Code of Conduct on Biosecurity for Biological Resource Centres: procedural implementation

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A globally applicable code of conduct specifically dedicated to biosecurity has been developed together with guidance for its procedural implementation. This is to address the regulations governing potential dual-use of biological materials, associated information and technologies, and reduce the potential for their malicious use. Scientists researching and exchanging micro-organisms have a responsibility to prevent misuse of the inherently dangerous ones, that is, those possessing characters such as pathogenicity or toxin production. The code of conduct presented here is based on best practice principles for scientists and their institutions working with biological resources with a specific focus on micro-organisms. It aims to raise awareness of regulatory needs and to protect researchers, their facilities and stakeholders. It reflects global activities in this area in response to legislation such as that in the USA, the PATRIOT Act of 2001, Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001; the Anti-Terrorism Crime and Security Act 2001 and subsequent amendments in the UK; the EU Dual-Use Regulation; and the recommendations of the Organization for Economic Co-operation and Development (OECD), under their Biological Resource Centre (BRC) Initiative at the beginning of the millennium (OECD, 2001). Two project consortia with international partners came together with experts in the field to draw up a Code of Conduct on Biosecurity for BRCs to ensure that culture collections and microbiologists in general worked in a way that met the requirements of such legislation. A BRC is the modern day culture collection that adds value to its holdings and implements common best practice in the collection and supply of strains for research and development. This code of conduct specifically addresses the work of public service culture collections and describes the issues of importance and the controls or practices that should be in place. However, these best practices are equally applicable to all other microbiology laboratories holding, using and sharing microbial resources. The code was introduced to the Seventh Review Conference to the Biological and Toxin Weapons Convention (BTWC), United Nations, Geneva, 2011; the delegates to the States' parties recommended that this code of conduct be broadly applied in the life sciences and disseminated amongst microbiologists, hence the publishing of it here along with practical implementation guidance. This paper considers the regulatory and working environment for microbiology, defines responsibilities and provides practical advice on the implementation of best practice in handling the organism itself, associated data and technical know-how.

Abbreviations: BRC, biological resource centre; BTWC, Biological and Toxin Weapons Convention; CBRN, chemical, biological, radiological and nuclear; EMbaRC, European Consortium of Microbial Resource centres; GBRCN, Global Biological Resource Centres Network; GMO, genetically modified organism; IUMS, International Union of Microbiological Societies; NGO, non-governmental organization; OECD, Organization for Economic Co-operation and Development; VBM, valuable biological materials; WFCC, World Federation for Culture Collections; WHO, World Health Organization.

Three annexes are available as supplementary material with the online version of this paper.

INTRODUCTION

Since the beginning of the millennium, advances in the life sciences have been so significant, so dramatically fast and beneficial, that it is justified to speak of the age of biology. Included in these advances is the improved understanding in microbiology through research on infection mechanisms, interactions of microbial communities, and evolution and co-evolution processes in many different habitats e.g. the human microbiome. Along with enormous progress in fundamental and applied microbiology, novel micro-organisms have been found and identified; the number of newly described microbial species is quickly growing. This is also true at the strain level, where many valuable specialized research collections are maintained by individual scientists or collaborating working groups. In addition to the scientific advances, the working environment has changed too. There is a clear movement towards quality assurance, quality management, documentation of complete process chains and the requirement to introduce working practices that protect laboratory workers, the environment and all those potentially exposed. This clearly adds to the increasing demands placed on service culture collections, which are there to '...conserve the microbial gene pool for future study and exploitation by mankind...worldwide recognition of this need has highlighted the need for centres of expertise in culture isolation, maintenance, identification and taxonomy...These demands alerted the World Federation for Culture Collections (WFCC) to the need for good practice in culture collections' (WFCC, 1999). The main mission of culture collections is to function as custodians of microbiological diversity, serve the worldwide scientific community and deliver authenticated biomaterial and associated data. This requires approved standards for operation and globally harmonized processes where possible, independent of the holdings or the size of a culture collection. However, culture collections are also research institutions, often performing fundamental or applied research and often in co-operation with renowned international scientists and depositors of novel species and strains. Microbial diversity includes a remarkable number of opportunistic pathogens and a small percentage of highly pathogenic ones. This requires culture collections that hold them to have highly standardized processes for biosafety and biosecurity. Biosecurity is 'more' than biosafety; where biosafety encompasses containment and workers' health protection, biosecurity aims toward the prevention of possible malicious misuse and demands additional operational management such as access control or export control. Biosecurity is ultimately governed by the non-proliferation approach of the Biological and Toxin Weapons Convention (BTWC). This convention is signed by 171 countries (ratified by 155) and as a result States' parties have enacted specific legislation or other measures to assure domestic compliance with the convention. Micro-organisms inherently bear a 'dual-use' potential and consequently most microbiologists are more or less affected by dual-use issues. One recognized possibility to raise awareness of responsibilities and institute best practice is by scientific communities adopting a compliant code of conduct.

In 2001, the Organization for Economic Co-operation and Development (OECD) developed biosecurity guidance for culture collections by facilitating them to introduce best practices while at the same time strengthening their global role and defining the Biological Resource Centre (BRC). It became clear that biosecurity required special attention by the OECD; in 2007 an expert group published the OECD best practice guidelines on biosecurity for BRCs. This document postulated a code of conduct to strengthen biosecurity and to implement the BTWC. From the very beginning it was an explicit goal to design the OECD best practices as well as the 'future code' (which is presented here) in an open manner, for wide use. Compliance signals that BRCs understand their responsibilities towards society. Like in other parts of the world e.g. the USA and Canada, the European Union followed-up by creating the EU Chemical, Biological, Radiological and Nuclear (CBRN) Action Plan on security of high-risk materials resulting in an EU list of high risk biological agents. The goal is to strengthen safety and security by reducing the possibility of threats to humans, animals and plants by pathogens and toxins and otherwise highly dangerous materials. The EU Commission adopted the CBRN Action Plan in 2009.

In developing this code of conduct, the requirements of national regulations and international convention were taken into account. Two other globally important publications were also considered fundamental for biosecurity: the World Health Organization (WHO) Laboratory Biosecurity Guidance of 2006 (WHO/CDS/EPR/2006.6) (WHO, 2006) and the International Union of Microbiological Societies (IUMS) Code of Ethics (IUMS, 2006). The latter states 'IUMS seeks that all its member societies adopt or develop a code of ethics to prevent misuse of scientific knowledge and resources'. Two other codes of conduct were taken into account: the Dutch Code of Conduct for Biosecurity (Royal Netherlands Academy of Arts and Sciences, 2008) and the DFG Code of Conduct on work with highly pathogenic micro-organisms and toxins (German Research Foundation, 2013). The code of conduct presented here is based upon the essential demands of these documents to provide principles that are broadly applicable and helpful for all microbiological institutions.

The code does not function as an 'additional' legal instrument, nor is it in conflict with any legal regulations. It highlights that export control measures are part of biosecurity and have a high legally binding character. The implementation of the code requires a suitable and adequate risk assessment; this will require further harmonized work in

the near future. The Microbial Resource Research Infrastructure (MIRRI; http://www.mirri.org) has undertaken to address this particular issue in collaboration with experts in the field. The spirit of this code is to function as a preventive beneficial instrument and to ease and harmonise processes in laboratories; although initially intended for BRCs, its use extends to all microbiologists and their institutions.

RELEVANT INTERNATIONAL CONVENTIONS AND ACTIVITIES

BRCs and the BTWC context

The BTWC aims at a complete prohibition of bio-weapons. After World War II, this convention was the first armament control and the only true disarmament convention. National governments are the enforcers of national and international legislation on the distribution of sensitive materials, usually controlled by their export offices. Their experts are important contact partners for scientists exchanging micro-organisms and, of course, for BRCs. The BTWC is the international basis for an implementation and control regime but lacks lists of the restricted material.

The *Australia Group* (established in 1985, currently 41 participants) encourages countries to impose export measures for control of dual-use goods. This globally important initiative is an informal group of countries committed to combating the proliferation of chemical and biological weapons; it defines common control lists of potential dual-use materials and hence, strengthens the BTWC. Several more items, including micro-organisms, might be added to the existing dual-use lists. Consequently, this will influence regional and national export control regulations (http://www.australiagroup.net/).

Because globally harmonised lists are not feasible, a single binding list is not possible. Also, the allocation into four risk groups for human pathogens, as defined by the WHO, cannot be internationally harmonized, for several reasons. For plant pathogens, the situation is even more complex as, for example, the climatic conditions and geographical spread for both pathogens and hosts lead to special regulations.

The possibility of using scientific knowledge for peaceful or malicious purposes reflects the dual-use dilemma and affects both publication of knowledge (critical know-how) and the biological materials themselves. The Geneva negotiations over a verification protocol for the demands of the BTWC require an effective new inter-sessional process. Responsibilities in the life sciences require on the one hand scientific openness and on the other a demand for security. Both are prerequisites for scientific work; the publication of findings and the exchange of bio-resources are essential for beneficial research. The Code of Conduct on Biosecurity for BRCs promotes awareness and strengthens the BTWC to minimize unintentional proliferation or malicious use of potential dual-use micro-organisms. Equally, the code promotes freedom of research.

The OECD BRC initiative

The OECD established an international expert task force on BRCs which developed a set of guidelines for biosecurity to address compliance with the regulatory environment, independent of the region of the world in which a BRC is located. In order to meet modern demands for the further advancement of biotechnology and life sciences, in 2001 the OECD introduced a new concept of repositories and providers of high quality biological materials and information: Biological Resource Centres. BRCs are considered to be a key element for sustainable international scientific infrastructure, which is necessary to underpin successful delivery of the benefits of biotechnology, and in turn ensure that these advances help drive economic growth. The OECD BRC initiative resulted in a published series of best practices for BRCs, including biosecurity guidance, to serve as a target for the quality management of culture collections (OECD, 2007).

The OECD biosecurity best practice guidelines provide for openness of information and uncomplicated exchange of material in conformity with international rules, and further recommend safeguards to prevent misuse of bioresources and information. Both aspects are equally important for life scientists; they should be balanced and mutually reinforcing. These guidelines are designed to be implemented in conjunction with the general OECD operational guidelines for all BRCs that are based on an understanding of the biological material and the operations of BRCs. They can be downloaded from the OECD website (http://www.oecd-ilibrary.org/science-and-technology/oecd-best-practice-guidelines-for-biological-resource-centres_9789264128767-en).

The OECD biosecurity best practice guidelines also provide guidance on how to implement the code of conduct for BRCs and, more generally, for institutions working with microbiological resources. Because of the open structure, these biosecurity best practice guidelines are in agreement with obligations under national and international laws and current regulations and propose a framework for risk assessment of materials held within an institution as well as suggestions for the management of potential risks. Of equivalent importance is a demonstrable culture of responsibility and awareness of security throughout an institution. The management and staff should also share a sense of responsibility for biosecurity and the institution should be able to demonstrate this. It is important to note that all of this reflects best practices and a reliable baseline for biosecurity implementation for all other institutions working with microbiological resources, beyond BRCs.

The OECD Biosecurity Best Practice Guidelines cover the following aspects:

- Assessing biosecurity risks of biological material.
- New acquisitions/reassessment of inventory.
- Biosecurity risk management practices.
- Physical security of BRCs.
- Security management of personnel.
- Security management of visitors.
- Incident response plan.
- Staff training and developing a biosecurity-conscious culture.
- Material control and accountability.
- Supply of material.
- Transport security (within a BRC and outside).
- Security of information.

THE OPERATIONAL ARENA: BRCS – INSTITUTIONS WORKING WITH MICROBIOLOGICAL RESOURCES

The mission of BRCs

BRCs under the Global Biological Resource Centres Network (GBRCN) are custodians of the (micro)biological species diversity and of data and information on these resources; as such they are an essential part of the international infrastructure underpinning biotechnology. They provide the scientific and industrial community with authentic biological materials required in research, application and teaching. BRCs protect investment in research by keeping the respective bio-resources stable for the future, being reliable suppliers. They also conduct research, offer training courses and consultation and provide expertise and knowledge. Many of them are certified by official certification bodies, according to international standards (for example ISO).

Some BRCs maintain hazardous bio-resources requiring appropriate infrastructures, profound knowledge of relevant bio-legislation including export control, the respective protective measures, and reliable risk analyses of existing and new deposits. Hence, the security of BRCs was considered vital by the OECD to protect 1) the individual BRC facilities and their staff, 2) the organizations and stakeholder networks they are embedded in: universities, state institutes, scientific societies, private institutions etc. and 3) the countries the BRCs are located in so that these countries support the world's freedom and global security. Today, several BRCs have committed themselves to the Code of Conduct on Biosecurity and it is expected that through actions of the WFCC others will follow.

To implement the code, individual BRCs will tailor the requirements formulated in the best practices to their specific needs: biosafety means ensuring appropriate containment of biological substances at the workplace and providing all required health and safety protection mechanisms, but biosecurity additionally involves institutional and personal security measures and procedures to prevent the loss, theft, misuse, diversion or intentional release of pathogens or parts of them, toxin-producing organisms and toxins (OECD, 2007). Access and supply of biomaterials, information and critical know-how must be controlled and protected, including the area of synthetic biology and bio-informatics. For the latter, a specific code is available, the IASB Code of Conduct for Best Practices in Gene Synthesis (IASB, 2009). Before delivering to third parties, BRCs will check the recipients and ensure that the whole transport chain is safe. Some bioresources are subject to the provision of relevant permits and licenses. Procedures must be followed to minimize the risk of inappropriate distribution. Traceability of cultures has to be ensured, especially of those capable of causing substantial harm to human or animal health or the environment.

Research

In the life sciences, there are codes of ethics in place, e.g. the IUMS code addressing all IUMS member societies to 'adopt or develop a code of ethics to prevent misuse of scientific knowledge and resources' (IUMS, 2006). The possibility of 'dual-use' of research results may present problems. Modern scientific approaches in fundamental research and application, including biomedical and infection research, require using the broad biodiversity of dangerous pathogens. Research results and their application are often not predictable. Therefore, BRCs will, in a process of ethical self-regulation and in a transparent way, evaluate possible consequences of research projects performed within their institutions and externally within collaborative projects to help control potential risks of misuse. Biosecurity measures shall extend to transfer of 'know-how' as BRCs are, like all other institutions working with microbiological resources, repositories of expertise and knowledge that could be misused. They are aware of the fact that national law of the country in which they are located applies to activities of visiting scientists from foreign countries, but additionally the visitor's country legislation might apply too. Such facts make clear that the code of conduct presented here does not convene other legislation, it only aims at compliance with legislation that already exists and at harmonized processes for broad application in the life sciences community.

Development and structure of the Code of Conduct on Biosecurity for BRCs

The Code of Conduct on Biosecurity for BRCs supports the principles formulated by the Inter Academy Panel Statement on Biosecurity: awareness, safety and security, education and information, accountability and oversight. It also fully supports the IUMS Code of Ethics against Misuse of Scientific Knowledge, Research and Resources. The code presented here was initiated by the GBRCN demonstration project (http://www.gbrcn.org) and European Consortium

of Microbial Resource centres (EMbaRC) project consortia with the aim that it was to be adopted by the culture collection community, but with the option for open and broader outreach.

Culture collections' activities on the biosecurity issue are remarkable (http://www.wfcc.info). The WFCC guidelines (first published in 1989 and now in its third edition) include seven paragraphs dealing with controlled access and supply of bioresources and the legal background. Documentation, tracking and working with end-user certificates are indicators of quality and reliability of service supply culture collections. Partners under the European Biological Resource Centre Network project developed information resource documents on various legislative issues including biosecurity ('Controlled Distribution of Dangerous Microorganisms – The Control of Dual-use Goods') to function as helpful guidance for culture collections and the scientific community (http://www.wfcc.info).

The Code of Conduct on Biosecurity for BRCs was agreed during the EMbaRC-GBRCN Workshop on Biosecurity, Utrecht, Netherlands, September 2011. Along with the code, the accompanying document 'Structure of the Code – the key issues' (see below) was agreed with the aim to demonstrate why and how this code had been developed. In December 2011, the code was introduced at the 7th Review Conference to BTWC, United Nations, Geneva, together with an NGO (non-governmental organization) statement (see annex I, available in IJSEM Online). The idea of the code was well received by the review conference.

STRUCTURE OF THE CODE – THE KEY ISSUES

The aim of this code is to help BRCs avoid any direct or indirect contributions to the development and production of potential biological weapons. It also raises awareness of potential dual use and the need to prevent malicious use.

There are several examples of codes and the first task was to determine exactly what form was needed for the BRC community. The OECD has created a web-based information resource (http://www.biosecurity.org) which provides an analysis of the different types of codes with examples: http://www.virtualbiosecuritycenter.org/codes-of-ethics/codes.htm.

A code is a set of conventional principles and expectations that are considered binding on any person who is a member of a particular group adopting the code, whether or not membership in that group is voluntary. A code is a unique regulatory instrument that should not be confused with a treaty, guideline or principle. There are also a number of descriptive terms that can be used instead of code (e.g. charter, oath, declaration, etc.) but these, according to the OECD, are essentially the same.

Codes can either be voluntarily binding or enforceable. A code can be voluntarily binding on a participant who chooses to be a member of any society or group that sponsors a code. Codes which have concrete consequences regardless of one's voluntary entry into compliance can be said to be enforceable. In general, three different types of codes can be distinguished, although some researchers have further categorized codes by their objectives and the level at which the code is binding.

- Aspirational (codes of ethics) – these set out ideals that practitioners should uphold.
- Educational/Advisory (codes of conduct) – go further than 'aspirational codes' by tying actions to guidelines which suggest how to act appropriately.
- Enforceable (codes of practice) – seek to further codify what is acceptable practice. Rather than attempting to sway or guide behaviour, enforceable codes are embedded within wider systems of professional and legal regulations.

There is much debate on the effectiveness of the voluntary 'aspirational' and 'educational' codes. However, the key aim of a code is prevention. It guides people's actions in a variety of different sectors and activities. There is no 'universal' code to guide the conduct of those involved in the life sciences.

The conclusion was that BRCs needed a binding code of conduct specific to their needs. The Code of Conduct on Biosecurity for BRCs is concise, simple, clear and addresses all laboratories holding dangerous organisms. The code preamble contains the ethical reasons and background that forms the code and this is followed by specific actions relevant to BRCs. The code offers a way to reconcile the various national and international approaches to biosecurity by setting a base line for actions associated with the specific activities of BRCs and culture collections to enable the reduction of the possibility of malicious use of their holdings and associated information. It offers clear benefits and delivers awareness. Entities adopting the code become trusted partners and demonstrate their awareness of the responsibilities of conducting safe science. Sharing the code with users raises their awareness of their need to be responsible in how they conduct their activities. Compliance also sends a signal to the authorities that BRCs understand their responsibilities towards society.

The code itself is a brief document without delivering details on its implementation and without citation of any legislation because of its global relevance. It covers seven key issues in the biosecurity context with the intention of protecting the individual facilities, the employees, all possible third parties involved and finally society itself from misuse of biomaterial, associated data and know-how.

A key text consulted was, besides the afore-mentioned established codes of conduct, the IAP (inter-academy panel on international issues, a global network of science academies; http://www.interacademies.net/) statement on biosecurity (http://www.interacademies.net/10878/13912.aspx).

CODE OF CONDUCT ON BIOSECURITY FOR BRCS

I. Preamble

Accumulated and advancing knowledge on biological systems offers substantial benefits to mankind, research and development in all areas of basic and applied biomedical and biotechnological sciences. However, this improved knowledge is intrinsically associated with the potential for dual application: for beneficial or malicious purpose. The possibility of using scientific knowledge for peaceful or non-peaceful purposes reflects the *dual-use dilemma* and confers a responsibility on both those with the knowledge and with the biological resources. The responsibilities of those engaged in the life sciences have an increasing role for in-depth implementation of the BTWC. Scientific openness and a sense of security are prerequisites for freedom of scientific work, publication of findings and exchange of bioresources to carry out activities in the life sciences. This code of conduct on biosecurity is to help microbial BRCs promote a basic ethical understanding of science compliant with the BTWC and raise awareness to prevent misuse in the life-sciences context.

This code intends to raise awareness on biosecurity within and outside BRCs and to clearly demonstrate that BRCs are fully compliant with national and international legislation and support the BTWC as an international norm prohibiting biological weapons. It is not the aim of this code to influence the range of bioresources maintained or life science activities performed at BRCs. Above all, this biosecurity code of conduct is meant to complement legislative procedures.

II. Scope

The aim of this code of conduct is to prevent microbial BRCs from directly or indirectly contributing to the malicious misuse of biological agents and toxins, including the development or production of biological weapons.

BRCs commit themselves to this code of conduct on biosecurity considering their specific situation and key role as an essential part of the international infrastructure underpinning biotechnology: providing the worldwide scientific and industrial communities with authentic biological materials required in research, application and teaching as well as related information and services. Being part of the scientific community they conduct activities in the life sciences, offer training courses, expertise and knowledge and they support the bioeconomy.

Many BRCs are entrusted with the collection and controlled supply of potentially hazardous bioresources. This requires high responsibility, well-established biorisk analyses and management, and appropriate BRC internal infrastructures, profound knowledge of relevant bio-legislation including export control, and respective protective measures. This code calls for implementation and compliance of awareness, accountability and oversight and targets all those engaged in life sciences activities: laboratory workers, managers, stakeholders and others.

III. Code

(1) Biorisk management.

- Integrate biorisk management throughout the organization and seek its continuous improvement.
- Assign adequate resources and responsibility to guarantee compliance with legal requirements, communication to staff and relevant third parties, and carry out reliable and appropriate risk assessment.

(2) Raising awareness.

- Devote specific attention in the education and further training of all staff on:
  - the dual use dilemma i.e. the risks of misuse of biological material, information and life sciences research
  - the requirements of regulations in this context.
- Provide regular training and carry out auditing to maintain up to date knowledge on biosecurity.
- Raise awareness of related third parties on their responsibilities.

(3) Reporting misuse.

- Encourage a culture of reporting misuse.
- Report any finding or suspicion of misuse of biological material, information or technology directly to competent persons or commissions.
- Protect persons reporting on misuse and ensure that they are not targeted for retribution as a consequence.

(4) Internal and external communication.

- Prevent access by unauthorised persons to internal and external e-mails, post, telephone calls and data concerning information about potential dual-use research or potential dual-use materials.
- Regulate the communication of sensitive information.

(5) Research and sharing knowledge.

- Assess possible dual-use aspects of research during the application for and the execution of research projects.
- Minimize the risk that publication of results on potential dual-use organisms will contribute to misuse of that knowledge.
- Consider biosecurity implications when sharing knowledge.

(6) Accessibility.

- Ensure physical security of and access control to stored potential dual-use material in accordance with its risk classification.
- Implement access control for staff and visitors where potential dual-use biological materials are stored or used.

(7) Supply, shipment and transport.

- Screen recipients of potential dual-use biological materials, in consultation with the relevant authorities and parties.
- Select transporters suitable to handle potential dual-use biological materials.
- Perform export control in accordance with applicable regulations.

THE DIFFICULTIES OF BIORISK ASSESSMENT – BALANCING THE RISKS

Central questions of biorisk assessment in practice

Suggestions for biosecurity risk assessment of biological material for BRCs. The following official documents are recommended for good practice in biosecurity risk assessment:

WHO Laboratory biosecurity guidance (WHO/CDS/EPR/2006.6) (WHO, 2006)

OECD Best Practice Guidelines on Biosecurity for BRCs (OECD, 2007).

Risk assessment as defined by the OECD best practice guidelines is 'the process of identifying sources of potential harm associated with the loss, theft, misuse, diversion or intentional release of pathogens or parts of them, and toxin-producing organisms as well as such toxins that are held, transferred and/or supplied by BRCs, assessing the likelihood that such harm will occur and the consequences if harm occurs'.

Therefore, risk assessment involves: the biological intrinsic risk, the risk of harm after loss or misuse and the consequences if harm occurs.

In practice, several factors may hamper biosecurity risk assessment as prescribed in the guidelines mentioned above, such as the difficulty of quantifying risk, lack of necessary data, difficulties in establishing causality in biological systems, or multiple risk factors (including dose of a pathogen after intake and uncertainty of dose–response predictions). While these facts must be accepted, biosecurity risk assessment under a code of conduct can still be performed in a responsible and acceptable way. Risk assessment in BRCs can only be based upon accessible (usually public) knowledge and it is the responsibility of the BRC to be up-to-date; discovering new facts about the potential use of an organism is not required. In case of new organisms without any data except identity, substrate and location, the usual and acceptable method is comparison with related, better known organisms in connection with the host. Therefore, best practice in the biosecurity context depends on the extent of known information on an organism to our best knowledge. Biosecurity management options concerning the organizational infrastructure and practical processes, e.g. export control (see annex II), are subject to national legal requirements to which BRCs must comply. These obligations and procedures cannot be fully generalized in detail and are not compromised by adoption of the principles of the code. Additionally, some national legislation provides lists of controlled organisms and requirements on data and sharing know-how; these take precedence (see below).

Risk assessment as described in the OECD Best Practice Guidelines on Biosecurity for BRCs. The OECD biosecurity expert group developed a scheme of physical security applicable to biosecurity risk levels within BRCs and has defined a matrix on biosecurity risk levels and physical security in a graded manner (Table 1).

The OECD best practice guidelines describe a model based on 'assessing biosecurity risks of biological material' using those biogenic/intrinsic factors that are known for a biomaterial. Biosecurity risk assessment is a multifactorial complex process. This matrix could mean that physical/technical safety and security (management procedures) should play a major role for covering the requirements because of biological uncertainties and causalities. The OECD best practice guidelines reflect best practice because risk evaluation of biological systems cannot be complete.

The WHO Laboratory biosecurity guidance document WHO/CDS/EPR/2006.6. This goes beyond the organism level and addresses VBM (valuable biological materials). The WHO biorisk management approach includes biosafety, laboratory biosecurity and ethical responsibility. Laboratory biosecurity is considered complementary to laboratory biosafety, biosafety practices reinforcing and strengthening laboratory biosecurity. These recommendations provide levels of protection for VBM, which are defined as follows: 'biological materials that require...administrative oversight, control, accountability and specific protective and monitoring measures in laboratories to protect their economic and historic (archival) value and/or the population from their potential to cause harm. VBM may include pathogens and toxins, as well as non-pathogenic organisms, vaccine strains, foods, GMOs (genetically modified organisms), cell components, genetic elements and extra-terrestrial samples'. Pathogens and toxins are an important subset of VBM. In contrast to the OECD best practice guidelines, the WHO document does not include a 'matrix' for risk assessment but

Table 1. OECD matrix on biosecurity risk levels and physical security

Biosecurity risk level	Physical security
Negligible or low	General security area (no special biosecurity requirements)
Moderate	Restricted area
High	High security area

suggests that the caretakers define the level of protection required. This is a very central option for scientists in microbiology, whether they are curators in BRCs or engaged in fundamental research.

Laboratory biosecurity risk assessment under the Laboratory Biosecurity Programme is mentioned as 'associated agent-based microbiological risk assessment and laboratory biosecurity risk assessment': the backbone of biosafety measures is a microbiological risk assessment, but laboratory biosecurity programmes additionally perform biosecurity risk assessments and strategies for their management. This is part of the biorisk assessment efforts; regular re-evaluation is necessary to respond to national and institutional standards. Risk assessments for research projects should be performed and records securely kept. Situations requiring risk assessment should be described. In biosecurity risk assessment, intelligence forces are complementing biosafety risk assessment with local threat assessments.

The difficulties of risk assessment in microbiology. Four elements are identified in risk assessment: hazard identification, exposure assessment, dose–response relationship and risk characterization. In other words: what can go wrong, how likely is it to go wrong and what are the consequences?

These questions seem simple, but microbial risks are not always fully understood, particularly given the hypothetical nature of some microbial risks in cases of intentional or accidental release. It is important that risk assessment processes are transparent.

Some suggestions for effective laboratory biosecurity risk assessment procedures under the Code of Conduct on Biosecurity for BRCs

Risk assessments are by nature intuitive to some extent, knowledge is necessarily often incomplete. Therefore, risk assessments need to be revisited when new knowledge becomes available, e.g. on host–pathogen interactions. Physical, technical, procedural and facility-specific operational measures will help with implementation of biosecurity, beyond the material-focused risk assessments e.g. items (organisms, toxins etc.) on national export control lists. The following recommendations may summarize the relevant steps:

- Focus on biosecurity/biothreat according to the aim of the code of conduct, with priority over the broader VBM definition given by the WHO because 'VBM' also has a focus on the 'value' of a certain biomaterial.
- It is a practical recommendation to use the biosafety risk group allocation and claim all risk group 3 and risk group 4 organisms as principally highly dangerous with potential consequences regarding biosecurity.
- Apply an appropriate physical security standard for all organisms allocated to the risk group 2 regardless of any known biosecurity threats/hazards of a specific biomaterial because principally all pathogens bear a risk that might be relevant in the biosecurity context.
- Compare all biomaterial that is kept in an institution with the list of the Australia Group and other (national) lists that might apply concerning dual-use goods. Lists are not exhaustive but form a legal basis.
- Consider potential economic harm to be caused by plant and livestock pathogens.
- If a BRC has a collection of specialized GMOs or other special collections, individual risk assessments per individual biological substance have to be performed.

The supplementary materials to this paper contain three annexes. Annex I is the NGO statement in original wording that introduced the code to the UN at the Seventh BTWC Review Conference. This may point out the situation of life scientists and the dual-use dilemma. Annex II aims at offering a helpful step-by-step flow scheme of export control and demonstrates how export control can be performed; it also contains an example of an end-user certificate, a document that is helpful to be on the safe side. Annex III shows a detailed checklist of practical items on biosecurity risk assessment and biosecurity risk management. This is the result of a comprehensive analysis under the GBRCN project aiming at finding out where possible gaps or weaknesses are for the implementation of the code. An example with fundamental importance is the issue regarding relevant authorities and their cooperation with institutions in the life sciences, here with a focus on BRCs.

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