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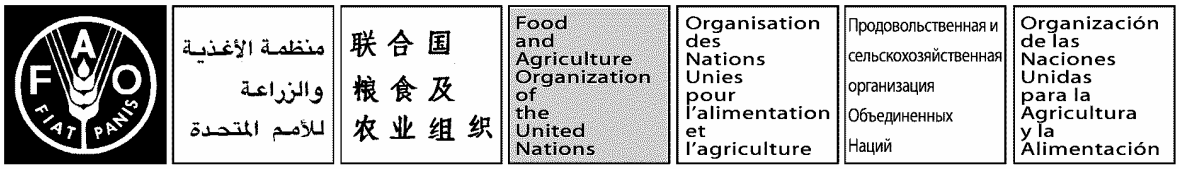

COMMISSION ON GENETIC RESOURCES FOR FOOD AND AGRICULTURE

THE USE AND EXCHANGE OF MICROBIAL GENETIC RESOURCES FOR FOOD AND AGRICULTURE

by

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This document has been prepared at the request of the Secretariat of the FAO Commission on Genetic Resources for Food and Agriculture by the Biodiversity Governance Unit at the Centre for Philosophy of Law at the Catholic University of Louvain, Belgium, as a contribution to the cross-sectoral theme, *Consideration of policies and arrangements for access and benefit-sharing for genetic resources for food and agriculture*, which the Commission will consider at its Twelfth Regular.

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ABOUT THIS PUBLICATION

The Commission on Genetic Resources for Food and Agriculture (the Commission), at its Tenth Regular Session, recommended that the Food and Agriculture Organization of the United Nations (FAO) and the Commission contribute to further work on access and benefit-sharing, in order to ensure that it moves in a direction supportive of the special needs of the agricultural sector, in regard to all components of biological diversity of interest to food and agriculture.

At its Eleventh Regular Session, the Commission agreed on the importance of considering access and benefit-sharing in relation to all components of biodiversity for food and agriculture, and decided that work in this field should be an early task within its Multi-Year Programme of Work (MYPOW). Accordingly, the Commission decided to consider arrangements and policies for access and benefit-sharing for genetic resources for food and agriculture at its Twelfth Regular Session (19-23 October 2009). To facilitate discussions and debate on access and benefit-sharing for genetic resources for food and agriculture at the Twelfth Regular Session, the Secretariat of the Commission has commissioned several background study papers on use and exchange patterns of genetic resources in the different sectors of food and agriculture. The studies provide an overview of past, current and possible future use and exchange patterns, as well as a description of terms and modalities for use and exchange of animal, aquatic, forest, micro-organism genetic resources; and of biological control agents. The current Background Study Paper deals with microbial genetic resources for food and agriculture. Cross-sectoral studies have been commissioned to analyse use and exchange patterns in light of climate change and to review the extent to which policies and arrangements for access and benefit-sharing take into consideration the use and exchange of genetic resources for food and agriculture in particular.

The broad ranges of studies are intended to provide insight, necessary to maintain, establish and advance policies and arrangements for access and benefit-sharing for biodiversity for food and agriculture. The studies may also contribute to the negotiations of an International Regime on Access and Benefit-sharing in the Ad Hoc Open-ended Working Group on Access and Benefit-sharing under the Convention on Biological Diversity.

ACRONYMS

ABS	Access and benefit sharing
AMGR	Agricultural microbial genetic resources
AnGR	Animal genetic resources for food and agriculture
ATCC	American Type Culture Collection
BCCM	Belgian Coordinated Collections of Microorganisms
BRC	Biological resource centre
CBD	Convention on Biological Diversity
CCCryo	Culture Collection of Cryophilic Algae
CGRFA	Commission on Genetic Resources for Food and Agriculture
CGIAR	Consultative Group for International Agricultural Research
COP	Conference of the Parties to the CBD
CRA	Italian Agriculture Research Council
DNA	Deoxyribonucleic acid
DSMZ	Deutsche Sammlung von Mikroorganismen und Zellkulturen (German Collection of Microorganisms and Cell Cultures)
ECCO	European Culture Collection Organization
FAO	Food and Agriculture Organization
GR	Genetic resources
ICARDA	International Center for Agricultural Research in the Dry Areas
IDA	International Deposit Authority
IPR	Intellectual property rights
ITPGRFA	International Treaty on Plant Genetic Resources for Food and Agriculture
MOSAICC	Micro-organisms Sustainable Use and Access Regulation International Code of Conduct
MoUs	Memorandum of Understanding
MTA	Material Transfer Agreement
MGR	Microbial genetic resources
OECD	Organisation for Economic Co-ordination and Development
PGRFA	Plant genetic resources for food and agriculture
PIC	Prior informed consent
RG	Risk group
UNEP	United Nations Environmental Programme
WFCC	World Federation of Culture Collections
WIPO	World Intellectual Property Organisation

WG-ABS	Ad Hoc Open-ended Working Group on Access and Benefit Sharing, established by the COP

GLOSSARY[2]

Microorganism: a microscopic organism (including viruses, bacteria, archaea, fungi, protists, microscopic plants (called green algae), and animals such as plankton)

Microbial culture: the growth of a microorganism on agar or other nutrient medium

Strain (in the context of culture collections): a pure microbial culture of descendants produced from one single ancestor, which all have the same genetic code (also called an isolate of that microorganism)

Type strain : when a species name is published, authors are required to designate a given strain as the *type* for that species ; the type strain should exhibit characters in agreement with those published in the species description, and, ideally, should be representative of the majority of strains belonging to the species.

Reference strain: in most cases more than one strain is needed to have a good representation of the genetic diversity of microorganisms within a species. That's why microbiologists also use reference strains (and not only type strains). Reference strains are those used in published taxonomic and physiological studies and are putatively representative of the species of which they are a member.

Culture collection: organization established to acquire, conserve and distribute microorganisms and information about them to foster research and education. Some important operating principles of culture collections which can be applied to "any culture collection regardless of size or economic standing" are (WFCC 1999)[3]:

- special preservation methods in order to ensure optimal viability, storage, purity and stability for individual strains; in particular, each strain should be maintained by at least two procedures, whenever practical;
- authentication (confirmation of the identity) and quality control of the strains upon deposit in the collection;
- records for each strain held, which should include at least the following categories of information: geographic location, substrate or host, date of isolation, name of person isolating the strain, depositor (or other source of the strain, such as another collection), name of the person identifying the strain, preservation procedures used, optimal growth media and temperatures, any data on biochemical or other characteristics, and any regulatory conditions applying;
- the capability of collections to meet all relevant national and international regulations concerning the control, transportation and health and safety aspects of resource handling and distribution.

WFCC culture collections: culture collections that are member of the World Federation for Culture Collections (WFCC). Any culture collection (defined as above) who wants to benefit from WFCC's education and information services, or who wishes to participate to one of its committees' activities can become member upon payment of a yearly fee of USD 100/year.

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[2] Based on WFCC 1999, Dugan and Tang 2004, Kurtzman and Labeda 2009, and Sigler 2004.

[3] These guideliness apply both to WFCC culture collection and non-WFCC culture collections. For the full list of guidelines, cf. WFCC 1999.

Research collections: culture collections of microorganisms offering services only in the institution under which the collection is established (for example a microbiology department in a university or a hospital).

Service collections: culture collections of microorganisms offering services both within and outside their own institution.

Patent collections: culture collections that are established as International Deposit Authorities for patent cultures (cultures that have to be deposited in conjunction with patent applications concerning microbiological inventions).

Safe deposits: some culture collections offer a safe deposit option. Under this option, a laboratory can deposit a culture to be maintained as a private deposit under conditions of secrecy, for which the collection charges a fee.

Public deposits: deposits that are not in the patent collections and not in the safe deposit collection.

EXECUTIVE SUMMARY

The important role of various components of global biodiversity in the improvement of agriculture and food production systems and the development of more environmentally and ecologically sound intensification has been increasingly recognized in the international debate. In particular the Commission on Genetic Resources for Food and Agriculture (CGRFA), at its Tenth Regular Session in 2005, *recommended that the Food and Agriculture Organization (FAO) and the CGRFA contribute to further work on access and benefit-sharing, in order to ensure that it move in a direction supportive of the special needs of the agricultural sector, in regard to all components of biological diversity of interest to food and agriculture.*

To facilitate the Commission's consideration of access and benefit-sharing policies in the special area of agricultural microbial genetic resources (AMGR), this study analyzes the exchange and use of microbial genetic resources in the different sectors of food and agriculture. A double set of case studies has been organized which provide the basic material of this report. A first set of case studies addresses specific cases of use of microorganisms in the agriculture and food sectors. Its aim is to analyze in detail the full research cycle involving *in situ* isolation, laboratory experimentation, *ex situ* conservation and distribution, and use.

A second set of case studies digs deeper into the question of the patterns of global interdependency by analyzing the exchange and distribution of microbial strains by culture collections. Based on these case studies, and the relevant literature in the field, this study addresses the following questions: What are the main patterns of global exchange and what are the main benefits of use and exchange of microbial genetic resources for food and agriculture? What are the current terms and modalities of exchange? What are the perceptions of the main stakeholders, and what are some of the promising initiatives by key players in the field?

1. Use and users of microbial genetic resources

The use and exchange of agricultural microorganisms present a wealth of opportunities for improvement of food and agricultural production systems, and for contributing to energy production and waste management in agriculture. The following areas where use of microorganisms currently plays an important role in agricultural have been identified in the study: (1) plant growth promotion through soil microorganisms, (2) in the understanding and surveillance of microbial plant pathogens (3) biological control, (4) beneficial symbiosis in the guts of ruminant livestock, (5) production of chemicals of direct benefit to agriculture, (6) workhorses in agro-industrial processes. Microorganisms also provide beneficial services in food production systems. Important areas of use that were identified are (1) fermentation, (2) probiotics, (3) production of chemicals of benefit to food production, and (4) understanding and surveillance of health hazardous microorganisms such as food toxins and food borne pathogens.

Users of microorganisms are both from public and private sector entities and farmers. AMGR are used in universities and professional schools for training and education, they are the basis of the services provided by culture collections, and are an important resource for research and development in university and private industry. They are vital components of agricultural production systems. Global distribution and exchange of well-documented microorganisms that are publicly available for research is organized by service culture collections. The most important of these are member of the World Federation of Culture Collections (WFCC)[4]. Prominent examples that are relevant in the field

[4] Cf. for an overview of the collections http://www.straininfo.ugent.be/About/index.php?cat=9&url=1. The map directly links to the websites of the individual collections (if existing) and to a short synopsis for every collection (although not always a recent one).

of food and agriculture are the US Agricultural Research Service Culture Collection and the UK based CABI Genetic Resource Collection, amongst others. These culture collections offer independent long-term access to authenticated biological materials, under strict quality control, and provide a standardized system for distributing materials among both public and private research institutions (Stern, 2004). Because of lack of capacity and high operating costs, the holdings of the culture collections only represent a small subset of the total holdings in the many more research collections. Therefore, for the service culture collections to function effectively as a publicly accessible infrastructure for life science research, they must hold materials with the greatest potential for follow-on research and overall scientific impact (*Ibid.*).

The vast majority of these collections are within the domain of the public sector:

- More than 80% of the more than 500 WFCC culture collections belong to public sector entities (universities or governments). The remaining are semi-governmental, and in some rare cases are within the domain of private non-profit or industry collections. All culture collections with major holdings in food and agriculture belong to the subgroup of the public sector or semi-governmental collections.
- The vast majority of materials distributed from culture collections – 77% according to a survey of 119 collections – are to public sector recipients. The remaining are distributed to the private sector for various uses, some of these being related to regulatory and identification purposes.

2. Global exchanges of genetic resources

Many countries are actively involved in collecting and exchanging microorganisms in the global arena. The majority of big culture collections are situated in OECD countries and that is also where the majority of collection, distribution and exchange takes place. The microbial strains from non-OECD countries however, represent an important and growing subset in the overall network of culture collections. In particular:

- The WFCC culture collections hold more than 1,4 million strains. The largest culture collection, with approximately 25.000 strains, holds less than 2 % of the total number of strains of the WFCC members. Moreover, each of these collections contains an important set of unique strains (an average of 40% of unique strain for the WFCC collections referenced on Straininfo.net). Intense collaboration and exchange amongst culture collections is a necessary consequence of this situation. Moreover, over the years all the culture collections distribute much more than they hold, contributing to a multiplier effect.
- More than 0.5 million strains are distributed a year by the WFCC culture collections alone. It is difficult to say how many strains are exchanged between research collections on an informal basis in the context of laboratories, but it is fair to say that the amount of strains exchanged between laboratories is probably even more. However, the latter are materials of still unknown scientific value and only conserved for ongoing research without the quality management and certified identification of the culture collections.
- In the case of an in-depth study of 10 major culture collections active in the field of food and agriculture (5 OECD, 5 non-OECD), an estimated 50% or more of the strains were acquired before the Convention on Biological Diversity (CBD) came into force. About 80-100% of acquisitions since then (at least in 2005, 2006, 2007 in the collections analyzed here) came without any conditions. For the OECD collections, in most cases, the country of origin was mainly from an OECD country (that is more than 50%), even if

a substantial part was non-OECD. For the analysed OECD collections, nearly all material was distributed to OECD countries (90-100%).

- Still a significant amount of materials is collected and held in developing country culture collections. For example, among the ten countries which worldwide hold the largest number of WFCC culture collections are Thailand and Brazil, with 57 and 46 collections each these, for a total number of 42.541 and 137.737 strains respectively.

3. Benefits of use and exchange of AMGR

The main benefit of use and exchange is the direct contribution to global and regional food security, through the focused screening and study of vast amounts of microbial resources from various regions of the world. Access to AMGR originally collected in other countries is an essential component of the process of discovering and adding value to AMGR. Therefore, the situation of exchange and use of microorganisms is characterized by a high level of interdependency. At present, microbial resources that are used in agriculture and food systems have been collected both from tropical and sub-tropical species-rich agro-ecosystems and from non tropical areas. A case in point are the microbes for bioremediation and species used in biological control of agricultural pests and in biological monitoring, which have emerged from ecosystems at a wide variety of latitudes and altitudes.

4. Terms and modalities for exchange of microbial genetic resources

Exchanges of microbial genetic resources (MGR) have historically occurred in an informal way between culture collections, laboratories and researchers worldwide. These informal exchanges (without any written contract governing the terms of provision or receipt of the material concerned) have facilitated research activities, and, as a consequence, science and exploitation of microbial resources have rapidly advanced. During last decades of the twentieth century, the increasing economic importance of biotechnology and the introduction of new legislation concerning the use and access to natural resources has subjected exchanges of genetic resources to increasing controls. Their access and distribution are submitted to many requirements and, therefore, exchanges are becoming more and more formalized. In particular:

- Depositors of microorganisms in culture collection are mostly from the own culture collection (approximately 45% of the depositors), or scientists working in other hospital and academic research collections (30% of the deposits). The remaining comes from other service culture collections (20%) or various other sources (5%).
- Culture collections are moving in the direction of using legal instruments: acquisition agreements when acquiring materials, material transfer agreements (MTA) when distributing them. However, over all, collections are in a state of transition. In this regard, they appear to be lagging behind collections of plant genetic resources for food and agriculture (PGRFA), which went through this transition 10-15 years ago.
- There is a general understanding on the fact that responsibility in relation to prior informed consent is on the depositor. Still, in most cases, depositors of MGR are not required to provide evidence of prior informed consent, even when the materials deposited are destined for subsequent redistribution.
- Many culture collections require recipients to negotiate subsequent agreements with the depositor before commercializing products based on materials received and in accordance with specific national laws concerning benefit-sharing.

- Most culture collections distribute materials for research purposes with MTAs specifying that the materials should not be further distributed by the recipient. This is often justified on the basis of the need to prevent circulation of improperly stored/mutated strains.

5. Awareness of users and providers on ABS issues in general

The awareness on access and benefit sharing (ABS) issues in general is very low in the field of MGR. At present, most of the collections are responding to the new legal framework on ABS, with particular regard to formulating appropriate MTAs. This process, in turn, raises important new questions. For example, the balance of private and public interests may be set differently by different institutions, and it is not clear to what extent any uniform MTA will emerge or what its contents will be. In particular, the result of a brief email survey and telephone interviews amongst culture collections indicate that :

- Knowledge of access and benefit-sharing related issues, including the CBD and how it should be implemented is low.
- Culture collections generally are not having difficulties as a result of access and benefit-sharing-related issues in the day-to-day management of their collections. This is equally true of culture collections who have, and have not, moved in the direction of adopting standard legal instruments and policies for acquiring and distributing MGR.

6. Initiatives of key players

In addition to adding value to the deposited microbial material, culture collections also serve as a conduit between providers, users, regulatory bodies, and policymakers. In particular:

- There are a number of international initiatives to promote: a) standardized, higher-level, quality controls on how collections maintain materials and manage digital information, and b) harmonization of access and benefit-sharing policies adopted by those same collections. The OECD guidelines for Biological Resource Centres (BRCs) and efforts to promote them globally is a good example of the former. The MOSAICC guidelines (Micro-organisms Sustainable Use and Access Regulation International Code of Conduct) and the Microbial Commons initiative are good examples of the latter.
- The European MOSAICC guidelines emphasize procedures for providers and recipients to ensure they are CBD compliant. The Microbial Commons initiative encourages the creation of a global pool of microbial genetic resources and information which would be subject to common terms and conditions for depositing, use and benefit-sharing, inspired in part by the multilateralism of the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA).

7. Future trends and issues

Microbes permeate the entire food and agricultural process. While the most visible role of agricultural uses of microorganisms is probably that of producing and delivering food, microbiology is critical to other agricultural sectors as well, for example for production of energy based on plant or other organic materials and for bioremediation of agricultural wastes. Microbial influences on food and agriculture produce both advancements and disasters, as some microorganisms present a threat to plant and animal health and contaminate food production processes.

Many elements of ongoing modernization and technological innovation interact with this use of microbial resources and will likely lead to important changes in the future. One of the main trends is the importance of practices that increase the microbial threats to food and agriculture described above. Regional and international shipment of agriculture products means that pathogens do not necessarily require natural dispersion. Further, intensive agricultural practices bring with them a set of undesirable consequences, which are likely to increase these threats, such as the selection for resistance by overuse of antibiotics and pesticides, or the evolution in animal production systems of new variants of zoonotic animal diseases.

Important change in use and potential benefit of microbial research is expected to occur from new scientific research approaches, such as the role of intensive computation in the integration of genetic, protein, metabolic and environmental data in microbial ecology and the use of Global Information Systems tools in tracking microbial dispersion. These emerging interdisciplinary approaches are likely to offer complementary approaches to biological control, by helping to protect beneficial organisms that may already be present in the environment, or by reinforcing innate host resistance through the use of probiotic microorganisms which fortify the host's innate immunity. They will probably also allow better targeting of the crop varieties to be used, based on the day to day surveillance of upcoming diseases and their dispersal rates. Another important trend is the development of new pesticides and transgenics, which now rely heavily on gene mining from microbes.

Use of microorganisms has a high potential for contributing to food security and poverty alleviation. They enable development strategies that can be based on locally available microbial material – provided that reference *ex situ* AMGR can be accessed from the culture collections – and are often less costly than the existing solutions developed for global markets, illustrated by examples discussed in this study from the local dairy industry and measures of biological control.

Global exchange of MGR has proven invaluable to researchers both in developing and developed countries. Frequent replication of the microorganisms under different environmental conditions leads to a population of microorganisms with a high variation in the genetic make-up. As a result, even if they are ubiquitous in nature at species level, there is a wide diversity of within species diversity associated with potentially interesting properties. Obtaining access to this diversity, spread as it is across international and continental divides, is essential for scientific research which turns on the ability to screen microbial populations for new applications or for basic understanding of the role and function of microbial diversity. The use of certified materials from the culture collections diminishes the costs from mistakes in cumulative research and decreases the search costs for finding appropriate materials. Therefore, the socio-economic benefits of the investment in culture collections are substantial.

Researchers from various countries deposit strains of national origin in foreign culture collections, which have acquired a special expertise and reputation. In turn, the same country will collect and receive strains in its own area of specialization. Access to these strains held *ex situ* is a necessary component of most microbial research. They are "knowledge bricks" which are crucial ingredients in the initiation of new lines of research and in the validation of local biodiversity screening or biodiversity analysis. Crucially, because of the high chances of mutation and evolution of microbial resources in *in situ* conditions, these *ex situ* reference organisms cannot be replaced by the study of similar *in situ* materials to validate the research findings.

The majority of exchanges of strains held in *ex situ* collections take place between OECD countries. As shown in this report, both the majority of provider countries and the majority of users of microbial genetic resources are situated in high-income countries. This is related to the fact that a

substantial part of collecting by public culture collections is done in the home country. The strains coming from developing countries however, represent an important and growing subset. On the other hand, as shown in this report, researchers from developing countries also regularly deposit in and acquire strains from high-income country collections.

At present, this situation of exchange of biological materials within a global commons, which prevailed during the early days of the emergence of modern life sciences, is facing a set of important challenges, which may hamper some of the most promising new scientific opportunities. Exchanges of MGR have historically occurred in an informal way, without the use of written contracts. However, the increasing economic importance of biotechnologies and new legislation concerning the use and access to natural resources, have subjected exchanges of genetic resources to increasing controls. Access and distribution are submitted to many requirements and therefore, exchanges are becoming subject to more and more formal forms of control. Moreover, as a response to financial restrictions on government spending for culture collections in some countries in the 1990s, and the growing commercial opportunities even for upstream research tools such as the strains held at the culture collections, some culture collections departed from the sharing and collaborating practices and have introduced unduly restrictive and more costly MTAs. This departure has been criticized by the scientific community.

If these trends continue, there is a serious risk of over protection and privatization of all biological resources on the same highly restrictive conditions that are only relevant for a handful of deposits with known or likely high payoff commercial opportunities (Reichman et al. 2008). This would have major impacts on access and distribution of microbial research materials in the life sciences. In particular, if the formal exchange becomes unduly restrictive, scientists might prefer to exchange strains in an informal way between research laboratories where the bulk of microbial research is done.

In parallel to these restrictive trends, most public culture collections are working to maintain the tradition of global distribution and exchange. There have been a number of initiatives to develop science-friendly MTAs that are designed under open access schemes, at least as far as the distribution for research and scientific purposes are concerned. For instance, both OECD and non-OECD collections include clauses of legitimate/legal exchange in their MTAs, which allow public culture collections that comply with strict quality management criteria to further distribute microbial research material that they have received from other public culture collections.

There is no evidence that formalization of the exchanges as such is leading to more restrictive license conditions, even if formalization might lead some collections to depart from the sharing ethos as illustrated in this report and introduces an important administrative burden. The interviews with culture collection managers confirmed that currently, distribution of strains is more complicated than in the past, mainly because new rules and regulations require a lot of administrative work, especially when dealing with distribution of strains to third-party countries. A minority of the respondents considered that there is some reluctance on the part of researchers to deposit strains since they think they may have economic value.

Some majors culture collections, such as the BIOTEC collection in Thailand and the DSMZ collection in Germany, expressed that it would be a good step forward to facilitate the exchange of MGR by reaching agreement on a global common policy for the distribution/deposit of the material, so that material is deposited/distributed under the same conditions/restrictions all around the world. These, and other points have led some commentators to think about the possibility of building of a global microbial commons with materials from the public culture collections which would be subject to common terms and conditions for depositing, use and benefit-sharing, inspired in part by

the multilateralism of the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA).

Policy development and understanding of ABS issues in the culture collections community is currently limited but improving, and will need to continue to evolve in the future. It must be noted however that, as considered in the Bonn guidelines, the facilitated access provided by culture collections constitutes itself a benefit measure in the context of benefit-sharing schemes, even though this is not necessarily directed to the original provider country. Further, within their global federation (the World Federation for Culture Collections, WFCC), and regional entities, such as the European Culture Collections' Organization (ECCO), culture collections have sought to devise harmonizing guidelines that would help to standardize procedures and provide a framework for compliance with the CBD and with growing legislation concerning biosafety and security. In particular, the MOSAICC guidelines (Micro-organisms Sustainable Use and Access Regulation International Code of Conduct) consider that designing a model MTA for the members of the WFCC would be a significant sector-based ABS approach for culture collections across the world, facilitating exchanges although its members operate in different legal systems. It even suggests the need for establishing common rules of access to MGR, complementary to national regulations on ABS and existing intellectual property rights (IPR) laws that would govern a "microbial commons" demarcated space. To the extent that such an efficacious standard MTA harmonizes the servicing of culture collections across the globe, it would lay the basis for a *de facto* commons for the global conduct of microbial research in the foreseeable future.

CHAPTER I: SCOPE OF THE STUDY

For millennia, people around the world have exchanged biological materials, mainly for food and agricultural purposes (Morgan 1979, Brush 1998). Crop domestication began about 12,000 years ago, and moved rapidly across continents and even inter-continentally. Colonialism and imperial trade in the 1500 and 1600s accelerated things rapidly, to the point where people were eating much the same staples all over the world (Braudel 1992). In the last century however, the emergence of *in vitro* cell culture technology and molecular biology has lead to a tremendous increase both in the quantities of biological resources exchanged and in the global interdependencies (Parry 2004). In particular, global distribution and exchange of microorganisms became an important component of contemporary life sciences. This movement is also related to several developments such as the introduction of ever more sophisticated techniques for storing, freezing and shipping samples; the genomics revolution; and the broader impact of globalization on the organization of research in the life sciences.

As a result, vast amounts of microbial genetic material are collected throughout the world and exchanged in collaborative networks for improvement of agriculture and food production systems. For instance, throughout the world, legume production such as soya or alfalfa (lucern) is improved through the use of nitrogen fixing bacteria, the root nodule bacteria. These bacteria are widespread throughout the world. Through the worldwide exchange of some well characterized and high performing strains of this bacterium, it is used in public and private research, for training and education, and commercially produced in large quantities in various countries of the world (CGRFA-11/07/Circ-3). Another example is related to the management of the threats from pathogenic microorganisms for agriculture and food production systems such as fungi causing root rot and stem rust diseases, or mycotoxin producing fungi, which are harmful for animal and human health. Some of these fungal pathogens can be transported by the wind, while others move with the international shipment of agricultural products. Through international collecting efforts, diagnostic and identification tools have been developed, which are used in early detection of the pathogens (Smith *et al.* 2008), and for detection of contamination in agriculture and food commodities (Doyle *et al.* 2005).

Further collecting efforts often play an important role in the monitoring of disease and screening for resistant genes in various cultivars, such as it is the case in the current stem rust outbreak in East Africa through the network of trap nurseries set up by the Consultative Group for International Agricultural Research (CGIAR) centre ICARDA (International Center for Agricultural Research in the Dry Areas).

The important role of various components of global biodiversity, including microbial genetic resources, in the improvement of agriculture and food production systems and the development of more environmentally and ecologically sound intensification, has been increasingly recognized in the international debate (Cassman and Wood 2005). In particular, the Commission on Genetic Resources for Food and Agriculture (CGRFA), at its Tenth Regular Session in 2005, *recommended that the Food and Agriculture Organization (FAO) and the CGRFA contribute to further work on access and benefit-sharing, in order to ensure that it move in a direction supportive of the special needs of the agricultural sector, in regard to all components of biological diversity of interest to food and agriculture.* At its Eleventh Regular Session in June 2007, while adopting its Multi-Year Programme of Work, the CGRFA *recommended that FAO continue to focus on access and benefit-sharing for genetic resources for food and agriculture in an integrated and interdisciplinary manner* and *agreed on the importance of considering access and benefit-sharing, in relation to all components of biodiversity for food and agriculture. It decided that work in this field should be an*

early task within its Multi-year Program of Work. The Commission accordingly will consider the development of policies and arrangements for access and benefit-sharing for genetic resources for food and agriculture as a priority in its Multi-Year Programme of Work, at its Twelfth Regular Session, to be held in October 2009.

To facilitate the Commission's consideration of access and benefit-sharing policies in the special area of microbial genetic resources, this study analyzes the exchange and use of microbial genetic resources in the different sectors of food and agriculture. In order to understand how an appropriate system for global, facilitated access to microbial genetic resources could work in the field of food and agriculture, it is imperative to have an overview of the current practices and the socio-economic benefits of use and exchange flows of these resources. Therefore, this study will address the following questions: What are the main patterns of global exchange and what are the benefits of use and exchange of microbial genetic resources for food and agriculture? What are the current terms and modalities of exchange, and how could they relate to the international access and benefit-sharing regime? What is the perception of the main stakeholders, and what are some of the promising sector-specific initiatives by stakeholders in the field? In this introductory chapter, a brief overview is given of the scope of the resources, and the categories of uses and users covered in the report.

1. GR covered: Microorganisms for food and agriculture

Microorganisms are at the basis of the ecosystems on which food production depends. Few of these organisms are domesticated but many are consistently associated with food production ecosystems. Agricultural production and food processing depend heavily on this "hidden" biodiversity as plants and animals cannot grow optimally without them. Good illustrations of this are the fungi and bacteria that establish mutually beneficial symbiosis with the roots of agricultural plants and the guts of ruminant livestock. Microorganisms play major roles in nitrogen fixation, as biocontrol agents, and in the degradation and recycling of organic matter in soils. Microorganisms also provide beneficial services in food processing.

An important feature of microorganism related to these uses is their high degree of multi-functionality. Indeed, most, if not all, microorganisms are used in all of these processes and across various industrial sectors. A good example is the case of free living soil microorganisms. Typically, these organisms play an important role in agriculture through nutrient recycling or degradation of toxic elements in the soil. On the other hand, these microorganisms produce antibiotics which are acting against other soil microorganisms which have important applications for human health. This feature of massive multiple uses characterizes many microorganisms that play an important role in agriculture and food processes, even at the strain level[5]. This is related to the fact that many important functions of microorganisms for use in agriculture and food are encoded in the accessory genome of the microbial strains. The accessory genome of the same strain can contain genes coding for functional properties relevant to various sectors of use, which enhances overall the fitness of the microorganism in various host environments.

[5] The multi-functionality can be illustrated by use patterns of one species distributed by a culture collection, the *Bacillus subitillis*, a very common and widespread soil bacteria (Fritze 2009). In the period 1991-2008 more than 4,000 samples were distributed of strains of this single species by the German Collection of Microorganisms and Cell Cultures (DSMZ). Thirty percent of these involved the type strain used for identification purposes, 10 % involved 3 reference strains (in particular for the detection of antibiotic residues in meat), and the remaining were related to diverse uses in food production (such as natto), biological control (anti-fungal activities), enzyme production and genetic experiments.

2. Categories of users and uses covered

For the purpose of this study, it is useful to distinguish some important categories of use of microorganisms in research and exploitation, which play an important role in food and agriculture-related uses.

Type strains : when a species name is published, authors are required to designate a given strain as the *type* for that species ; the type strain should exhibit characters in agreement with those published in the species description, and, ideally, should be representative of the majority of strains belonging to the species. The Bacterial Code requires the deposit of new type strains in at least two culture collections in two different countries. No such code exists today for yeast, fungi, plasmids or algae[6].

Common uses of type strains: in systematic and taxonomy, and for quality control of commercial systems for identification of microorganisms.

Reference strain: in most cases more than one strain is needed to have a good representation of the genetic diversity of microorganisms within a species. That's why microbiologists also use reference strains (and not only type strains). Reference strains are those used in published taxonomic and physiological studies and are putatively representative of the species of which they are a member. Many organizations (such as the American Society for Testing and Materials, the Deutsches Institüt für Normung, etc.) publish protocols mandating the use of specific reference strains, for example for testing antimicrobial susbstances or testing of resistance of materials to microbial degradation.

Common uses of reference strains: materials testing (for its resistance to microbial degradation), quality control of food, testing of antimicrobial substances and quality control of diagnostic kits.

Other specific strains : many given strains are used for specific properties that they exhibit. Common uses are use of microorganisms as food ferments, biocontrol agents, plant growth promotors, or biotechnology workhorse (use of microorganisms for the compounds they produce or for the biological processes they enable).

Users of microorganisms are both from public and private sector entities and farmers. They are used in universities and professional schools for training and education and are an important resource for university and private industries' laboratories where they are conserved in research collections. They are a vital component of agricultural production systems. The most important and already well identified microorganisms are distributed and exchanged worldwide through the various services provided by the culture collections. The latter perform a key role in the overall research cycle in microbiology and are an important intermediary between the providers and users of microbial genetic resources. Initially constituted as collections of repositories of materials in the 1960s, the functions of the culture collections have gradually expanded to include systematic standardization and authentication of research materials, development of research tools to enhance the productivity of research and proactive knowledge management for both public and private entities (Stern 2004: 11). This is reflected in the concept, elaborated in 1999 by the OECD working party on biotechnology of culture collections as Biological Resource Centers, which are defined as collections of culturable organisms (e.g. micro-organisms, plant, animal and human cells), replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs), viable but not yet culturable organisms, cells and tissues, as well as databases containing molecular, physiological and structural information relevant to these collections and related bioinformatics (OECD 2001: 7). Through the culture collections network, strains are distributed and made available for research and development with marginal distribution costs, often

[6] The Bacterological code is a product of the International Committee on Systematics of Prokaryotes (ICSP), a IUMS (International Union of Microbiological Societies) ComCoF.

with the possibility to further distribute the strains to qualified third parties (cf. infra ch. III section 2.4.) and with major benefits for the development of downstream applications.

CHAPTER II: USE AND GLOBAL EXCHANGE OF AGRICULTURAL MICROORGANISMS AND THEIR BENEFITS

1. Use of microorganisms and microbial genetic resources

Many classifications have been proposed in the literature to cover these various services. However, to the best of our knowledge, these classifications are all limited to a set of specific applications, and do not cover the entire breadth of the microorganisms that play a role in agriculture and food production systems. By combining the information of these various classifications (Colwell 2002, Doyle *et al.* 2005, CGRFA-11/07/Circ.1, CGRFA-11/07/Circ.2, CGRFA-11/07/Circ.3, Kuo and Garrity 2002), this report considers a broader list of categories which shows the full scope of the microbial genetic resources to be considered. This list has been discussed with microbial experts at two workshops (cf. section 3 infra), and substantially enhanced and improved by researchers at Bioversity International and FAO. Further fine tuning of this list is currently in progress. It should be noted that one microorganism can belong to more then one group, for example a biocontrol agent typically can also be a plant pathogen of another crop).

Table 1. Main functional groups of microorganisms relevant to food and agriculture

Functional groups	**Services**
Agriculture	
Plant symbionts	Promote plant growth by enabling nutrient recycling and facilitating nutrient acquisition by plants For example : • plant symbionts enable nitrogen fixation after establishing inside root nodules of legumes
Microorganisms for bioremediation	Reduces pollution by accelerating the degradation of toxic elements from air, aquatic and terrestrial systems
Rumen organisms	Facilitate rumen digestion of plant material and prevent certain digestive diseases
Biological control agents	Control pests and diseases by acting either as pathogens/natural enemies of weeds, fungi, insects, nematodes, or as competitors of other pest micro-organisms. Some of these microbial biological control agents are also known to be pathogenic for humans and animals
Primary metabolites producers	Primary metabolites can be of direct benefit to agriculture. Amino acids and vitamins are for example used as additives in animal feed
Plant pathogenic micro-organisms	Cause pests and infectious diseases / Control pests (in which case micro-organism is classified as a biological control agents)

Food	
Anti-spoilage agents	Fermentation enables food preservation, adds nutritional value, flavour and texture to the food product, and ensures it is less hospitable to other micro-organisms, including pathogens and spoilage-causing micro-organisms
Primary metabolites producers	Primary metabolites can be of direct benefit to food production, for example they are - used as feed supplement - used as flavour enhancer
Probiotics	Favour human and animal health by improving digestion, reducing lactose intolerance, strengthening the immune system and preventing gastro-intestinal infections (and thus, in the case of livestock, less required veterinary interventions, which may be cost saving)
Health hazardous micro-organisms	For example • Food borne pathogens cause (severe) illnesses in humans and animals, such as diarrhea, cholera, salmonella and various forms of hepatitis • Microorganisms that produce food toxins which can cause severe illnesses in humans and animals

As can be seen from table 1, food and agriculture microbiological science and technology present a wealth of opportunities for improvement of food and agricultural production systems, and for contributing to energy production and waste management. In agriculture, three specific areas where use of microorganisms and microbial research currently play an important role are (1) the exploitation of interactions with beneficial microbes that are of direct benefit to agricultural plants and animals (such as in plant growth promotion or bioremediation), (2) the development of various means of biocontrol and (3) the building of surveillance networks for plant pathogens (Doyle *et al.* 2005).

First, microorganisms are directly beneficial to agriculture and plants. The classic examples are the symbiosis between legumes and rhizobia and the complex mixture of bacteria that enable ruminants to extract sufficient nutrients from a diet of grasses. However, for the few classic examples of mutualism in agricultural systems, there are likely to be many more interactions taking place in agricultural systems. More knowledge of microbial ecology and mutual interactions will likely help to advance agricultural organisms' nutrient use and pathogen resistance, or could help to improve drought resistance and salt tolerance of plants. An example is the study of the loss of microbial diversity in soil after application of fumigants. Early results show the possibility to use bacterial species to restore the degraded soil (Benedetti 2009). This and similar approaches were limited in the past by the scope of the culturable microbial communities, but are likely to become an important area of research with the advent of environmental genomics (or metagenomics) and increasingly powerful computational tools.

Second, through biological control, relatively harmless microorganisms (or their metabolic products) that inhibit or kill a harmful organism are mass produced and applied to food or crops as a protective measure. Biocontrol agents control pests and diseases by acting either as pathogens/natural enemies of weeds, fungi, insects, nematodes, or as competitors of other pest micro-organisms. Some of these microbial biological control agents are also known to be pathogenic for humans and animals. One particular field of research is the use biocontrol against

microbial pathogens. However, in spite of some important successes, such as for example the use of nontoxic strains of the fungus *Aspergillus* competing with toxic strains in biocontrol in cotton and peanut fields (Azizmohseni 2009), large scale production of biological control microorganisms against microbial pathogens is still a difficult process, and their performance in field setting is often unpredictable as a match with each local ecosystem's condition is needed. Nevertheless, better understanding of these processes can lead to better ways to controlling them though alternative means. In one case, better understanding of the role of *Pseudomonas* bacteria in causing root rot in Cocoyam – an important staple crop in tropical and subtropical areas – led to the formulation of new farming practices that better suppressed the disease (Höfte 2009). Overall, the biggest application of biocontrol is inundative biocontrol, using biopesticides (mostly against insects) with numerous commercialized products. Understanding microbial causes of disease and spoilage can lead to more environmentally friendly pesticides, or the formulation of improved drugs for immunization of animals against pathogens. For instance, foot and mouth diseases of livestock comes in about 80 different serotypes around the world, each one of them being serologically different. An animal resistant to one serotype through vaccination or exposure will still have an immune system that is unprepared for most of the other serotypes. This means that vaccines must be highly specific to the strains involved.

A third area of importance in the use of microorganisms and microbial research is the surveillance for microbial pathogens and microorganism that pose hazards to health. Surveillance of disease outbreaks relies on a variety of technologies and approaches, mainly based on accurate modelling of pathogen spread and coordination and networking between the different entities handling surveillance operations. It also depends on practical detection technologies, which ideally can test for multiple organisms in single test, so that it can be applied *in situ* to complex materials, such as soil, food and fecal materials. Robust systems for disease surveillance advance the capability to respond to microbial threats, thereby reducing damage. For example, planting of certain genotypes of wheat in North America is guided each year by a forecasting system that observes what wheat rust virulence types are appearing in the South, which results in recommendations as to what available resistant genotypes will do best in the upcoming planting season.

Direct use of microorganisms in the field of food production systems is also an important area where microbial science and technology can bring an important added value. For instance, fermentation often leads to inactivation of spoilage causing microbes and thereby enhances the shelf-life of the food. A time-honoured example of this principle is the production of yoghurt. However, beneficial microbes cultivated in food can provide added value far beyond delay or prevention of spoilage. Indeed, many of these microbes have beneficial "probiotic" properties that can help exclude disease-causing organisms and prevent infections.

Many elements of ongoing modernization and technological innovation interact with this use of microbial resources and will likely lead to important changes in the future. One of the main trends is the importance of practices that increase the microbial threats to food and agriculture described above. Regional and international shipment of agriculture products means that pathogens do not necessarily require natural dispersion. Further, intensive agricultural practices bring with them a set of undesirable consequences, which are likely to increase these threats, such as the selection for resistance by overuse of antibiotics and pesticides, or the evolution in animal production systems of new variants of zoonotic animal diseases. However, important change is also expected to occur from new scientific research approaches, such as the role of intensive computation in the integration of genetic, protein, metabolic and environmental data in microbial ecology and the use Global Information Systems tools in tracking microbial dispersion. These emerging new interdisciplinary approaches are likely to offer complementary approaches to biological control, by helping to protect beneficial organisms that may already be present in the environment, or by reinforcing innate host

resistance through the use of probiotic microorganisms which fortify the host's innate immunity (Doyle *et al.* 2005: 12-13).

2. Global exchange of microbial genetic resources

To understand the patterns of global exchange of microbial genetic resources, and the way they relate to each other, it is necessary to give a brief introduction of the particular nature of microorganisms (especially in contrast to plants and animals) and the collections of microbial strains. Microorganisms are ubiquitous and found in every ecological niche, performing recycling roles and interacting with other living forms in ways that we are only beginning to understand. Their total numbers are only known approximately (Colwell 2002). Their study requires systematic authentication of collected biomaterials in *ex situ* research collection and preservation of certified biomaterials for cumulative follow on research – insofar as this is technically possible. The *in situ* conservation is not sufficient for organizing systematic research into microorganisms and their applications for a number of reasons, in particular because (WFCC 1996, Fritze 2008):

- Microorganisms replicate frequently; this may lead to changing populations in the environment and, if not expertly preserved, also *ex situ*;
- Microorganisms cannot be accurately enumerated;
- Estimation of a 'base line' for inventorying purposes of Microorganisms is not possible; Microorganisms may be transferred across borders by wind, water, the movement of animals or humans;
- Microorganisms cannot be tracked and monitored conventionally, they are difficult to fingerprint for identity/non-identity checks, scope for piracy exists;
- Microorganisms are unlikely to be depleted by sampling (however the loss of hosts could lead to the loss of dependent microbial species; examples are known for fungi);
- Strains of one and the same species of microorganisms have been recorded to occur in a number of geographical locations; few species may occur in only one country;
- Within a species of microorganism, strains may show slight genetic variation, also e.g. depending on sampling time, thus individual strains are of considerable significance in terms of genetic expression;
- Microorganisms may be found equally in 'gene-rich' countries as in 'industrial' regions; and
- Microorganisms require special equipment, technologies and taxonomic skills for their study.

Microorganisms that are isolated from the environment are typically conserved in culture collections. These microbial strains form the basis of much of our knowledge of microbial diversity and are the living archival material for future study. Because of the high cost of isolation and the extraordinary scope of the microbial diversity, the main efforts have been on the collection and identification of the microbial diversity of the microbial species with known scientific and commercial value. Therefore, the situation is to a certain extent similar to the situation of plant genetic resources for food and agriculture (PGRFA), where collecting efforts in seed germplasm have been targeted to the diversity of the main high value staple crops, and where lots of orphan crops and neglected and underutilized species, which are not the target of breeding efforts, are not in *ex situ* collections. However, unlike the situation for plant breeding , only a tiny percentage of microbial diversity has even been identified – probably less than 2% for bacteria, archea and

viruses, and between 5 and 10 % for fungi[7] – and only a small fraction of this known diversity can actually be effectively cultured. The rest is *in situ* and part of it will remain that way for a very long time. Researchers are still going back to collect *in situ* for local microbes to be studied and bring them into the culture collections.

2.1. The role of the culture collections in the global distribution and exchange of microbial genetic resources

Global distribution and exchange of microorganisms that are publicly available for research is organized by the service culture collections, the most important of which are member of the World Federation of Culture Collections (WFCC) (cf. http://wdcm.nig.ac.jp/hpcc.html, accessed 1st June 2009)[8]. Prominent examples that are relevant in the field of food and agriculture are the US Agricultural Research Service Culture Collection and the UK based CABI Genetic Resource Collection, amongst others. These culture collections offer independent long-term access to authenticated biological materials, under strict quality control, and provide a standardized system for distributing materials among both public and private research institutions (Stern, 2004). Because of lack of capacity and high operating costs, the holdings of the culture collections only represent a small subset of the total holdings in the many more research collections. Therefore, for the service culture collections to function effectively as a publicly accessible infrastructure for life science research, they must hold materials with the greatest potential for follow-on research and overall scientific impact (*Ibid.*). Many more materials are shared upon confidential basis between research collections (cf. section 2.2. below), but without complying with the same stringent public quality management protocols.

It is the historical mission of culture collections to organize the collection, authentication, maintenance and distribution of strains of microorganisms and cultured cells. The use of certified materials from culture collections diminishes the costs from mistakes in cumulative research (Furman and Stern 2006) and decreases the search costs for finding appropriate materials (Evenson and Kislev 1976, Gollin *et al.* 2000, Visser *et al.* 2000). The situation of the culture collections is characterized by a high level of interdependency. The largest culture collection, with approximately 25.000 strains, holds less than 2% of the total number of strain holdings of the WFCC members and only an estimated 1.5% of the total biodiversity of unique strains holdings in the WFCC collections. Intense collaboration and exchange amongst culture collections is a necessary consequence of this situation.

2.2. Sources and providers of genetic resources: Understanding the research cycle

The exact line between service culture collections – which offer services both within and outside their own institution, such as distribution and identification services – and research collections – which only develops activities in the institution under which the collection is established (for example a microbiology department in a university or a hospital) – is sometimes difficult to draw.

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[7] Some estimates of the number of microorganisms (the Bacteria, Archaea, viruses, and microbial Eucarya (protists, fungi and algae)) exists in the literature. Current estimates of numbers of prokaryotes, which include the Bacteria and Archea, range from 300,000 to 1 million species or more. About 5000 species of Bacteria and Archea have been described, but there are many orders of magnitude more awaiting discovery. Estimates are that there are 500,000 species of viruses. Only about 1% of them has been described. Between 5% and 10% of the ca. 1.5 million species of fungi have been described – as have 40,000 of the 100,000 – 200,000 protozoan species. Only 10% of the estimated 400,000 species of microbial algae have been described (Colwell 2002).

[8] A more complete and direct access to the culture collections can be obtained through Straininfo.net (cf. text at footnote 1 above).

Minimal features of service culture collections, which distinguish them from research culture collections, are the existence of a public catalogue listing the holdings of the collection, standard procedures for delivery of the strains and a set of recognized quality management standards that guarantee the identity and authenticity of the strains that are delivered (Stern 2004). Some culture collections have even higher standards, and develop a set of additional services. However, for the purpose of this report, we will use these minimal features as the drawing line between the service culture collections and the research collections.

The majority of agricultural microbial genetic resources (AMGR) coming into the culture collections is from *in situ* sources, as the bulk of biodiversity is not yet known. To uncover this wealth of materials and knowledge, collections specialize in specific areas of research and collaborate with each other for the exchange of the basic research tools and materials, or in the form of partnerships for collaborative research. Some resources are acquired by the service collections as the direct result of their own collecting from *in situ* settings. Other resources come from researchers from academic and hospital research collections who collect strains directly *in situ* and who want to deposit their materials upon publication of research results. A small part comes from other culture collections. A survey conducted in 2005 amongst culture collections that are members of the WFCC provides some more information on the relative importance of the various sources and providers (cf. figure 1).

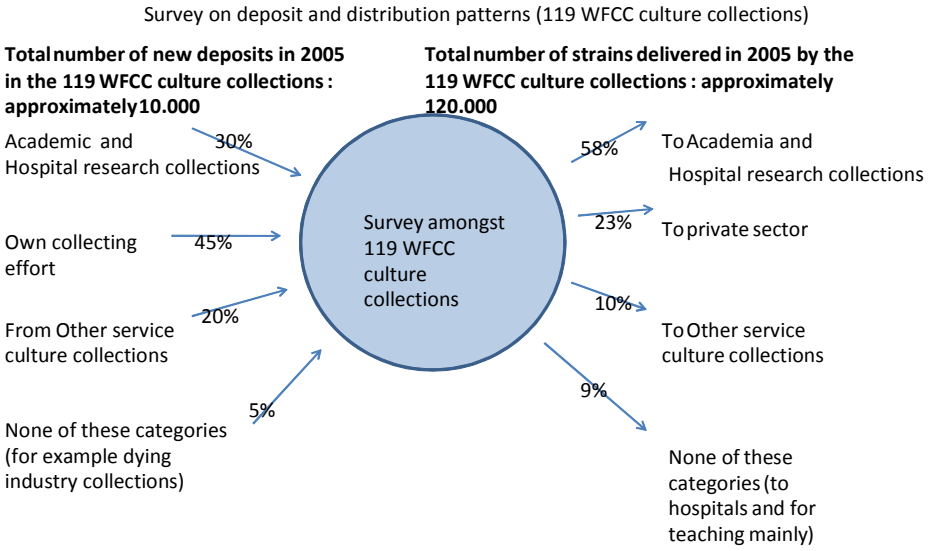

Figure 1. Providers and users of microorganisms (source of the data: Stromberg *et al.* 2006).

As illustrated by the survey, research collections play an important role in providing strains to the culture collections. Therefore, it is important to understand their specific characteristics and their role in the overall research cycle, especially when compared to the service culture collections. When the strains are collected through the own collecting effort of the culture collection (45% on average), they are usually characterized and directly deposited in the culture collection without any intermediaries. However, when they come from research collections or from single scientists, often strains of a same organism are handled by several collaborating scientists in the same project, before being officially deposited in the service culture collections. Moreover, not all strains of the research collections are deposited in the service culture collections. Indeed, the research collections

are holding vast collections of less well documented strains, which are of unknown scientific value, or strains which are the object of ongoing research that is not yet published or kept for future follow-on research. These collections usually have an in house database with a local numbering system for tracking and future reference. As extensively reported in the two expert workshops, the research collections exchange strains with collaborating scientists on an informal basis and under the implicit understanding that these strains will only be used in the laboratory of the collaborating scientists.

2.3. Global patterns of exchange

To obtain more information on the global patterns of exchange a quantitative survey was submitted to the culture collections that participated the second set of in-depth cases studies (cf. annex 2, part B). Because of the vast amount of data to gather (an average of 800 database entries per year to be analyzed) only some collections that had detailed in-house data bases were able to provide this data.

In this section we will briefly summarize the results of this quantitative study. Nine collections provided detailed quantitative data on patterns of exchange for the years 2005, 2006, and 2007; with a detailed list of provider and recipient countries. All these collections have important accession and distribution activities in the agriculture and food sectors, except for one (labelled cc9), which we have included as a control variable. The two tables below synthesize the findings of this quantitative questionnaire on patterns of exchange, for the accessions in 2005, 2006 and 2007, and for the distribution of strains in 2005, 2006 and 2007. We have labelled the names of culture collections in the table with numbers, in order to respect the anonymity of the research protocol. The results that are analyzed come from the following WFCC collections (indicated with their WDCM number[9]):

Asia
- Persian Type Culture Collection, PTCCI, WDCM124, Iran
- BIOTEC Culture Collection, National Center for Genetic Engineering and Biotechnology, WDCM783, Thailand
- Bioresource Collection and Research Center, Food Industry Research and Development Institute, (BCRC) WDCM59, from Taiwan

Europe
- Culture Collection, University of Goteborg (CCUG), WDCM32, Sweden
- BCCM/LMG Bacteria Collection, WDCM296, Belgium
- BCCM/MUCL Mycotheque de l'université Catholique de Louvain, WDCM308, Belgium
- HAMBI Culture Collection, WDCM779, Finland
- All-Russian Collection of Microorganism, Institute of Biochemistry and Physiology of Microorganisms, Russian Academy of Sciences (VKM), WDCM 342, Russian Federation
- Coleccion Española de Cultivos Tipo (CECT), WDCM412, Spain

America
- Universidade Federal de Pernambuca, Micoteca do Departmento de Micologia (URM), WDCM 604, Brazil

[9] Cf. http://wdcm.nig.ac.jp/wfcc.

	CC1	CC2	CC3	CC4	CC5	CC6	CC7	CC8	CC9	CC10	CC11
Total numbers of strains in CC	N/A	N/A	N/A	N/A	N/A	approx. 2000	N/A	20000		540	2500
% deposited before 1993 (est)	51	N/A	90	N/A	35	40	50	40	50	90	50
access 05	436	886	55	2812	104	32	272	150	736	0	108
%without restrictions	98	N/A	100	86	79	98	100	N/A	100	0	100
%with res, non-commercial	2	N/A	0	0	0	2	0	N/A	0	0	0
%other-restrictions	0	N/A	0	14	21	0	0	N/A	0	0	0
Depositors											
national %	65	45	98	86	70	100	99	N/A	57	nr	100
foreign %	35	55	2	14	30	0	1	N/A	43	nr	0
Number of foreign countries	18	14	1	3	8	0	1	N/A	23	nr	0
Country of origin		*		*	*						*
national %	26	10	98	98	60	53	99	N/A	N/A	nr	41
foreign %	74	90	2	2	40	47	1	N/A	N/A	nr	59
Number foreign countries	43	42	1	3	16	8	1	N/A	N/A	nr	19
unknown	35	1	0	19	-	0	0	N/A	N/A	nr	-
access 06	548	803	66	4161	252	41	185	150	651	0	70
%without restrictions	98	N/A	100	95	82	97	100	N/A	100	0	100
%with res, non-commercial	2	N/A	0		0	2	0	N/A	0	0	0
%other-restrictions	0	N/A	0	5	18	1	0	N/A	0	0	0
Depositors											
national %	27	52	98	97	87	100	100	N/A	62	nr	83
foreign % (countries)	73	48	2	3	13	0	0	N/A	38	nr	17
Number of foreign countries	18	12	1	1	7	0	0	N/A	25	nr	2
Country of origin		*		*	*						*
national %	2	8	98	98	65	54	100	N/A	N/A	nr	8
foreign %	98	92	2	2	35	46	0	N/A	N/A	nr	92
Number of foreign countries	44	34	1	4	21	6	0	N/A	N/A	nr	7
unknown	26	1	0	0	-	0	0	N/A	N/A	nr	-
access 07	431	650	80	5010	141	53	324	297	687	0	32
%without restrictions	96	N/A	100	98	66	99	100	N/A	100	0	100
%with res, non-commercial	4	N/A	0	0	0	1	0	N/A	0	0	0
%other-restrictions	0	N/A	0	2	34	1	0	N/A	0	0	0
Depositors											
national %	37	73	98	95	75	100	100	N/A	59	nr	100
foreign % (countries)	63	27	2	5	25	0	0	N/A	41	nr	0
Number of foreign countries	21	10	1	4	11	0	0	N/A	25	nr	0
Country of origin		*		*							*
national %	12	15	97,5	84	N/A	51	100	N/A	N/A	nr	0
foreign %	88	85	2,5	16	N/A	49	0	N/A	N/A	nr	100
Number of foreign countries	46	47	1	7	N/A	10	0	N/A	N/A	nr	4
unknown	25	1	0	21	N/A	0	0	N/A	N/A	nr	-

* Information on the country of origin of a certain number of strains did not appear in the CC database.

Table 2. Deposits in the 11 culture collections of the survey (previous page). The survey shows the number of new deposits in the culture collections in 2005, 2006, and 2007. The depositor can be a microbial scientist not affiliated to the culture collection, but he/she can also be a scientist working at the culture collection and collecting microorganisms in various countries:

- % without restrictions = the depositor authorizes the collection to distribute the microorganism for all uses without restrictions
- % with restriction for non-commercial use = the depositor authorizes the collection to distribute the microorganisms for non-commercial use only
- % other restrictions = the depositor has specified other restrictions;
- % Depositors national = the depositors are from the same country as the county where the culture collection is situated;
- % Depositors foreign = the depositors are from another country;
- Number of foreign countries = number of countries in the group of foreign depositors;
- National Country of origin = the microorganism that is deposited has been collected in the same country as the culture collection;
- Foreign country of origin = the microorganism has been collected in another country;
- Number of foreign countries = number of countries in the group of microorganisms from foreign countries;
- Unknown = number of strains for which the country of origins is unknown (amongst the total number of deposits).

	CC1	CC2	CC3	CC4	CC5	CC6	CC7	CC8	CC9	CC10	CC11
2005											
strains distributed	2911	420	192	395	4046	N/A	174	4288	44585	0	107
recipients countries											
national %	23	68	96	19	94	N/A	100	N/A	N/A		87
foreign %	77	32	4	81	6	N/A		N/A	N/A		5
Number of countries	44	12	5	4	23	N/A		N/A	N/A		5
2006											
strains distributed	2089	1011	748	410	3788	660	523	4000	4190	0	72
recipients countries											
national %	28	67	30	19	95	100	100	N/A	N/A		85
foreign %	72	33	70	81	5			N/A	N/A		15
Number of countries	40	24	6	5	22			N/A	N/A		6
2007											
strains distributed	3454	1724	331	236	4148	811	210	4743	4360	0	56
recipients countries											
nationals %	23	74	95	63	96	100	100	N/A	N/A		86
foreign %	77	26	5	37	4			N/A	N/A		15
Number of countries	42	29	3	6	19			N/A	N/A		2

Table 3. Distribution patterns in the 11 culture collections of the survey :

- Strains distributed : number of strains distributed by the culture collection;
- % recipient countries national: % of the strains that are distributed to recipients situated in the same country as the culture collection
- % recipient countries foreign: % distributed to foreign countries

- n. countries : total number of recipient countries for all the strains distributed in that year.

General information: All the collections of the sample are big collections, hosting between 2,000 and 20,000 strains. They all host a great amount of pre-1993 strains; in five of them at least 50% is pre-1993.

Number of deposits in the collection for the years 2005, 2006 and 2007*:* in all collections, the number of deposits is fairly regular over the years; a collection having large capacity for acquiring new strains continues to acquire strains on a regular basis.

Percentage of deposits without restrictions, with restrictions for non-commercial use only or with other types of restrictions: nearly all accessions in the collection are deposited without restrictions; the data for cc4 and cc5 on "other restrictions" are related to the fact that these collections reported in this category the "safe deposits" in the collection. By definition, these safe deposits are not publicly available – often they are safeguards in early research stages for entities without conservation infrastructure – and are not part of the global access and exchange infrastructure.

List of depositor countries and the respective number of accessions/country: the vast majority of deposits is done by national depositors (if evaluated over the 3 years); nevertheless, except for 4 collections, all collections receive a significant amount of deposits from foreign depositors as well. The deposit pattern varies enormously from one year to another, probably in part depending on the organization of the research collaborations.

List of countries of origin: the majority of deposits come from national origin (if evaluated over the 3 years); nevertheless, except for 2 collections, all collections also receive a significant amount of strains from foreign countries. Again this pattern varies a lot from one year to another. From the data that was collected, it is clear that in many cases national depositors do deposit material that is not from national origin, that is they deposit material which comes from collecting missions in other countries.

Further comments: an in-depth analysis of the list of the depositor and provider countries that was provided by the culture collections shows that the majority of strains deposited from other countries of origin in OECD collections come from OECD countries (>50%). Nevertheless, the percentage of strains to OECD collections with an origin in non-OECD countries represents an important subset. The origin of strains in the non-OECD collections is mainly from their own country. For non OECD countries, the data from 2005, 2006 and 2007 shows that every year depositors from countries such as India, the Philippines and China, and to some extent Latin American countries such as Brazil, Columbia and Uruguay, deposit directly strains from their countries in the OECD collections that were studied. This can be for reasons of lack of capacity or to comply with the obligation to deposit strains of new species of bacteria (type strains) at least in two different culture collections (for example if they chose to deposit one of the backup copies in a collection in an OECD country).

Patent deposits: the data collected here were too limited. However, in those collections that are patent deposit authority (5 in our sample), the absolute number of strains deposited a year is extremely small (in most cases only a dozen strains a year) compared to the number of strains in the accession and distribution data.

Recipients of materials (clients): except for one collection (cc4) all collections distribute significantly more strains than they acquire. This is related to the fact that the same strains are often distributed more than once. Of the 7 collections that provided detailed data on distribution, 5 (3 OECD countries and 2 non-OECD countries) distribute the majority of their strains to foreigners

and 2 (1 OECD country and 1 non-OECD country) mainly to nationals. An analysis of the list of recipient countries (for the part of the strains that are provided to foreigners) shows a different result to the case of the deposit patterns: for OECD collections nearly all the strains (90 to 100%) are provided to OECD countries, for non-OECD collections analyzed here, the results are mixed. Some distribute strains only to rational recipients; others distribute a substantial part to foreign countries.

Patterns of exchange in the field of food and agriculture: The second part of the questionnaire asked the culture collection managers to focus on the subset of depositor and recipient organizations active in the field of food and agriculture. This part was particularly difficult for the collections to fill in, because it requires to recompile information from various databases. For instance, it requires identifying for each strain if it was accessioned or distributed to entities that belong to the food and agricultural sector. These data are often encoded (if existing at all) in different data sets: the client database, which covers various sectors of use, the depositors database and the database of accessions and distributed strains which encodes the countries of origin and destination. Five culture collections provided some data on this part of the questionnaire, while only 1 provided a list of data for each distributed strain in 2005, 2006 and 2007 associating the country of origin with the recipient country in the cases of use for food and agricultural purposes. This information is too incomplete to draw conclusions. However, it allows to cross-check some of the information of the general questionnaire. The answers confirm that all the collections surveyed have a substantial number of depositing and recipient organizations that are active in the field of food and agriculture, the vast majority of them being in the non-commercial sector and for research purposes. The detailed list of countries of origin for each distributed strain (for 1 collection) confirms the pattern of the general questionnaire: most foreign strains come from OECD countries and are distributed to OECD countries; however non-OECD nations also regularly deposit and acquire strains from OECD collections. This is consistent with the fact that unlike plant genetic resources for food and agriculture (PGRFA) and animal genetic resources for food and agriculture (AnGR), there is no greater concentration of *in situ* microbial diversity in tropical, developing countries. A case in point are microbes for bioremediation and species used in biological control of agricultural pests and in biological monitoring, which have emerged from ecosystems at a wide variety of latitudes and altitudes (Beattie *et al.* 2005).

2.4. Interdependence between developing and developed countries on the global scale

Most microorganisms are extremely widespread, can easily be transported by host organisms or various means such as wind and water, and show an amazing degree of local diversity and variation. The combination of these features leads to various patterns of interdependency between countries that are users and providers of microbial genetic resources, meaning that all countries are reliant on materials originally from other countries. This section discusses two categories of global interdependence: (1) interdependence in access to *in situ* MGR, and (2) interdependence between *ex situ* collections.

An important difference with PGRFA, is that AMGR already moved or were moved around the globe much more independently (by transportation through the air, the water or in some cases the subsurface magma), long before the acceleration of the global dispersal as a result of human use and exchange of genetic resources. Only in some rare cases, the spread of microorganisms has been limited. This is mainly the case when the spread of microorganisms is limited due to barriers to dispersal or due to the functional specialization of certain microorganisms which can only live in very specific environments (Zengler 2008). In these cases, microorganisms are endemic (Bull 2003), such as certain microorganisms from hot springs with specific bio-chemical characteristics or from the polar circles. Accessing a strain of those endemic microorganisms for further study or

exploitation creates a situation of interdependence between the user countries and the provider country where the hotspot of endemic microbial diversity is situated[10].

However, in most of the cases, microorganisms are not endemic but widespread in nature. This situation appears to be closest to the scenario with plant genetic resources for agriculture, where germplasm has spread around the world as a result of the way humans have developed and used them. As a consequence, studies relying on microbial diversity, have to access strains from all over the world, typically to constitute a sub-set of strains that are representative of the biodiversity of the species. Moreover, screening a wide variety of single strains increases the chance to access the overall diversity of accessory genomes, which encode many important functions of microorganisms for use in agriculture and food (cf. supra ch. I, section 1). Examples where access of strains from various locations is necessary are the building of diagnosis networks of microbial diseases, or research for identifying new probiotic bacteria in the dairy industry for example.

A second category of interdependency is very important in the case of microorganisms, which is interdependence between *ex situ* collections. As shown in the previous section, scientists do deposit some genetic resources in foreign culture collections, because of lack of local capacity or because the expertise in a certain area of microbial research is concentrated in a culture collection in another country. Again, this situation is similar to the situation in PGRFA where a network of specialized CGIAR centers has been created to exploit in the best possible way economies of scale and international cooperation. In the case of AMGR, this pattern of specialization and cooperation between national collections is created in part by the high cost of isolation, characterization and conservation of microbial strains and by the impressive amount of microbial species to be studied. As a result, as stated also in the introduction, even the largest culture collection in the world holds less than 2% of the total diversity of strains that have been currently isolated and conserved in the culture collections.

3. Benefits of use and exchange of AMGR

The current system of global exchange of microbial genetic material provides already major socio-economic benefits in various sectors related to food and agriculture such as improvement in crop production through nitrogen fixing bacteria or decreased use of chemical pesticides by the development of biological control agents. These benefits depend upon access to a wide variety of microorganism from various geographical areas and countries. However, the need to access materials from other countries, and the degree of interdependency between countries, widely varies with the type of material exchanged and the role of this material in the overall research cycle.

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[10] Two important features characterize these endemic free living microorganisms. First, even if they are specific to certain exceptional environments, this does not mean that they will appear only in one location. For instance, hot spring or cold environments microorganisms that are found in one location can be found in other similar environments as well, such as the cryophillic algae found in alpine mountain regions discussed below. When microorganisms are restricted to certain biogeographical regions, they will typically be quite rare because of the exceptional character of the bio-physical conditions in these regions and their geographical isolation. Second, because of the specific nature of these environments, the "host regions" of endemic organisms can be much more easily identified than in the case of the majority of widespread and highly flexible microorganisms. This might have some advantages in the context of the institutional design of an access regime, as it is much easier to regulate these well identified regions, as long as they fall within national jurisdictions. One notable example of this is the Yellowstone nature park, where the park authority was able to bargain on a specific regime with culture collections such as the American Type Culture Collection (ATCC) who wanted to claim full ownership over the strains deposited from the hot springs in the nature park (cf. also infra at note 18). Nevertheless, similar organisms might be found in other hot springs in the world, therefore it is not possible to prove with certainty that certain microorganisms came originally from the Yellowstone hot spring, after it leaves the ATCC culture collection.

This section will provide an overview of these needs and practices and build a typology of the various situations of global interdependency that are relevant for the international regime. It is based on two expert workshops that have been held in February and March 2009 in Brussels on this topic, with high-level representatives from both the microbial science community and culture collections' community. Participants came from developing and high income countries. Most of the discussion below is based on the presentations at these expert workshops. This has been completed with a survey of the literature and follow-up interviews (for a detailed list of presentations, cf. annex 1 to this report).

3.1. Benefits from global access to in situ MGR

There is a growing recognition that microbes can exhibit biogeographical patterns in spite of their widespread availability. This means that these microorganisms are only available in certain specific habitats and cannot be found elsewhere on earth. At the present state of microbial research, not enough is known on microbial life in order to explain the reasons of these patterns. However, it is possible to indicate some features that make some microorganisms to be a better candidate for being endemic, rather than widespread.

More chance to be ubiquitous (non exhaustive list)	**More chance to be endemic to a specific environment (non exhaustive list)**
Generalists: showing a variety of functional properties, able to grow in wide range of environments	Specialists: specialized in a function useful in a specific and limited environment
Living in association with plants and animals that can move (or be moved) long distances	Living in association with plants and animals that have low dispersal rate
Moved around the world by humans purposefully for direct use, or inadvertently, for example, being introduced, undetected, with new planting materials, etc.	
Inhabiting habitats, e.g., the stratosphere or the sea, where the potential of long-range transport is high (such as certain fungi causing crop diseases)	In habitats with stringent growth conditions and little potential for transport (hydrogeologically isolated) (for e.g. polar habitats).

Table 4. Some features that contribute to widespread *versus* restricted global availability of microorganisms in nature (based on Fierer 2008).

In general, the field of microbial biogeography is still in its infancy (Fierer 2008). In spite of constant evolution in this field, in particular made possible by the genomics revolution, some important explanatory factors of biogeographical patterns can be identified (*Ibid.*). One of this is the dispersal rate (mainly the passive dispersal, by different types of propagules) of the microbial material, another environmental selection and finally the sexual cycle and the reproduction rate. If the dispersal rate is low or the dependence on a specific environment very high then the chance of having organisms that are endemic will increase. If the reverse is true, then the chance of having widespread availability will increase. We illustrated in table 4 several of the main features that contribute to restricted availability to certain environments or to widespread availability.

The term "diversity" can be confusing here in that it encompasses different meanings. Typically local diversity is referred to as alpha diversity, whereas the total species richness over continents and biomes is referred to as gamma diversity (Fierrer 2008). We know that most microbial communities have high local (alpha) diversity; however there is currently some debate regarding the gamma diversity of microbes[11]. However, it can be said that if microbes would have no biogeography, the discovery of new microbial taxa should be far less common than has been observed (*Ibid.*). The complexity of this situation is further exacerbated by the fact that many species are actually representing a group of intra-species complexes which can have very different properties (cf. for a clear example the detailed analysis of the *Burkholderia cepacia* species complex in Mahenthiralingam et al 2000). Therefore, much of the microbial diversity should also be studied at the intra-species level.

The following situations of interdependence in access to *in situ* materials that are important for the agriculture and food were highlighted at the workshops:

(1) Analyzing microbial diversity of pathogenic and beneficial microorganisms

The basic benefits of the global exchange in these cases is the access to a population of strains that is representative of the within biodiversity of the species. This allows in turn the development of scientific descriptions and molecular biology diagnostic tools for identification of economically important pathogens (cf. for detailed examples in the agriculture and food sector, annex (a)).

(2) Accessing microbial biodiversity for screening for interesting strains

Single strains might have specific properties that provide major benefits in the exploitation of the microorganism in food and agriculture. By screening large populations of potentially interesting strains these can be identified, conserved and then cloned for mass production. Major examples in this category are the screening for optimal biocontrol agents in agriculture or the screening for bacteria and fungi in food fermentation such as lactic acid bacteria in the dairy industry, or yeast in the bread industry (cf. for detailed examples in the agriculture and food sector, annex (b)).

(3) Accessing endemic microorganisms

For free living microorganisms, there are nevertheless some clear cases where one might expect to find free living microorganisms with strong geographical specificity, such as microorganisms whose growth is only possible in very cold or very hot environments with few dispersal possibilities, or bacteria with a low dispersal rate such as soil bacteria; or microorganisms from isolated geographical regions with very specific biochemical properties (cf. for detailed examples in the agriculture and food sector, annex (b)).

3.2. Benefits from global access to ex situ AMGRs

Because of the high cost of characterization and conservation, and of the investment in the human resources, culture collections have developed a network of collaborating organizations which have specialized in various areas of microbial research. This specialization and coordination has lead to a functional interdependency in access to *ex situ* strains on a global scale.

[11] More hard data is needed to assess the validity of the competing hypotheses in this field. Fortunately, sequencing efforts have been increasing at an exponential rate, and public databases are now filled with sequences of microbial small-subunit rRNA genes from a wide range of habitats and locations. We should be able to use these sequence data to quantify the degree of overlap in microbial assemblages between habitats (Fierer 2008).

Countries deposit strains of national origin in foreign culture collections, which have acquired a special expertise and reputation. In turn, the same country will collect and receive strains in its own area of specialization. Some of the *ex situ* strains held at these specialized and internationally recognized reference culture collections become reference organisms used and referred to in most follow-on research, resulting in an ever broadening body of validated scientific knowledge related to that organism. Access to these reference organisms held *ex situ* in service culture collections is a necessary component of most microbial research. They are "knowledge bricks" which are crucial ingredients in the initiation of new lines of research and in the validation of local biodiversity screening or biodiversity analysis. Crucially, because of the high chances of mutation and evolution of microbial resources in *in situ* conditions, these *ex situ* reference organisms cannot be replaced by the study of similar *in situ* materials to validate the research findings.

The case of the development of biological control agents for cocoyam presented at the workshop illustrates this interdependence in the field of agriculture (Höfte 2009, Perneel *et al.* 2007). Cocoyam (*Xanthosoma sagittifolium* (L.) Schott) is a tuber crop used to feed more than 200 million people living in the tropics and subtropics. The tubers provide carbohydrates in the human diet and also contain substantial amounts of proteins, fat and essential vitamins. Cocoyam production, however, is seriously impaired by the cocoyam root rot disease caused by the fungus *Phytium myriotylum* Drechsl. As fungicides have not been sufficiently effective against cocoyam root rot and may have adverse effects on environment and human health, biological control is considered a preferred strategy. The *Pseudomonas aeruginosa* PNA1, isolated from the chickpea rhizosphere in India, and conserved at the ICRISAT CGIAR in India, has shown to efficiently suppress cocoyam root rot by the production of antibiotics and biosurfactants. Based on the access to this prior knowledge, and by using the ICRISAT strain to compare the results of the research, a screening programme was set up in Cameroon. Through focused screening of local pseudomonas bacteria from cocoyam fields in Cameroon, specific pseudomonas bacteria were identified as effective biocontrol agents. On this basis, new farming strategies for combating the fungi have been introduced, such as the use of a compost of oil palm containing the pseudomonas bacteria and joint cultivation of white and red cococyam.

This focused screening program, in spite of only involving local strains, is crucially dependent on access to *ex situ* reference strains held abroad. The use of the Indian strain was needed as a reference strain at various instances of the screening and characterization process (Perneel *et al.* 2007). These features of interdependency were also highlighted in two other cases presented at the workshops, with major benefits for developing countries.

A first case concerned the development of inoculants for silage fermentation in Indonesia, through screening of local strains of *Lactobacillus plantarum* collected in the farmers' fields (Widyastuti 2009). Through screening of these strains, high-quality native strains were selected and developed for commercialization for farmers in orders to reduce their dependence on expensive silage bought from silage companies. Strains JCM 1057 from the Japan Collection of Microorganism and NRIC 1067^{T} from the Nodai Research Institute Culture Collection in Japan were included as reference strains of the research. In this case, the isolation, selection and development of silage inoculants was possible by using locally available microbial resources, but access to foreign strains was necessary for validation of the results and calibration of the tools used in the screening process.

The second case concerns the development of inoculants for soya production at the Grassland Culture Collection in Zimbabwe (Murwira 2009). The original inoculant for soya production in Zimbabwe was introduced for mass production in 1964 from the US Agricultural Research collection. A programme of re-isolation of strains, which evolved from this initial strain on the farmers' fields in Zimbabwe, was set-up to isolate strains that are better adapted to local conditions.

Comparison with the original strains from the US (USDA 110 and USDA 122) was necessary to control and validate the identification of potential new inoculants.

These cases illustrate the role of access to reference materials from other countries as a condition for initiating and validating local research and exploitation projects. However, it is important to stress that the functional interdependency is not only limited to access to *ex situ* AMGR, but includes access to research tools, technical skills and global databases. Indeed, increasingly, molecular biology and bioinformatics become key components of microbial research. In one case presented at the workshop, a project in Georgia for developing starter cultures for Matsoni yoghurt (Chanishvili 2009), the results were obtained through a combination of screening of local strains and use of international digital databases. In this case, identification of strains from local farmer markets was done based on the analysis of morphological and bio-chemical characteristics and on a comparison of the genetic sequences to the sequences publicly available in the International Nucleotide Sequence Database (GenBank/Embl/DBJ) (Uchida *et al.* 2007). This successful development of starter cultures was made possible through the training of young scholars in foreign culture collections, the availability of molecular biology research tools in an international collaboration with Japan and access to the databases on the Internet. Therefore, even if the access to original materials is crucial in many cases, global functional interdependence on research materials should be situated in the broader context of international collaboration for training, technology transfer and access to global database infrastructures.

4. Conclusions

Food and agriculture microbiological science and technology present a wealth of opportunities for improvement of food and agricultural production systems, and for contributing to energy production and waste management. In agriculture, three areas where use of microorganisms and microbial research currently play an important role are (1) the understanding and combating of microbial pathogens and health hazardous microorganisms, (2) the building of surveillance networks and (3) the exploitation of interactions with beneficial microbes that are of direct benefit to agricultural plants and animals, and to food production processes.

Important change in use and potential benefit of microbial research is expected to occur from new scientific research approaches, such as the role of intensive computation in the integration of genetic, protein, metabolic and environmental data in microbial ecology and the use of Global Information Systems tools in tracking microbial dispersion. These emerging interdisciplinary approaches are likely to offer complementary approaches to biological control, by helping to protect beneficial organisms that may already be present in the environment, or by reinforcing innate host resistance through the use of probiotic microorganisms which fortify the host's innate immunity. The new developments show high potential for contributing to food security and poverty alleviation. They enable development strategies that can be based on locally available microbial material – provided that reference *ex situ* AMGR can be accessed from the culture collections – and are often less costly than the existing solutions developed for global markets, illustrated by the examples from the local dairy industry and alternative measures of biological control.

All countries are actively involved in collecting and exchanging strains in the global arena**.** The main providers of microbial genetic resources to the culture collections are the culture collections (approximately 45%), which engage extensively in their own collecting efforts, and the university research collections (approximately 30%). The users are both situated in the public sector (approximately 77%, mainly for research and training at universities) and the private sector (approximately 23%). Strains that are acquired by private sector entities at culture collections are mostly general reference strains also used in public research, such as type strains and reference

strains, which show important public good properties. However, some strains are also acquired directly for use in commercial applications, but most of the high performing industry strains are held at the private industry collections under conditions of trade secrecy.

The majority of exchange take place between OECD countries. As shown in this report, both the majority of provider countries and the majority of users of microbial genetic resources are situated in OECD countries. This is related to the fact that a substantial part of collecting by culture collections is done in the home country. The strains coming from non-OECD countries however, represent an important subset. This situation is very different from the situation of PGRFA, where the majority of materials currently held in genebanks around the world were originally collected from developing countries (and the majority of materials send out from those genebanks – the international public genebanks of the IARCs of the CGIAR at least) are distributed to developing countries.

In summary, the situation of exchange and use of microorganisms is characterized by a high level of interdependency. The main form of interdependence is related to within species diversity of ubiquitous microorganisms, used in biodiversity studies and screening, but some forms of interdependency relate to rare cases of endemic strains, such as in the case of the polar circles. Genetic erosion of microbial diversity is very difficult to assess at the present state of microbial science, but the disappearance of ecosystems with very specific biochemical conditions is likely to contribute to the disappearance of unique species. Moreover, further uniformization of agricultural production systems is likely to decrease overall soil diversity, which increases in turn the dependence on some remaining regions of high microbial diversity in certain species. Finally, much of the efforts to conserve the microbial diversity, and to benefit from the important services it provides, also depend on broad access to the *ex situ* strains in the culture collections that are the basis of taxonomic research and for validated cumulative follow-on research on previous scientific findings.

CHAPTER III: CURRENT PRACTICES OF EXCHANGE OF AMGR

1. Introduction

The main purpose of this chapter is to provide information on the existing terms and modalities for distribution and exchange of agricultural microbial genetic resources (AMGR) in order to assess to what extent the existing legal framework and the contractual practices grant or deny access to AMGR, and provide a fair sharing of the benefits generated from their use.

Exchanges of MGR have historically occurred in an informal way between culture collections, laboratories and researchers worldwide. It may be said that, in fact, one of the strengths of the current system of global exchange is the high level of collaboration in the scientific microbial community, as shown by the numerous global and regional initiatives of the science unions and the culture collections federations, and within international organizations, such as OECD.[12] Informal exchanges have facilitated research activities, and, as a consequence, science and exploitation of such resources have rapidly advanced.

During the last decades of the twentieth century exchanges have risen considerably. However, the increasing economic importance of biotechnologies and new legislation concerning the use and access to natural resources, have subjected exchanges of genetic resources to increasing controls. Access and distribution are submitted to many requirements and therefore, exchanges are becoming subject to more and more formal forms of control, and ultimately restrictions on access.

Four areas have been identified where there are potentially increased restrictions on access. These are: the contractual practices of the culture collections, patents involving microorganisms, the impact of national access and benefit sharing (ABS) measures, and the norms of science. First, as a response to financial restrictions on government spending in the 1990s (Stern 2004), and the growing commercial opportunities for upstream research tools, such as the microbial strains held at the culture collections, some culture collections have departed from the sharing and collaborating practices.

Examples of restrictive license practices may be found in some material transfer agreements (MTAs) used by culture collections for distributing strains. Perhaps the most notable recent example is the MTA used by a private non-profit member of WFCC (see infra section 2.1) that permits the use of the strain in the purchaser's laboratory only. This can be justified on the basis of the need to prevent circulation of improperly stored/mutated strains. However, the restriction applies to all recipients of that collection, that is also for strains that are ordered by other culture collections and collaborating scientists in common research projects.

Second, recently there has been an increasing number of applications for patents in developed countries involving specific uses of microbial material, mainly patents on processes involving microorganisms, research tools and specific properties of certain genes (Oldham 2004). The number of patent deposits involving microorganisms has remained overall fairly stable over the last 15 years (with roughly 2,500 patent deposits worldwide a year, and a total of 1,250 strains deposited worldwide a year in the International Deposit Authority (IDA) authorities, cf.

[12] See, for example, the European Culture Collections' Organisation (ECCO) (http://eccosite.org/) or the WFCC initiatives; the OECD Best Practice Guidelines for Biological Resource Centres; or projects like MOSAICC (http://bccm.belspo.be/projects/mosaicc/) or the Global Biological Resource Centre Network (http://www.gbrcn.org/index.php).

http://www.wipo.int/ipstats/en/statistics/micros/deposits_ida.html). Nevertheless, even if this amount is only a tiny fraction of the strains deposited in the culture collections (cf. supra ch. II section 2.3, table 2), this does not take away from the fact that access to patented uses of microorganisms remains an important concern for developing countries (vid. infra section 2.2).

Other limitations to the use and re-use of the materials derived from the implementation of very restrictive and inoperative access and benefit-sharing national measures, mostly in developing countries, make it increasingly difficult to access genetic materials even when this access is for non-profit research (infra section 2.3). Finally, it is worth noting that the sharing paradigm, which has characterized the scientific community, has been eroding over the past several years due to growing interests in patenting by scientific institutions (GRAIN 2006: 79-82).

These trends might have major impacts on access and distribution of microbial research materials in the life sciences. If the formal exchange system becomes unduly restrictive, scientists might prefer to exchange strains in an informal way between their in- house research collections where the bulk of microbial research is done. As shown in chapter II, these research collections play an important role in the overall research cycle, because it is there where the first selection and screening of reference materials is done. It is difficult to estimate the size of the research collections, but as they constantly process vast amounts of raw and still unspecified materials, they probably have much bigger holdings than the culture collections. However, they lack the quality management and the long-term conservation of strains of the culture collections, which is required for certified follow-on research and quality management purposes in both the public and private sectors.

Other possible consequences that have been documented with regard to increasing restriction on access to genetic materials, is the problem of research chill, that is, the result of private sector-like conditions imposed on academic research, bio-collecting efforts, including marine bioprospecting (Greer and Harvey 2004: 168-170), and increasing distribution prices of culture collection holdings.

If these trends continue, there is a serious risk of over protection and privatization of all biological resources on the same highly restrictive conditions that are only relevant for a handful of deposits with known or likely high payoff commercial opportunities (Reichman *et al.* 2008). Likely, this scenario would continue to allow (and encourage) informal, relatively unrestricted exchanges among a handful of club members, but would limit the amount of material that is effectively available to, and used by the global research community. The researchers that operate outside the confines of the clubs working on specific sets of materials would then be excluded.

In parallel to restrictive trends, some culture collections are working to maintain the tradition of global distribution and exchange. There have been a number of initiatives to develop science-friendly MTAs that are designed under open access schemes, at least as far as the distribution for research and scientific purposes is concerned (vid: infra sections 2.3.2 and 2.4). This represents a clear sign of the scientific community`s interest to preserve the open access philosophy to collections of MGR.

Microbial genetic resources share some of the characteristics of global public goods, notably the global interdependence (see supra chapter 2, section 3). These, and other points have led some commentators to think about the possibility of building a microbial commons (Reichmann *et al.* 2008; and *infra* footnote 24). Sharing strategies are indeed fundamental for research on certain kinds of AMGR. Facilitating access to MGR may help to better authenticate and characterize them, to preserve microbial genetic diversity and to enhance the use and distribution of MGR for research, as well as their use and distribution by developing countries (CGRFA-11/07/Circ.3: 16, 20 et seq.). The need for global coordination to facilitate the exchange and fair use of MGR has also been

highlighted in connection with the Convention on Biological Diversity (CBD) discussions on an International Regime on access and benefit-sharing, and in other fora (see infra sections 2.3.1 and 2.4 *in fine*).

2. Current terms and modalities for exchange of MGR

Access to microbial genetic resources from the culture collections is granted under terms and modalities that vary widely between countries, and, within the countries, between the larger collections – which have formal arrangements for access – and smaller collections – which often do not use written contracts for access arrangements. As a general trend, more and more collections, both in developing and developed countries, are moving towards formal arrangements, but very few explicitly clarify their responsibilities in regards to ABS. This section reviews the reasons why the collections are moving from the informal to a more formal set of arrangements, and evaluates the impact of the ABS legislation upon these arrangements.

2.1. The historical informal sharing and access regime for non-commercial purposes

Previous studies have shown that informal exchanges among scientists and/or culture collections represent a very large percentage of the exchanges. Informal distribution of strains occurs without any written contract governing the terms of provision or receipt of the material concerned, under the presumption that the strains will only be used for non-commercial purposes (Stromberg *et al.* 2006). This has been confirmed by the surveys organized for this report (cf. infra under 2.3.1. and chapter IV). Some collections even distribute material only on an informal basis. This is especially true for the smaller and specialized collections. Other collections are using or have recently started to use standard forms for depositing as well as for distribution of strains for non-commercial purposes. However, these standard forms are not systematically used in all the collections for all their transactions.

As regards the distribution of strains for commercial purposes, bilateral agreements negotiated on individual and case by case basis are generally concluded. Commercial purpose is here understood as the distribution of the material for the purpose of profit. It may include the sale, leasing, exchange, license, or other transfer of material for profit purposes. In general, patents will also trigger the negotiation of commercial distribution clauses. Use of reference or type strains for test and identifications purposes, without selling them to third parties, is generally not understood as a trigger of commercial distribution clauses.

This historical informal system affords the culture collections only two unsatisfactory options, namely, either to use case by case formal contracts, only relevant for a handful of strains in the culture collections with known or likely high payoff commercial opportunities, or to allow informal, relatively unrestricted exchanges among a handful of club members for the bulk of the transactions with the strains.

2.2. Three models of a self-regulatory approach

The principal advantage of the existing informal networks is to lower transaction costs while allowing re-use and further distribution of the research materials with few, if any, of the strings attached to them out of concerns about unknown future commercial applications (Reichman et al. 2008). At the same time, the tacitly recognized quality management standards observed by trusted members of the club guarantee the authenticity and integrity of the materials exchanged.

Despite their presumed efficacy, however, these informal networks exhibit a number of serious disadvantages (*Ibid.* and Stern 2004). They are necessarily limited in size because, absent a personal

relationship built on trust, the participants would not willingly sustain the case-by-case costs of verifying compliance with acceptable quality standards. They would also expose themselves to the risk that unknown third parties could free-ride on the underlying tacit norms that support the system, without affording reciprocal access to collections of equal quality on equivalent terms. If third parties were allowed to extract materials from the club's resources, moreover, the original providers would lose control over them and thereby forfeit the ability to claim either reputational or commercial benefits from ensuing research uses and commercial applications.

Given the commoditizing pressures on microbial science, moreover, the stability of the informal system over time will likely be diminished as more and more contributors might succumb to high-protectionist MTA offered by the few non-profit and private members of WFCC, as shown below through the example of the MTA of the American Type Culture Collection.

The adoption of quite restrictive access measures in several developing countries, as a reaction to the excesses of bioprospecting and patenting by developed countries (Safrin 2004), further threatens the efficacy of an informal regime. These access procedures have reportedly lead to increasing difficulty to access materials from culture collections in developing countries[13]. The deposit of materials which were collected *in situ* in developing countries has become also increasingly difficult, both for deposits in developing and developed countries collections.

In particular, these access procedures can lack transparency and be quite complicated, involving lengthy delays in obtaining genetic materials (UNEP/CBD/WG-ABS/5/3 2007: 12–13; Roa-Rodriguez and van Dooren 2008). Scientists both from developed and developing countries have repeatedly expressed concern about the harm that restrictive access regulations might have on scientific research (Jinnah and Jungcurt 2009: 464).

To offset these negative trends, therefore, some WFCC members have developed formal MTA that formalizes the basic norms and benefits of the informal club system, along with the obligations and responsibilities that support them. These formal MTA are however only a first step and are hampered today by the wide variety of license conditions adopted in these formal MTAs.

2.2.1. The American Type Culture Collection model

More than 80% of the WFCC collections belong to public sector entities (universities or governments). The remaining are semi-governmental (8%) and in some rare cases, are private non-profit (4%) or private industry collections (1%).

Restrictive license conditions are more likely to occur in the case of private non-profit collections or private industry collections. One example is the policy adopted by the American Type Culture Collection, which is a private non-profit collection, today receiving only 15% of its core funding from direct government grants (Stern 2004). The ATCC model is rather the exception than the general rule, both because it is one of the rare private non-profit collections and because of its restrictive license policy. However, because of the dominant historical role of this collection it still attracts considerable interest both from other collections in developing and developed nations[14].

The ATCC collections' Material Transfer Agreement requires that the material be used for research purposes only and be used within the purchaser's investigators laboratory. It permits the use of material for industry sponsored academic research (research sponsored by a for-profit organization

[13] Cf. Workshops on Analysing Patterns of Exchange and Use in the Global Microbial Commons, Brussels, 18-19th February 2009 and 25th-26th March 2009.

[14] An example for example are the many partnerships that ATCC is building with developing countries' collections, such as the Eliava Institute of Bacteriophage, Microbiology & Virology collection in Tbilisi, Georgia (Chanishvili 2009).

carried out at a non-profit organization and by the non-profit organization's employees). In this case, the authorized use extends only to the academic research carried-out at the non-profit organization and by the non-profit organization's employees. According to the MTA, any non-profit purchaser using the biological materials in connection with industry sponsored academic research should notify the industrial sponsor that any use of the biological materials by the industry sponsor will require a separate license from the collection and/or its contributors and that collection and/or its contributors are under no obligation to license any biological materials to any such industry sponsor. The MTA explicitly states that the purchaser must not distribute, sell, lend or otherwise transfer to a person or entity the biological material, without prior written agreement of the collection. Any commercial use of the biological material is strictly prohibited without its prior written consent.

All these requirements depart from traditional practices of exchanges among culture collections and scientists and, different from the examples illustrated below, do not recognize the so-called legal/legitimate exchange. This departure has been criticized by the scientific community[15]. The ATCC collection argues in its defence that the main reason to restrict transfer is to ensure the quality of the research material[16], to prevent circulation of improperly stored/mutated cultures. However, the restriction applies to all recipients of that collection, that is also for strains that are ordered by other public culture collections and collaborating scientists in common research projects.

The MTA also deals with ownership and intellectual property rights (IPR). Different from other culture collections, the collection categorically affirms its "ownership" on the materials deposited in and distributed from its collection. Hence, with the notable exception of Yellowstone nature park[17], its MTA states that the collection and/or its contributors retain ownership of all right, title and interest in the distributed materials, progeny, unmodified derivatives and distributed materials contained or incorporated in modifications. It also recognizes that the purchaser retains ownership of: (a) modifications (except that the collection retains ownership rights to distributed material included therein) and (b) those substances created through the use of distributed material, but which do not contain that material.

On the other hand, the MTA recognizes that use of material may be subject to the intellectual property rights of a third person, the existence of which rights may or may not be identified in the collection catalogue or website. The culture collections makes no representation or warranty regarding the existence or the validity of such rights. Thus, the purchaser has the sole responsibility for obtaining any intellectual property licenses necessitated by its possession and use of the materials.

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[15] See, for example, the letter signed by H. Trüper and B. Tindal, members of the Judicial Commission of the International Committee for Systematics of Prokaryotes: Material Transfer Agreements of Culture Collections Threaten Prokaryote Taxonomy, published in ASM News, vol. 71, n. 6, 2005, 259-260. When criticizing these clauses both scientists states: "Research nowadays uses complex techniques so that virtually no laboratory can perform all possible experiments. Cooperation among laboratories at national and international level is essential, and would be severely hindered, if the same cell material needs to be studied. It is common practice between scientists to freely exchange such materials while keeping the culture collection strain numbers […]These so-called "agreements" are different from the past policy of ATCC and now effectively inhibit the transfer of strains between the ATCC and other internationally recognized service collections. The consequences are particularly significant for type strains. In the past, the Judicial Commission of the ICSP has, via the Bacteriological Code, striven to make all type material available to the scientific community as widely as possible. The strategy of depositing strains in two different service collections in two different countries was introduced to combat the growing restrictions on the distribution of type material based solely on economic grounds."

[16] Perrone and Soriano, Material Transfer Agreements Serve a Critical Function, in Microbe, September 2005 http://www.asm.org/microbe/index.asp?bid=37457.

[17] Cf. infra footnote 19.

Finally, although in the contract the purchaser acknowledges and agrees that the use of certain material may be subject to third party restrictions, the ATCC MTA does not contains any reference to the Convention of Biological Diversity and/or the prior inform consent. Third party terms may have been specified in the ATCC deposit forms. If so, the ATCC will make them available for review by purchaser upon request.

2.2.2. The European Culture Collection Model

Last February 2009 was adopted the ECCO core Material Transfer Agreement for the supply of samples of biological material from the public collections. The main purpose of the agreement is to make biological material available from ECCO collections under the same core conditions, by means of its implementation by the ECCO members - either as such or integrated in the members' respective more extended documents. The MTA will be reviewed and revise at regular intervals and whenever necessary. It contains specific clauses dealing with the purpose of the use (mainly focus on research activities), intellectual property rights, liability, safety and security.

The ECCO core MTA applies to the distribution of the material to end-users, intermediaries or those involved in the so called legitimate exchange. Recipients must not sell, distribute or propagate for distribution, lend, or otherwise transfer the material to any others, except those acting as intermediaries and those involved in legitimate exchanges. Legitimate exchange is defined as the transfer of the material between scientists working in the same laboratory, or between partners in different institutions collaborating on a defined joint project, for non-commercial purposes. This also includes the transfer of material between public service culture collections/BRCs for accession purposes, provided the further distribution by the receiving collection/BRC is under MTA conditions equivalent and compatible to those in place at the supplying collection.

The ECCO MTA requires the material to be used only for non-commercial purposes. Commercial purposes are defined as the use of the material for the purpose of profit. According with the information provided for some experts involved in the drafting of the ECCO MTA, commercial uses would surely include patents applications. In case the recipient desires to use the material or modifications for commercial purpose(s), it is the responsibility of the recipient, in advance of such use, to negotiate in good faith the terms of any benefit sharing with the appropriate authority in the country of origin of the material, as indicated by the collection's documentation. In principle, the ECCO agreement does not impose the collection to be involved in the benefit sharing negotiations.

In any case, recipients of the material should acknowledge the collection as the source of the material in any and all publications that reference the material.

Finally as in the other models, the agreements state that it does not grant any rights under any patents, propriety, intellectual property, or other rights with respect to the material.

2.2.3. A developing country model: the BIOTEC culture collection

As an example of MTAs used in developing countries we have chosen the MTA adopted by the BIOTEC Culture Collection, National Center for Genetic Engineering and Biotechnology (BIOTEC), Thailand. BIOTEC uses 2 standard material transfer agreements, one for general distribution of materials to customers (hereinafter BIOTEC MTA1), and another one for exchange of materials between BRCs and other culture collections which allow recipient collections to further distribute the materials to third parties (herinafter BIOTEC MTA2).

The BIOTEC MTA1 requires the material to be used only for research and education. The material may be distributed to co-workers, but always under the recipient's direct supervision. Its release to colleagues in other institutions can be granted after BIOTEC written permission and following the signing of an appropriate copy of the MTA1 between the third party and BIOTEC.

As regards commercial users, if the recipient desires to use the material for commercial purposes, BIOTEC agrees, in advance of such use, to negotiate in good faith with recipient to establish the terms of a commercial license. To this end, they use to sign a Memorandum of Understanding negotiated on individual basis.

Note that the BIOTEC MTA1 explicitly acknowledges the freedom of the recipient to file patent application(s) claiming inventions made by the recipient through the use of the material. It should notify the CC upon filing a patent application claiming modification(s) or method(s) of manufacture or use(s) of the material. The recipient must acknowledge BIOTEC as the source of the material and data in any and all publications and patent applications based on or relating to the material, replica, or derivatives thereof and any research thereon.

Finally, as far as pre-existing IPRs, the MTA explicitily states that that the material is or may be the subject of a patent application and that no express or implied licenses or other rights are provided to the recipient under any patents, patent applications, trade secrets or other proprietary rights of BIOTEC, including any altered forms of the material made by BIOTEC.

Conditions under the MTA2 are quite similar. Main difference refers to subjective scope of the agreement that only applies to other BRCs. Thus, the MTA2 allows further distribution of the material under the recipient's direct supervision or the recipient's appropriate agreement. As in the case of the ECCO core MTA, this second model facilitates the exchange and distribution of strains by the scientific community.

2.3. Potential impact of access and benefit sharing legislation on the self-regulatory arrangements

The three MTA models for accessing strains from culture collections surveyed in the previous section are based on self-regulation. These and other self-regulatory arrangements are extensively discussed in the numerous global and regional initiatives of the microbial science unions and the culture collections federations, and within international organizations, such as OECD. Guidelines and principles developed by the WFCC (WFCC, 1999) and the OECD (OECD, 2001) contribute to the further development of the MTAs, and community pressure (such as membership on important WFCC and OECD committees, or inclusion / exclusion in common research projects) plays an important role in the compliance with the terms and conditions that are proposed in these guidelines.

The self-regulatory arrangements have some important shortcomings however. They do not (and mostly do not intend to deal) with the problem of access and benefit sharing. At most they offer some administrative support for facilitating the ABS regime, such as through their extensive catalogues reporting the detailed source of every strain and the tracking of the provenance of the strain if they have been acquired from another culture collection. Some collections also offer to play the role of an intermediary in ABS negotiations, if a recipient wants to distribute strains acquired at their collection for profit purposes. A second important shortcoming, as seen from the above analysis of the three models, is the lack of standardisation of many the license conditions between the collections. This adds to the legal uncertainty in this field, especially for international transactions with strains. Finally, as for any regime based on self-regulation, it is inherently fragile.

Any collection might decide to opt out of the regime at any moment, when its perception of potential benefits of introducing more restrictive license conditions outweighs its fear of ostracism from the community.

This section evaluates the impact that a higher level set of legal rules, negotiated on the international level in the context of the current ABS negotiations, might have on this self-regulatory regime. First, some of the common features of the self-regulatory arrangements developed in the WFCC collections are presented. Then the interaction with the introduction of ABS regulation is discussed.

2.3.1. State of play: common features of MTAs in WFCC collections in developing and developed countries

To assess the common features of MTAs used in WFCC collections an in-depth survey based on written questionnaires and phone interviews was organized for a representative set of culture collections in developed and developing countries. WFCC culture collections were selected and contacted according to pre-designed criteria – in particular, the volume of deposits in the food and agriculture sector and the geographical diversity. The following 16 collections participated to this survey (indicated with their WDCM number)[18]:

Africa
- Grasslands Rhizobium Collection, MAR, WDCM34, Zimbabwe

America
- Universidade Federal de Pernambuca, Micoteca do Departmento de Micologia (URM), WDCM 604, Brazil
- CIAT Rhizobium Collection, Centro Internacional de Agricultura Tropical, WDCM53, Colombia.

Asia
- Microbial Type Culture Collection and Gene Bank (MTCC), Institute of Microbial Technology (IMTECH), WDCM773, Chandigarh, India
- Persian Type Culture Collection, PTCCI, WDCM124, Iran
- International Center for Agricultural Research in the Dry Areas, ICARDA, Syria
- Bioresource Collection and Research Center, Food Industry Research and Development Institute, (BCRC) WDCM59, from Taiwan
- BIOTEC Culture Collection, National Center for Genetic Engineering and Biotechnology, WDCM783, Thailand

Europa
- BCCM/LMG Bacteria Collection, WDCM296, Belgium
- BCCM/MUCL Mycotheque de l'université Catholique de Louvain, WDCM308, Belgium
- DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, (DSMZ), WDCM274, Germany
- HAMBI Culture Collection, WDCM779, Finland
- All-Russian Collection of Microorganism, Institute of Biochemistry and Physiology of Microorganisms, Russian Academy of Sciences (VKM), WDCM 342, Russian Federation
- Coleccion Espanola de Cultivos Tipo (CECT), WDCM412, Spain
- Culture Collection, University of Goteborg (CCUG), WDCM32, Sweden

[18] Cf. http://wdcm.nig.ac.jp/wfcc.

- CABI Genetic Resource Collection, IMI, WDCM214, UK

2.3.1.1. Accession/Deposit of MGR

Culture collections usually hold public and safe deposits. The following paragraphs focus on public deposits.

Most of the culture collections have accession or deposit forms for public deposits to be used worldwide. The "accession form" is the very first document attached to strains entering a collection. Appropriate use of this form facilitates the management of the microorganisms throughout its *ex situ* lifespan. (MOSAICC 2009: 8). In some cases (mostly when a scientific cooperation exists among two or more research centres) depositing of material may be based in bilateral agreements.

In general, deposit forms do not include specific restrictions. When the depositor imposes a restriction either the material is deposited as a safe/restricted deposit, or a second model of accession form is used. When a second model of accession form exists, it generally states that the material may be distributed only for research purposes at the premises of the end-user. If the deposit is made as a consequence of a bilateral agreement, there may be restrictions on the use of the material. One culture collection does not tolerate any restriction. There is a general understanding on the fact that responsibility in relation to the Prior Informed Consent (PIC) is on the depositor. This is very clearly explained in the note published in the DSMZ webpage.

It is the responsibility of end users/depositors to ensure that these undertakings are complied with.

Notice to DEPOSITORS

As a consequence of ratification of the Convention on Biological Diversity (CBD) it is your responsibility as depositor to ensure the MGR were collected with the Prior Informed Consent (PIC) of the country of origin and that the deposit of the strains in an open collection does not infringe any national obligations. DSMZ will not accept deposits without disclosure of the country of origin (see DSMZ- accession form).

Notice to RECIPIENTS

End user obligations under the CBD

It is the responsibility of all recipients of DSMZ cultures who reside in countries that are signatories to the CBD to ensure that the use of organisms received complies with the general requirements of the CBD and with any regulations drawn up by your own country. It is also in customer's interest to keep traceability records where DSMZ cultures are subsequently passed on to a third party and to ensure the third party is made aware of its obligations under the Convention. DSMZ accepts no responsibility for the breach of any requirements relating to the CBD.

* http://www.dsmz.de/dsmz/main.php?contentleft_id=40.

Either deposit forms or the general information delivered for public deposits are used to specify that strains deposited are to be accessible to researchers or industries according to the applicable MTA. Usually, forms for public deposit do not include any clause referring to IPRs, confidentiality, access and benefit-sharing or reporting on the use of the material. Once again, there are exceptions regarding deposits made in virtue of cooperative research agreements that often deal with these issues.

2.3.1.2. Distribution of material

a. The use of Material Transfer Agreements (for research and education)

Most culture collections have a (standard) MTA for distribution of strains or have the intention to draft an MTA in the near future. Standard MTAs are used for worldwide distribution of strains, although in some cases specific permission is required to send the material abroad; obtaining that permission may take a few months.

All but two MTAs explicitly permit the use of material for research and education.

Examples of permitted uses

"RECIPIENT may use the MATERIAL in any lawful manner for academic research, teaching or quality control purposes. Any COMMERCIAL USE of the MATERIAL requires the prior written authorization of the PROVIDER. Such approval will not be unreasonably withheld."

"The use of the genetic resource provided to you by CABI and all replicates and derivatives are for research or teaching purposes only.[…] The Customer shall not distribute, sell, lend or otherwise transfer the genetic resource to any third party. Any commercial use of the genetic resource provided by CABI is prohibited without CABI's prior written authorization."

As a general rule, MTAs do not allow the redistribution of the materials to third parties, but most of the analyzed MTAs allow, under certain conditions, redistribution of material by culture collections or in the research group. MTAs refer to this possibility as a legal or legitimate exchange (for example in the case of the ECCO agreement surveyed above). The BIOTEC culture collection has a specific MTA for exchange of materials between culture collections, which allows recipient collections to further distribute the materials to third parties.

Examples of definition of legitimate/legal exchange

"LEGITIMATE EXCHANGE: The transfer of the MATERIAL within the Research Group. LEGITIMATE EXCHANGE also includes the transfer of MATERIAL between named culture collections/biological resources centres for accession purposes, provided that further distribution by the receiving culture collections/biological resources centre is under MTA provisions compatible and equivalent as those in place at the supplying collection."

"Legal Exchange: Transfer of Material between scientists working at the same laboratory or between partners from different organizations collaborating in a joint non-commercial project. It also includes the transfer of Material between culture collections/Biological Resource Centers

for the purposes of availability; further distribution by recipient collections/BRC is in accordance with the terms and conditions of MTA (Material Transfer Agreement) available at delivering collection."

The main purpose of these kinds of limitations on further distribution is to limit the distribution in cascade/in series. They facilitate the tracking of the MGR and ensure that MGR keep their original quality and characteristics. These are the main reasons that led the Micro-organisms Sustainable Use and Access Regulation International Code of Conduct (MOSAICC)[19] to recommend that the MTA by default prohibit further down-the-line transfers (MOSAICC, 2009: 9-10) (cf. also infra ch IV, section 2).

b. Other agreements (commercial use and scientific collaboration)

As regards commercial applications, most MTAs require a separate authorization by the culture collection and/or the depositor. A commercial application may be understood as the use of the material for the purpose of profit. It includes the sale, leasing, exchange, license, or other transfer of material for profit purposes and also research activities if they are for profit purposes.[20]

Examples of definitions of commercial uses/purposes

"COMMERCIAL USE: the use of the MATERIAL for the purpose of profit. COMMERCIAL USE shall include the sale, leasing, exchange, license, or other transfer of MATERIAL for profit purposes. COMMERCIAL USE shall also include uses of MATERIAL to establish service business activities, to manufacture products, to perform contract research, or to conduct research activities for profit purposes." (BCCM/LMG MTA)

"Commercial Purposes: Any sales of the product or services with the purpose of profit earning using the Material".

"Commercial use" means the use or exploitation of the genetic resources or genetic resource, with the object of, or resulting in, financial gain, and includes but is not limited to the following activities: sale, applying for, obtaining or transferring intellectual property rights or other tangible or intangible rights by sale or license or in any other manner, commencement of product development, conducting market research, and seeking pre-market approval."

Although some culture collections consider patents as commercial applications that are incompatible with their MTAs, other culture collections tolerate the filing of patents in their standard MTA for non commercial uses. One MTA even explicitly states that the recipient will be the owner of these patents and the owner of modifications and intellectual property contained in modifications.

"The RECIPIENT is free to file patent application(s) claiming inventions made by the RECIPIENT through the use of the MATERIAL but agrees to notify BIOTEC upon filing a patent application claiming modification(s) or method(s) of manufacture or use(s) of the MATERIAL. The RECIPIENT agrees to acknowledge BIOTEC as the source of the

[19] Accessible on http://bccm.belspo.be/projects/mosaicc/docs/code.pdf.

[20] For the definition of commercial use vid also MOSAICC 2009: 8.

MATERIAL and data in any and all publications and patent applications based on or relating to the MATERIAL, replica, or derivatives thereof and any research thereon."

"Recipient has right to draw up patents for inventions made by Recipient using Material or its Modifications. Recipient will be the owner of these patents.

Recipient is the owner of Modifications and intellectual property contained in Modifications."

On the contrary, another MTA explicitly states that the user may not seek intellectual property rights and protection under patent law.

When MTAs refer to future negotiations on commercial use, they also state potential obligations on benefit-sharing in accordance with specific national ABS laws. Most of them contain clauses requiring recipients to go back and negotiate new terms when the recipient is moving into a commercialization mode. That is the potential commercial user has to contact the cultural collection, which has the original depositor's contact details. In most cases, contracts for commercial uses are directly agreed between the depositor and the end-user. None of them have clauses such as in the International Treaty on Plant Genetic Resources (ITPGRFA) which establish, in advance, royalty percentages, which may become higher under certain conditions. Benefit-sharing is agreed *ex post* through bilateral negotiations. Moreover, MTAs do not require any reporting obligations, except those dealing with commercial uses or patents filing (cf. supra).

Culture collections are usually not mentioned as a beneficiary of the benefit-sharing clauses. The only benefit-sharing clauses included in the analyzed MTAs, which included the culture collection as a recipient of the benefits, concerns the acknowledgment of the culture collection in publications or in patent applications. However, benefit-sharing measures may be included in specific contracts dealing with commercial uses or collaborative research projects.[21]

21 For an example of a public-private agreement for the benefit-sharing related to the use of MGR see: Case Study 2. The Kenya Wildlife Service (KWS), The International Centre for Insect Physiology and Ecology (ICIPE), and Novozymes and Diversa (Verenium) Corporation: Agreements in the Industrial Biotech Sector; in https://www.cbd.int/meetings/wgabs-06/documents.shtml.

Another legendary commercial ABS case in the sector of microbes, was the Yellowstone-Diverse Cooperative Research and Development Agreement (CDRA), signed in 1997. The agreement, challenged before the courts, was finally sanctioned (Edmonds Institute et al., v. Babbitt: US District Court for the District of Columbia: Memorandum opinion, 1999 and Order and Final Judgement', 2000). It may be considered a fundamental example of the benefit-sharing experience for the US national parks. According to the National Park Service (NPS) general conditions for scientific research and collecting permit (on https://science.nature.nps.gov/research/ac/ResearchIndex) collected specimens are federal property. The NPS does not convey ownership of biological specimens collected on National park system. The reasons are explained in the following terms: "NPS biological specimens have ongoing and increasing public benefit and value for park resource management, science, and education. The NPS has authority to control, possess, and manage these collections, which are federal property. As long as these collections conform to NPS mission and policy, we have no desire or authority to convey them to other entities. While we do not convey specimens, we do encourage their use, including through long-term repository loans". (See: https://science.nature.nps.gov/research/ac/html/CollectionFAQ) The conditions also state that specimens collected and research results derived from collected specimens are to be used for scientific or educational purposes only, and may not be used for commercial or other revenue-generating purposes unless the permittee has entered into a CRADA or other approved benefit-sharing agreement with the NPS.

In accordance with this policy, ATCC holds the National Park Service special collection where microorganisms isolated from national parks in the United States are deposited and from where they are made available under specific accession forms and MTAs for this collection. The forms may be accessed on http://www.atcc.org/Portals/1/Pdf/DepositForms/NPS_Bact_Deposit_Form.pdf and

http://www.lgcstandards-atcc.org/Portals/5/LgcPromochemOffices/NPS_MTA.pdf.

"The RECIPIENT agrees, in advance of such use, to negotiate in good faith with the intellectual property rights owner(s) to establish the terms of a commercial license; taking also into account specific national laws regarding article 15.7 of the Convention on

Biological Diversity as to conditions concerning benefit-sharing.."

2.3.1.3. Ownership

One of the most controversial issues on the questionnaire was the one related to the ownership of the material deposited in the public deposits of the culture collections. It should be noted that far from the affirmative assertion on ownership ATCC analyzed above (cf. supra), the culture collections interviewed have shown a much more complex perception of the ownership of the MGR deposited in their premises. Thus, while two collections affirmed that their institutions were the owners of the material, three collections considered that the owner was the country where the culture collection is hosted, and two other collections indicated that it was the country were the material was collected. Very different, two culture collections participating in the study considered the material as international common goods owned by all human-kind.

Other culture collections of the 16 collections that were interviewed indicated multiple ownership: one collection, for example, considered that the owners of the material are the country where the material was collected, the scientist who isolated the material and the depositor. Other culture collections considered that no-one is the owner of the material but that a bundle of rights exist in relation to the country where the material was collected, the institution where the material was collected, the institution where the material was isolated, the culture collection where the material is deposited and the depositor. In a similar way, two culture collections answered this question in a negative way: clearly neither the depositor nor the recipients nor the host institutions have any right of ownership on the material. The remaining four collections of our sample did not express any opinion on this issue.

Culture collections have also been questioned about what would happen if the culture collection stops to exist: Two collections responded that there is no clear response to this question, while three other collections considered that the material would remain subject to the host institution control (in both cases a university), and six collections stated that the culture collection and its material would remain subject to their country's national government and that the material must be transferred to another culture collection in the countries. Two collections considered that the material should be transferred to another collection anywhere in the world. The remaining three collections of our sample did not express any opinion on this issue.

2.3.1.4. Practical problems for deposit/distribution of MGR. In particular the CBD

Culture collections have also been asked about the difficulty or problems they face for the deposit/distribution of material. Generally speaking, they have not indicated serious concerns in relation to intellectual property rights. Only one collection warned about the possibility of patenting a type strain. Another collection reported on the fact that when a patent is taken on a new process or method related to a strain of the public collection, the patent applicant often requests that the

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So, for example, in the corresponding MTA the recipient recognises that the material is property of the US Government. For more information on the Yellowtone-Diverse CDRA and in general on the National Park Service experience, see Kerry et al. 1998, and Scott 2004: 177-199.

material is taken out of the public domain. However, once the material is in the public domain, it is no longer possible to patent the material. Finally, one collection was aware of the fact that users were filing patents in relation to their strains without informing the collection, even if this was not in accordance with its MTA. As indicated above, MTAs do not normally include reporting or monitoring obligations. They only require the user who wishes to make a commercial use of the strain to contact the culture collection. However, one culture collection confirmed that they were aware of commercial applications developed from the strains they have distributed, and had not received any information about this from any of the recipients. Some of the culture collections noted that they do not have the technical means to verify if final users are complying with the conditions provided for in the MTAs. Unfortunately, no information has been requested as concerns the reporting obligations for commercial or research agreements negotiated on an individual basis.

A more contentious issue is the one dealing with the Convention on Biological Diversity (CBD). During the last few years, most of the collections have started to take into account the requirements of the CBD in their deposit forms. The policy it is quite similar in all the culture collections. All of them ask about the country of origin, being a mandatory field in almost all cases. Although one curator considered this information as very relevant for scientific purposes, another one has criticized the scientific basis to determine what the (scientific) origin of the strain is. As stated by DSMZ, the CBD was mainly formulated with animals and plants in mind. It does not fully appreciate the complicated issues relating to microorganisms and their dissemination.[22] Information on PIC is also required in most of the deposit forms. Nevertheless, this field is not considered mandatory by the culture collections interviewed and, in fact, it is quite uncommon to get the information on it from depositors. For example, two big culture collections have confirmed that since 1993, they have received this information only on two occasions. In only one case (amongst the culture collections interviewed) the culture collection rejected accepting a strain because prior informed consent-was not obtained conform with the CBD.

2.3.1.5. Trends

Ten of the 16 interviewed culture collections confirmed that currently, distribution of strains is more complicated than in the past, mainly because new rules and regulations require a lot of administrative work, especially when dealing with distribution of strains to third-party countries. A minority of the respondents considered that there is some reluctance on the part of researchers to deposit strains since they think they may have economic value.

Most of the culture collections expressed that it would be a good step forward to facilitate the exchange of MGR by reaching agreement on a global common policy for the distribution/deposit of the material, so that material is deposited/distributed under the same conditions/restrictions all around the world.

2.3.2. Impact of access and benefit sharing legislation

Materials that are deposited in the culture collections, with the exception of the ATCC and some private industry collections, are collected under the presumption that they will remain accessible for further distribution under the relatively non-restrictive license conditions surveyed in the previous section. However, in a system entirely based on self-regulation (as it is the case for the MTAs surveyed above), every party can decide at any moment to opt out of the system of relatively non-restrictive license conditions and seek private rents or advantages for their organization by doing so. Indeed, under the principle of national sovereignty, every host country has the authority to decide

22 http://www.dsmz.de/dsmz/main.php?contentleft_id=40.

upon the ownership status of the *ex situ* and *in situ* resources within its national boundaries[23]. An example of such "opting out" that was reported in the surveys at the basis of this report are the introduction of restrictions by ATCC on the use of its materials, without any prior informed consent of the depositors and even if these materials are originally collected in other developed and developing countries. Another often cited example is the difficulty to collect new materials from Brazil, due to the restrictions introduced by its national ABS legislation.

The adoption, on the international level, of a set of legally binding rules to govern the transactions with microbial resources would potentially alleviate some of these problems with the legal uncertainty and lack of standardization that characterizes the system of self-regulation. On the basis of the discussions in this chapter, major contributions for addressing these problems can be expected from measures which:

- provide for a standardized solution to the benefit-sharing with the original providers of the strains to culture collections, instead of the current solutions based on case by case negotiations or *ex post* arrangements;
- provide for a clarification of the rights of the recipients of strains from culture collections, by introducing legal obligations and rules for the use of deposit forms[24] (as many deposits are made by scientists from outside the culture collections, and even from other countries to comply with the obligation to deposit type bacterial strains in two collections in two different countries);
- support further standardization of the license conditions used in the various MTAs both for commercial and non-commercial research purposes.

Moreover, in the absence of a mutually agreed set of rules, countries might unilaterally adopt a set of rules in the context of their national ABS legislations that would have negative consequences for the self-regulatory arrangements. In particular, ABS rules that put restrictions on access to type strains and reference strains might have dramatic consequences for both developing and developed countries. Access to these strains is crucial for certain industry sectors that rely on these strains and is a key component of the basic scientific research infrastructure both in the public and private sectors. Another major negative consequence could be to put undue legal restrictions on the legitimate or legal exchange clauses for exchange of strains between culture collections, such as the one adopted by the BIOTEC collection in Thailand or the ECCO standard agreement.

Most of the issues to be addressed in developing a mutually agreed set of rules for the distribution of microbial strains are of a high technical nature. They imply an in depth knowledge both of the legal issues involved, of the realities of the various stakeholders in developing and developed countries, and of the way that scientific research and innovation in microbiology contributes both to economic development and to deeper understanding of biological processes. Therefore, further progress is only to be expected through intense collaboration on the international level between all the parties involved.

3. Effects of legal or technological restrictions on use and exchange of MGR

At present, culture collections are facing a set of important challenges, which may hamper some of the most promising new scientific opportunities made possible by current advances in screening and in increasing availability of full genome sequencing of entire microorganisms.

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[23] For the general principle, see Universal Declaration of State Sovereignty over Natural Resources (1967). See also General Assembly resolution 1803 (XVII) of 14 December 1962, "Permanent sovereignty over natural resources."

[24] Cf. for the impact of deposit forms on possible restriction for use the discussion in chapter 2, section 2.3.

The most important obstacle is the quality management of the culture collections' holdings and the associated costs. DSMZ (German Collection of Microorganisms and Cell Cultures) estimates that approximately 20% of all cell lines used in tumour research are misidentified, and literally thousands of studies based on faulty cell lines have been published. This problem is not as acute for all types of microbial materials. Thanks to the efforts to develop systematic tests for cell culture identification and certified standard reference strains at the collections, microbiologists have been able to limit their exposure to contamination. As a consequence, the costs of culturing these strictly quality-managed research strains is quite high. High estimates by two major culture collections for adding a bacterial culture to a collection and conserving it at least 20 years range from US $2,500 to US $10,000 depending on the type of material (OECD 2001). For most strains that do not require special treatment however, the average cost in large culture collections is far less, estimated around US $ 250 - 300 (WFCC representative, personal communication, 27 March 2009). These are rough estimates that significantly vary from one collection to another. They are far below the losses that can be incurred by investments in follow-on research on faulty research findings, as was the case of 10 years of follow-on research on contaminated cell lines in the so-called HeLa scandal in the 1950s (Stern 2004: 12-13). Therefore, the socio-economic benefits of the investment in culture collections are substantial.

A second major impediment to exchange is related to biosecurity issues. An important characteristic of some microorganisms, which makes working with them more complicated, is their potential to harm humans, animals, plants or to impact other aspects of the environment. According to the potential risks associated, they are classified into risk groups and/or governed by quarantine, sanitary, import and export regulations. Risk Group (RG) 1 characterizes the organisms with no harmful potential, risk group 2 with only minor harmful potential, while risk group 3 and 4 present higher levels of risk. For bacteria and fungi the largest percentages are covered by those organisms with no or only minor harmful potential. In the EU, only around 1% and less than 0.01% are allocated to the pathogenic group RG3 and RG4, 80% of bacteria and 99% of fungi are in RG1, and approximately 19% of bacteria and less than 1% of fungi are in RG2.

A set of various other impediments have been mentioned by culture collection mangers and microbial scientists, but no strong evidence exists for other impediments that are faced systematically by many collections. We will discuss some of these impediments in more detail in chapter IV.

4. Conclusions

Exchanges of AMGR have historically occurred in an informal way between culture collections, laboratories and researchers worldwide. These informal exchanges have facilitated research activities, and, as a consequence, science and exploitation of microbial resources have rapidly advanced. During the last decades of the twentieth century, the increasing economic importance of biotechnology and the introduction of new legislation concerning the use and access to natural resources have subjected exchanges of genetic resources to greater controls. Their access and distribution are submitted to many requirements and, therefore, exchanges are becoming more and more formalized. There is however, no evidence that the formalization as such is leading to more restrictive license conditions, even if formalization might lead some collections to depart from the sharing ethos as illustrated in this chapter and introduces an important administrative burden.

Most of the culture collections have accession or deposit forms for public deposit to be used by depositor and recipients, no matter where they are located in the world. The "accession form" is the very first document attached to strains entering a collection. Appropriate use of this form will facilitate management of the microorganisms throughout its *ex situ* lifespan.

Most of the culture collections have an MTA for distribution of strains, or have indicated the intention to draft an MTA in the near future. MTAs are used for worldwide distribution of strains, although in some cases specific permission is required to send the material abroad. As a general rule, MTAs do not allow the redistribution of the materials to third-parties, but, with the exception of the MTA of ATCC, most of the analyzed MTAs allow, under certain conditions, redistribution of material by culture collections or within the research group. This has been observed both in the developing and developed country WFCC collections. MTAs refer to this possibility as a legal or legitimate exchange.

Due to the global interdependence on microbial genetic resources, which was clearly established in the second chapter of this report, a global approach to the access, distribution and use of microbial genetic resources is needed. This is supported by the opinion of most of the culture collections interviewed in this study. However, the current approach of the collections is based on self-regulation, which leads to the lack of legal certainty and the lack of standardisation discussed extensively in this chapter. The adoption, on the international level, of a set of legally binding rules to govern the transactions with microbial resources and supporting measures for further standardization could potentially alleviate some of these problems

In particular, more work should be done in relation to the commercial use of AMGR, both in public sector and private sector organisations. While the transfer of materials for research purposes has been standardized to a certain degree, thanks to the initiatives of culture collections and existing networks, the conditions for the transfer of material for commercial purposes are decided on a case-by-case basis, which entails a high-level of transaction costs, and no overall solution has been negotiated for dealing with ABS obligations.

CHAPTER IV: STAKEHOLDERS' VIEWS

1. Perceptions, awareness of users and providers of ABS in general

As stated in the previous chapter, culture collections are increasingly taking steps to build a coordinated MTA policy. This policy is highly relevant for dealing with the high-level of interdependency between countries for access to microbial genetic resources for food and agriculture highlighted in this report. This last chapter briefly focuses on these initiatives and the perceptions on ABS issues that drive the actors involved in them.

This section will report on the perceptions of the culture collections' scientists and managers on ABS issues and on its impact on distribution and exchange of microbial genetic resources. It is based on a short email survey that was addressed to the culture collections which are member of the WFCC. Its aim was to identify the main obstacles to the depositing and distribution of strains and to gather information about the understanding and perception of ABS issues. A first set of questions concerned the list of obstacles (ABS related, technical or cost obstacles) perceived by the culture collections, their knowledge of obstacles perceived by clients and the resulting trends that they perceive in number of deposits and distribution of strains (questions 1 to 3). The second set of questions was related to the degree of formalization of the current exchange system, the usefulness of a documentation system and the presence and understanding of ABS rated rules (questions 4 to 6). Forty-three out of the 238 collections contacted by email fully completed the questionnaire, 20 from Europe, 6 from North America, 6 from South America, 5 from Asia, 5 from Australia and 1 from Africa (for a complete list of the culture collections, cf. Annex 3 to this report. This email survey was complemented by 16 telephone interviews on relations with users and providers of resources, 9 of them belonging to culture collections and 7 to pure research collections (cf. annex 4 to this report). The telephone interviews gave some more precise indications on the relation of culture collections with the providers and the users concerning ABS issues. The results of the email surveys are summarized under (a) to (d), and the results of the telephone interviews are summarized under (e) to (g).

(a) Sources of MGR: The profile of the culture collections that answered the email survey is quite similar to the more general profile of culture collections obtained in a previous survey of 119 collections (cf. figure 1 chapter II above). Most microorganisms are sourced by researcher collecting and by acquiring strains at research collections from universities. The second source, though less important, are strains from other culture collections and from industry.

(b) Obstacles to exchange and resulting trends: A wide variety of obstacles to exchange were mentioned in the survey. The main general obstacles to exchange are too strict (or even absurd) biosecurity regulation and restrictions on use, imposed by or upon the depositor (17 and 16 out of 42 answers respectively).

The specific obstacles related to technical issues were in the majority related to shipment (technical shipment, quarantine, regulation of receiving country) (19 out of 36 answers). Obstacles related to costs and awareness are much less prominent. Some collections do not perceive major cost or are aware of obstacles (respectively 13 out of 40 and 26 out of 37), while others id mentioned a specific set of costs and awareness as obstacles without a clear dominant pattern. No clear results were obtained in relation to the costs that clients perceive.

Perceived obstacles do not seem to result in a decrease in the number of exchanges. About half of the respondents saw an increase in the number of exchanges of MGR as a trend, while a little less

than half of the respondents regard the trend as stable, and only a few see a decrease in the exchange of MGR in future.

(c) Formal character of the exchanges of MGR: In half of the culture collections, the majority of exchange is formal, that is based on written agreements (more than 80% formal exchanges, 20 out of the 38 answers). Approximately 25%, were only involved in informal exchanges (without written forms, less than 5% formal exchange, 9 out of the 38 answers), while the remaining 25% were situated in between. It is important to note that there is no correlation between the formal/informal character of exchange and the fact that the collection is situated in an OECD country or a non-OECD country. The same proportion of formal/ informal is found both in the OECD sub-group and the non-OECD sub-group of the sample. This confirms the high degree of heterogeneity of the culture collections, where a substantial amount of collections move in the direction of ABS compliant systems of accession and distribution with formal MTAs, while others are still in a process of transition from operation as a research collection with informal processes of exchange, to a fully developed culture collection that is integrated in the international environment.

On the question of the usefulness of formal documentation, no clear results were obtained. Most elements of documentation were indicated as being useful by one or another collection, and no single set of criteria is clearly indicated as the most important.

(d) Rules of access and benefit-sharing: The results on the presence and knowledge of ABS rules on the part of the respondents also reflect the heterogeneity in the formal/informal character of the exchanges. Half of the collections have ABS rules in the institutions (21 out of 43 respondents), while the others don't know about ABS or don't have any rules. The level of understanding of ABS reported by the respondents is estimated as average or very poor in general: only 6 out of 31 respondent organizations considered they have a 'very good' understanding of ABS rules and regulation; 2 out of 21 respondents stated the knowledge on ABS was very poor in their country in general; and only 3 out of 38 indicated their knowledge of ABS was very good or good with the clients of the culture collections. There is thus, substantial room for improvement in understanding of ABS rules both within and outside the culture collections.

In general, the culture collections do not perceive many ABS-related obstacles to exchange, both for those who already implement a formal set of rules that aim to take into account the ABS provisions, and those who are still involved in informal exchanges. However, even for those who are moving in the direction of an ABS compliant system, the level of understanding of ABS is evaluated to be very poor or average in many of the cases.

(e) Relations with providers: In all the cases, the culture collections explicitly mentioned that no permit for depositing in the collections was required when collecting in their own country, which is where the majority of their collecting is undertaken. No collections mentioned specific obstacles with ABS issues when collecting in other countries, except for one case that was experienced in one collection (but for that collection it was an exceptional situation). This is also confirmed by the presentations on AMGR made during the workshops, where ABS related obstacles with collecting strains were clearly mentioned in some specific cases, for exchange with countries with strict ABS regulations.

(f) Relations with commercial clients: Most culture collections mentioned problems with ABS in relation to the commercial clients of the culture collection. It was clearly stated by most collections that commercial clients do see benefit-sharing as a serious obstacle to acquiring strains at a collection. In some countries, it was mentioned that companies go elsewhere in order to avoid these issues, in other cases the culture collections were able to impose formal agreements, which include

benefit-sharing obligations on the commercial partners in spite of their reluctance. One collection mentioned problems of monitoring the downstream use of strains by private companies that are acquired in the context of a formal benefit-sharing agreement.

(g) The situation of the research collections: The case of the research collections is quite different. The respondents clearly stated that here exchanges are clearly restricted to non-commercial research purposes and to use in the recipients laboratory only. The provision of strains is done in the frame of research collaboration. When the collection is done in the home country, in nearly all the cases no permission is required (only one exception). When collecting is done in other countries, permission for collecting is presumed to be obtained from the partner organisation in the provider country. Mostly, exchange to other parties is entirely informal. In one case, a formal letter was explicitly signed, stating that the strains should be used for scientific purposes only. Knowledge of ABS is overall very poor; if not entirely absent on the part of scientist managing research collections.

2. Initiatives of key players

Culture collections at the national and regional levels have long played a crucial role in conserving MGR and facilitating access to, and distribution of such materials for research and development. In addition to serving as a conduit among providers, users, regulatory bodies, and policymakers, culture collections also add value to the deposited biological material (and thus to the corresponding research initiatives) by means of the internal services they provide.

Consistent with this view of their role, the culture collections have been developing common rules and principles to govern their services from accession of biological material to its authentication, preservation and maintenance, through to its ultimate release to the scientific community (Fritze 2008). Within their global federation (the World Federation for Culture Collections, WFCC), and regional entities, such as the European Culture Collections' Organization (ECCO), have sought to devise harmonizing guidelines that would help to standardize procedures and provide a framework for compliance with the CBD and with growing legislation concerning biosafety and security.

One important milestone was the 1996 WFCC Information Document, which specified "special characteristics of microorganisms that distinguish them from plants and animals" and the consequences of such characteristics for inventorying, tracking and benefit-sharing (Fritze 2008). This document also recommended "that access to *ex situ* microbial genetic resources should remain unimpeded for the purposes of scientific research, industrial application, education and health care" (Fritze 2008). A voluntary code of conduct was also being drafted to introduce access and benefit-sharing procedures (Fritze 2008). More recently, the project known as Micro-organism Sustainable Use and Access Regulation International Code of Conduct Micro-organisms Sustainable Use and Access Regulation International Code of Conduct (MOSAICC)[25] focused attention on the need for Model Material Acquisition Agreements and Model Transfer Agreements for the use of culture collections, as well as research scientists in their roles as depositors or recipients of microbial strains.

MOSAICC presents a very remarkable step forward concerning the access and distribution of MGR and the Convention of Biological Diversity. This code of conduct was developed by the Belgian Coordinated Collections of Microorganisms (BCCM) in 1997, with the support of the European Commission, and the involvement of twelve partners from various sectors in both developed and developing countries. Its main purpose is to facilitate access to microbial genetic resources (MGR)

[25] Accesible on http://bccm.belspo.be/projects/mosaicc/docs/code.pdf.

and to make possible the identification of the individuals or groups that are entitled to be scientifically or financially rewarded for their contribution to the conservation and sustainable use of the MGR, so to conclude of benefit-sharing agreements.

MOSAICC proposes a system that works through two key elements: the Prior Informed Consent (PIC) and the Material Transfer Agreement (MTA). Thus, it provides microbiologists with some guidelines to obtain and comply with the information concerning the PIC[26] and to establish MTAs for access to and transfer of MGR, access to and transfer of technology, fair and equitable sharing of benefits as well as for technical and scientific co-operation. It also aims to assist authorities of countries providing MGR by suggesting procedures to issue PIC for access to MGR and to monitor the transfer of such MGR, to enable fair and equitable sharing of the possible benefits arising from their utilisation.

It should be said that MOSAICC has inspired some MTAs already in use. Concepts such as the legal/legitimate exchange used in some of the MTAs analysed in the survey (see infra section 2.4.3) have their roots in this important initiative.[27] An example of this is the European Culture Collections' Organization (ECCO) draft MTA. After some years of discussion, ECCO agreed on the core contents for an MTA to be used for the supply of strains from culture collections. The still draft MTA contains common definitions and procedures, including for the implementation of a system of legitimate exchange. It contains specific clauses dealing with the purpose of the use (mainly focus on research activities), intellectual property rights, liability, safety and security. The main purpose of the agreement is to facilitate exchange of biological materials among culture collections. Unfortunately, the final text has not been adopted yet.[28]

Very importantly, for the purposes of this study, MOSAICC considers that designing a model MTA for the members of the World Federation for Culture Collections (WFCC) would be a significant sector-based ABS approach for the culture collections community across the world, facilitating exchanges although its members operate in different legal systems. It even suggests the need for establishing common rules of access to MGR, complementary to national regulations on ABS and existing IPR laws that would govern a "microbial commons" demarcated space (MOSAICC 2009: 7).

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[26] See MOSAICC 2009: 3-4.

[27] It is worth to say that MOSAICC does not use the term "legitimate exchange" but it contains some provisions that refer to the a similar idea. So, the Code of Conduct (MOSAICC 2000: 9-10) recommends to distinguish between two types of material transfer:

- I. Transfer where further distribution is excluded (MTA excluding distribution to 3rd parties);

- II. Transfer where further distribution is allowed (MTA allowing distribution to 3rd parties);

The choice between these two types of transfer will be determined by the capacity of the users as well as of the suppliers for keeping records of the individuals or institutions from where or where to they transfer MGR.

I. When they choose a MTA excluding distribution to 3rd parties, provider and recipient agree that the recipient cannot distribute the MGR to anybody outside his/her institution. A MTA excluding distribution to 3rd parties stops the further distribution of the MGR along a chain of contacts. From the provider's side, the monitoring of the distribution of the MGR is limited to the registration of one recipient. In cases where scientists other than the original recipient would like to acquire a strain of the same MGR, they can apply to the original provider. Provisioning of strains from the original source also guarantees the quality of the MGR. This option is recommended for transfers between individuals or institutions who's primary mission is not the *ex situ* conservation and valorisation of MGR. The MTA excluding distribution to 3rd parties will also be used in case of fast-track procedure.

II. MTA allowing distribution to 3rd parties is in use when MGR are transferred to a recipient that is a culture collection or when both recipient and provider are culture collections. The terms of the transfer will be consistent with the best practices of culture collections and set in the framework of collaborative agreements, when such agreements exist.

[28] For more information see: Fritze 2008 .

This position has also been supported by the Microbial Commons initiative. The latter initiative has encouraged through a set of international workshops the creation of a globally shared pool of microbial genetic resources and information, which would be subject to common terms and conditions for depositing, use and benefit-sharing, inspired in part by the multilateralism of the International Treaty[29].

3. Conclusions

In general, the culture collections do not perceive many ABS related obstacles to exchange. This was observed both for the culture collections which already implement a formal set of rules that aim to take into account the ABS provisions, and for those who are still involved in informal exchanges. However, for all the stakeholders involved in the global sharing and exchange regime, the level of understanding of ABS was poor or very poor in the majority of the cases. There is thus substantial room for improvement on the understanding of ABS rules both in culture collections, at university research collections and within private companies.

Most culture collections mentioned problems with ABS in relation to the commercial clients of the culture collection. It was clearly stated by most collections that commercial clients do see benefit-sharing as a serious obstacle to acquiring strains from a collection. However, the situation strongly varies from one collection to another. In some cases, it was mentioned that companies go elsewhere in order to avoid benefit-sharing issues, but in other cases the culture collections were able to agree upon formal agreements, which include benefit-sharing obligations with their commercial partners.

The case of the research collections situated at the universities or hosted by the culture collections is quite different. In these instances, most of the exchange to other parties is entirely informal, and is intended for non-commercial research purposes and for use only within the recipients' laboratory. In one case, a formal letter was explicitly signed stating that the strains should be used for scientific purposes only.

At present, most of the collections are responding to the new legal framework on access and benefit-sharing, with particular regard to formulating appropriate MTAs for the culture collections or by increasingly considering formal use of licenses for the university research collections. This process, in turn, raises important new questions. For example, the balance of private and public interests may be set differently by different institutions, and it is not clear to what extent any

[29] The first international meeting of the microbial commons initiative was held the 7th and 8th of July 2005 at the University Foundation in Brussels, Belgium. It was coordinated by the BIOGOV Research Unit of the Centre for Philosophy of Law at the Université catholique de Louvain and the Laboratory of Microbiology at Ghent University, and carried out under the Interuniversity Attraction Poles program financed by the Belgian Science Policy and the REFGOV integrated project of the 6th European Framework Program in Research and Development. The web-based proceedings of the workshop can be found at http://biogov.cpdr.ucl.ac.be/bioinf/. A selection of papers of this workshop has been published as a special issue in the International Social Science Journal (Dedeurwaerdere 2006). The second international meeting was held in Ghent the 12th and 13th of June 2008. This meeting was part of an international undertaking and collaboration between the Belgian Science Policy, Science Commons, StrainInfo.net, Genomics Standards Consortium, Bioversity International and the US national committees of CODATA, IUMS and IUBS and was focused on the building of an integrated infrastructure in microbial research dealing with issues such as bioinformatics, intellectual property rights, material transfer agreements, text mining and integration with genomics databases. The web-based proceedings of this second international meeting can be found at http://www.microbialcommons.ugent.be/. A selection of articles of this meeting will be published as a special issue in the International Journal of the Commons (Dedeurwaerdere 2009). A third international meeting will be organized 8th and 9th of October 2009 at the US National Academies Board by the Board on Research Data and Information. It will address topics such as models to lower the transaction costs and support access to and use of microbiological materials and digital resources from the perspective of publicly funded research, public-private interactions, and developing country concerns. It also will have at least two sub-theme breakout sessions focusing on research and applications in food and agriculture and on energy and environment, with the goal of stimulating more research and implementation of improved legal and institutional models for publicly funded research in microbiology.

uniform MTA will emerge or what its contents will be. It is this concern, indeed, that to a large degree prompted undertaking of this report. To the extent that an efficacious standard MTA harmonizes the servicing of culture collections across the globe, it lays the basis for a *de facto* commons for the global conduct of microbial research in the foreseeable future.

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ANNEX: EXAMPLES OF GLOBAL INTERDEPENDENCY IN ACCESS TO *IN SITU* AMGR

(a) Analyzing microbial biodiversity of pathogenic and beneficial microorganisms

Two examples from research on important plant pathogens maintained at the collection of the Plant Pathogen Centre in Rome highlight some of the features of the benefits of exchange of microorganisms in a situation of geographical interdependency (Barba 2009).

The first example concerns *Tilletia indica*. This fungus is an important plant pathogen which causes a cereal disease known as Karnal bunt (named after a district in India where the disease was first reported in 1931). It is a fungal disease of wheat which is economically very important. One percent of grain infection is considered to be enough to discard a commercial lot for human consumption. The disease has been first observed in Asia, but has now also been reported in various areas in Mexico, USA, Brazil and South Africa. The exchange and study of a wide variety of *Tilletia indica* is important for a number of reasons. First, availability of several strains of *Tilletia* spp. allows comparing morphological properties of spores produced by the fungus. Recognizing the spores is crucial, as the spores of the *Tilletia indica* can be confused with the spores of related *Tilletia* species which are not causing the Karnal bunt. Second, comparison of DNA extracted from different fungal species allows the use of molecular diagnosis tools to identify the *Tilletia indica*. Several tests and diagnostic tools are currently developed based on the DNA of a representative sub-set of strains of *Tilletia* from various countries.

The second example presented at the workshop concerns a virus, the plum pox virus. This virus causes an important disease of stone fruits such as plums. Fruits of infected plants cannot be commercialized. It was first observed on plum trees in Romania in 1943, but has spread since then to all continents: in 1986 it was observed in Egypt and Tunisia, in 1992 in Chile, in 1995 in Lithuania and it has now reached as far as China (2000) and Argentina (2004) (Barba 2009). Benefits from global exchange which are similar to the *Tilletia* case are the development of diagnostic and identification tools. Other benefits are the possibility to compare the virulence of strains from various geographical origins and hence to make a correct risk analysis assessment. Finally, some of the access to strains needs also to be purely local. Indeed, isolation and identification of pathogenic strains of the plum pox virus in the area where the crop is cultivated may provide better guarantees for success in breeding for resistance.

Other cases of microbial biodiversity research have been presented at the workshops which provide information on the research cycle that leads to identification and diagnostic protocols. In general, the development of protocols requires access to a large number of *in situ* microorganisms, often from various species, and a limited set of *ex situ* strains obtained from culture collections as control strains. Finally, only one or a few strains are selected for conservation in the culture collections and some strains are temporarily conserved in research collections for follow-on research. For example, in the case of a collaborative research project on wine grape contamination by *Aspergillus niger*, 99 strains from 107 vineyards throughout Europe were collected and submitted for analysis (Perrone *et al.* 2008, Lima 2009). From these strains, around 11,000 fungal strains were isolated from 39 different genera. From these strains, 56 that belong to the new non-toxic *Aspergillus* species *Aspergillus uvarum* were selected for in-depth analysis and compared to 28 reference strains ordered at existing culture collections. Finally, a type strain from this species was selected and deposited at 4 different culture collections. The remaining strains of the 56 are kept in two research collections, hosted respectively in Italy by the Institute of Sciences of Food Production and in the UK by CABI Bioscience Genetic Resource Collection.

The bulk of strains used in the early stages of research (such as the 56 strains in the case of *Aspergillus niger*) are kept in the research collection for future reference. They are not preserved under the same strict quality management procedures as in the culture collections, but are distributed upon request to other scientists for replication of the research findings or follow-on research. Information on these strains is available through personal networking at international conferences, and through the research collection numbers that are mentioned in the publications on these species.

(b) (b) Accessing microbial biodiversity for screening for interesting strains

Some cases that were presented at the workshop where screening for interesting strains are relevant on a broad geographical scale (Giraffa 2009, Azizmohseni 2009). This is the case of microorganisms able to grow in a wide variety of environments, such as certain biocontrol agents used in agriculture. Another important case is *Lactobacillus plantarum* which is used as a silage inoculant, in food fermentation in the dairy and olive industry, and, more recently, as a probiotic and as a vehicle for therapeutic compounds in the gastro-intestinal tract. Some of these strains can be accessed through the culture collections, when screening projects already have led to published research results. However, these are only a tiny fraction of the relevant biodiversity. Access to large amounts of *in situ* microorganisms is needed as a source of biodiversity to find new interesting strains, and to provide a solid platform for basic studies (such as collaborative projects in comparative genomics, screening platforms etc.) and applications. These are collected in the research collections of the laboratories that perform the identification and do the screening of the sub-set of strains that belong to the target species to be studied. The exchange of strains between these research collections is mainly organized through inter-laboratory agreements and within the frame of international cooperation. In the absence of cooperative agreements, which are based on mutual benefit and reciprocity between the researchers, few strains are shared amongst researchers and competition amongst researchers is very high. Also, in one case reported at the workshop from Iran, sharing of strains for developing a biocontrol agent against alfatoxin producers, based on research results of strains in Africa, was made impossible because of the difficulty to obtain import permits in the current international context (Azizmohseni 2009).

The analysis of a specific research project, the screening of *Lactobacillus plantarum* in food biotechnology (Giraffa 2009) allows comparison with the amount of strains available in the culture collections and in research collections. *Lactobacillus plantarum* has a long history of safe use and can persist in a wide variety of ecological niches. The largest culture collection holdings are around 30 strains for each specialized culture collection (for the BCCM-LMG collection in Belgium (36), the Institut Pasteur in France (29) and the Moroccan Coordinated Collection of Microorganisms (36) (data from www.straininfo.net, accessed 26th May 2009). These are already well characterized strains, deposited upon completion of international research projects from all over the world (for example in the case of BCCM strains coming from Yugoslavia, Italy, Belgium, Nigeria, Congo, Egypt, Malaysia) and distributed through the formal material transfer agreement (MTA) mechanism (cf. supra ch. III, section 2.4). Both the number of strains and the organizations involved is in sharp contrast to the situation in the research collections, which are holding the bulk of strains prior to characterization and publication of research results. For instance in Italy alone, the collections of the Agriculture Research Council (CRA) hold approximately 300 identified strains of *Lactobacillus plantarum* to be characterized (in the CRA-FLC) and 50 strains from dairy, olive and wine fermentations (in the CRA-cluster collection). Other Italian research institutions hold approximately 300-400 strains to be characterized. Currently, efforts are underway to pool these resources and to benefit from economies of scale in investing in research equipment for screening.

Similar efforts for coordination and formal cooperation on *Lactobacillus plantarum* are also developed on the international level. One example brought up at the workshop is the collaboration between the university of Nairobi in Kenya, the Jomo Kenyatta University of Agriculture also in Kenya, and the Technology and the Federal research centre for Nutrition and Foods in Germany (formerly BfEL, now the Max Rubner Institute). In this project, 130 strains from Masai fermented milk have been screened for probiotic properties. The aim of this international collaboration is to provide technical assistance for selecting microbial strains with functional properties for standardized production and for improvement of quality and safety of existing traditional fermented food products in Kenya (Mathara *et al.* 2004, Holzapfel 2002). This project was partly based on the 2002 FAO-WHO guidelines for the evaluation of probiotics in food (FAO-WHO 2002). Based on the special equipment that was available in the German laboratory, it has been shown that a number of *Lactobacillus plantarum* strains from the Masai traditionally fermented milk showed probiotic potential (Mathara *et al.* 2008). These strains are good candidates for multifunctional starter cultures. The research results of this collaboration have been published as a co-authored publication of the Kenyan Laboratories and the German laboratory (*Ibid.*), and the 130 strains that have been used in the research are conserved at the Max Rubner research collection. Through the joint publication, the research results remain available in the public domain for further follow-on research and development of standardized starter cultures in the Kenyan dairy industry. No information was available at the workshops with respect to the conditions under which the strains were collected from the Masai by the Kenyan and German research institutions.

(c) Accessing endemic microorganism

An example of interdependency in accessing endemic microorganisms presented and discussed in-depth at the expert workshop concerns a collection of microorganisms form extremely cold environments at the Culture Collection of Cryophilic Algae (CCCryo) in Potsdam, Germany (Leya 2009) and microorganisms collected through bioprospecting missions in Antarctica (cf. www.bioprospector.org). In general, the cryophilic microorganisms collected in these environments show high potential commercial value. They are used in various sectors of biotechnology, because of their capacity to produce enzymes under unusual cold circumstances, but are also widely used as food and feed supplements. Examples from bioprospecting in Antarctica in the case of food and agriculture are microorganisms producing anti-freeze proteins in ice cream, such as *Pseudomonas synxanthas*, or plant promoters that express themselves at very low temperature, such as *Deschampsia antartica.*

The cryophilic algae collected by CCCryo can only grow under certain conditions of temperature and mainly originate from expeditions to the Arctic (Spitsbergen) and Antarctic (King-George-Island) performed by the host institution of the Culture Collection (the Fraunhofer Institute for Biomedical Engineering). Furthermore algal strains are being cultured, which were collected in various alpine regions of our earth, such as the European and New Zealand Alps, the Rocky Mountains or the High Tatra Mountains. In the case of the expedition to Spitsbergen, Norway, the collecting was done in a protected area and did require a special collecting permit. The collector had to specify in advance the objective of the mission, the number of strains that would be taken and where they could be accessed upon deposit. Similar permits were required for biocollecting in Antarctica. What is interesting in these cases is that full tracking of the source of each microorganism has been successfully organized, and prior informed consent requested and given (by the Norwegian government or the party to the Antarctic Treaty organizing the collecting respectively) to collect and deposit the organisms in both public and private culture collections.

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