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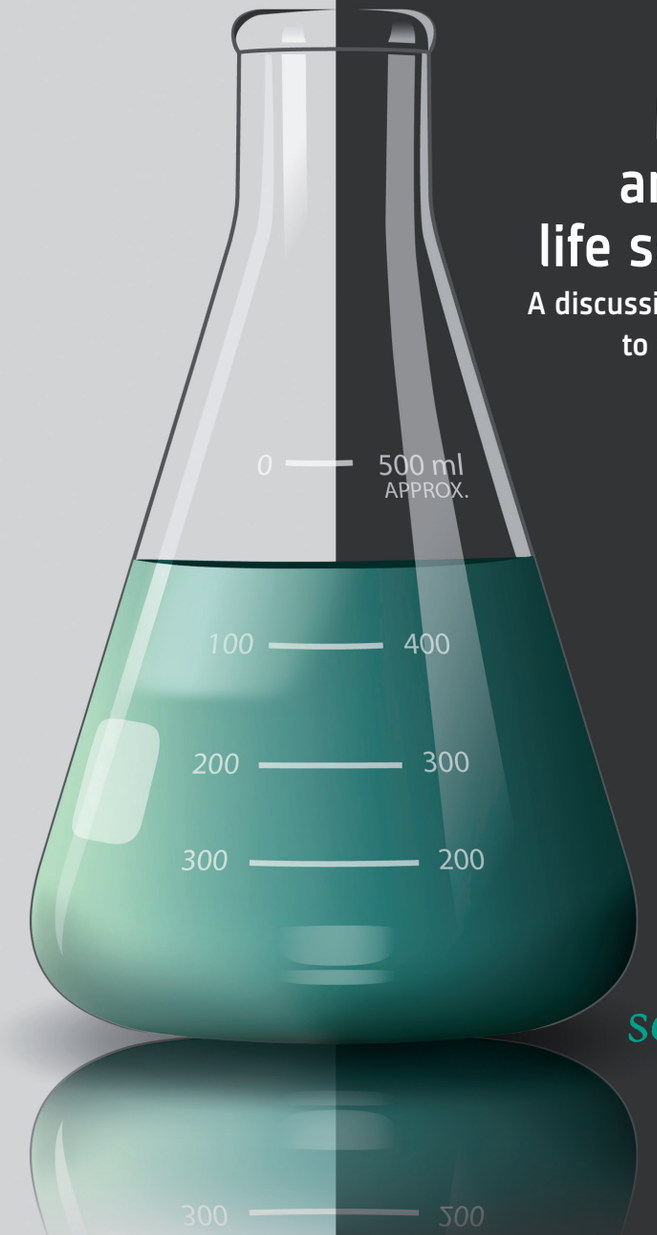

Misuse potential and biosecurity in life sciences research

A discussion basis for scientists on how to address the dual use dilemma of biological research

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Contents

Introduction

Why discuss the misuse potential of biological research?

Research in the life sciences produces knowledge and technologies that significantly benefit human, animal, and environmental health as well as the sustainable management of ecosystems. At the same time, certain discoveries emerging from the life sciences are capable of causing harm to people and the environment if used improperly or with ill intent. This is known as the "dual use dilemma" – arguably inherent to all forms of innovation.

Concerns about bioterrorism and recent technological advances in gene synthesis and gene editing have brought the dual use nature of biological research into public focus. The potential for misuse is especially apparent with respect to research on human pathogens. Although less obvious, there is also misuse potential in connection with research involving animal and plant pathogens – or involving no pathogens at all. Indeed, awareness of such misuse potential is needed in virtually all research fields involving use of biological material and development and application of new technologies.

Life science research can also be misused in ways that may not directly threaten human health and safety, the environment, or national security, but could threaten the well-being and dignity of isolated individuals or specific groups. For instance, genetic information and other health-related data could be used in a way that discriminates against certain individuals or stigmatizes particular communities. Athletes' use or misuse of pharmaceuticals or neurotechnologies to obtain an unfair advantage in sports competitions is another example. Indeed, it is important to remain aware and to carefully consider all possible misuses of life science research (for more, consult the references[1–4]). However, this document focuses in particular on the need to discuss *security-related risks*[a] *of life science research* – a realization emerging from the recent history of biological weapons and so-called bioterrorism.

a In a strict sense, the term „risk" is numerically defined as a combination of the probability of occurrence of harm and the severity of that harm. However, we use the term "risk" here and throughout this document in a more broad and colloquial sense to designate the potential of negative consequences. We do not suggest that this potential can or should be quantified.

Have "biocrimes" happened or is it just hype?

Rudimentary biological weapons have been used for centuries. For instance, during the so-called French and Indian War (1754–1767) in North America, British military authorities gave blankets carrying smallpox to Native Americans in a deliberate effort to provoke an outbreak.[5] During and after World War II, several countries established large-scale biological weapons programmes.[6] In 1972 the international community agreed on the Biological and Toxin Weapons Convention, banning the development, production, possession, and use of biological weapons by state powers. With the anthrax attacks in the US in 2001, a week after September 11, the focus and concern shifted from state-led bioweapon programmes to bioterrorism. To date, there have been very few proven cases of terrorists expressing interest in biological agents, much less trying to acquire them. A comprehensive report on biological weapons in the twentieth century points to approximately 30 cases of biological agents being used or acquired for illicit purposes by non-state actors.[7] Eight of these cases stem from terrorist groups, and only one bioterror case is known to have resulted in harm to people (see also list below). The remaining cases involved individuals acting on narrower criminal motives such as murder, extortion, or revenge ("biocrimes"). The most common biological agents implicated in acts of bioterrorism and biocrime have been anthrax strains, HIV, and the ricin and botulinum toxins. Criminals and terrorists acquired the biological agents by various means: whether from legitimate suppliers, natural sources, self-manufacturing, or theft. The corresponding report concludes that bioterrorist attacks are low probability events, but carry potentially major consequences if they occur.

A selection of biosecurity-related events:

1925 The **Geneva Protocol** prohibits the use of chemical and biological weapons in international armed conflicts.

1972 The **Biological and Toxin Weapons Convention** bans the development, production, and possession of biological weapons.

1984 Followers of the guru Bhagwan Shree **Rajneesh** deliberately contaminate salad bars in Oregon with *Salmonella* bacteria causing severe food poisoning in over 700 people.

1993 Members of the Japanese religious cult **Aum Shinrikyo** release anthrax spores in Tokyo, but luckily no one is harmed.

2001 Letters containing **anthrax** spores are mailed to media offices and senators killing five people and infecting 17 others and leading to heightened concern about bioterrorism.

2002 Researchers report having reconstructed **poliovirus *de novo*** from chemically synthesized oligonucleotides[8], demonstrating that it is possible to create a pathogen from commercially available synthetic building blocks.

2005 The influenza virus responsible for the **1918 flu** pandemic is successfully reconstructed[9, 10], raising questions in regards to the safety and scientific value of such experiments versus the potential for misuse.

2012 Two independent research groups report **gain-of-function experiments on H5N1**, sparking an intense international debate.[11, 12]

What strategies are being considered internationally?

Since the 2001 anthrax attacks in the US, prevention of bioterrorism has been a concern of governing bodies worldwide.[13] Strengthening oversight of research in the life sciences is one key element discussed in this context. Proposed measures range from legally binding, government-led "top down" approaches – such as international treaties and national laws – to "bottom up" self-regulatory initiatives. Self-regulation does not mean that individual scientists decide for themselves what procedures to follow but that there are checks and balances on research agreed within the scientific community.[14] These can for instance take the form of guidelines, standards, and codes of conduct.

In the US, a policy introduced in 2014 requires all institutions receiving federal funding for research in the life sciences to review the potential for misuse of each related project.[15] The responsibility for these reviews and appropriate mitigation plans is given to an institutional review entity such as a biosafety committee. In Europe, many countries have begun evaluating the need for biosecurity laws to strengthen their research oversight in a top-down manner, with Denmark representing the first country to actually put such regulations into force. Under the Danish regulation, any institution or company that possesses certain biological materials or equipment and technology – as defined in a list of controlled items – must obtain a license from the Danish biosecurity agency. The institution or company must additionally obey certain biosecurity procedures such as keeping an

inventory and allowing inspections.[16] In Switzerland, the Federal Office for the Environment (FOEN) recently mandated a legal study that has identified regulatory gaps in the Swiss legislation and a number of possibilities to address them.[17]

In contrast to these country-level regulatory measures, expert bodies in Europe and the US have repeatedly suggested that bottom-up awareness-raising approaches could offer even better protection by sensitizing individual researchers and research institutions to risks. Codes of conduct have been proposed as an effective measure to foster responsible behaviour.[18–20] Several national and international institutions have developed individual codes, while others have incorporated requirements on the possible misuse of biological research within more comprehensive codes of ethics (see Appendix 1). Taken together and condensed, these codes of conduct emphasize the following general rules:

- Be aware and assess your own research
- Refrain from research where the potential for harm is disproportionate to the potential benefits
- Modify research and/or publications to reduce risks
- Report and document risks
- Know and use guidelines and safe practices
- Be alert and raise concerns (also about others' research)
- Protect sensitive material and data
- Train others and serve as a role model

What is the purpose of this document?

This document is intended to aid discussion of the potential for research misuse among scientists and support staff involved in research with biological materials, regardless of their background, discipline, or role. It was developed as a result of workshops with life scientists from Swiss academic institutions on ways of addressing the misuse potential of biological research (see also p. 35).[21] In these workshops, life scientists had expressed their interest in having a basis for discussing the risks of possible life science research misuse together with colleagues, supervisors, students, and staff.

Life scientists have the competence and knowledge to evaluate the potential for misuse of life science research. They are generally committed to conducting their work safely, conscientiously, and with integrity. Nevertheless, even research conducted with the best of intentions bears potential for misuse by others, so the possible risks must be considered, discussed, and subjected to impact assessments.

The document at hand provides a basis for life scientists to reinforce their commitment to conduct research responsibly and to support others in doing the same according to a bottom-up approach. It highlights six issues that should be considered when designing, conducting, and communicating research projects. Each issue is illustrated with examples from actual research projects, which can also be used as discussion material, and with statements from life science researchers made in the context of the above-mentioned workshops.

Definitions

Biocrime:[b] threat or use of biological agents by individuals or groups motivated by traditional criminal motives such as murder, extortion, or revenge.

Biorisk:[c] combination of the probability of occurrence of harm and the severity of that harm where the source of harm is a biological agent or toxin.
Note: The source of harm may be an unintentional exposure, accidental release or loss, theft, misuse, diversion, unauthorized access, or intentional unauthorized release.

Biosafety:[c] containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents and toxins, or their accidental release.

Biosecurity:[c] protection, control, and accountability for biological agents and toxins within laboratories, in order to prevent their loss, theft, misuse, diversion of, unauthorized access or intentional unauthorized release.
Note: The term biosecurity has different meanings in different contexts and is often used in the context of preventing importation of plant or animal diseases into a country. Therefore, in the context of misuse prevention in biological research, sometimes the term laboratory biosecurity is used.

Bioterrorism:[b] threat or use of biological agents by individuals or groups motivated by political, religious, ecological, or other ideological objectives.

Dual use research:[d] Research conducted for legitimate purposes that generates knowledge, information, technologies, and/or products that can be utilized for benevolent or harmful purposes.

Dual use research of concern (DURC):[d] Research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security.

b Definition from W. S. Carus in "Bioterrorism and biocrimes"[7]

c Definition from the European Committee for Standardization[22]

d Definition from the United States government policy for institutional oversight of life sciences dual use research of concern[15]

Six issues to consider

1. Be aware that life science research can be misused

Research in the life sciences affords immense benefits to society and the environment, but it also carries risks. These risks include not only unintentional or accidental exposure to hazardous biological material, but also the *intentional misuse* of such materials or related data, knowledge, and technologies generated from research. In the hands of people wishing to cause harm, these materials, data, or technologies could pose threats to human, animal or plant health, agriculture or the environment.

In many cases, research endeavours or technologies that promise the greatest advances also bear the greatest potential for harm. For example, genome editing technologies such as CRISPR/Cas9 could revolutionize many areas of research and industry including therapeutic development, crop improvement, and control of disease-transmitting insects. However, the same advantages that make CRISPR/Cas9 such a powerful tool for researchers – its simplicity, efficiency, and inexpensiveness – could also play into the hands of those who wish to misuse it to do harm (Figure 1).

Virtually all technologies can be misused to cause harm – consider a simple kitchen knife, for example. The universality of this "*dual use dilemma*", however, offers no justification for ignoring it. In life science research, the potential for misuse of scientific findings is especially apparent with regard to experiments with hazardous biological material such as highly pathogenic organisms and toxins. However, it is crucial to note that technologies or knowledge posing human-health risks can also emerge from research on non-human pathogens or from research not involving pathogens at all. Examples include research on vectors to deliver genetic material (Figure 2), on brain-enhancing drugs and technologies, on cell toxins for cancer treatment, or on gene drives for altering insect populations (Figure 1), just to name a few. Further, the possible threats are not limited to human health, but also include animal and plant health, agriculture and the environment.

Voices from the scientific community:

> It's the awareness that is important […]. Once the scientific community is aware, it will inspire self-regulation; if everybody were aware of the possibility that something could go wrong, then people would say: Did you think about your experiment? That is something we should aim for.

> It's always good to think about these questions – we have a responsibility towards the public and for the sake of credible science.

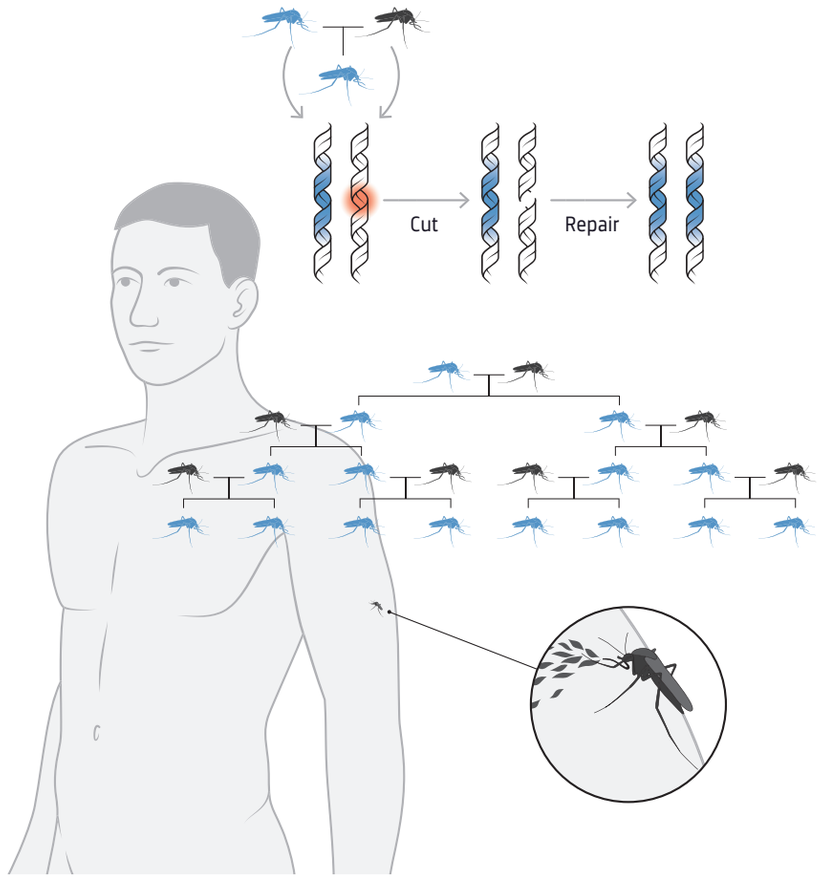

Figure 1. Gene drives, a technology based on CRISPR/Cas9, convert heterozygote carriers of a genetic modification into homozygotes (blue). In this way, they promote the spread of genetic modifications within a population by ensuring they are inherited. Applied to mosquitoes, gene drives could potentially be used to eliminate diseases such as malaria. However, it is also feared that they could be misused to deliberately deliver new diseases or toxins to humans. For more, see Example 1 on p. 28 (Illustration adapted from Oye et al 2014).[23]

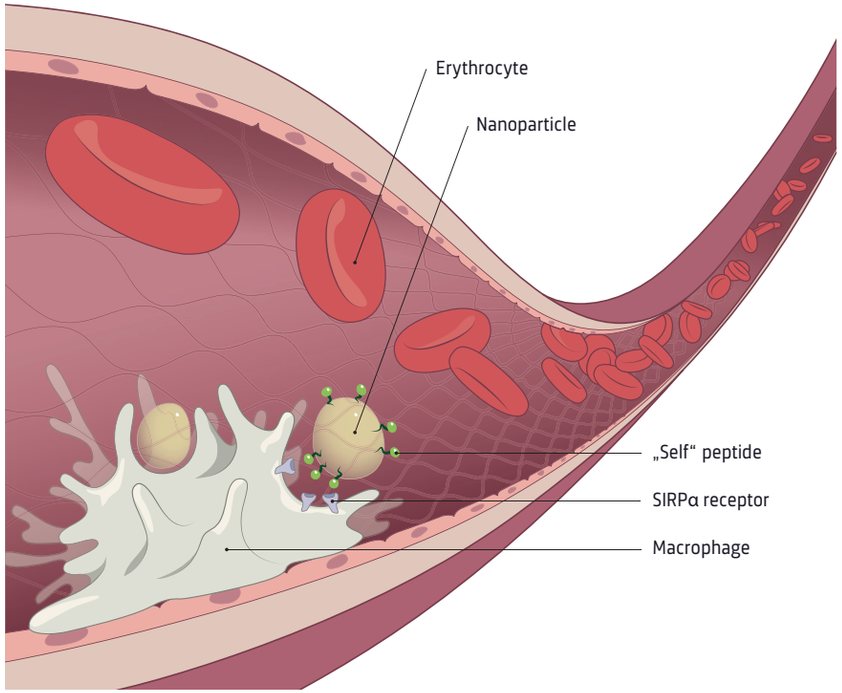

Figure 2. By attaching a "self" peptide to conventional nanocarriers, researchers succeeded in reducing clearance by the immune system (macrophages) and thus increasing the efficiency of cargo delivery. Enhanced delivery efficiencies could allow patients to take medicines at lower doses or less frequently, thereby improving convenience and safety. However, the same method could also be misused to facilitate delivery of toxins or pathogens. For more, see Example 2 on p. 28.

2. Assessing misuse potential

Assessing the potential for misuse of research is not an easy task. Quantifying risks requires knowledge of the likelihood and consequences of misuse, including detailed information on potential perpetrators and their intentions. Researchers seldom have such information, and even security experts frequently disagree in their assessments. In a recent study, for instance, experts' estimate of the likelihood of a large-scale biological weapons attack occurring in the next 10 years ranged between 0 and 100 percent.[24] Nevertheless, despite these difficulties, efforts should be made to identify and to carefully consider the misuse potential accompanying any such research endeavour. Indeed, some observers suggest that ongoing reflection and explicit discussion offer the best protection against potential harm.[25]

Many materials and technologies used in the life sciences could be misused for malevolent purposes, but certain types of research bear more potential for causing harm than others. Research that provides knowledge, products, or technologies that could be *directly* misused to pose a *significant threat* has been termed "*dual use research of concern*" (DURC). Relatedly, the US National Academy of Sciences (NAS) has proposed seven classes of "*experiments of concern*", illustrating the kinds of research that could pose significant risks if misused (Box 1).[26] The seven classes only address microbial threats and the NAS openly states that a wider range of experiments should be gradually incorporated as medical, veterinary, and agricultural research develops. The list may be used as a starting point to identify research projects that require especially thorough risk assessments and management. However, it should not be considered exhaustive. Further, not every experiment falling into one of the seven classes automatically constitutes DURC. In short, the list cannot be a substitute for individual risk assessments on a project-by-project basis.

One possible process for assessing the misuse potential of a given biological research endeavour is shown in Figure 3.

Box 1. Seven classes of experiments of concern

As proposed by the US National Academy of Sciences in its 2004 "Fink report"[26]

The proposed seven classes include experiments that:

1) Would demonstrate how to render a vaccine ineffective.
2) Would confer resistance to therapeutically useful antibiotics or antiviral agents.
3) Would enhance the virulence of a pathogen or render a non-pathogen virulent.
4) Would increase the transmissibility of a pathogen.
5) Would alter the host range of a pathogen.
6) Would enable the evasion of diagnostic/detection modalities.
7) Would enable the weaponization of a biological agent or toxin.

In cases of research of particular concern, temporary suspension of experiments may be warranted to enable a thorough risk assessment, discussion of findings, and implementation of mitigation measures.

Voices from the scientific community:

> It's impossible [to prove that your research has no misuse potential], but it's still worthwhile for a researcher to think about it and to weigh the pros and cons […] Even if there is no definite answer, it is worthwhile to explore this possibility.

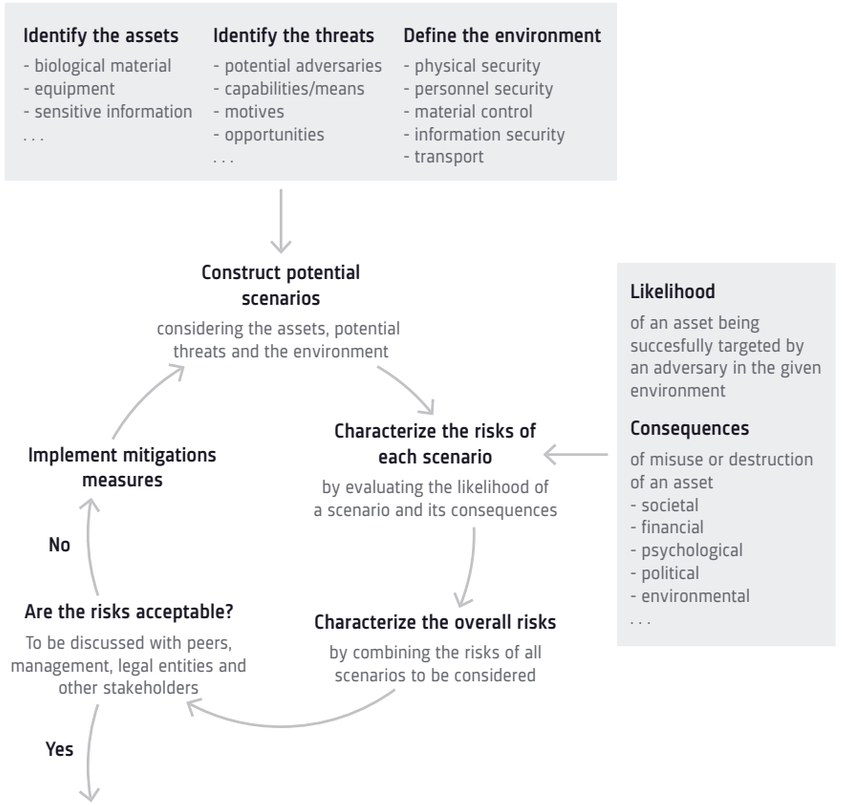

Figure 3. One possible procedure for risk assessment. The proposed process is based on the "Laboratory Biosafety and Biosecurity Risk Assessment Technical Guidance Document" of the Sandia National Laboratories and the International Federation of Biosafety Associations.[27] In their discussion of assets, the authors refer not only to biological materials, equipment, or sensitive information with potential for misuse as a biological threat, but also to materials that are of high value to the owner and should therefore be safeguarded.

3. Designing and following safe and secure strategies

When designing research, scientists should choose the safest, most secure possible way of addressing a given research question or achieving a desired result. In this context, *biosafety* refers to measures implemented to prevent unintentional exposure to biological hazards or their accidental release. *Biosecurity* describes measures to prevent unauthorized access, theft, or misuse of biological materials or their intentional release. The two sets of measures address different risks, complement each other, and overlap in some areas. Overall, effective biosafety practises may be considered the foundation of biosecurity (Figure 4). *Biorisk management* covers both biosafety and biosecurity. It promotes responsible, safe, and secure operations in institutions where work with biological material takes place. Biorisk management directly involves the people who deal with biological materials and related techniques as part of their daily activities.[28, 29]

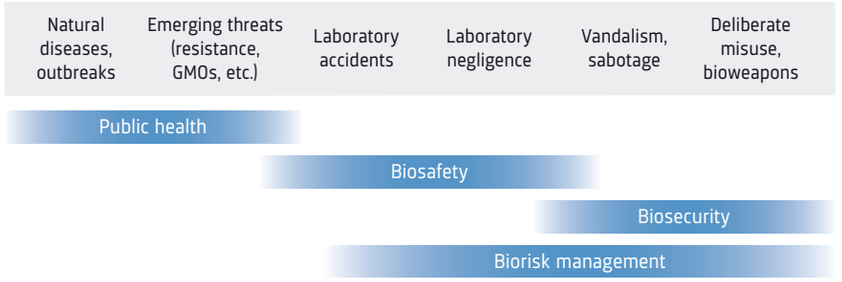

Figure 4. Spectrum of biological risks and their control. (Illustration based on Stroot and Jenal 2011)[28]

Life science researchers in Switzerland are subject to specific sets of laws and regulations governing their work. Swiss legislation primarily addresses *biosafety* aspects of research (see Appendix 2). Denmark, by contrast, has already established comprehensive *biosecurity* legislation – it is one of the first countries to do so.[30] When designing a biorisk management strategy for a project, measures that go beyond legal requirements should always be considered in light of regulatory gaps.

Designing safer, more secure research could mean, for example, selecting different organisms or different strains of organisms, such as attenuated strains or vaccine strains. This sort of strategy could reduce the potential for damage from both *unintentional* and *intentional* releases, thereby addressing some – but not all – biosecurity concerns (see Example 4, p. 30).

Designing research projects to eliminate all potential for misuse is scarcely possible. In cases where high risks for misuse remain, scientists should consider implementing specific safeguards to mitigate the risks. These safeguards might include, but are not limited to: introducing added security measures when recording, storing, and shipping biological materials; placing biological material exclusively under the responsibility of particular staff and collaborators; regularly checking inventories; and enhancing IT security on behalf of data storage and electronic communications (see also Box 2).

Voices from the scientific community:

> Biosafety is well taken care of, but no one is aware of biosecurity. I have never heard of any discussion at any level about biosecurity.

> I think [the idea that you can design research in a secure way] is wishful but useful thinking.

> We have biosafety on level 3 and 4 where for instance nobody can get in without a card. Or the windows are bulletproof. It's an access control and it covers both biosafety and also biosecurity.

Box 2. Biosecurity measures

The following measures should be considered when designing a biosecurity strategy. Many of them address both biosafety and biosecurity concerns.

- Inventory of valuable biological material such as organisms, patient- and RNA/DNA samples
- Physical security of equipment and biological material
- IT security of computers, data, access codes, etc.
- Transport security
- Access control
- Personnel management
- Incident response and reporting
- Development and maintenance of security-specific policies and procedures
- Evaluation and revision
- Training and education
- Internal audits
- External inspections

4. Treating unexpected findings carefully

Research can take unexpected turns and lead to unanticipated discoveries (Figure 5). This unpredictability might even be seen as essential to research. Relatedly, those involved in a given research project should stay alert for unanticipated findings that increase the need for biosafety and/or biosecurity.

Unexpected observations should always be taken seriously and treated carefully. Researchers who make unexpected discoveries with biosecurity implications should consider alerting their collaborators and the scientific community in a secure way (see Issue 5, p. 23 for more on secure communication).

Given this natural unpredictability, the possible consequences of a research project should be assessed not only in its initial stages, but also over the entire course of the implementation process and even following completion (see Issue 2, p. 15). Biosafety and biosecurity strategies should be adapted accordingly.

Voices from the scientific community:

> Research is unpredictable, especially in basic curiosity-driven research, which can lead in completely unexpected directions – so there is always a risk that the research you're doing can have an unexpected outcome.

> If you find something exceptional [that has misuse potential], don't just throw it out, but treat it correctly so that nobody else does it again and doesn't know that it might be dangerous. That is also part of research ethics.

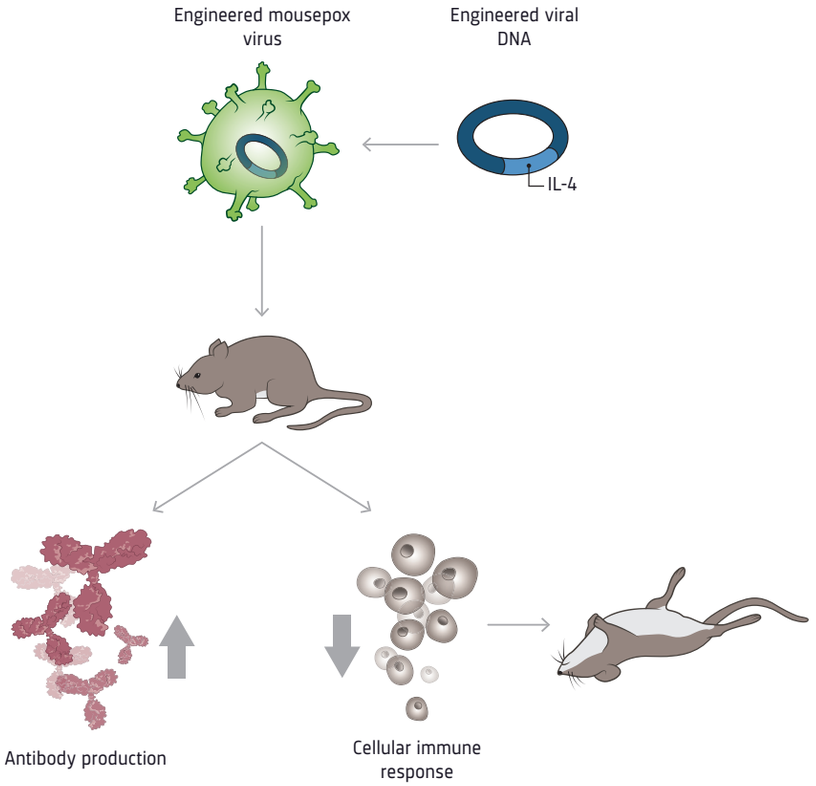

Figure 5. In order to develop a mouse contraceptive for pest control, Australian scientists intended to boost antibody production by infecting mice with viruses expressing the immune regulator interleukin 4 (IL-4). Unexpectedly, the modified mousepox virus completely suppressed the cell-induced immune response and was uniformly lethal. The researchers thus had unintentionally created a more virulent mousepox virus, raising concerns that these results could also be adapted to human poxviruses. For more, see Example 3 on p. 29.

5. Communicating results responsibly

Potential for misuse exists not only for harmful biological materials, but also for information on how to prepare these materials such as methodological protocols or genomic sequences of pathogens. There has been much debate about whether access to protocols and data to reproduce research findings of particular concern should be restricted (Figure 6).[31] Some argue that withholding detailed instructions and information from the public domain is warranted in certain cases, and that such findings should only be shared in restricted scientific circles. Others argue that these strategies involve too many complications and are not suitable for preventing misuse. Moreover, they caution against measures that interfere with scientific freedom as well as transparency and reproducibility, two pillars of the scientific system, required for knowledge sharing and self-correction. Restrictions could hinder research progress in areas where it is greatly needed (for an ethical discussion on scientific freedom and biosecurity see [32]).

Reflections on how to responsibly communicate research results should be made at an early stage, ideally at the start of any research project. These reflections should consider not only how to deal with publication in scientific journals, but also how to deal with communication at scientific meetings and with the general public.

One recent example illustrating a possible strategy for communicating research results with misuse potential is provided by US researchers' discovery of a new type of botulinum toxin in 2013. Since the researchers claimed that the new toxin type could not be neutralized by any available antitoxins, they reached an agreement with journal editors and US authorities to withhold certain genetic information from publication until appropriate countermeasures were developed.[33, 34]

Overall, strategies for communicating research with misuse potential could include the following (see also [35]):

– Explicitly raising awareness of the misuse potential of research by adding contextual information to relevant publications

– Modifying the content of a publication so as to remove information of particular concern from the rest of the scientific information

– Delaying open communication until conditions are met such that the information no longer poses the same degree of risk (as in the example described above)

– Strengthening informal communication networks in order to exchange information of particular concern only within targeted scientific communities

Voices from the scientific community:

> There is no limit for publication right now – if something is publishable, it will be published. Should we limit what we are publishing or not? That's for scientists to discuss.

> In my opinion, information is the most important tool we have to fight natural threats such as infectious diseases in the future. The value of publication is much higher than the risk because then the community can jointly think about potential threats. We shouldn't exclude our brightest minds from this because that might be hindering our chances of fighting future threats.

> Communication should not be restricted, but it's important that people think about it and ask for advice […] for example, researchers should ask for help when preparing press releases. [Steps should ensure] that crazy people don't get any crazy ideas [from published research].

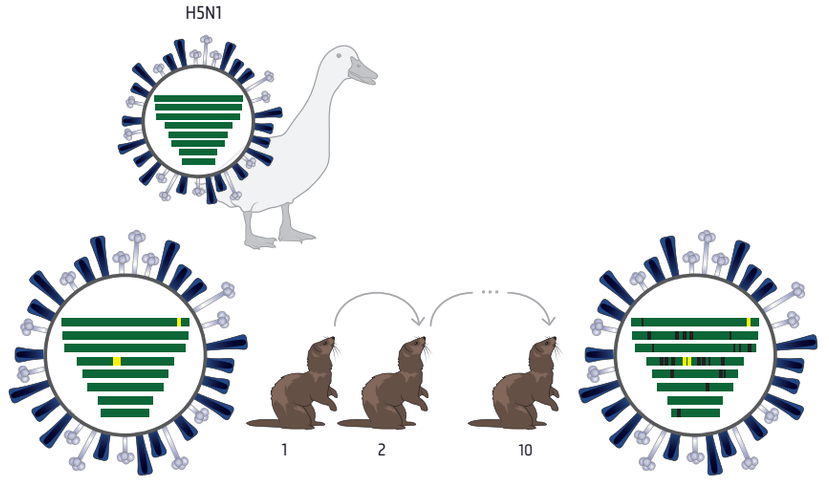

Figure 6. By 2012, two research groups had independently created a new version of the avian flu H5N1 virus that was able to spread through the air between ferrets. To achieve this, one of the research teams had first introduced three specific mutations (yellow bars) into a H5N1 wild-type variant. After ten serial passages, this engineered strain had accumulated additional mutations (black bars) allowing air-borne transmission. These studies sparked controversy in the scientific community about whether such "gain-of-function" experiments should be performed at all and how the results should be communicated. For more, see Example 4 on p. 30 (Illustration adapted from Herfst et al 2012).[11]

6. Educating and overseeing

Education and training in biosecurity are among the most effective strategies to anticipate and prevent misuse of life science research.[26] To date, however, biosecurity does not receive enough attention in the education of many young academics in the life sciences.[21, 36] Internationally, several bodies have proposed relevant educational materials to fill the gap (see "educational resources" on the next page).

Other important measures to prevent misuse include fostering responsible research practices and scientific integrity more generally and cultivating an atmosphere of trust at research institutions and in research groups.

Voices from the scientific community:

> Ethical questions regarding science are usually not discussed [as part of the university curriculum]. We had some courses during my master's [studies], but there was very little and there was no general course. We need more education – a lot of students are not aware of this dual use problem.

> We have students from 23 different nations in our institute with very different educations and they are very young and not aware of these issues; as PIs, we have to be the role models.

> It's important to create a nice atmosphere so that students feel comfortable to come and tell us if something goes wrong; we try to create a lab where people collaborate rather than compete.

Some educational resources:

- National Science Advisory Board for Biosecurity (2010) Enhancing responsible science. Considerations for the development and dissemination of codes of conduct for dual use research. Appendix B. An educational tool
  http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb/reports-and-recommendations
  A set of slides introducing the topic of dual use research of concern and providing a framework for risk assessment and management, guidance on communicating research, as well as a number of fictional case studies.

- Federation of American Scientists. Case studies in dual use biological research.
  http://fas.org/biosecurity/education/dualuse/index.html
  An online tool presenting six case studies of actual research that raised concerns about the potential of misuse.

- National Institutes of Health. Dual use research: A dialogue.
  http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/dual-use-research-of-concern/dialogue
  A 7-minute video to raise awareness of the potential of misuse of life science research.

- Rappert B, Dando M, Chevrier M. Dual use role-playing simulation.
  http://projects.exeter.ac.uk/codesofconduct/BiosecuritySeminar/Education/index.htm
  A set of slides and instructions to facilitate a role-playing exercise in which participants answer questions about experiments with misuse potential as well as measures to reduce risks.

- Whitby S, Novossiolova T, Walther T, Dando M (2015) Preventing biological threats: what you can do. A guide to biological security issues and how to address them.
  Novossiolova T (2016) Biological security education handbook: The power of team-based learning.
  www.bradford.ac.uk/social-sciences/peace-studies/research/publications-and-projects/guide-to-biological-security-issues
  Two comprehensive books on biosecurity education, which provide in-depth information as well as team-based learning exercises. The material is primarily aimed at undergraduates in life sciences and their lecturers, but can also be useful to scientists at other stages of their career.

Examples

1. Genome editing in wildlife populations

CRISPR/Cas9 technology has been heralded as a revolutionary, game-changing gene-editing technique due to its simplicity, flexibility, precision, efficiency, and low cost.[37] One of the many possible applications of CRISPR/Cas9 technology is that of genetically altering entire populations of sexually reproducing organisms through gene drives. CRISPR/Cas9-based gene drives convert heterozygote carriers of a genetic modification into homozygotes. In this way, they promote the spread of genetic modifications among populations much faster than simple genetic inheritance. They can even increase the frequency of genetic modifications that reduce the reproductive capacity of their carrier. Such gene drives could be used, for instance, to eliminate malaria by altering the *Anopheles* mosquito genome, to reverse the development of pesticide resistance, or to eradicate invasive species.[23] In 2015, Valentino Gantz and Ethan Bier first demonstrated the validity of the CRISPR/Cas9-based gene drive approach in a proof-of-concept study using *Drosophila* fruit flies[38], and, in collaboration with Anthony James, did so a second time using *Anopheles* mosquitoes.[39] In addition to concerns about biosafety – for example, the ecological consequences of accidentally releasing modified insects into the wild – these experiments also raise questions about the potential for misuse of this new technology with malicious intent. For instance, it is feared that CRISPR/Cas9-based gene drives could be misused to alter insects to deliver diseases or toxins to humans. They could also be employed to cause damage to agriculture, for example, by eliminating pollinators or by rendering plant pests resistant to insecticides.[40]

2. Improved drug delivery using aerosolized micro- and nanoparticles

Inhalation of aerosolized drugs is an effective way to deliver medicines for respiratory diseases and lung disorders. In 1997, David Edwards and his research team reported on a new type of aerosol consisting of large porous particles. These porous particles appeared to greatly increase the efficiency of drug delivery as they deeply penetrated into the lungs and remained bioactive over a much longer period of time than other aerosols on the market. Such enhanced efficiencies would allow patients to take medicines at lower doses and less frequent intervals, thereby improving convenience and safety.[41] Only several years later, in the wake of the 2001 anthrax attacks, it became obvious that the same delivery method could also be misused to facilitate deep lung penetration of toxins or pathogens.

More recently, nanoparticles have also been intensively investigated as drug delivery systems and as carriers for genetic material. As nanoparticles are taken up by cells more easily than larger molecules and can cross tissue barriers (e.g. the blood-brain barrier), their potential for efficiently delivering bioactive molecules is unprecedented. However, delivery efficacy can be constrained, among other things, when nanoparticles, like any other foreign particles, are recognized, neutralized, and cleared by the immune system, in particular by macrophages. In 2013, Dennis Discher and his colleagues found a way to slow down this clearance by macrophages. They designed a short peptide based on the human transmembrane protein CD47 that is recognized by macrophages as a "marker of self", thus quelling a response. Attaching these "self" peptides to conventional nanoparticles significantly delayed clearance and enhanced drug and dye delivery.[42] Due to its short length of only 21 amino acids, the "self " peptide can be relatively easily synthesized and attached to various carriers to increase persistence.[43] While these advances facilitate better delivery of therapeutics, for example to fight tumour cells or infectious diseases, they could in principle also be misused to enable delivery of harmful biological material.

3. Unexpected lethality of mousepox virus

Australian scientists Ronald J. Jackson and Ian Ramshaw sought to develop a contraceptive for mice as a means of pest control.[44] For this, they inserted the mouse egg shell protein ZP3 into the mousepox virus – a virus that usually causes a mild infection in mice. They hypothesized, firstly, that the infected mice would develop an immune response against the virus extending to ZP3; and secondly, that the anti-ZP3 antibodies would subsequently attack the eggs in the ovaries of female mice, causing sterility. Their strategy appeared to work quite well in some mouse strains but in others, antibody production was found to be inadequate. In an attempt to boost the immune response among all mice, the scientists inserted the gene encoding the immune regulator interleukin 4 (IL-4) into the mousepox virus, since prior research suggested IL-4 could increase antibody production. Unexpectedly, the mousepox virus expressing IL-4 completely

suppressed the cell-induced immune response in mice and was uniformly lethal. Further, even mice that were vaccinated against mousepox were killed by the newly engineered virus.[45] Since viruses of the pox family are closely related, concerns arose that these research results could be used to increase the virulence of poxviruses infecting humans (e.g. eradicated smallpox) and dangerously render vaccines ineffective.

4. Mammalian transmissibility of bird flu virus

The highly pathogenic bird flu virus (avian influenza A virus H5N1) is only transmissible between birds, but can occasionally infect mammals including humans in cases of intense exposure. To find out whether H5N1 could mutate to become transmissible between mammals, virologists performed so-called gain-of-function experiments. A team led by Ron Fouchier in the Netherlands applied genetic modifications to a wild-type H5N1 variant followed by serial passages in ferrets, creating a new version of the virus that could spread through the air between ferrets.[11] A group led by Yoshihiro Kawaoka in the US achieved the same mammalian transmissibility by creating an H5N1-H1N1 chimeric virus and adding specific mutations.[12] While these new versions of H5N1 were not lethal to the ferrets, the two studies raised serious concerns about possible misuse of the findings. As a result, the NSABB – the US government advisory committee on biosecurity and dual use research – initially recommended that important details be omitted from the papers before publication. An agreement was eventually reached on revised texts that nonetheless remained comprehensive, including description of the specific mutations linked to increased transmissibility as well as detailed methodology. Both studies were finally published in 2012. In the wake of this controversy, leading influenza scientists agreed to a voluntary moratorium on such research to enable discussion of its benefits, risks, and possible measures to minimize dangers. One way of reducing the risks of gain-of-function experiments may involve development of so-called molecular biocontainment strategies. A research team in the US, for example, has created an H5N1 strain that can replicate in ferrets but not in humans.[46] Further research is needed, but this molecular containment strategy holds promise for safer experiments with highly pathogenic viruses.[47] A strategy like this can reduce the risk of harm from both unintentional and intentional virus releases. However, it cannot prevent individuals with malevolent intentions from replicating the experiments with virus strains that are pathogenic to humans.

Appendix

1. Codes of conduct and guidelines

Several national and international institutions have developed codes of conduct, statements, or guidelines addressing the misuse potential of biological research. The Virtual Biosecurity Center, an initiative of the Federation of American Scientists, hosts a comprehensive database of relevant publications.[48] The most relevant codes and statements consulted when developing this document are shown in Table 1.

Source	Title	Year
BBSRC, MRC, Wellcome Trust	Position statement on dual use research of concern and research misuse	2015
Deutsche Forschungsgemeinschaft (DFG)	Verhaltenskodex: Arbeit mit hochpathogenen Mikroorganismen und Toxinen	2013
Robert Koch Institute	Dual use potential of life sciences research. Code of conduct for risk assessment and risk mitigation	2013
Do-it-yourself biology community (DIYbio.org)	DIYBio code of ethics	2011
US National Science Advisory Board for Biosecurity (NSABB)	Considerations in developing a code of conduct for dual use research in the life sciences	2010
Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita	Codice di condotta per la biosicurezza	2010
Max Planck Society	Guidelines and rules of the Max Planck Society on a responsible approach to freedom of research and research risks	2010
Royal Netherlands Academy of Arts and Sciences (RNAAS)	A code of conduct for biosecurity	2008
InterAcademy Panel (IAP)	IAP statement on biosecurity	2005
International Union of Microbiological Societies (IUMS)	IUMS code of ethics against misuse of scientific knowledge, research, and resources	2005
American Society for Microbiology	Code of ethics	2005

Table 1. A selection of codes of conduct and guidance documents addressing the misuse potential of biological research.

2. Swiss legal documents addressing biorisks of research in the life sciences

Listed below are the main Swiss laws and ordinances addressing biorisks of research in the life sciences. Further information can be found on the websites of the FOPH and the FOEN. The relevant Swiss regulations mainly emphasize the biosafety aspects of research. Biosecurity issues are seldom addressed. Export rules involving goods and information with dual use potential are a notable exception; these also include certain research data and results. By contrast, Swiss laws and ordinances on the handling of biological agents overwhelmingly focus on biosafety. Nevertheless, as discussed under Issue 3 (p. 18), biosafety measures can have spillover effects on biosecurity. For example, limiting and controlling access to certain biological materials reduces the likelihood of both unintentional and intentional release.[17]

Gene Technology Act (814.91)
Environmental Protection Act (814.01)
Containment Ordinance (814.912)
Deliberate Release Ordinance (814.911)
Ordinance on Protection of Employees from Dangerous Microorganisms (832.321)
Major Accidents Ordinance (814.012)
Goods Control Act (946.202)
Goods Control Ordinance (946.202.1)
Epizootic Diseases Act (916.40)
Epizootic Diseases Ordinance (916.401)
Agriculture Act (910.1)
Plant Protection Ordinance (916.20)
Cartagena Ordinance (814.912.21)

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How this document was developed

This document was developed by a working group of the Forum for Genetic Research of the Swiss Academy of Sciences, with the support of additional experts in the life sciences, laws and regulations, and biosafety and biosecurity.

Further document input was obtained in three workshops held in the spring of 2016 in Bern, Lausanne, and Zurich. In total, over 40 life scientists from Swiss academic institutions came together to discuss ways of addressing the misuse potential of biological research.

The workshops centred on the following discussion points:
- What is your conception of misuse of biological research?
- What cases of misuse are you aware of in your research field that involved biological material?
- Do you already discuss potential misuse of research with your colleagues?
- Do you assess the misuse potential of your research? How do you prevent misuse of your research?
- What kind of institutional rules do you have to prevent misuse of biological material?
- Do you or anyone else at your institution train young scientists in biosecurity?
- Do you consider biosecurity issues when hiring new staff?

Lively workshop discussions revealed the need for increased reflection and education to foster awareness of biosecurity and to reaffirm commitments to responsible behaviour. Participants expressed support for use of bottom-up approaches drawing on educational tools and guidance documents. By contrast, they expressed doubts about imposing more formal, stringent controls – whether involving codes of conduct, biosecurity committees, or biosecurity laws – due to difficulties in properly defining misuse of biological research.[21]

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The Swiss Academies of Arts and Sciences link sciences regionally, nationally and internationally. They specifically engage in the fields of early warning and ethics and advocate for an equitable dialogue between science and society.

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