sector, and the lack of clear
regulatory status of these food “ingredients”.

This consideration emphasizes the need to reach a harmonized approach,
especially in the context of international trade.

   used in the feed/food sector - new or modified strains - a different application of strains already in use.
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