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Review Article

Building and implementing a multi-level system of ethical code for biologists under the Biological and Toxin Weapons Convention (BTWC) of the United Nations

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ABSTRACT

The recent global COVID-19 pandemic has had profound economic and social impacts on the world. It has highlighted an urgent need to strengthen existing international biosecurity governance mechanisms to prevent the misuse and malicious abuse of life science research and maintain international biological arms control norms. Biologists are at the front line of biotechnology development and are key to maintaining biosecurity awareness and moral self-discipline. As an important first step, biologists need to actively participate in the formulation and implementation of relevant biosecurity policies and measures to ensure their effectiveness and sustainability. Furthermore, efforts should be made to advocate for and promote the establishment of an ethical code of conduct for biologists to share safety responsibilities for global biosecurity. To maximize the impact of this ethical code of conduct, an effective approach to implementing codes of conduct for biologists at both national and international levels should be established under the framework of the Biological and Toxin Weapons Convention (BTWC).

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1. Background

Recently, significant progress has been made in developing cutting-edge biotechnology, such as gene-editing technology, protein engineering, and synthetic biology. Although biotechnology development has highly benefited society, countries all over the world are also facing risks arising from the potential misuse and abuse of these technologies. Furthermore, as biotechnology has become increasingly accessible, the threshold for biological weapon production has significantly decreased, thereby increasing the risk of accidental and deliberate use of the knowledge and materials to harm humans, animals, plants, or the environment. Thus, extensive discussions have been conducted among the international community on balancing the two major themes of biotechnology, development and security, and coordinating these themes to deal with the challenge of the coexistence of hope and danger.

While striving to improve their regulatory biosecurity systems, governments of each country also require a platform for collective action. Unknown risks related to biotechnology and biosecurity often lead to an inevitable lag in legal consequences and effective penalties. Moreover, as many uncertainties still exist in the current development and application of biotechnology, its safety can only be speculatively assessed based on unknown possible risks, which presents a further challenge for legal enforcement. In fact, technologies that have been fully discussed and assessed for risks within the scientific community could present unknown threats and risks to humanity. Therefore, legal disputes cannot be effectively enforced because there is a lack of necessary judicial determination of causality, resulting in "red line" breaches. For example, at the Meeting of Experts for the Biological and Toxin Weapons Convention (BTWC) in August 2015, Swiss scientist Dr. Cedric Invernizzi presented a report entitled "*CRISPR/CAS: An Adaptive Bacterial Immune System is Becoming a Game Changer in Genetic Engineering,*". This raised concerns on the potential risks of CRISPR-Cas 9 gene editing technology as it potentially had "...irreversible and unpredictable risks with unknown consequences for other species."[1] These concerns were confirmed only a few years later when the world's first genetically edited baby was completed by a Chinese researcher, Mr. He Jiankui, in 2018, which sparked an intensive international debate on the safety and ethics of biological research.[2]

Current risks of biosecurity are primarily related to human misuse and abuse and stem from the out-of-control behavior of relevant subjects under the comprehensive action of internal and external environments. Thus, the autonomy of the relevant stakeholders is an important feature present in biological sciences, that is absent from other field, such as that of nuclear technology.[3] Biologists are the first line of defense against the misuse of biotechnology; therefore, their biosecurity awareness and moral self-discipline is key to prevention. For future safety, it is the responsibility of biologists to be proactive in terms of the development and application of biotechnology, while pursuing bold research and prudently promoting biological sciences. Researchers should effectively reduce the potential risks arising from the knowledge, tools, and technologies required to conduct such research and ensure that it is only used for peaceful and sustainable development. Accordingly, increasing efforts should be made to advocate for and promote the establishment of a code of conduct for biologists to share safety responsibilities for global biosecurity. This will cultivate a sense of professional responsibility and historical mission among practitioners, encourage the role of the scientific community in self-disciplining, and promote the orderly participation of multiple parties in the process of biosecurity governance. This will ultimately prevent biological risks, while obtaining full benefits of biotechnology.

2. Statement of problem

During the meeting of experts at the BTWC in 2005, representatives from 23 scientific organizations, research institutions, and companies around the world participated in an informal exchange at an open session on "Discussing and Promoting Consensus and Effective Action on the Content, Promulgation, and Adoption of a Code of Conduct for Scientists," which represented a broader consensus among biologists and international scientific organizations to establish a self-discipling code against biosecurity risks. In 2009, the National Academies of Sciences of the U.S. also stated that "individual awareness is important, as is education and training, to create and maintain a culture of trust and responsibility that is central to sustaining good scientific conduct."[4] In the same year, the Global Partnership Working Group issued a recommendation for a "*Coordinated Approach in the Field of Global Knowledge Proliferation of Weapons of Mass Destruction and Encouraging Scientists Participation*," noting that "closer attention now needs to be paid to engage scientists and raise their awareness and sense of responsibility to prevent the diversion of their knowledge in legitimate scientific disciplines for unintended malicious purposes, strengthen the framework to prevent the dissemination of sensitive information, promote cooperation, and advance common non-proliferation goals."[5] However, current codes of conduct in life sciences are difficult to implement because there is little empirical evidence to link them with positive changes in scientists' behaviors suggesting their effectiveness may be limited.[6] After investigating the Code of Conduct for Dutch Scientists, some researchers argued that "the rapidly evolving codes and guidelines may deceptively simplify moral awareness to a matter of compliance rather than see it as a constituent element of professionalism, character, and responsibility."[7]

In 2011, the National Scientific Advisory Board on Biosafety (NSABB) of the U.S. released a report following a 6 y study. The report entitled "*Strengthening Responsible Science: Considerations for the Formulation and Dissemination of a Code of Conduct for Dual-use Research*" pointed out three key elements to ensure the effectiveness of a code of conduct: guarantees of strong institutions and resources, firm commitment to and active dissemination of the code, and the full demonstration of the code through discussion.[8] Similarly, the Federal Expert Security Advisory Group (FESAP) of the U.S. made recommendations for "*Strengthening emphasis on biosafety, laboratory biosafety, and responsible behavior culture in life sciences*" in 2015.[9] To ensure the acceptability and effectiveness of these codes of conduct, organizational culture related to biological risk governance, responsible scientific research, compliance with relevant laws, regulations, guidelines, and policies, and emphasizing the values and beliefs of life science research practitioners is necessary at all institutions. The concept of a biosafety and biosecurity culture (as a subset of organizational culture) is multilayered and complex,[10] and must be imbibed by all stakeholders in any organization. Therefore, collective self-governance mechanisms need to be widely implemented.

In 2018, the Chinese government and the Implementation Support Unit (ISU) of the BTWC jointly organized an international workshop in Tianjin China on "Building a Global Biosafety Community with a Shared Future: Developing a Code of Conduct for Biologists." Approximately 100 representatives from over 20 countries, including the US, Russia, Britain, Germany, India, Pakistan, Brazil, the Netherlands, and Switzerland, attended meetings, as well as the Organization for the Prohibition of Chemical Weapons, the World Organization of Animal Health (OIE) and other relevant international organizations, 10 universities and research institutions, including the National Academy of Sciences, Johns Hopkins, Stanford, Oxford, and Bradford University, attended the meeting.

Extensive discussions were held on core issues such as basic principles, target groups, effective implementation, and sustainable development of an Ethical Code of Conduct for Biologists formulated under the framework of the BTWC, but no unified consensus was reached.

Therefore, in this paper we intend to discuss the following main issues:

i) Past Codes of conduct that have been developed in life science research.
ii) The BTWC's advancement of the formulation of a code of conduct for biologists.
iii) The stakeholders currently involved in responsible life science research and their responsibilities under the code of conduct.
iv) Building a multi-level system of ethical code for biologists under the BTWC with an effective implementation strategy.

The active participation of biologists in the formulation and implementation of relevant biosecurity policies and measures is key to effective and sustainable biosecurity governance.[11] Here, we review the development of codes of conduct in life science research and present the necessity for formulating a code of conduct for biologists under the framework of the BTWC. We then propose an approach to implement codes of conduct for biologists at both national and international levels under the framework of the BTWC, with the aim of ensuring more effective implementation.

3. Code of conduct for life science research

A code of conduct is a formal and systematic set of rules, responsibilities, norms, and expectations of appropriate behavior.[10] In life sciences, codes of conduct raise awareness on dual-use issues and social responsibility, promote best practices, and reinforce the norm against the use of biological agents for bioterrorism or biowarfare.[12] The earliest concept of these codes of conduct can be traced back to the Hippocratic Oath from the 5th-3rd century BCE. As the foundation of ancient Greek professional ethics, the Hippocratic Oath is a professional ethics framework for the medical profession, with four key principles: gratitude towards the teachers; prescription of regimens for the good of patients according to one's ability and judgment; refrain from harm and abusing professional convenience to do unethical or illegal things; and– respecting and protecting personal privacy and business secrets. The earliest modern medical ethics code is the *Code of Conduct for Hospitals and Medical Staff*, drafted by the British medical ethicist Thomas Percival for Manchester Hospital in 1794. One of the key components of the codes was the introduction of the relationship between medical staff and hospital funding, in addition to the doctor-patient relationship included in early medical ethics. In 1847, based on this code, the American Medical Association (AMA) formulated medical ethics education standards and codes, which included the responsibilities of doctors to patients, obligations of patients to doctors, doctors' responsibilities to other doctors and their peers, responsibilities of the medical profession to the public, and obligations of the public to the profession.

Since the 20th century, the rapid progression of medicine has increased the moral responsibilities of medical professionals, and increasing international collaboration and medical practices across countries has highlighted the need to formulate unified international, medical, ethical norms for medical staff. In 1946, the International Military Tribunal at Nuremberg created the well-known *Nuremberg Code*, which formulated the basic principles for human experimentation: "the experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature." The Nuremberg Code laid the foundation for research on human and animal subjects in life science research. In 1949, the World Medical Association (WMA) passed the *International Code of Medical Ethics of WMA* in London, which further clarified the contents of three items: a general code for doctors, the duties of doctors to patients, and of doctors to other doctors. The Tuskegee syphilis experiment scandal of the U.S. Department of Public Health (PHS) secretly studying the effects of syphilis on the human body using 400 African American black men as test objects since 1932, accelerated the development of biomedical ethics. In 2000, the European Science Foundation issued the landmark science policy document, Good Scientific Practice in Research and Academics, proposing that scientific institutions worldwide should establish domestic scientific research codes for scientists. In 2003, the All European Academies, a joint European organization composed of 53 national scientific and humanities institutions, created the Memorandum of Scientific Integrity (2003). Based on this, the European Science Foundation and the All European Academies issued the European Code of Conduct of Research Integrity as a consensus document in 2010, which was further supported by 31 other research foundations from 22 countries at the Second World Conference on Research Integrity. This code stipulated a formal code of conduct and practical principles for systematic research in natural sciences, including medicine, life sciences, humanities, and social sciences.

To date, codes of conduct (including ethical codes) in life science research have mainly been formulated by academic organizations or professional associations at the national (regional) and international level. According to research by Burnette and Connell, "establishing and attaching importance to a culture of ethical and safe behavior, and implementing effective biological risk management seem like possible ways to prevent the abuse of biological materials and significantly improve control of potential risks in the life science research community at the national level."[13] Since 2005, with increased attention on biosecurity from governments around the world, more organizations have been engaged in building and promoting codes of conduct in life science research. For example, the Royal Society of the UK, the Wellcome Trust, and British Medical Association (BMA) released two reports in the same year: *Do No Harm: Reducing the Potential for the Misuse of Life Science Research,*[14] and Biotechnology, Weapons and Humanity II,[15] in which the importance of codes of conduct was discussed. In 2005, the AMA published *the Code of Medical Ethics: Guidelines to Prevent Malevolent Use of Biomedical Research.*[16] The Dutch government entrusted the Royal Netherlands Academy of Arts and Sciences with formulating the Netherlands Code of Conduct of Biosecurity in 2006, which covered awareness raising, research and publication policies, accountability and supervision, internal and external communication, accessibility, and shipping and transportation for life sciences researchers.[17] In 2008, the Deutsche Forschungsgemeinschaft (DFG) also formulated a code of conduct titled the *"Use of Highly Pathogenic Microorganisms and Viruses for Germany*", which was further updated in 2013.[18] The American Society for Biochemistry and Molecular Biology (ASBMB) and American Society for Microbiology (ASM) formulated codes of conduct for their members, prohibiting the abuse of sciences in the process of exploring biochemistry, molecular biology, and microbiology.[16] In 2015, the Indonesian Academy of Sciences formulated its domestic code of conduct on biosecurity with the help of the Royal Netherlands Academy of Arts and Sciences.[19] Recently, with the assistance of the German government, the Tunisian government formulated a code of conduct for its domestic biological science research in 2019.[20] In 2020, the National Academy of Medicine, the National Academy of Sciences, and the Royal Society

released a consensus study report, "*Heritable Human Genome Editing* (HHGE)", which recognized that the International Commission on the Clinical Use of Human Germline Genome Editing and was specifically tasked with defining a responsible pathway for clinical use of HHGE, should a decision be made by any nation to permit its use.[21]

At the international level, the International Committee of the Red Cross issued a document entitled "*Preventing the Abuse of Life Sciences: From Ethics and Law to Best Practice*" in 2004.[22] In the same year, members of the Asia-Pacific Economic Region (APEC) discussed the introduction of the same code of conduct for scientists.[23] In 2005, the InterAcademy partnership (IAP) panel formulated *the Statement on Biosecurity*, which proposed awareness, safety and security, education, information, accountability, and supervision principles on the basis of scientists' autonomy of responsible research.[24] In the same year, the Organization for Economic Cooperation and Development (OECD) issued *the International Future Plan for Promoting Responsible Management in Life Science*,[25] and took *the European Code of Conduct on Biosecurity* as a specific initiative of the organization, aiming to revise and supplement laws and regulations to prevent scientific abuse and raise awareness of biologists' responsibilities in Europe.[26] In 2006, the International Union of Microbiological Societies adopted *the Code of Ethics against Misuse of Scientific Knowledge, Research Results and Resources*.[27] In the same year, the World Medical Association (WMA) updated the WMA International Code of Medical Ethics in South Africa. In 2010, the World Health Organization (WHO) formulated the guiding document *Responsible Life Sciences Research for Global Health and Safety*. In 2019, the World Organization of Animal Health (OIE) issued *the Guide to Responsible Behavior in Veterinary Research*, formulating a governance framework model to mitigate biosecurity risks, which emphasized interaction among multiple stakeholders in the field, and the importance of raising awareness of biosecurity risks.[28] In addition, organizations representing amateur scientists, such as DIY Bio, formulated *codes of conduct* to regulate their own members in 2011.[11]

In addition, the biotechnology industry has started to introduce self-regulation models centered on products and services. For example, based on the understanding that reducing the safety risks of gene synthesis technology is in line with their long-term economic interests, the two major international industry associations of commercial gene synthesis, the International Association of Synthetic Biology and the International Gene Synthesis Consortium, provided guides and necessary software for their members to screen new customers and DNA synthesis orders, and promised to only purchase synthetic genes from companies that abided by the code of conduct, so as to strengthen self-regulation,[29] and prevent the abuse of synthetic biology technology to construct dangerous viruses or bacterial pathogens from scratch.

Although many countries and international professional organizations have formulated codes of conduct, they vary greatly in terms of breadth, depth, and purpose.[30] The general state of current codes of conduct for life science research have the following characteristics:

i) To date, no unified code of conduct applicable to all biologists or for interdisciplinary sciences has been created. This has created challenges in integrating various normative resources and improving the effectiveness of the code of conduct for life science research across a wide spectrum of research fields.
ii) Different levels of attention to biosecurity or prevention of biotechnology abuse are observed in the content and structure of the codes.
iii) Three different types of codes co-exist and complicate further implementation: ideal codes (codes of ethics) that mainly stipulate the scientific beliefs that practitioners should adhere to for biological research, such as standards of integrity, honesty or objectivity; educational (advisory) codes that add to ideal codes by guiding research through guidelines and suggestions; and executable codes that indicate acceptable research behavior, and are often connected with the legal system to ensure effective implementation.[31]

4. The BTWC advances the formulation of a code of conduct for biologists

In October 2001, the United Nations (UN) and its Anti-terrorism Policy Working Group recommended that the BTWC should develop a code of conduct for biologists. As the first international weapons control standard to completely ban biological weapons systems, and the only multilateral agreement adopted by the United Nations General Assembly in the field of international biosecurity governance, the BTWC has continued to promote a code of conduct for biologists as a binding resolution adopted by all state parties for nearly 20 y. During the 5th Review Conference of the State Parties to the BTWC in 2002, a consensus was reached following an intersessional work program to discuss and promote common understanding and effective action by the state parties on topics including "the content, promulgation and application of a code of conduct for scientists."[32] In 2004, the State Parties to the BTWC first introduced the topic "*Code of Conduct for Scientists on the Safe and Ethical Use of Biological Sciences*." During the BTWC Experts Meeting in 2005, one of the themes was formally established to "discuss and promote consensus and effective action on the content, promulgation, and adoption of a code of conduct for scientists," to which the German government submitted a working document entitled "Code of Conduct in Life Sciences and Its Application in Universities," (working paper no. 12). It proposed that a code of conduct "should include an important element: the obligation to understand possible dual uses of biomedicine and bioscience research." Since then, the BTWC has directed more attention to discussing the establishment and implementation of codes of conduct. In the final document of the 6th Review Conference of the State Parties to the BTWC in 2006, the state parties reached a consensus on "recognizing the importance of a code of conduct and self-regulatory mechanisms to raise biosecurity awareness among relevant practitioners and called upon the State Parties to seek to prevent misuse of bioscience and biotechnology research that may be used for purposes prohibited by the BTWC through the development of a code of conduct."[33] Then in 2008, a special topic was established and dedicated to "supervision, education, raising awareness, and adopting and/or developing a code of conduct to prevent potential misuse prohibited by the BTWC in the context of advances in bioscience and biotechnology research" during the Meeting of State Parties to the BTWC.[34] The Experts Meeting at the BTWC in 2012 established "Voluntary Codes of Conduct and Other Measures to Encourage Responsible Conduct by Scientists, Academia, and Industry" as one of the important topics.[35] During the 2015 Meeting of the State Parties to the BTWC, the Chinese government submitted a working paper on the development of a model code of conduct for biologists under the BTWC. Subsequently, the working document "*Code of Conduct for Biologists (Model)*" was formally submitted to the 8th Review Conference of the State Parties to the BTWC in 2016, jointly by the Chinese and Pakistan governments as working paper no. 30 of the BTWC. Notably, in this meeting, the state parties reached an important consensus to "encourage the promotion of a culture of responsibility among relevant national professionals and the voluntary development, adoption, and promulgation of codes of conduct."[36]

These efforts were expedited in the 2017–2021 inter-sessional work program of the 9th Review Conference of the BTWC. The actions included:

i) recommendations during the Annual Meeting of State Parties to the BTWC in 2017 to strengthen the scientific and technical review process of the BTWC, such as establishing a designated review body and a formulation of a code of conduct for biologists.[37] In the meeting, the Center for Biosafety Research and Strategy at Tianjin University, a non-government organization (NGO) involved in the drafting of the "Code of Conduct for Biologists (Model)" submitted by the Chinese and Pakistan governments, issued a call for the promotion of a code of conduct under the framework of the BTWC.
ii) The Chinese government and the Implementation Support Unit (ISU) of the BTWC and the Center for Biosafety Research and Strategy at Tianjin University jointly organized an international workshop on "*Building a Global Biosafety Community with a Shared Future: Developing a Code of Conduct for Biologists*" in Tianjin, China in June 2018.
iii) Finally, a full-floor discussion themed "*Voluntary Codes of Conduct*" was held during the 2018 Annual Meeting of Experts on Developments in the Field of Science and Technology Related to the BTWC (MX2) in August. A side meeting on "*Developing a Code of Conduct for Biologists*" was also presented by a group of scientists and policy researchers from China, the United Kingdom, and Netherlands. Recently, experts from the Center for Biosafety Research and Strategy at Tianjin University shared their thoughts on the urgency, significance, and implementation of codes of conduct at the 2020 and 2021 Annual Meeting of Experts on Developments in the Field of Science and Technology Related to the BTWC (MX2).

The recent global outbreak of COVID-19 pandemics further demonstrated that global biological security threats are primarily due to the rapid economic and social development of many countries as well as increasing globalization. Therefore, strengthening international codes against any possible malicious use of science and technology is urgently required.[38] With the rapid development of bioscience and biotechnology, as well as challenges, such as unstable global security, the adoption of a "Code of Conduct for Biologists" as a resolution at the upcoming 9th Review Conference of the State Parties to the BTWC in 2022 becomes increasingly important for the world to strengthen international biosecurity consensus and achieve substantive international cooperation.

5. Why should an ethical code of conduct for biologists be formulated and implemented under the framework of the BTWC?

Biosecurity risks caused by biotechnology misuse and abuse are often complex, superimposed, and intertwined with diverse military, economic, and social security threats and the hidden dangers contained within them are not fully understood. Additionally, conflicts between the accumulation of biotechnology and the legal system inevitably arise, thereby increasing supervision challenges. It has previously been pointed out that "laws and norms complement each other. Implementing norms through formal laws and regulations is a slow and arduous task, which often meets considerable resistance. It is therefore difficult to complete this work by enforcing laws."[39] Thus, effective supervision of biosecurity risks arising from life science research may require a combination of "hard" and "soft" laws. Briefly, hard law refers mainly to conventions, laws, and regulations, while soft law refers to voluntary norms and codes. Governance tools such as codes of conduct, moral standards, and education are soft laws and informal measures, whose implementation focus on self-management by relevant institutions and personnel.[11] Countries throughout the world are going through a process of trial and error to deal with biosecurity threats, which requires soft laws to oversee researchers on the frontiers of biotechnology and improve the efficiency of biosecurity governance through easily adjustable and controllable mechanisms before other national biosecurity governance rules can be issued. Advantageously, the formulation of soft law involves fewer restrictions on people as well as less time and space requirements than hard laws, and more active participation and joint consultation, which may compensate for the insufficiency of traditional hard laws for fairer and more just biosecurity governance, better strengthening human rationality to restrain the abuse of technical capabilities and illegal acquisition of economic benefits, and protecting public safety while ensuring progress in scientific and technological research and industry innovation in accordance with laws and regulations.

The self-management model of the code of conduct proposed by the gene synthesis industry provides a useful template for biosecurity governance. However, this model, based on market interests, is not necessarily applicable to academia or many scientists and researchers working for governments where cultivating and establishing a responsible culture through moral education may be more valuable and practical.[40] Practical experience showed that one common issue of codes of conduct in life science research, whether at the national (regional) or international level, was that it was often difficult to guarantee effective implementation because the code is voluntary and lacks a strict implementation mechanism. In many cases, biosecurity threats caused by biotechnology development have global consequences. Therefore, it is necessary to take a consistent and comprehensive approach to formulate ethical decisions related to biotechnology safety risks and social responsibilities due to the diverse cultural, social, religious, and economic backgrounds of different countries, particularly at the international level.[41] *The Hague Code of Ethics*, which is an international model to regulate the behavior of chemical researchers, has benefited from its formulation and implementation in accordance with the principles of the Chemical Weapons Convention, so that it can be endorsed as a responsible scientific research principle in chemistry. Similar to chemistry, although codes of conduct for biologists are aimed at individual scientists, most biologists still serve in traditional scientific research institutions such as universities and governments, with the exception of a few amateur DIY Bio scientists,. Even when research funds are from private sources, the influence of the government on domestic enterprises cannot be ignored. When signing the BTWC in 1969, President Nixon stated "Scientists across the world, regardless of language, race or background, belong to a common society. They are not developing biological weapons that one country may use against another, but are now fully committed to fighting the enemy of all mankind – disease."[42] From Nixon's statement, biologists seemed set free by the BTWC.[43] However, judging from the process of vaccine development undertaken by countries around the world in response to the outbreak of COVID-19 in 2020, especially the plan approved by the UK Department for Business, Energy & Industrial Strategy to deliberately infect participants with COVID-19 to better understand the virus,[44] the research behavior of individual scientists is still influenced by the policies of their countries and institutions.

It is worth noting that self-management cannot be completed solely by individual behavior, and it relies on bodies or platforms with execution authority. Surveys show that many life science researchers still lack awareness of the misuse and abuse risks asso-

ciated with their own research.[45] Dealing with this challenge may require a systematically organized "prevention network" that integrates stakeholder demands into a coherent policy and regulatory framework to prevent unintentional or deliberate release of biological agents and toxins.[16] Since its establishment in 1974, the BTWC has gradually formed a prevention network universally recognized by all state parties to eliminate the threat of biological weapons, prevent their spread, and promote the peaceful use of biotechnology. For example, since August 2007, the BTWC used the Implementation Support Unit (ISU), as a conduit to facilitate the flow of information between science and security communities. This played an important role in increasing awareness of the Convention and its provisions in policy, technical, and public forums.[46] Taking advantage of its close ties with biologists, the ISU organizes, co-organizes, and participates in major international conferences and other activities in the life science research field to successfully improve scientists' awareness of the potential risks of abuse and intentional injury, and promote scientists' participation in the implementation of responsible science behavior. However, the effectiveness of the BTWC is currently restricted by the "mismatch between the rapid progress of technological change and slower, multilateral negotiations."[47] With biotechnology research and application continuing to progress quickly and rapidly at a global scale, it has become necessary to carry out international coordination of governance measures through or under the auspices of the UN or other multilateral agencies.[42] Therefore, to address the effective implementation of a code of conduct for biologists in the life science research field, practicing them under the framework of the BTWC seems a viable solution.

Although the BTWC is an agreement among states rather than individuals, its functionality increasingly depends on the professional knowledge and judgment of individual scientists. This is particularly in the era of fast-progressing biotechnologies with obvious beneficial and risky dual-use characteristics. Furthermore, it is important for scientists who engage in the assessment of biosecurity or biosecurity threats to understand which acts are appropriate and which should be prohibited.[48] Subsequently, scientists are obligated to explain their assessments to decision makers and put forward constructive solutions. Reports from the National Science Advisory Board for Biosecurity (NSABB) of the U. S. and other organizations have found that codes of conduct can effectively improve understanding of biosecurity risks. Moreover, the process of formulating the code educates researchers[49] thereby promoting the key goals of the BTWC.

6. Responsible life science research and respective responsibilities under the code of conduct

Recently, the idea of formulating an international code of conduct has been raised multiple times in the review and expert meetings of the BTWC, resulting in heated discussions on its usefulness and implementation on an international, national, or institutional scale.[50] According to a working paper jointly submitted by the Chinese and Pakistani governments at the latest Review Conference of State Parties, biologists and all relevant personnel engaged in bioscience research and related activities should abide by nine basic principles during research and application of aforementioned research: ethical standards; legal constraints; research integrity; respect for experimental subjects, scientific research projects and processes; constraints on dissemination of results; roles in popularization of scientific research; institutional responsibility; and roles in international exchange. The formulation of a code of conduct is only the first step towards self-management by biologists, the challenge remains the promotion of the true adoption and implementation of these codes. To overcome this challenge, the responsible research that needs to be conducted and the main stakeholders involved must be identified.

a. Professional researchers. These individuals, including researchers, post doctorates, undergraduates, and postgraduates who work in universities, private enterprises, non-profit organizations, and government research laboratories, are the most important beneficiaries of the codes of conduct. According to the InterAcademy partnership (IAP), "scientists are obliged not to do any harm. Therefore, they should always bear in mind potential consequences, and that their research may be harmful. They should realize that the goodwill of individuals cannot completely prevent the abuse of science."[51] Resnik and Shamoo argued that the responsibilities of scientists should also include not conducting or publishing research that is harmful or dangerous to others, not sharing dangerous biological materials, maintaining the confidentiality of research, reporting and informing the public of suspicious activities, educating other researchers and students on bioterrorism, assisting in formulating policies related to bioterrorism, and promoting research on response to bioterrorism.[52] According to the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists by the Center for Biosafety Research and Strategy at Tianjin University, the Johns Hopkins Center for Health Security and the Interacademy Partnership (IAP), which revised the previous working paper no. 30 "*Code of Conduct for Biologists (Model)*" jointly submitted by the governments of China and Pakistan at the 8th review conference of the State Parties to the BTWC in 2016, professional scientists or scientific institutions, including research, funding, and regulatory bodies, have the following responsibilities.

i) To respect human life and relevant social ethics, responsibly use biosciences for peaceful purposes that benefit humankind, promote a culture of responsible conduct in biosciences, and guard against the misuse of science for malicious purposes, including harm to the environment.
ii) To be aware of and observe applicable domestic laws and regulations, international legal instruments, and norms relating to biological research, including those on the prohibition of biological weapons.
iii) To promote scientific integrity and prevent misconduct in research, and be aware of the multiple applications of biological sciences, including their potential use for developing biological weapons.
iv) To protect the welfare of both human and non-human research participants and apply the highest ethical standards in research conduct, fully respecting research subjects.
v) To identify and manage potential risks in pursuit of benefits of biological research and processes, while considering potential biosecurity concerns at all stages of scientific research. To put oversight mechanisms and operational rules in place that prevent, mitigate, and respond to risks and establish a culture of safety and security.
vi) To maintain a well-educated, fully trained scientific community that is well versed in relevant laws, regulations, international obligations, and norms. To provide education and training that includes input from experts from multiple fields, including social and human sciences, to provide a more robust understanding of the implications of biological research.
vii) To raise awareness on potential biosecurity risks that might result from deliberate misuse of research. For scientists and scientific journals to strike a balance, when disseminating research findings, between maximizing benefits and minimizing harm.
viii) To play an active role in encouraging public understanding and interest in biological science and technology, including its potential benefits and risks. Communicating scientific

facts and addressing concerns, uncertainties, and misunderstandings to maintain public trust. Advocating for peaceful and ethical applications of biosciences and working collectively to prevent the misuse of biological knowledge, tools, and technologies.

ix) To identify the potential for misuse of bioscience research, and ensuring that expertise, equipment, and facilities are not used for illegal, harmful, or malicious purposes at any stage of research. Establishing a training system for scientists and appropriate mechanisms and processes to monitor, assess, and mitigate potential vulnerabilities and risks in scientific activities and dissemination.

x) To encourage international cooperation and collaboration in the pursuit of peaceful innovation in, and applications of, biosciences, and promoting learning and exchange opportunities to share best practices in biosecurity. Furthermore, to actively provide relevant expertise and assistance in response to potential biosecurity threats.

b National Scientific Institutions. Scientific institutions consist of scientists selected for outstanding research. They actively work with regulators in their countries to formulate codes of conduct for biologists and present independent expert aid to government regulatory decisions. In particular, fair judgments on policy decisions in terms of science, must be free from the influence of political, industrial, or other special interests. Scientific institutions communicate and share information with those of other countries and global convention organizations, while condemning any academic misconduct by domestic biologists in public on behalf of domestic academia. The National Academy of Sciences, the most honorable academic institution in each country, should organize regular reviews of its research and provide guidance for responsible scientific research. The Engineering and Medical Responsibility Committee of the U.S. National Academy of Sciences issued Cultivating Research Integrity guidelines in 2017, which contains reviews for "responsible research behavior" proposed by the National Institutes of Health (NIH), and basic principles put forward for educational evaluation of responsible research.[53]

c. National-level Scientific Societies Scientific societies are associations authorized by law, and their members are usually professionals in relevant fields. The government typically grants self-management to these societies, as long as their professional knowledge is commensurate with public interests.[26] Due to the nature of these professional societies, they are in the best position to understand the potential risks of relevant research. They are also beneficial for forming codes of conduct for their members in specific sub-fields. National scientific societies in specific sub-fields should take the initiative to introduce and explain biosecurity risks from the field to government regulators and scientific academies. They should participate in the formulation of domestic codes of conduct for biologists, and provide their practical progress to professional associations at the international level as policy reserves. For example, the International Union of Microbiological Societies (IUMS) adopted the Code of Ethics against Misuse of Scientific Knowledge, Research Results and Resources in 2006, which is based on the previous achievements of the American Society for Microbiology (ASM) on the topic.[54] In the case of any academic misconduct, scientific societies representing the relevant field should cooperate with national scientific academies in public condemnation.

d. International scientific societies and academic organizations During research, scientists transcend national and political boundaries to establish contacts and form organizations with colleagues from different countries based on common interests.[54] This process includes strengthening scientific undertaking, promoting cooperation among scientists, and providing independent advice on key global issues. For instance, the Global Partnership Working Group and the International Union of Microbiological Societies (IUMS) have been important advocates for self-awareness of biosecurity risks among biologists and formulated codes of conduct for their members. International scientific societies have significant advantages in dealing with international agreements under the global framework, as they can establish a transnational dialog, which gathers scientists from academia and industry, scientific and technical members of state party delegations, and security policy experts from different countries to promote consensus on certain issues.[12] They should therefore also bear the responsibility of publicly condemning any academic misconduct in biological research.

e. Research Institutions Research institutions, including government research institutions, universities, non-profit research institutions, and private enterprises with R&D capabilities, are high-level organizations for biological research. Ideally, each institution should establish its own institutional biosafety[55] and ethics committees[56] with the following mandates:

i) Formulate their codes of conduct;
ii) Represent all necessary professional knowledge in the field (when the above conditions are not available internally, they should be obtained externally);
iii) Have the right to make final review decisions;
iv) Obtain clear mandates, such as funds and time, to ensure the implementation of review tasks;
v) Consist of scholars from related fields but remain independent to eliminate potential conflicts of interest (external experts can be selected).

In addition, research institutions should be responsible for monitoring risks and conducting biosecurity risk assessments during the conduction of research. For any unpredictable results during research, or changes in understanding of the risks due to developments in the field, reassessment should be organized immediately. Moreover, research institutions should assume the responsibility of providing education and training to ensure that all researchers are fully aware of all potential risks and should "formulate education and training programs by providing a guiding framework to determine the roles and responsibilities of professional researchers in risk prevention and control, and evaluate individual performance,"[57] and improve researchers' abilities to prevent biosecurity risks through a combination of classes, practicals, and field training under the guidance of tutors.[58] Finally, to ensure that researchers can truly understand and implement the codes of conduct, institutions must ensure that their members recognize and accept the legal responsibilities and consequences of violating the codes,[59] and improve their own evaluation and promotion systems. For example, the American Public Health Service Act requires all research institutions that have received funding from the U.S. federal government since 1985 to formulate internal policies for scientific misconduct.[10]

f. Sponsors. Research funding typically comes not only from government agencies but also from businesses and non-profit organizations. Accordingly, sponsors can be classified as grant or contract sponsors. As the major funding source, governments usually have the dual identities of grant and contract sponsors in life science research. As a sponsor, the government should ensure that all biological research projects funded have carried out sufficient risk assessment and feasibility analysis on possible health and social threats, and should help researchers and institutions formulate prevention, emergency, and education programs compatible with risk management and control. For example, the largest funding agency for life sciences research, the NIH, requires instruction in RCR as a condition of funding for all trainees, fellows, partici-

pants, and scholars receiving support through the NIH.[60] Although businesses and non-governmental organizations may lack the capability to assess all biosecurity risks, they should be responsible for ensuring that researchers who receive the funding have the ability to identify, assess, and manage potential biosecurity risks.

g. Regulators. Some scholars have proposed that "it is inevitable that top-down government supervision will be required before academia has reached a full consensus, that is, an effective match between self-regulation and public opinion".[11] The current trend in the governance of bioscience and technology risks is to establish country-level biosecurity measures. Governance tools include soft law and informal measures, such as professional standards, codes of ethics, and education, as well as awareness measures.[61] In addition, as specialized institutions are responsible for managing and carrying out biological research, regulatory authorities should promote legislation at the national level to avoid temporary, ineffective, and uncoordinated supervision.[11] Regulators should also be responsible for formulating and promulgating relevant regulatory rules. For example, in 2008, Israel passed the Regulation of Research into Biological Disease Agents, establishing the Hazardous Biological Agents Committee as a national regulator responsible for assessing the risks posed by the proposed experiments to the health, welfare, and safety of the Israeli. The regulator should assess all possible risks related to biosecurity and ethics before the projects are approved.[62] Regulators should also serve as important participants in formulating domestic codes of conduct. In addition to formulating and implementing hard law measures, the U.S. government also plays an important role in soft law.[16] The formulation of soft laws requires regulators to actively communicate and negotiate with academia and private businesses. For example, when the biannual List of Selective Agents and Toxins review was carried out in 2010, the U.S. government adopted a more transparent approach, inviting academic scientists to participate in the policy revision, including researchers and project leaders in the review working group, and taking suggestions from the public.[63]

h. Scientific publishers and other disseminators. It is not enough to rely solely on moral education to strengthen the responsibility of biologists.[64] As a platform for the publication of research results, scientific publishers and other disseminators bear the responsibility to restrict or prohibit the dissemination of research that could be abused by state and non-state actors and threaten public health. Publishers should ensure that the biosecurity risks of the research results and processes are fully evaluated during the peer review process, and that proper social dissemination of scientific research is adopted to avoid misunderstandings among the public. In 2003, the editors of several major scientific journals issued a joint statement calling for a careful review and publication of safety-sensitive research related to microbiology, infectious agents, public health, and plant and agricultural systems.[65] Other platforms, such as online social media, which are increasingly becoming an alternative form of research dissemination, should be treated the same as traditional scientific publishers. Ultimately, the responsibility for disseminating scientific achievements falls on everyone who participates in knowledge transmission chains.[66]

7. Building a Multi-level system of ethical code for biologists under the Biological and Toxin Weapons Convention (BTWC) of the United Nations with effective implementation

The recent global COVID-19 pandemic has had profound global economic and social impacts. The upheavals have highlighted the fact that we live in an interconnected world and that science occurs in a societal context. We are more aware of the need to improve biological security against natural, accidental, and deliberately caused disease, and the question of biological security has therefore been pushed up the global governance agenda in a way that is rarely possible. It is thus urgent to strengthen existing international biosecurity governance mechanisms to prevent the malicious abuse of life science research and maintain international biological arms control norms. Awareness is growing among state parties that a code of conduct may be necessary, under the framework of the BTWC, for professionals engaged in life science research from the government, academia, and industry to strengthen biosecurity education, awareness, and publicity.[11] The participation of the global life scientific community in the formulation of a code of conduct for biologists under the framework of the BTWC can help reduce the risks that may be incurred due to accidental or intentional abuse of life science research. In the context of global pandemics, the 9th Review Conference of the State Parties to the BTWC in 2022 will be crucial for all state parties to reach a consensus on a code of conduct and its effective implementation. Although the code of conduct for biologists is voluntary, it is an important supplement to the domestic laws and regulations in life science research of all countries and the existing codes and guidelines of international academic organizations. The industry security standards formulated by international organizations, such as the International Organization for Standardization (ISO), have in fact become international laws and regulations, and their contents have later been transformed into domestic regulations in many countries.[10] Here we argue that to improve the culture of biosafety, biosecurity, and responsible conduct, the life sciences will have to pay more attention to lessons learned in other fields and adapt those tools and frameworks.[67] In the process of seeking effective implementation of these codes, it is not enough to create only the responsibility framework to produce a set of governance measures; systematic creation of an implementation system of ethical codes at both international and domestic levels is also necessary (Fig. 1).

8. Effective approaches of development and implementation of code of conduct at an international level

In accordance with Article XII of the BTWC, a review conference of the state parties is held every five years to review its implementation and discuss scientific and technological progress relevant to the BTWC.[68] Therefore, formulation of a code of conduct for biologists under the framework of the BTWC requires all state parties to first achieve a consensus on the purpose, principles, content, and implementation of the code at the annual Meetings of Experts (MX) and Meetings of State Parties (MSP), and then reach a BTWC resolution.

a. The code should serve as an ideal (ethical code) for the principles of integrity, honesty, and objectivity in biological research. This will help raise awareness among biologists of the power of biotechnology and the ethical responsibilities that arise from it. Simultaneously, it establishes the ideals of scientific research behavior and indicates behaviors that should be punished according to the law.[42] This ethical code constitutes a principal guidance for state parties to establish their own domestic codes.

b. The code should draw lessons from past laws and regulations on the biosecurity of state parties. It is worth noting that state parties have been exploring the possibility of defining individual engagement in activities that should be prohibited by the Convention as national criminal offenses since 2005,[69] and some of the widely accepted codes of conduct in the past have been used by courts to establish legal standards.[70] In particular, in 2021, as a response to biosecurity and biosafety issues in China, the China Biosafety Law (CBL) leaned towards using laws to regulate bioethical issues in this field.[54] Therefore, a code of conduct will also provide a reference for state parties to formulate, revise, and update their national laws and regulations for biosecurity.

c. The codes should take full account of all existing codes of international academic organizations and professional societies.

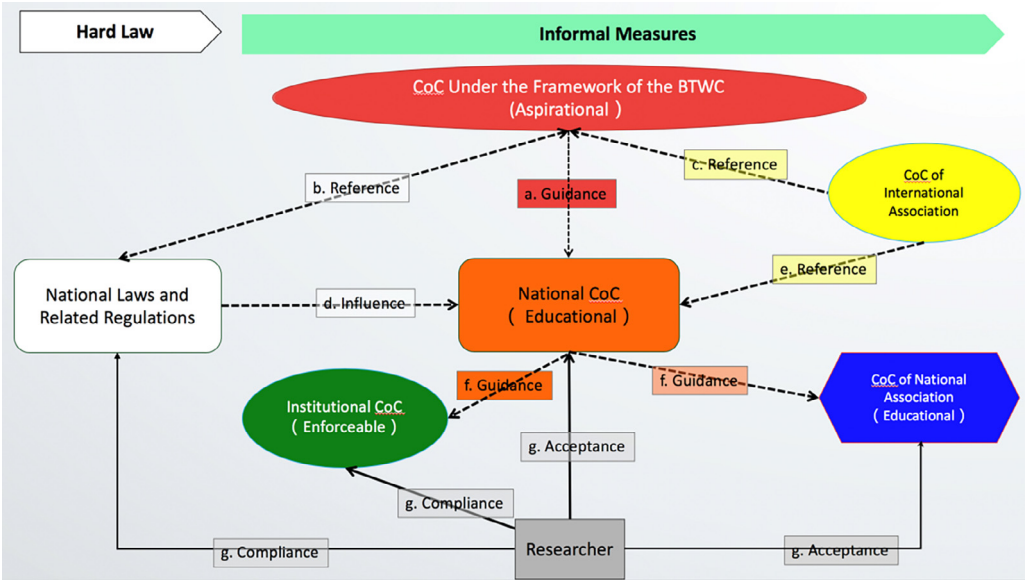

Fig. 1. System for implementation of an ethical code of conduct for biologists.

Global platforms such as the IAP are particularly valuable when dealing with international conventions, as they provide an effective mechanism for scientists worldwide to participate.[66] For example, in 2015, state parties reached a resolution on the formulation of *the Hague Code of Ethics* for Chemical Weapons Convention to promote a culture of responsible behavior in chemistry research and prevent the misuse of chemical technology. As a principal guide for global chemical research activities, the Hague Code of Ethics has been recognized by the International Union of Pure and Applied Chemistry (IUPAC) and the International Council of Chemical Associations (ICCA) and plays an important role in regulating all responsible chemical research.

9. Effective approaches of development and implementation of code of conduct at a domestic level

The formulation of an ethical code of conduct for biologists within the framework of the BTWC would further reaffirm the strong commitment of state parties to the objectives of the BTWC and strengthen the efforts of all state parties in promoting biosecurity education, awareness, and advocacy at the domestic level.[71] To fulfill goal, state parties must first formulate their national codes of conduct (educational or advisory) based on this code, which will provide specific guidelines for life science research in their own countries. However, it is worth noting that codes of conduct alone are not enough to reduce risks arising from biological research. In some countries and organizations, such as the EU, policymakers still do not consider self-regulation and norm construction as viable alternatives to hard law.[3] In fact, an integrated approach including both soft and hard laws may be necessary in some cases.[72] In this context, dialogue, communication, and cooperation between the governments as regulators and the audience of the code of conduct is important, and an appropriate balance between top-down legal regulation and bottom-up autonomy of the scientific community must be reached.

10. Effective approaches of development and implementation of code of conduct at a national level

National-level codes of conduct are often influenced by national laws and policies. Hard and soft law are not mutually exclusive, but rather mutually influential management measures for governing biological research risks. Voluntary standards and codes of conduct can often be made more effective through criminal law to punish damage caused by accidental misuse or intentional abuse.[73] In this process, regulators, as the main developers of hard law and important participants in the formulation of soft law, need to take advantage of their organizational capability and adopt a more transparent approach to open dialogue with all stakeholders. During this discourse, regulators, scientists, and other stakeholders should openly discuss the potential risks of scientific research and propose measures that reduce identified risks, including responsible research by scientists and sound regulatory policies by regulators.[74] In addition, the public should be encouraged to openly express their views.

These codes of conduct should be integrated with those of international academic organizations previously implemented. The Statement on Biosecurity issued by the IAP in 2005 has a great influence on national-level codes, and it could serve as a good reference for drafting guidelines for specific items. For example, the Responsible Behavior of Global Research Institutions report published by the InterAcademy Partnership Council in 2012 stated that researchers should fully consider the potential harmful consequences of their research when first planning a project.[54] Referring targeted and specific guidance from international academic organizations will mean that more scientists can participate in the process of formulating codes of conduct of their own countries, thus enhancing their sense of ownership of the codes.[75] Based on the experience of international academic organizations in including the scientific community, establishing a culture of responsible biological research, and defining standards of research regulation, many countries have invited experts from international academic organizations to share their experiences in formulating codes of conduct. In 2008, the U.S. government invited international scientific organizations such as the IAP to convene a workshop on incorporating biosecurity risk education into a training program for biologists.[76]

National-level codes of conduct should also guide the establishment of internal codes of conduct for individual research institutions, domestic academic organizations, and sub-fields according to their needs. Academic organizations are more likely to be involved in promoting responsible scientific research by highlighting the exemplary behaviors of scientific leaders within their own organization and[97] this requires the creation of specific educational

guidelines and recommendations. For research institutions where biological research is conducted, "institutions with better-developed biosecurity programs tend to be more likely to introduce and implement an internal responsible biosafety culture,"[77] i.e., to become "a Highly Reliable Organization (HRO) with a good performance record. . .to ensure its members' compliance through supervision."[78] Therefore, the effectiveness of their codes of conduct is determined by the institutions' ability to prevent and control risks, by adopting enforceable codes – that is, institutions should clarify what are and are not acceptable research behaviors in the specific content of the code.

As the subjects of the codes of conduct for scientific research, biologists should first consciously comply with all legal rules and standards on scientific research in their countries, and consciously resist illegal acts such as deliberately neglecting and ignoring laws and regulations and circumventing supervision.[79] Since most biological research occurs within a biologist's country, domestic level codes act directly on them. According to the above elaboration, national-level codes, internal codes of institutions, and codes of academic organizations differ in design based on their different purposes. Biologists are expected to accept the specific educational guidelines and recommendations provided by national and domestic academic organizations, and adhere to the enforceable codes formulated by research institutions, which are responsible for regulating the entire research process.

11. Conclusion

As the formulation and implementation of a code of conduct, the fundamental guideline for life science research worldwide, is influenced by the laws and policies of state parties, the experiences of relevant international academic organizations should be utilized. Ideally, for an ethical code of conduct for biologists, a resolution reached by all state parties of the BTWC should guide each state party to develop their national codes based on their own needs and circumstances. Moreover, it is recommended that research institutions and academic organizations at all levels formulate their own codes and implement the responsibilities of biologists based on this and their own national codes of conduct. The effectiveness of the codes depends on how well they are implemented by the scientific community,[53] especially the distribution of governance responsibilities, which could represent a huge challenge because each committee and organization will have its own subculture and established norms and practices.[10] Thus, further research on how to effect self-discipline under the framework of the BTWC at different levels, in terms of formulation of subjects and procedures, and implementation of and compliance with rules, needs to be conducted. The global outbreak of COVID-19 pandemic over the past 2 y, and the upcoming 9th Review Conference of the BTWC in 2022 has increased the urgency for this and introduced a rare historical window to advocate responsible life science research at a global level. As the first step toward this goal, a consensus resolution among the state parties will be valuable in raising awareness and participation levels of the scientific community and making effective and collective efforts to build a global code of conduct for biologists.

Conflict of interest

The authors declare no conflict of interest.

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