TERROR
Strengthened preparedness and response to biological and chemical terror attacks

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WP8 Novel Threats

D8.2: Synthetic Biology - Risk assessments and recommendations for future governance guidelines

Authors:	Lead author: Didier Breyer[1] Co-authors: Aline Baldo[1], Tone Bjordal Johansen[3], Fanny Coppens[1], Mats Forsman[2], Else Marie Fyske[4], Elisabeth Henie Madslien[3], Jessica Jones[5], Franck Limonier[1], Saskia Rutjes[6]
Affiliations	[1] Sciensano; Belgium [2] Swedish Defence Research Agency; Sweden [3] Norwegian Institute of Public Health; Norway [4] Norwegian Defense Research Establishment, Norway [5] UK Health Security Agency; United Kingdom [6] Rijksinstituut voor Volksgezondheid en Milieu (RIVM), The Netherlands
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Terms and abbreviations

AG	Australia Group
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
ARG	Antimicrobial Resistance Gene
Biological agent	A microorganism, virus, biological toxin, particle or otherwise infectious material, either naturally occurring or genetically modified, which may potentially cause infection, allergy, toxicity or otherwise create a hazard to humans, animals or plants (WHO, 2024).
Biosafety	Containment principles, technologies and practices that are implemented to prevent unintentional exposure [of humans, animals and the environment] to biological agents or their inadvertent release (WHO, 2024).
Biosecurity	Policies, principles, technologies and practices implemented for the protection and control of and accountability for biological material, technology and information or the equipment, methods, skills and data related to their handling. Biosecurity aims to prevent intentional or accidental unauthorized access to, and loss, theft, misuse, diversion or release or even weaponization of such commodities (WHO, 2024).
DURC	Dual Use Research of Concern
DIYbio	Do-It-Yourself biology
CBRN	Chemical, Biological, Radiological or Nuclear
CRISPR/Cas/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats. Cas stands for "CRISPR associated" and refers to a group of nucleases such as Cas9 which is an RNA guided nuclease widely used in gene editing.
Desktop DNA/RNA synthesizers	Desktop machines that can synthesize fragments of DNA/RNA
Gibson assembly	Molecular cloning method that allows for the joining of multiple DNA fragments in a single, isothermal reaction (Gibson et al., 2009).
GoF research	Gain-of-Function research refers to genomic alterations in organisms to enhance biological functions, e.g., pathogenesis, type of host, etc.
Homology searches	Homology searching is an essential part of making inferences about where a biological sequence came from, and/or what it does. What a researcher will often do is search this sequence

	against some reference database of annotated sequences to learn what function the sequence performs and/or what organisms are likely to encode this sequence in their genome (https://readiab.org/database-searching.html).
LoF research	Loss-of-Function research refers to genomic alterations in organisms that result in a decrease of biological functions e.g., decreasing a pathogen's ability to cause disease.
WGS	Whole Genome Sequencing

Key Findings

The literature review conducted prior to this work highlighted various potential risks associated with developments and applications in the field of synthetic biology. These include modifying existing pathogens, re-creating extinct pathogens or designing new pathogens, including bacteria producing harmful effector proteins. The accelerated technological developments within this field, combined with the widespread availability of knowledge and technology, raise concerns about the potential for misuse or the possibility of an intended incident.

Many recommendations have already been made on this subject. As authors of this report, we choose to build upon the literature review and other relevant literature by structuring the recommendations according to different stakeholders. Our objective is to reflect the diverse range of players involved in the governance of the biosecurity of synthetic biology, including scientists, scientific institutions and academia, publishers of scientific journals, funding bodies, professional organizations, the private sector, governments, and international bodies. We emphasize the vital need for consultation and coordination among these players.

To address biosecurity and dual-use concerns in synthetic biology effectively, it is essential to adopt an interdisciplinary and intersectoral approach. Governance in this area must bring together multiple stakeholders with various roles and responsibilities, operating at different levels (individual, institutional, national, regional, and international), and consider the scientific, economic, social, political, and ethical aspects of synthetic biology.

It is the responsibility of governments and the European Commission (EC) to ensure that these stakeholders fulfil their roles and responsibilities so that the risks of misuse in synthetic biology research and applications are properly assessed and managed. This can be achieved through various approaches, including the implementation of legally binding measures where necessary. In doing that, governments and EC should balance the need to protect human and animal health and the environment from synthetic biology risks with the freedom of research and the need for innovation in this field. Regulatory frameworks should be adaptable to the rapid advancements in synthetic biology while remaining relevant and effective.

EC plays a central role in creating policies and regulatory frameworks that enable a harmonized and consistent approach across all Member States to complex challenges. Additionally, EC and

governments can negotiate international agreements, participate in global forums, and advocate regulatory frameworks that reflect EU values and standards. This harmonization is crucial to prevent a fragmented approach to biosecurity and dual-use concerns in synthetic biology.

Many recommendations, including our own, call for increased awareness, screening, and identification of research that may be diverted, either intentionally or accidentally. Establishing a clear framework for effective risk assessment with accessible, rapid, and easy-to-use procedures is necessary for genuine supervision. In this context we advocate the need for developing a **European biosecurity platform**, consisting of biosecurity experts from all EU Member States, that may facilitate the coordinated development of policies, guidelines and tools required to address biosecurity and dual-use concerns in synthetic biology. The current European Biosecurity Regulators Forum (EBRF) may be a good fundament to further develop this platform.

In summary, an appropriate model for managing the risks of synthetic biology involves continuous risk assessment, the involvement of all stakeholders and legal sources, and measures ranging from risk awareness for individual scientists to laboratory guidelines, codes of conduct, national laws, and European and international provisions.

Objectives

Relevant risk assessments will be written to inform Member States on the most pressing risks posed by synthetic biology.

Recommendations made on the governance of synthetic biology to prevent or minimize misuse of this technology, for the benefit of Member States.

Background

Joint Action TERROR

The European Union (EU) plays an important role in counter-terrorism activities. While primary responsibility for security measures lies with individual Member States, the EU provides a borderless perspective that encourages cooperation and coordination through numerous policy frameworks.

EU Regulation 2022/2371 (EU, 2022) seeks to build a stronger EU health security framework by improving coordination between the European Commission and other EU agencies. The regulation

was formally adopted during the lifecycle of Joint Action TERROR and repeals Decision N° 1082/2013/EU on serious cross-border threats to health. It provides the framework to improve preparedness and to strengthen the response capacities to health emergencies of biological, chemical, environmental, and unknown origin.

The 2009 Commission Working document 'Bridging Security and Health' identified areas that could be strengthened. It states, among other issues, that Member States preparedness in health would benefit from sharing lessons learned and best practices in, among other issues, cross-sectoral support, and coordination.

To support this, Joint Action TERROR's main objectives were to address gaps in health preparedness and to strengthen cross-sectoral work with security, civil protection, and health sectors response to biological and chemical terror attacks.

Joint Action TERROR aimed to build upon work undertaken for the Health Programme and other relevant EU programmes and exercises in particular Joint Action "Strengthened International Health Regulations and Preparedness in the EU" (SHARP) and the Joint Action "Healthy Gateways".

Overview of Synthetic Biology and Recent Advancements

The term 'synthetic biology' has not been clearly defined. One can refer to the operational definition chosen in 2014 by three European scientific committees (SCENIHR et al. 2014): "*SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms*". The Convention on Biological Diversity further clarified that "*While there is no internationally agreed definition of 'synthetic biology', key features of synthetic biology include the de novo synthesis of genetic material and an engineering-based approach to develop components, organisms and products.*" (https://www.cbd.int/doc/meetings/cop/cop-12/information/cop-12-inf-11-en.pdf). This scientific field has become ubiquitous in the modern world, underpinning many biological applications.

Synthetic biology was recognized as a separate technological domain in the early 2000's and has since played an important role in the development of novel tools and products across multiple sectors, such as health, environment, food/agriculture and energy (Tan et al., 2021; Voigt, 2020). Advancements within DNA synthesis, sequencing, assembly techniques and genome editing have opened for new opportunities in the modification and recreation of biological systems (Juhas, 2023). Important

milestones include the introduction of the Gibson isothermal DNA assembly method in 2009 (Gibson et al., 2009), creation of a bacterial cell based on a chemically synthesized genome in 2010 (Gibson et al., 2010) and the discovery of the CRISPR/Cas9 system and critical components to enable targeted DNA-cutting and editing *in vitro* in 2010/2011 (Deltcheva et al., 2011; Jinek et al., 2012). The researchers discovering the gene editing precision of CRISPR/Cas9 (Charpentier and Doudna) was later awarded the Nobel Prize in Chemistry in 2020 (*Genetic scissors: a tool for rewriting the code of life*).

Examples of recent advancements and opportunities within the biomedical field include the engineering of cell factories to enhance the production of various pharmaceuticals from microorganisms, in diagnostics, as nanocarriers or in vaccine development (Yan et al., 2023). A multitude of other applications are being discovered in other areas such as environmental protection, agriculture, and food production, but it is beyond the scope of this report to give a full overview of this rapidly evolving field.

Novel beneficial applications which may affect humans, animals, and the surrounding environment, have urged the need for critical assessments and international debate on the ethical aspects and biosecurity concerns of synthetic biology. The potential widespread use and impact of this technological field, calls for engagement and debate across countries and disciplines to consider the risks and benefits ensuring a sound and responsible development.

To contribute to this process, we performed a literature review on technological advancements within synthetic biology and the potential for misuse covering the period January 2016 to February 2022 (Johansen et al., 2024). In the following sections, the main risks associated with developments and applications of synthetic biology are presented and discussed. Recommendations are then addressed to the various players involved in the governance of the biosecurity of synthetic biology.

Identified risks

As Deliverable 8.1 of the EU Joint Action TERROR, a literature review was completed ahead of this report to explore the state of scientific knowledge on the misuse-potential of synthetic biology (Johansen et al., 2024). Table 1 provides a summarised list of risks identified from the literature review.

Table 1: Risks identified from Synthetic Biology Literature Review, produced as part of Joint Action TERROR

Risk	Description	Evidence
1	Editing microorganisms to increase their pathogenicity by adding toxins, virulence factors and/or genes associated with antibiotic/ drug resistance.	(Carter & Warner, 2018; Cummings et al., 2021; Dieuliis & Giordano, 2017; Holm, 2017; Imperiale et al., 2018; Kobokovich et al., 2019; Walsh, 2018; Wang & Zhang, 2019)
2	Modification of zoonotic agents to increase their transmissibility to humans.	(Carter & Warner, 2018; Cummings et al., 2021; Holm, 2017; Walsh, 2018).
3	Creating novel infectious agents with unknown disease potential (*de novo* synthesis).	(Cello et al., 2002; DiEuliis et al., 2017; Koblentz, 2017; Noyce & Evans, 2018; Noyce et al., 2018; Tumpey et al., 2005)
4	Do-It-Yourself (DIY) biology / DIY laboratories.	(Keulartz & van den Belt, 2016; Meyer & Vergnaud, 2020; Sarpong et al., 2020)
5	Increased accessibility of gene editing and sequencing technology and knowledge, lower costs and increased simplicity of use (easy-to-use CRISPR–Cas9 gene editing kits at affordable prices).	(Smalley, 2018; Sneed, 2017)
6	Design of proteins with new functions, facilitated by the ongoing deep learning revolution in 3D structure prediction.	(Keulartz & van den Belt, 2016; Pilizota & Yang, 2018)

7	Publicly available databases populated with genomes of highly virulent pathogens, including those with AMR and toxin-encoding genes. The sharing of detailed information furnishes comprehensive insights into pathogens, encompassing details about their origin, transmission routes, virulence factors (e.g., toxins), and antimicrobial resistance (AMR) which could potentially be misused to create dangerous pathogenic bioweapons.	(Nwadiugwu & Monteiro, 2022; Smith & Sandbrink, 2022; Vinatzer et al., 2019)
8	Information sharing on advances in synthetic biology (e.g., scientific publications) might inspire terrorists by demonstrating what is technically possible and how to do it.	(Meyer & Vergnaud, 2020)
9	Increasing convergence of the life sciences with other scientific fields (e.g., chemistry, artificial intelligence and nanotechnology).	(Dixon et al., 2022; Smith at al., 2022; Trump et al., 2021a)
10	Spreading of misinformation (minimization vs. exaggeration of risks in the public debate).	(Melin, 2021)

Risk assessment

Synthetic biology technologies are developed for beneficial purposes and offer substantial and valuable advances in various fields such as medicine, energy, or environmental remediation. However they can also be misused or repurposed for malicious intentions by people with relevant knowledge and adequate facilities and equipment, and potentially cause harm to humans, animals, plants and agriculture, and the environment (NAS, 2018). Potential threats include the ability to modify pathogens, e.g. by increasing their transmissibility, their virulence or make them resistant to common antibiotics used for treatment. The technology can also be used to re-create extinct pathogens or design new pathogens (Trump et al., 2021b). Such research with potential for harmful misuse, is termed Dual-Use Research of Concern (DURC) (Rath et al., 2014). Various related terms are also used to describe the dual-use potential of biological research, such as gain-of-function (GOF) research, gain-of-function research of concern (GOFROC), or enhanced potential pandemic pathogen (ePPP) research (Saalbach, 2022).

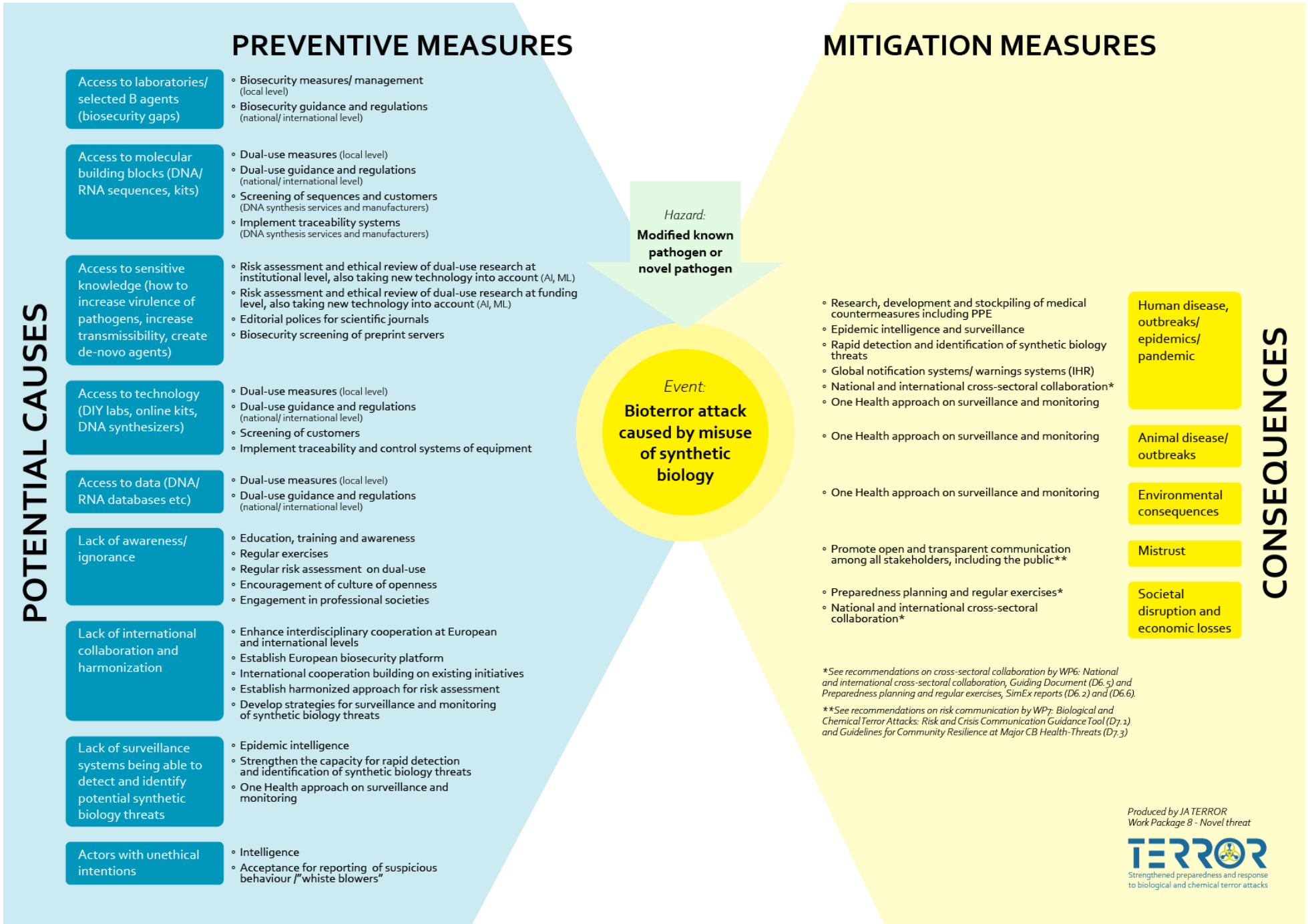
In the literature review performed in Deliverable 8.1 of this EU Joint Action (Johansen et al., 2024), being limited to open sources, we found no examples of synthetic biology being accidentally or deliberately used to cause harm. However, we did find several examples of synthetic biology being used to recreate or modify highly pathogenic agents for beneficial or research purposes. This observation, combined with the accelerated technological developments within this field, including the availability of open science and sequence databases, raises concerns about the potential for misuse (Li et al., 2021; Sun et al., 2022). The rapid development within artificial intelligence and machine learning further gives opportunities for combining the available information in new and more accessible ways which increases the risk of misuse (Melin, 2021).

The consequences of infectious diseases can be severe regardless whether the origin of disease is natural, accidental, or intentional (Franconi et al, 2018; NATO, 2012). The COVID-19 pandemic demonstrated the enormous effects a pandemic can have worldwide, and the origin of the virus is still debated. We probably will never know with full certainty if the pandemic had a natural origin, was the result of a laboratory escape or even more controversially a result of an engineered virus escaping from research (see e.g. Alwine et al., 2023). With the growing number of laboratories and research projects using synthetic biology techniques, the probability of unforeseen incidents is likely to increase, whether they result from a lack of knowledge, accidents, negligence or misuse.

As highlighted by the WHO in its global guidance framework for the responsible use of the life sciences, the risks arising from developments in the life sciences and converging technologies need to be recognized and mitigated (WHO, 2022). This can be complicated by the fact that governance and oversight frameworks for managing the risks posed by science and technology often lag behind developments and innovations in the life sciences. The reasons for this include the rapid development and diffusion of biotechnology capabilities, the lack of biorisk governance structures in many countries and the increasing convergence of life sciences with other scientific fields (e.g. chemistry, artificial intelligence and nanotechnology).

Identification of risks/hazards (what can go wrong) is usually the first step in the process of assessing biological risks. However, proceeding to the next steps of evaluating and characterizing the current risks of synthetic biology (e.g. how likely is the risk of misuse and what would be the consequences/damage potential), is challenging in the context of bioterrorism/biowarfare since it requires extensive and up-to-date knowledge about several factors, such as technological maturity, cost, and availability, implementation of risk mitigation measures and insight in the actor, intent, capability, target population and threat landscape (threat assessment). While the identification of risks/hazards and relevant risk mitigation measures were partly covered by the above-mentioned literature review, assessing the threat landscape and potential target groups is outside the scope of this project. However, a simplified bow-tie approach (Figure 1) could be used as a tool to visualize the risks of misuse of synthetic biology identified in the literature review (see Table 1) and relevant risk mitigation measures/barriers. To analyse the "risk level" of given biosecurity scenarios, it is possible to generate a probability-impact matrix, as suggested by SIPRI 2023 (Himmel, 2023) This would imply the development of specific threat scenarios, including information about the agent, technology/mechanism of modification/creation, subjects affected, treatment/detection capabilities and type of actor (state *vs.* non-state).

Figure 1: Bowtie diagram illustrating the risk analysis of a bioterror scenario involving synthetic biology. Potential causes and possible preventive measures as well as potential consequences with mitigation measures are described.



Summary of recommendations

Table 2: Summary of recommendations and the identified risks that they contribute to mitigate (see table 1 for corresponding risk numbers).

Recommendations		**Risk (number correlates to risk identified in Table 1)**
1. Individual scientists		1 - 10
2. Scientific institutions	2.1. Education and awareness	1 - 10
	2.2 Training	1, 2, 3, 5, 6
	2.3 Ethics	1, 2, 3, 6, 8
	2.4 Biosecurity management	1 - 9
3. Journal Editors and platforms of peer-reviewed literature		8, 9, 10
4. Research funding bodies		8, 10
5. Nucleic acid (DNA/ RNA) synthesis services and manufacturers		4, 5, 7, 9
6. Professional / non-governmental organisations		4, 8, 9, 10
7. Governments (national, EU, international)	7.1 Cooperation	7, 9
	7.2 Regulatory	4, 7, 8
	7.3 Biosecurity Assessment	1 - 9
	7.4 Surveillance and Monitoring	1 - 9
	7.5. Detection	1 - 9
	7.6. Emergency Planning	1 - 9
8. Interdisciplinary and cross-sectoral levels		9, 10

Recommendations

1. At level of individual scientists

In a nutshell :

1. Educate scientists about the biosecurity and dual-use risks of synthetic biology and integrate risk considerations into every stage of their research.
2. Secure the ability for scientists to report major risks or ethical issues, with research institutions embedding ethical considerations into their policies.
3. Encourage scientists to actively participate in societal discussions on synthetic biology, with such involvement being recognized and valued in their career development.

Scientists must be informed, educated, and made aware of the risks associated with the use of synthetic biology, particularly regarding biosecurity and dual-use considerations, as well as about existing policies and regulations. They must be aware of the necessary balance between exploring technical possibilities and considering known or potential risks. This responsibility should apply to all scientific disciplines concerned with synthetic biology (not just biologists, but also, for example, bioinformaticians). Consideration of risks related to the uses of synthetic biology should be a constant reflex, both as a preliminary step and during the conduct of any research activity.

If they identify major biosecurity or dual-use risks or other ethical issues during their scientific work in the field of synthetic biology, it is important that scientists are able to draw the attention of their responsible authorities (the role of "whistle-blowers" - INRA, 2014). This must be reflected in institutional rules and practises in the research institutions (see recommendations in section 2).

Scientists should also be encouraged to make their voices heard in societal discussions surrounding synthetic biology. Active participation in discussions on biosecurity, biosafety, and dual-use should be recognized and valued in the evolution of a scientific career within the EU. Given their knowledge and experience in the field, scientists can foster an environment conducive to both the advancement of research and the safety of its applications. By engaging in these debates, scientists can ensure that any regulations put in place are based on reasoning underpinned by transparent scientific facts assessing the potential dual-use applications and risks. While policymakers play an important role, incentives for engaging the voices of active researchers are pivotal for compliance.

2. At level of scientific institutions

2.1. Education and awareness

In a nutshell:

1. Provide researchers with the tools and training needed to integrate biosecurity and dual-use considerations into their work.
2. Integrate biosafety and biosecurity aspects into the curricula for life sciences and synthetic biology students.
3. Promote a culture of openness and ethical conduct by encouraging discussions on biosecurity and ethical concerns.
4. Establish clear institutional policies and guidelines on biosecurity and dual-use aspects of synthetic biology.

As mentioned before, researchers in synthetic biology must be made aware of the biosecurity and dual-use aspects of their research. Scientific institutions (in particular universities and other institutions that educate future researchers in the life sciences) must provide them with the means to conscientiously integrate risk considerations into their research work, with the aim of achieving self-regulation among scientists. This can be seen as a risk-benefit analysis of research projects in which the risks of potential misuse are weighted against the assumed potential benefits of scientific innovation.

Both the biosafety and the biosecurity aspects must be integrated from the start in the curricula for students engaged in life sciences and synthetic biology. Courses should cover topics such as dual-use research, ethical implications, risk assessment, and regulatory frameworks. They should be considered an overarching principle, to be integrated in every aspect of the researcher's work. An interdisciplinary approach is essential. For example, computer science students working in bioinformatics should also be aware of biosecurity issues. This interdisciplinarity can foster broader collaborations to address biosecurity challenges effectively.

A culture of openness and responsibility about the research that is performed, and of ethical conduct, should be strived for, by encouraging the discussion of the above-mentioned topics during lab meetings, seminars or workshops. Students and researchers should be encouraged to share their concerns and discuss best practices with peers and seniors. As the academic world is heavily focused

on the publication of peer-reviewed articles in scientific journals, mentors and promotors should encourage the students to include a discussion on the potential biosecurity or ethical implications of their work when preparing a scientific article for submission.

To ensure a unified approach among the different research departments and even labs of the same institution, clear institutional policies and guidelines on the biosecurity and dual-use aspects of synthetic biology should be established. These should provide procedures for conducting risk assessment, managing biological material, but also for reporting potential biosecurity issues. Researchers who feel that their biosecurity concerns are not addressed adequately within their lab or department, should be able to turn to an established authority within the institution without fear of negative consequences. This encourages vigilance and accountability within the research community.

2.2. Training

In a nutshell:

1. Invest in comprehensive training programs on biosecurity measures for researchers, PhD students, and technical staff in synthetic biology, to equip participants with the skills to manage and mitigate biosecurity and dual-use risks.

Scientific institutions involved in synthetic biology research must invest in training and capacity building related to biosecurity measures. A structured program will provide comprehensive education and practical experience in biosecurity related to synthetic biology, ensuring that participants are well-prepared to address biosecurity challenges in their research and professional activities.

Creating a comprehensive training program for biosecurity in synthetic biology involves several key components. Researchers (scientists), PhD students, and technical staff in scientific institutions must have the knowledge and skills necessary to manage and mitigate biosecurity risks associated with synthetic biology. They must be aware of the manipulations carried out in their institution (current trends, future directions). Training should cover classical biosafety aspects, and also address regulatory and ethical considerations, as well as aspects concerning the protection of sensitive biological data, their storage, and potential cybersecurity threats to synthetic biology research.

Training can take various forms: workshops, case study analyses with ethical dilemmas and societal impact, practical exercises (role-playing scenarios), simulation exercises, and group discussions. It can use already existing tools, such as the Biosecurity Resource Toolbox of the European Biosecurity

Regulators Forum (https://ebrf.eu/toolbox.html) or the WHO laboratory biosecurity guidance (WHO, 2024).

2.3. Ethics

In a nutshell:

1. Integrate biosecurity and dual-use concerns into ethical reviews and develop tailored ethical guidelines for synthetic biology to ensure that only safe and ethically sound research projects are approved.
2. Oblige researchers to submit their research projects to, and to seek guidance from, local ethics committees.

The ethical considerations associated with synthetic biology extend well beyond safety issues (see, for example, INRA, 2014). The societal impact of this innovative technology remains a contentious topic. Biosecurity and dual-use concerns should be integral to ethical reviews, ensuring that only safe and ethically sound research projects are approved within scientific institutions. Given the unique nature of developments in synthetic biology, it would be beneficial to develop ethical guidelines specifically tailored to this field. Sensitive projects should undergo regular monitoring to detect and address any deviations from ethical standards or potential safety risks.

Researchers must submit their projects to local ethics committees and seek guidance from these committees when working on potentially controversial applications. They must be held accountable for adhering to ethical guidelines.

More generally, it is important for institutions to ensure that all their research activities are carried out in accordance with the Responsible Research and Innovation (RRI - Responsible Research and Innovation (RRI) - ERA4HEALTH) approach promoted by the EU.

2.4. Biosecurity management

In a nutshell:

1. Integrate potential concerns related to DURC into risk assessments for synthetic biology research.
2. Adopt a precautionary and proportionate approach to mitigate biosecurity risks, including secure storage, robust traceability, and stringent access controls for biological materials.

3. Clearly define roles and responsibilities within scientific institutions to ensure effective biosecurity management.
4. Appoint a biosecurity officer to monitor compliance with biosecurity policies and liaise with national regulatory bodies.
5. Encourage scientists to apply available tools (such as the WHO Laboratory biosecurity guidance or standard ISO 35001:2019) to enhance biosecurity management.

In Europe, biosafety is governed by a comprehensive and restrictive legal framework, based on Directives 2009/41/EC (EU, 2009) and 2001/18/EC (EU, 2001). This covers good microbiological practices, appropriate containment levels and additional measures to ensure the safety of the general population and the environment.

Although there are currently no specific regulations on biosecurity at EU level, potential concerns related to DURC should be considered when assessing the risks of synthetic biology research. As recommended by other organizations (e.g., NSABB, 2023), an integrated approach should be implemented for overseeing research in the field of synthetic biology that presents significant biosecurity concerns, including DURC.

Scientific institutions should adopt a precautionary and proportionate approach to mitigate these risks while supporting research in the field. This approach includes secure storage of biological materials with robust traceability, stringent access controls, ensuring that data related to synthetic biology research is securely stored and transmitted, preventing unauthorized access or leaks that could facilitate misuse, addressing potential cyber threats and latest developments in AI. Biosecurity leaks and incidents should be reported consistently and systematically to the authorities, with a view to promote the best possible biosafety practices. Mechanisms could be implemented to monitor the compliance with the biosecurity policies within the institution. This could include regular audits, inspections, the use of a digital inventory system to track the biological material, or electronic notebooks for the transparency and community oversight of the experiments performed.

The roles and responsibilities of various actors within scientific institutions should be clearly defined, inspired, for example, by what has been put in place in the United States (NSABB, 2023; OSTP, 2024). In this regard, a staff member could be appointed to the role of biosecurity officer, similarly to the role of biosafety officer. In addition to the monitoring and ombudsman tasks already mentioned, this

person would also be responsible for liaising with national regulatory bodies in order to stay informed of the latest regulations and guidelines.

Biosecurity management within scientific institutions should be based on various tools available, such as the WHO Laboratory biosecurity guidance (WHO, 2024) or standard ISO 35001:2019(en) (ISO, 2019). The first complements the WHO Laboratory biosafety manual by covering the biosecurity part of the biological risk management lifecycle and providing key considerations and best practices for institutional, national and international levels, including regulatory oversight. The second specifically addresses hazards associated with laboratories where biological materials are handled at all containment levels. It defines the requirements and guidance for laboratories or any other organization that handle biological agents to control and reduce any risks associated with their use encompassing all relevant law.

3. At the level of Journal Editors and platforms of peer-reviewed literature

In a nutshell:

1. Scientific journal editors should continue to implement editorial policies, review processes, and best practices to identify articles related to synthetic biology that can contain information that may be misused or pose significant biosecurity threats.
2. Improve and review editorial policies regularly, and update them as necessary to maintain responsible and safe communication on synthetic biology.
3. Preprint servers must implement biosecurity screening policies.
4. Consider the potential benefits of legal obligations imposed by authorities to strengthen biosecurity measures in scientific publications.

Scientific papers, including those related to synthetic biology, can contain information that may be misused or pose significant biosecurity threats. Most scientific journal editors and chief editors have adopted editorial policies, review processes, and best practices to identify such articles. There are two main challenges in this area: (i) balancing the benefits of publication for the research community and society with the risks of malicious use of published information; and (ii) determining whether the current non-binding measures implemented by journal editors are sufficient or if legal obligations should be imposed by authorities. In the US, the National Science Advisory Board for Biosecurity

(NSABB) can advise policymakers, research institutions, and researchers about the conduct, oversight, and communication of sensitive research (NAS, 2017).

Even in the absence of a binding framework, it is crucial that scientific journal editors continue to ensure that research in synthetic biology is communicated responsibly, complementing the efforts made by researchers and scientific institutions (see previous recommendations). The current editorial policies could still be improved, for example by:

- Harmonizing the criteria and guidelines used by editors to assess biosecurity risks in synthetic biology research.
- Providing ongoing training to journal editors to enhance their ability to identify potential biosecurity risks in synthetic biology research.
- Using an interdisciplinary network/panel of experts to evaluate high-risk publications. This group should include biologists, bioinformaticians, modelers, ethicists, and other competent experts. A unified group for all journals would ensure a more consistent and better-coordinated approach.
- Regularly reviewing editorial policies to adapt them to scientific research advances and the evolving risk assessment landscape.

Biosecurity oversight should also be implemented by preprint servers (e.g., BioRxiv - www.biorxiv.org, medRxiv - www.medrxiv.org). With the COVID-19 crisis, the use of preprints - the rapid publication of articles in repositories outside the traditional peer review system - in medical and biological research has increased considerably. It is vital that preprint servers also apply screening policies in terms of biosecurity and malicious use, including for synthetic biology research.

4. At the level of research funding bodies

In a nutshell:

1. Funding bodies should require all grant applications for synthetic biology research to include a comprehensive review of potential biosecurity risks, dual-use concerns, and risk mitigation strategies, ensuring only projects meeting adequate biosecurity standards receive funding.
2. Regularly review risk assessments throughout the research lifecycle for funded synthetic biology projects to address emerging risks promptly.

Establishing a transparent process for assessing biosecurity and ethical risks throughout synthetic biology research programs, starting from the design stage and involving funding bodies, is essential

for ensuring responsible and secure research practices. This involves integrating biosecurity and ethical considerations into the grant application process, continuous monitoring, and fostering collaboration between researchers and funders.

This approach has already been implemented in the US, particularly within the framework of the "Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential" (OSTP, 2024). This policy outlines the organizational framework for research oversight and defines the roles and responsibilities of research entities (e.g., principal investigators and research institutions) and funding or sponsoring entities (e.g., federal funding agencies).

Similarly, funding bodies in the EU should be encouraged to:

- Require that all grant applications for synthetic biology research include a detailed review of potential biosecurity and ethical risks (such as dual-use concerns), unintended consequences and potential benefits, as well as clear risk mitigation strategies. Only projects that meet adequate biosecurity standards should receive funding.
- Ensure that applicant institutions have clear institutional policies and guidelines on the biosecurity (incl. dual-use aspects) of synthetic biology (see recommendations in section 2).
- Increase expertise, awareness and common understanding of risk and ethical issues in synthetic biology research among screeners, reviewers and auditors.
- Mandate that funded projects in synthetic biology research conduct ongoing risk and ethical assessments throughout the research lifecycle. This includes periodic reviews and updates to the initial risk assessment as the project evolves. Any emerging risks should be promptly addressed to prevent potential misuse.
- Establish regular communication with scientific institutions to facilitate open dialogue and shared responsibility for biosecurity in synthetic biology research.

While these recommendations probably can be implemented by government funding bodies, it may be more challenging to enforce them at the level of funding by private companies or non-profit organizations.

5. At the level of nucleic acid (DNA/ RNA) synthesis services and manufacturers

In a nutshell:

1. Providers of synthetic nucleic acids should extend homology searches for potentially dangerous sequences to include sequences known to contribute to pathogenicity or toxicity, even if not derived from high-risk pathogens.
2. AI technologies should be integrated in screening systems to improve algorithms that can identify 'risky' patterns in synthetic nucleic acid sequences.
3. Manufacturers of benchtop DNA synthesizers should ensure the legitimacy of customers, implement traceability systems for the equipment, and integrate robust control systems to prevent the synthesis of dangerous sequences.
4. Authorities should consider implementing clear guidelines, incentives, and/or regulations to reinforce biosecurity measures, fostering collaboration between companies, scientific institutions, and governments to share information on flagged sequences and suspicious orders.

Guided by a framework established by the U.S. Department of Health and Human Services (HHS, 2023), suppliers of synthetic nucleic acids and manufacturers of benchtop nucleic acid synthesis devices have been encouraged since 2010 to voluntarily screen orders for potentially dangerous sequences and verify customers to ensure they are legitimate users. Most gene synthesis companies and organizations (in 2018, it represented approximately 80% of gene synthesis capacity worldwide) currently adhere to the protocol developed by the International Gene Synthesis Consortium (IGSC - https://genesynthesisconsortium.org/). Screening relies on searching for homology between an ordered nucleic acid sequence and the sequences of high-risk pathogens in a reference list. This approach has limitations in the context of synthetic biology, particularly because it could allow the creation of new pathogens or the reconstitution of extinct pathogens that are not on the reference list.

The effectiveness of screening ordered sequences to identify potentially dangerous sequences could therefore be improved. Various recommendations have already been made on this topic (see e.g., HHS, 2023; NAS, 2024):

- Extend, as soon as technically possible, the homology search to include sequences known to contribute to pathogenicity or toxicity, even if they are not derived from high-risk pathogens.

However, a database with such sequences, if developed, should be used with great caution to prevent leaks and malicious use.

- Encourage the screening of nucleic acid sequences shorter than the current screening window length (200 nucleotides), including short single stranded DNA (ssDNA). Such short sequences can, in some cases, be intended to construct longer nucleic acids that can themselves constitute a potentially dangerous sequence.
- Work towards a better understanding of the relationship between sequence and function.
- Work towards a better harmonisation of the content and implementation of screening protocols.
- Consider how the development of AI technologies could on the one hand positively contribute to develop algorithms that learn and recognize 'risky' patterns, but on the other hand increase risks of evading safeguards in place.

In recent years, benchtop DNA nucleic acid synthesis equipment have emerged. Such equipment could allow users to synthesize DNA in their own laboratories, bypassing the need to order from centralized providers and the associated screening of potentially dangerous sequences. In this case, too, recommendations have been made (HHS, 2023):

- Control customers by benchtop nucleic acid synthesizer manufacturers to ensure their legitimacy and the suitability of the equipment for their needs. Controls could also be implemented for the specific reagents used with this equipment.
- Implement a traceability system by manufacturers throughout the lifecycle of this equipment (for example, to record the transfer to a new user).
- Ensure by scientific institutions that this equipment is accessible only to users with a legitimate need.
- Integrate various control systems into this equipment by manufacturers: user authentication, recording of synthesized sequences, integrity of synthesized sequences, impossibility of synthesizing risky sequences, etc. Such controls should be implemented considering (cyber)security aspects (for example, not storing risky sequence databases on the equipment itself to prevent malicious use), intellectual property protection, user identity, and ethics.

As suggested by international non-governmental organisations, authorities could consider the need for a more binding approach for such controls (clear guidelines, incentives, regulations...) in addition to best practices, to ensure that all suppliers and manufacturers effectively apply controls according to the same rules (Helena, 2023 - https://helena.org/projects/helena-biosecurity; IBBIS - https://ibbis.bio/). This could go hand in hand with increased collaboration between companies,

scientific institutions, and governments at an international level for sharing information on flagged sequences and suspicious orders.

6. At the level of professional / non-governmental organizations

In a nutshell:

1. Professional / non-governmental organizations should continue to facilitate the exchange of best practices and the implementation of codes of conduct for biosecurity in synthetic biology.
2. Professional / non-governmental organizations should serve as channels to educate, inform, and promote self-regulation among specific stakeholders, such as DIY biologists.
3. Promote collaboration between professional / non-governmental organizations and governmental authorities to ensure a coherent and comprehensive approach to biosecurity governance in synthetic biology.
4°Consider establishing a professional society in synthetic biology to develop protocols and standards, promote ethical practices, foster collaboration between academia, industry, and governments, and increase public trust and biosecurity awareness.

An increasing number of professional and non-governmental networks and organizations play a significant role in the oversight and governance of biosecurity related to the use of synthetic biology. In the EU, several national associations have been founded to better represent the interest of stakeholders (see e.g., Donati et al., 2022). At broader level, notable examples include groups such as the European Synthetic Biology Society (EUSynBioS - https://www.eusynbios.org/), the European Molecular Biology Organisation (EMBO - https://www.embo.org/), the International Risk Governance Council (IRGC - https://irgc.org/), the European Synthetic Cell Initiative (SynCellEU - https://syntheticcell.eu/), the European Research Infrastructure on Highly Pathogenic Agents (ERINHA - https://erinha.eu/), the iGEM Foundation (https://igem.org/), Helena (https://helena.org/projects/helena-biosecurity), the International Biosecurity and Biosafety Initiative for Science (IBBIS - https://ibbis.bio/), the Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNET - https://inspection.canada.ca/en/science-and-research/science-collaborations/biosafety-level-4-zoonotic-laboratory-network), the Global Health Security Agenda (GHSA - https://globalhealthsecurityagenda.org/), the International Gene Synthesis Consortium (IGSC - https://genesynthesisconsortium.org/), the International Federation of Biosafety Associations (IFBA -

https://internationalbiosafety.org/), the InterAcademy Partnership (IAP - https://www.interacademies.org/).

Despite the highly fragmented institutional landscape and often unclear roles and responsibilities, the contribution of these actors to the oversight and governance of biosecurity in synthetic biology should be recognized and encouraged. They play a pivotal role in facilitating the exchange of best practices and implementing codes of conduct (see e.g., the iGEM Safety and Security Program – Millet et al., 2020). In certain cases, these organizations and networks serve as vital channels for specific stakeholders to educate, inform, and promote self-regulation. For example, in the context of Do-It-Yourself biology, where amateur biologists engage in synthetic biology outside of traditional public or private laboratories, these networks help fill the gap where official regulations and controls may be challenging to enforce.

To enhance the effectiveness of biosecurity measures in synthetic biology, promoting collaboration between these actors and governmental authorities is essential (see also section 7). This cooperation can ensure a more coherent approach to governance, leveraging the strengths of both formal and informal networks to address the complex challenges posed by synthetic biology.

The creation of a professional society in the field of synthetic biology could provide an additional governance strategy related to biosecurity, bridging the gap between "bottom-up" governance (researchers, scientific institutions, specialized professional organizations) and "top-down" governance (governments) (Weir and Selgelid, 2009). A professional society could serve as a unified platform for establishing protocols and standards, offering educational resources and training or certification programs to professionals in synthetic biology, and promoting ethical and responsible research practices. It could also enhance public trust through transparency and awareness initiatives, effectively communicating the benefits and risks associated with synthetic biology.

7. At the level of governments (national, EU, international)

7.1. Cooperation

In a nutshell:

1. Governments should enhance cooperation at European and international levels to address the risks of synthetic biology, ensuring consistent management of threats across sectors. International cooperation can build on existing general principles and initiatives, such as horizon scanning, adopting

coordinated multidisciplinary approaches, supporting relevant international organizations, and using informal groups for open discussions and reinforcing biosecurity measures.
2. A European biosecurity platform could be established, comprising experts from all EU Member States to coordinate policies, guidelines, and tools for strengthening biosecurity.

Cooperation between governments, both at the European and international levels, is crucial to address the risks associated with the malicious use of synthetic biology and ensure that advancements in synthetic biology and the associated risks are consistently managed. This cooperation is all the more necessary as several sectors are potentially involved (see section 8) Concerted efforts to improve surveillance, information sharing, training, communication and capacity building will contribute to a better protection of public health and the environment.

At EU level, a former project funded by the European Commission ("The preparation of a biosecurity toolbox to strengthen European Biosecurity", specific contract HOME/2019/ISFP/FW/CBRN/0005) recommended to develop a European biosecurity platform consisting of biosecurity experts with delegates from all EU Member States. The current European Biosecurity Regulators Forum (EBRF) may be a good fundament to further develop this platform. This biosecurity platform may foster a web of policies, approaches and measures that strengthen biosecurity within Member States, and facilitate the coordinated development of policies, guidelines and tools required to address identified gaps.

Enhanced cooperation between member states would allow the European Union to have greater impact and credibility in the context of international cooperation, which is also crucial. This collaboration could lead to bilateral and/or multilateral agreements enabling countries to share their experiences on critical issues related to synthetic biology and the measures implemented to mitigate the risks of malicious use. Furthermore, this cooperation must also contribute to capacity building in developing countries.

Collaborative efforts at international level can build on a series of existing general principles and initiatives, such as:
- Carrying out horizon scans or scenario assessments, to help governance players proactively identify new developments and the associated risks. For example, the Subsidiary Body on Scientific, Technical and Technological Advice for the Convention on Biological Diversity has established a broad and

regular process for analysing, monitoring, and evaluating the latest technological developments in synthetic biology (https://www.cbd.int/synbio).

- Having a coordinated, multidisciplinary approach that promotes transdisciplinary policies and actions, covering humans, non-human animals, plants and agriculture, and the environment (WHO, 2022) (see also section 8).

- Supporting and contributing to the work of relevant international organisations insofar as it can facilitate access to information needed for biological risk assessment, training, responsible science, risk mitigation, regulatory development and other relevant activities.

- Using existing informal groups to promote open discussions on the biosecurity aspects of synthetic biology and contribute to establish mutually reinforcing biosecurity regulatory measures. For example, the IEGBBR (International Experts Groups of Biosafety and Biosecurity Regulators - IEGBBR) has developed a mobile application that describes the regulatory framework and policy of its eleven member countries in a very detailed manner, to serve as examples for countries developing or adapting their regulations and/or policies related to biosafety, biosecurity and dual-use. Other relevant informal groups include the Biological Security Working Group (BSWG) of the Global Partnership Against Weapons of Mass Destruction and the Australia Group (AG) (https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/index.html). The latter seeks to harmonize export control of sensitive dual-use goods and technology to prevent development and proliferation of chemical and biological weapons. In addition to the 42-member states of the AG, the European Union also meets at the plenary annual meeting.

7.2. Regulatory

In a nutshell:

1. Regulation 2022/2371 (EU, 2022) provides a generic regulatory framework to improve preparedness and strengthen response capabilities to health emergencies, including synthetic biology threats, through coordinated EU and national plans.
2. At the national level, governments should strengthen, including to a legally-binding approach, the measures taken by relevant stakeholders to ensure that risks of malicious use in synthetic biology research are properly assessed and managed.

3. Regulatory frameworks should be proportionate (the need to protect human health and the environment *vs.* the freedom of research and need for innovation) and adaptive (evolving with synthetic biology advancements).
4. At the EU level, governments should work to harmonize national strategies and regulatory policies to ensure a coherent approach, and consider adopting a specific EU biosecurity regulatory framework.
5. At the international level, governments and the EC should apply existing agreements and treaties to prevent the misuse of synthetic biology technologies, promote enhanced cooperation and harmonization in biosecurity, support the implementation of best practices and standards developed by international bodies, and identify potential institutional and regulatory gaps globally.

Regulatory policies fall under the purview of national governments, which play a crucial role in defining standards for managing biological risks within their jurisdictions, as well as implementing and enforcing relevant policies (WHO, 2022). Government actions (top-down) complement the initiatives of other actors (bottom-up). Governments can operate at two levels:
- National Level: Through laws, binding statutes, decrees, etc.
- International Level: By participating in the work of international bodies, where they agree on harmonized and shared principles and standards, possibly legally binding.

The malicious use of synthetic biology spans multiple legal domains, such as criminal law (criminalizing bioterrorism), emergency law, national security law (police, customs, etc.), public health law, and environmental law. Consequently, numerous regulations and policies are potentially associated with biosecurity and dual-use research management. This legal fragmentation is compounded by a lack of harmonization among governments regarding whether biosecurity, including synthetic biology, introduces sufficiently new risks to warrant specific regulations and oversight.

A few countries, including the United States, Russia, the United Kingdom, Japan, Australia, China, Denmark and the Netherlands, have adopted specific approaches to biosecurity: national strategies, special legislation, and/or dedicated administrative bodies. For example, since 2013, the Netherlands has a Biosecurity Office responsible for studying biosecurity risks and formulating governance measures to mediate between the government and stakeholders. At the European Union level, there is currently no specific biosecurity regulation. However, Regulation 2022/2371 (EU, 2022) provides a generic regulatory framework to improve preparedness and strengthen response capabilities to

health emergencies, including those linked to the malicious use of synthetic biology. An EU prevention, preparedness and response plan and recommendations are to be developed that will complement national prevention, preparedness and response plans. These plans will be regularly assessed by the European Centre for Disease Prevention and Control (ECDC). The regulation also establishes a strengthened Health Security Committee to combat serious cross-border threats to health.

At the national level, governments should:

- Implement adaptive regulatory frameworks that can evolve with synthetic biology advancements, ensuring regulations remain relevant and effective, considering when relevant all scientific, economic, social, political, and ethical aspects.
- Ensure regulatory frameworks strike a balance between the need to protect human health and the environment and the freedom of research and need for innovation.
- Enhance regulatory control (permits, inspections) as necessary. This is also particularly relevant for DIYbio locations, since these would most likely be the labs setup/used by a terrorist cell (this should be done in cooperation with the security sector).
- Consider strengthening the measures taken by scientific institutions (see section 2) by implementing an academic training curriculum for scientists in the life sciences promoting a responsible biological science research culture. The curriculum should be designed to raise the level of understanding of biosecurity, including dual-use, and ought be incorporated into standard educational courses.
- Consider, including to a legally-binding approach, strengthening the measures taken by other stakeholders (private companies, research funding bodies) to ensure that the risks of malicious use in synthetic biology research and applications are properly assessed and managed.
- Establish a national inventory of dangerous pathogens and document information on institutes that store or maintain dangerous pathogens (Vennis et al., 2021).
- Map relevant biosecurity stakeholders in their country. This would help in raising awareness and get commitment from the 'higher decision-making levels'.
- Stay in contact with the DIYbio community to monitor activities and ensure these groups adhere to biosecurity and biosafety standards and legal requirements, and implement responsible practices in synthetic biology.

At the EU level, governments and the EC should:

- Work to harmonize national strategies and regulatory policies to ensure a coherent approach, reduce current fragmentation among different governance and surveillance frameworks, and clarify areas of responsibility among various actors.
- Consider the adoption of a biosecurity regulatory framework to facilitate the above harmonisation.

At the international level, governments and the EC should:

- Apply existing agreements and treaties that contribute to preventing the misuse of synthetic biology technologies and ensuring global health and environmental security, such as the WHO's International Health Regulations 2005 (IHR), the Biological and Toxin Weapons Convention (BTWC), the United Nations Security Council Resolution 1540 (UNSCR1540), and the Cartagena Protocol on Biosafety.
- Use international forums to work towards enhanced cooperation and harmonization in biosecurity, particularly in promoting information sharing and coordinating responses to threats to address cross-border biosecurity challenges.
- Support the implementation of best practices, standards, and non-legally binding instruments developed by international bodies such as the World Health Organization (WHO), the World Organisation for Animal Health (OIE), the Food and Agriculture Organization (FAO), and the UN Biorisk Working Group (UN-BRWG). These non-legally binding instruments (e.g., WHO's Laboratory Biosecurity Guidance, 2024) can be a flexible and effective means of strengthening on-the-ground governance, as they are formulated more technically and are more "readable" for experts in the field compared to the often general language of conventions and treaties (Venis et al., 2022).
- Identify potential institutional and regulatory gaps globally in the landscape of biosecurity and synthetic biology governance.
- Interact with key stakeholders such as scientific journal editors, synthetic nucleic acid suppliers, and equipment manufacturers, and consider the possible implementation of a more binding approach alongside the best practices adopted by these actors.

7.3. Biosecurity assessment

In a nutshell:

1. Governments should collaborate with international organizations to develop a standardized and widely accepted biosecurity risk assessment process for synthetic biology, incorporating technological advancements and artificial intelligence.

2. The risk assessment process should be adaptive and inclusive, covering not only threats to human health but also potential adverse effects on animals, plants, and related products.
3. This process should integrate existing norms and standards, such as the WHO Laboratory Biosecurity Guidance and ISO 35001:2019, and complement biosafety risk assessments.

The assessment of biosecurity risks, particularly in relation to the malicious use of pathogens, traditionally relies on the categorization of biological agents into classes (CDC - https://emergency.cdc.gov/agent/agentlist-category.asp) or lists (HHS-USDA - https://www.selectagents.gov/sat/list.htm). Biologicals agents are classified based on the overall evaluation of various criteria (see for example Rotz et al. 2002). The agents included in classes/lists may change as new information is obtained or as new evaluation methods are established.

Some authorities and authors have suggested revising this approach in the context of assessing the risks of the malicious use of synthetic biology research and applications. This reassessment is motivated by the fact that the threats created by such research and applications could surpass the severity of any biological agent listed. Different approaches have been proposed:

- Reviewing the relative levels of hazard or inclusion criteria of the aforementioned classes/lists since technological advances may lead to a general increase in the potential for bioterrorism for many biological agents. Synthetic biology products could thus represent a greater threat than natural biological agents (MacIntyre et al., 2020).
- Determining a level of concern or hazard based on four factors: the usability of the technology, usability as a weapon, requirements of the actors (access to expertise, resources…), considering the recreation of pathogenic viruses and the modification of existing bacteria as the highest level of concern (NAS, 2018).
- Considering the type of research conducted, particularly any research that can reasonably be expected to pose a significant threat with broad potential consequences for public health and safety, agricultural crops and other plants, animals, the environment, materials, or national security, or that can reasonably be expected to create, transfer, or use a high-risk biological agent resulting from the enhancement of transmissibility or virulence in humans of a pathogen (NSABB, 2023; US, 2024).
- Enabling users to quickly identify potential dual-use aspects in their research (Dual-Use Quickscan of the Dutch Biosecurity Office - https://dualusequickscan.com/en/).

To better assess and thus manage emerging risks related to synthetic biology applications, governments should collaborate, in consultation with international organizations, to develop a biosecurity risk assessment process (covering the risks of malicious use of synthetic biology) that meets at least the following characteristics:

- Be standardized, reproducible, and as widely accepted as possible in the international community.
- Be adaptative to take into account technological advancements, including the use of genome editing methods (e.g., CRISPR-Cas) or developments enabled by artificial intelligence in synthetic biology.
- Integrate artificial intelligence into the biosecurity risk assessment process.
- Apply not only to synthetic biology products that may pose a serious threat to human health but also to those that may have severe adverse effects on animals or plants or on animal or plant products.
- Be based on the best available information at the time, while recognizing that the assessment of synthetic biology research and applications may involve a significant degree of uncertainty.
- Consider existing norms and standards, such as the WHO Laboratory biosecurity guidance (WHO, 2024) or standard ISO 35001:2019(en) (ISO, 2019).
- Complement biosafety risk assessment.

7.4. Surveillance and monitoring

In a nutshell:

1. Establish collaborative networks and joint research initiatives to develop integrated, multidisciplinary strategies for surveillance and monitoring of synthetic biology applications.
2. Enhance data sharing by adopting FAIR principles to ensure epidemiological data is accessible, interoperable, and usable by relevant stakeholders, thereby improving global responses to biological threats.
3. Utilize existing international epidemiological surveillance networks, such as GISAID and WHO's GOARN, as models to identify potential synthetic biology threats and inform biosecurity strategies.
4. Implement specific monitoring mechanisms for synthetic biology research to identify dual-use concerns.
5. Consider surveillance and monitoring associated with synthetic biology concerns in a One Health perspective, emphasizing the interconnectedness of human, animal, and environmental health.

To address the challenges posed by novel synthetic biology applications, it is essential to set up collaborative networks or joint research initiatives to foster a multidisciplinary approach to

surveillance and threat assessment. This collaboration can lead to the development of integrated strategies that combine expertise from various fields, ensuring a more robust response to emerging threats. Regular communication and information sharing among experts can help identify potential risks early, and develop effective mitigation strategies.

Data sharing is a very important part of epidemiological surveillance. In this context, the interoperability of the different databases and their accessibility for the stakeholders concerned are critical aspects. Adopting the FAIR principles (Findability, Accessibility, Interoperability and Reusability) can facilitate this process. These principles ensure that data is not only collected and stored, but is also easily accessible and usable by scientists, public health officials and other relevant stakeholders. High level of data sharing can significantly improve the global response to emerging biological threats.

In Europe, the European Centre for Disease Prevention and Control (ECDC) plays an essential role in identifying, assessing and communicating current and emerging threats to human health posed by infectious diseases (https://www.ecdc.europa.eu/en). Consideration of potential biological threats from synthetic biology applications could also be inspired by or build on existing international epidemiological surveillance networks, such as the Global Initiative on Sharing All Influenza Data (GISAID - https://gisaid.org/) and the World Health Organization's (WHO) Global Outbreak Alert and Response Network (GOARN - https://goarn.who.int/).

Monitoring research activities in synthetic biology is also crucial to identifying potential dual-use research of concern. Establishing specific monitoring mechanisms can help identify and assess the risks associated with such research. This proactive approach can prevent the misuse of synthetic biology and ensure that its applications remain safe and beneficial.

The considerations above must be seen in a One Health perspective, as a significant amount of emerging and re-emerging diseases are zoonotic (WHO, 2022; ECDC - https://www.ecdc.europa.eu/en/one-health). Therefore, the management of suspicious biological incidents requires an intersectoral and interregional cooperation between health, veterinary and environmental authorities, as well as law enforcement agencies.

7.5. Detection

In a nutshell:

1. Strengthen the capacity for rapid detection and identification of synthetic biology threats by developing proactive response measures such as metagenomic and environmental detection methods.
2. Continuously develop and refine computer-based tools, including whole genome sequencing (WGS) and next-generation sequencing (NGS), to monitor synthetic biology-derived agents through unusual genetic patterns.
3. Educate and prepare genomics-proficient laboratories to address synthetic biology threats, ensuring they engage in continuous training and proficiency tests for up-to-date skills and knowledge.
4. Utilize advanced bioinformatics and artificial intelligence (AI) tools to identify unusual genetic sequences, leveraging machine-learning algorithms to rapidly analyse vast datasets for real-time threat detection.
5. Develop and deploy innovative synthetic biology-based detection tools, such as highly sensitive biosensors and CRISPR-based diagnostics, alongside internet-connected sensors to enhance surveillance across healthcare, environmental, and agricultural settings.

States should strengthen their capacity to respond to potential threats linked to synthetic biology by enabling the rapid detection and identification of synthetic biology products that could be used maliciously. The current public health system already offers a range of tools to recognize outbreaks of new pathogens, whether natural or artificial. However, these tools primarily constitute a reactive approach, often triggering a public health response only after the population has developed symptoms (as observed during the Covid crisis). It is therefore essential to work towards establishing proactive response measures. Despite current limitations, metagenomic and environmental detection methods have high potential for better early identification of synthetic biology-derived agents, complementing traditional public health systems.

Computer-based approaches offer several tools to support the early detection of synthetic biology threats. These approaches should be continuously developed and refined. The use of whole genome sequencing (WGS) and next-generation sequencing (NGS) should be reinforced to detect, identify, and monitor synthetic biology-derived agents by examining unusual patterns of virulence genes, antimicrobial resistance genes, and other genetic alterations indicative of synthetic engineering. In

this context, (existing) networks of genomics-proficient laboratories should be educated and prepared to address the potential threats posed by synthetic biology, enabling the rapid detection and identification of synthetic biology-derived agents. These laboratories should engage in continuous training and regular proficiency tests to keep their skills and knowledge up to date.

Advanced bioinformatics and artificial intelligence (AI) tools could be exploited to identify unusual genetic sequences that are indicative of synthetic biology applications. Machine learning algorithms may be able to detect patterns and anomalies that traditional methods might miss. These algorithms can analyse vast datasets rapidly, providing real-time information on potential threats. This approach is especially relevant given the speed at which synthetic biology applications are developed, creating novel organisms that may not be detected by existing detection methods.

Synthetic biology itself can also be used to develop new detection tools. For instance, highly sensitive biosensors and CRISPR-based rapid diagnostic tools can detect pathogens at lower concentrations and more quickly than traditional methods. These innovative tools can be deployed in various environments, from healthcare facilities to agricultural sites, providing a comprehensive surveillance network. The use of internet-connected sensors can also facilitate data collection from diverse sources, enhancing the overall surveillance capability. Environmental sensors can monitor for unusual biological activity, while sensors in healthcare settings can track disease outbreaks in real-time. Agricultural sensors can help detect pathogens that may impact food security, providing an early warning system for potential biological threats.

7.6. Emergency planning

In a nutshell:

1. Regularly conduct joint case-study exercises with multidisciplinary teams from various member states to test and refine response strategies for synthetic biology-related incidents.
2. Invest in research and development of medical countermeasures, including vaccines and therapeutics, eventually through public-private partnerships and international funding mechanisms to ensure effectiveness against synthetic biology threats.

States should be prepared to respond to an incident involving synthetic biology. Review of challenges and good practices in preparedness and response plans in the health sector and between the health, security and civil protection is provided in JA TERROR deliverables 5.1 and 6.5 respectively.

Joint case-study exercises should be regularly conducted, involving multidisciplinary teams from various member states, to test and refine response strategies and ensure a robust response capability.

The development of medical countermeasures is challenging, but it is important to note that currently available medical countermeasures, such as vaccines and therapeutic treatments, could be less effective, or even ineffective, in the event of health issues related to synthetic biology threats. Governments should also invest in research and development of medical countermeasures, including vaccines and therapeutics, through public-private partnerships. International funding mechanisms and incentives can encourage pharmaceutical companies to prioritize the development of these essential tools.

8. At interdisciplinary and cross-sectoral levels

In a nutshell:

1. Foster interdisciplinary collaboration among scientists, governments, the private sector, and the public to address biosecurity and dual-use concerns in synthetic biology.
2. Leverage existing cross-sectoral collaboration models and establish common frameworks to coordinate efforts in detecting and preventing the misuse of synthetic biology.
3. Promote open and transparent communication among all stakeholders, including the public, to build trust and ensure comprehensive understanding and regulation of synthetic biology risks and benefits.

To effectively address biosecurity and dual-use concerns in synthetic biology, it is crucial to adopt an interdisciplinary approach that avoids working in silos. This requires fostering collaboration at multiple levels, including scientists, governments, the private sector, and the public. As highlighted by WHO (2022), governing biorisks cannot be done by a single group of stakeholders; instead, it needs to bring together multiple stakeholders with different roles and responsibilities, working together at different levels (individual, institutional, national, regional and international) and from different geographical regions. Continuous intelligence gathering and horizon scanning (early detection and assessment of emerging technologies or threats) should be key components of this approach, enabling stakeholders to stay ahead of emerging threats and trends in synthetic biology (see e.g., Dixon et al., 2022).

The implementation of this approach can leverage existing models of cross-sectoral collaboration, ensuring that the full scope of potential risks is considered and that effective strategies are developed to address these risks. This collaboration is necessary as several sectors are potentially involved, for instance : The security sector by monitoring and assessing malicious and terrorist threat signals, e.g. by screening the darknet; The health sector by assessing the health risks and relevant mitigation measures for a given threat; Civil protection by contributing in mass casualty events (triage, decontamination…). Establishing common frameworks and agreements among these sectors can help coordinate efforts in detecting and preventing the misuse of synthetic biology. More information on cross-sectoral collaboration can be found in the deliverables of JA TERROR WP6, and more specifically D6.5.

Collaboration must also take place between different scientific disciplines. The convergence of biology, chemistry, engineering, and computing is crucial for a comprehensive understanding of synthetic biology risks. The "One Health" approach, which emphasizes the interconnectedness of human, animal, and environmental health, also provides a useful framework for addressing the complex biosecurity challenges posed by synthetic biology.

Open and transparent communication between all relevant stakeholders is also a key element. Creating platforms for these discussions, such as public forums, workshops, and interdisciplinary conferences, can help build trust and ensure that all voices are heard. Engaging the public in these discussions is particularly important to ensure that the benefits and risks of synthetic biology are understood and that societal values and concerns are considered in the development and regulation of synthetic biology (see also Deliverable D7.1).

References

Alwine JC, Casadevall A, Enquist LW, Goodrum FD, Imperiale MJ. (2023). A Critical Analysis of the Evidence for the SARS-CoV-2 Origin Hypotheses. *mSphere.* 8(2):e0011923. https://doi.org/10.1128/msphere.00119-23

Carter SR, Warner CM. (2018). Trends in Synthetic Biology Applications, Tools, Industry, and Oversight and Their Security Implications. *Health Secur.* 16(5):320-333. https://doi.org/10.1089/hs.2018.0067

Cello J, Paul AV, Wimmer E. (2002). Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science.* 297(5583):1016-8. https://doi.org/10.1126/science.1072266

Cummings CL, Volk KM, Ulanova AA, Lam DTUH, Ng PR. (2021). Emerging Biosecurity Threats and Responses: A Review of Published and Gray Literature. *In: Trump BD, Florin MV, Perkins E, Linkov I, editors. Emerging Threats of Synthetic Biology and Biotechnology: Addressing Security and Resilience Issues [Internet]. Dordrecht (DE): Springer; 2021.* Chapter 2. Available from: https://doi.org/10.1007/978-94-024-2086-9_2

Deltcheva E, Chylinski K, Sharma CM, Gonzales K, Chao Y, Pirzada ZA, Eckert MR, Vogel J, Charpentier E. (2011). CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. *Nature*. 471(7340):602-7. https://doi.org/10.1038/nature09886

DiEuliis D, Berger K, Gronvall G. (2017). Biosecurity Implications for the Synthesis of Horsepox, an Orthopoxvirus. *Health Secur.* 15(6):629-637. https://doi.org/10.1089/hs.2017.0081

DiEuliis D, Giordano J. (2017). Why Gene Editors Like CRISPR/Cas May Be a Game-Changer for Neuroweapons. *Health Secur.* 15(3):296-302. https://doi.org/10.1089/hs.2016.0120

Dixon TA, Freemont PS, Johnson RA, Pretorius IS. (2022). A global forum on synthetic biology: the need for international engagement. *Nat Commun* 13, 3516. https://doi.org/10.1038/s41467-022-31265-9

Donati S, Barbier I, García-Soriano DA, Grasso S, Handal-Marquez P, Malcı K, Marlow L., Westmann C, Amara A. (2022). Synthetic biology in Europe: current community landscape and future perspectives. *Biotechnology Notes*, 3, 54-61. https://doi.org/10.1016/j.biotno.2022.07.003

EU. (2001). Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 17.4.2001, p. 1–39. https://eur-lex.europa.eu/eli/dir/2001/18/oj

EU. (2009). Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. OJ L 125, 21.5.2009, p. 75–97. https://eur-lex.europa.eu/eli/dir/2009/41/oj

EU. (2022). Regulation (EU) 2022/2371 on serious cross-border threats to health and repealing Decision No 1082/2013/EU. OJ L 314, 6.12.2022, p. 26-63. https://eur-lex.europa.eu/eli/reg/2022/2371/oj

Franconi R, Illiano E, Paolini F, Massa S, Venuti A, Demurtas OC. (2018). Rapid and Low-Cost Tools Derived from Plants to Face Emerging/Re-emerging Infectious Diseases and Bioterrorism Agents. *Defence Against Bioterrorism.* 23:123–39. https://doi.org/10.1007/978-94-024-1263-5_10

Genetic scissors: a tool for rewriting the code of life. Retrieved 16/09/24 from https://www.nobelprize.org/uploads/2020/10/popular-chemistryprize2020.pdf

Gibson DG, Glass JI, Lartigue C, Noskov VN, Chuang RY, Algire MA, Benders GA, Montague MG, Ma L, Moodie MM, Merryman C, Vashee S, Krishnakumar R, Assad-Garcia N, Andrews-Pfannkoch C, Denisova EA, Young L, Qi ZQ, Segall-Shapiro TH, Calvey CH, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC. (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. *Science*. 329(5987):52-6. https://doi.org/10.1126/science.1190719

Gibson DG, Young L, Chuang RY, Venter JC, Hutchison CA 3rd, Smith HO. (2009). Enzymatic assembly of DNA molecules up to several hundred kilobases. *Nat Methods.* 6(5):343-5. https://doi.org/10.1038/nmeth.1318

HHS. (2023). Screening Framework Guidance for Providers and Users of Synthetic Nucleic Acids. U.S. Department of Health & Human Services. https://aspr.hhs.gov/legal/synna/Documents/SynNA-Guidance-2023.pdf

Himmel M. (2023). Biosecurity Risk Assessment in the Life Sciences: Towards a Toolkit for Individual Practitioners. Publisher: SIPRI, Stockholm. https://doi.org/10.55163/EGCN8815

Holm S. (2017). The Bioethicist Who Cried "Synthetic Biology": An Analysis of the Function of Bioterrorism Predictions in Bioethics. *Camb Q Healthc Ethics.* 26(2):230-238.https://doi.org/10.1017/S0963180116000827

Imperiale MJ, Howard D, Casadevall A. (2018). The Silver Lining in Gain-of-Function Experiments with Pathogens of Pandemic Potential. *Methods Mol Biol.* 1836:575-587. https://doi.org/10.1007/978-1-4939-8678-1_28

INRA. (2014). Avis du Comité consultatif d'éthique pour la recherche agronomique commun à l'Inra et au Cirad sur la biologie de synthèse. 36 pages. https://www.inrae.fr/actualites/avis-biologie-synthese

ISO. (2019). ISO 35001:2019. Biorisk management for laboratories and other related organisations. https://www.iso.org/standard/71293.html

Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science.* 337(6096):816-21. https://doi.org/10.1126/science.1225829

Johansen TB, Madslien EH, Forsman M, Ekström F, Fykse E-M, Keersmaecker SD, Roosens N, Vanneste K, Fraiture M-A, Palyi B, Knepr-Segina M, Zmak L, Tabain I, Janković H, Jones J. (2024). Novel threats: State of the art of Synthetic Biology. In EU (Ed.)

Juhas M. (2023). Synthetic Biology in Microbiology. *In: Brief Lessons in Microbiology. Springer, Cham.* https://doi.org/10.1007/978-3-031-29544-7_7

Keulartz J, van den Belt H. (2016). DIY-Bio - economic, epistemological and ethical implications and ambivalences. *Life Sci Soc Policy.* 12(1):7. https://doi.org/10.1186/s40504-016-0039-1

Koblentz GD. (2017). The De Novo Synthesis of Horsepox Virus: Implications for Biosecurity and Recommendations for Preventing the Reemergence of Smallpox. *Health Secur.* 15(6):620-628. https://doi.org/10.1089/hs.2017.0061

Kobokovich A, West R, Montague M, Inglesby T, Gronvall GK. (2019). Strengthening Security for Gene Synthesis: Recommendations for Governance. *Health Secur.* 17(6):419-429. https://doi.org/10.1089/hs.2019.0110

Kupferschmidt K. (2017). Labmade smallpox is possible, study shows. *Science.* 357(6347):115-116. https://doi.org/10.1126/science.357.6347.115

Li J, Zhao H, Zheng L, An W. (2021). Advances in Synthetic Biology and Biosafety Governance. *Front Bioeng Biotechnol.* 9:598087. https://doi.org/10.3389/fbioe.2021.598087

MacIntyre CR. (2020). Reevaluating the Risk of Smallpox Reemergence. *Mil Med.* 185(7-8):e952-e957. https://doi.org/10.1093/milmed/usaa084

Melin A. (2021). Overstatements and Understatements in the Debate on Synthetic Biology, Bioterrorism and Ethics. *Front Bioeng Biotechnol.* 9:703735. https://doi.org/10.3389/fbioe.2021.703735

Meyer M, Vergnaud F. (2020). The rise of biohacking: Tracing the emergence and evolution of DIY biology through online discussions. *Technological Forecasting and Social Change.* https://doi.org/10.1016/j.techfore.2020.120206

Millett P, Isaac CR, Rais I, Rutten P. (2020). The synthetic-biology challenges for biosecurity: examples from iGEM. *The Nonproliferation Review.* 27(4–6), 443–458. https://doi.org/10.1080/10736700.2020.1866884

NAS. (2017). National Academies of Sciences, Engineering, and Medicine; Policy and Global Affairs; Committee on Science, Technology, and Law; Committee on Dual Use Research of Concern: Options for Future Management. Dual Use Research of Concern in the Life Sciences: Current Issues and Controversies. *Washington (DC): National Academies Press (US).* https://doi.org/10.17226/24761

NAS. (2018). National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Board on Life Sciences; Board on Chemical Sciences and Technology; Committee on Strategies for Identifying and Addressing Potential Biodefense Vulnerabilities Posed by Synthetic Biology. Biodefense in the Age of Synthetic Biology. *Washington (DC): National Academies Press (US).* https://doi.org/10.17226/24890

NATO. (2012). NATO Science for Peace and Security Series A: Chemistry and Biology - Biopreparedness and Public Health. Springer Ed. https://www.springer.com/series/7106

Noyce RS, Evans DH. (2018). Synthetic horsepox viruses and the continuing debate about dual use research. *PLoS Pathog.* 14(10):e1007025. https://doi.org/10.1371/journal.ppat.1007025

Noyce RS, Lederman S, Evans DH. (2018). Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One.* 13(1):e0188453. https://doi.org/10.1371/journal.pone.0188453

NSABB. (2023). Proposed Biosecurity Oversight Framework for the Future of Science. A Report of the National Science Advisory Board for Biosecurity. https://osp.od.nih.gov/wp-content/uploads/2023/03/NSABB-Final-Report-Proposed-Biosecurity-Oversight-Framework-for-the-Future-of-Science.pdf

NTIbio. (2023). Benchtop DNA Synthesis Devices: Capabilities, Biosecurity Implications, and Governance. https://www.nti.org/analysis/articles/benchtop-dna-synthesis-devices-capabilities-biosecurity-implications-and-governance/

Nwadiugwu MC, Monteiro N. (2023). Applied genomics for identification of virulent biothreats and for disease outbreak surveillance. *Postgrad Med J.* 99(1171):403-410. https://doi.org/10.1136/postgradmedj-2021-139916

OSTP (Office of Science and Technology Policy) (2024). United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential. https://www.whitehouse.gov/ostp/news-updates/2024/05/06/united-states-government-policy-for-oversight-of-dual-use-research-of-concern-and-pathogens-with-enhanced-pandemic-potential/

Pilizota T, Yang YT. (2018). "Do It Yourself" Microbial Cultivation Techniques for Synthetic and Systems Biology: Cheap, Fun, and Flexible. *Front Microbiol.* 9:1666. https://doi.org/10.3389/fmicb.2018.01666

Rath J, Ischi M, Perkins D. (2014). Evolution of different dual-use concepts in international and national law and its implications on research ethics and governance. *Sci Eng Ethics.* 20(3):769-90. https://doi.org/10.1007/s11948-014-9519-y

Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. (2002). Public health assessment of potential biological terrorism agents. *Emerg Infect Dis.* 8(2):225-30. https://doi.org/10.3201/eid0802.010164

Saalbach KP. (2022). Gain-of-function research. *Adv Appl Microbiol.* 120:79-111. https://doi.org/10.1016/bs.aambs.2022.06.002

Sarpong D, Ofosu G, Botchie D, Clear F. (2020). Do-it-yourself (DiY) science: The proliferation, relevance and concerns. *Technol. Forecast. Soc. Change.* 158. https://doi.org/10.1016/j.techfore.2020.120127

SBSTTA. Subsidiary Body on Scientific, Technical and Technological Advice. https://www.cbd.int/synbio

SCENIHR et al. (2014). SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), SCCS (Scientific Committee on Consumer Safety), SCHER (Scientific Committee on Health and Environmental Risks), Synthetic Biology I Definition, Opinion, 25 September, 2014. https://health.ec.europa.eu/publications/synthetic-biology-i-definition_en

Smalley E. (2018). FDA warns public of dangers of DIY gene therapy. *Nat Biotechnol.* 36(2):119-120. https://doi.org/10.1038/nbt0218-119

Smith JA, Sandbrink JB. (2022). Biosecurity in an age of open science. *PLoS Biol.* 20(4):e3001600. https://doi.org/10.1371/journal.pbio.3001600

Sneed A. (2017). Mail-order CRISPR kits allow absolutely anyone to hack DNA. *Scientific American*, *2*. https://www.scientificamerican.com/article/mail-order-crispr-kits-allow-absolutely-anyone-to-hack-dna/

Sun T, Song J, Wang M, Zhao C, Zhang W. (2022). Challenges and recent progress in the governance of biosecurity risks in the era of synthetic biology. *Journal of Biosafety and Biosecurity*, *4*(1), 59-67. https://doi.org/10.1016/j.jobb.2022.02.002

Tan X, Letendre JH, Collins JJ, Wong WW. (2021). Synthetic biology in the clinic: engineering vaccines, diagnostics, and therapeutics. *Cell*, *184*(4), 881-898. https://doi.org/10.1016/j.cell.2021.01.017

Trump BD, Florin MV, Perkins E, Linkov I. (2021a). Biosecurity for Synthetic Biology and Emerging Biotechnologies: Critical Challenges for Governance. *In: Trump BD, Florin MV, Perkins E, et al., editors. Emerging Threats of Synthetic Biology and Biotechnology: Addressing Security and Resilience Issues [Internet]. Dordrecht (DE): Springer; 2021.* Chapter 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK584259/

Trump BD, Galaitsi S, Pollock M, Volk KM, Linkov I. (2021b). Promoting Effective Biosecurity Governance: Using Tripwires to Anticipate and Ameliorate Potentially Harmful Development Trends. *In: Trump BD, Florin MV, Perkins E, et al., editors. Emerging Threats of Synthetic Biology and Biotechnology: Addressing Security and Resilience Issues [Internet]. Dordrecht (DE): Springer; 2021.* Chapter 14. Available from: https://www.ncbi.nlm.nih.gov/books/NBK584248/

Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solórzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, García-Sastre A. (2005). Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science*. 310(5745):77-80. https://doi.org/10.1126/science.1119392

Vennis IM, Bleijs DA, Brizee S, Van Den Berg HHJL, Kampert E, Rutjes SA, Van Passel MWJ. (2021). Systematic approach towards establishing a National Inventory of Dangerous Pathogens. *Glob Health Action.* 14(1):1971866. https://doi.org/10.1080/16549716.2021.1971866

Vinatzer BA, Heath LS, Almohri HMJ, Stulberg MJ, Lowe C, Li S. (2019). Cyberbiosecurity Challenges of Pathogen Genome Databases. *Front Bioeng Biotechnol.* 7:106. https://doi.org/10.3389/fbioe.2019.00106

Voigt CA. (2020). Synthetic biology 2020–2030: six commercially-available products that are changing our world. *Nat Commun*, *11*(1), 6379. https://doi.org/10.1038/s41467-020-20122-2

Walsh PF. (2018). The Biosecurity Threat Environment. *Intelligence, Biosecurity and Bioterrorism.* 19:21–57. https://doi.org/10.1057/978-1-137-51700-5_2

Wang F, Zhang W. (2019). Synthetic biology: Recent progress, biosafety and biosecurity concerns, and possible solutions. *J. Biosafety and Biosecurity*. 1(1):22-30. https://doi.org/10.1016/j.jobb.2018.12.003

Weir L, Selgelid MJ. (2009). Professionalization as a governance strategy for synthetic biology. *Syst Synth Biol.* 3(1-4):91-7. https://doi.org/10.1007/s11693-009-9037-4

WHO. (2022). Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
Available at : https://www.who.int/publications/i/item/9789240056107

WHO. (2024). Laboratory biosecurity guidance. https://www.who.int/publications/i/item/9789240095113.

Yan X, Liu X, Zhao C, Chen GQ. (2023). Applications of synthetic biology in medical and pharmaceutical fields. *Signal Transduct Target Ther.* 8(1):199. https://doi.org/10.1038/s41392-023-01440-5