BIOSAFETY AND BIOSECURITY:
POLICY LANDSCAPE AND RECOMMENDATIONS 2024

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Michael E. DeBakey Institute
Scowcroft Institute of International Affairs
College of Veterinary Medicine & Biomedical Sciences
School of Public Health
The Bush School of Government & Public Service

Biosafety and biosecurity are paramount when working with deadly pathogens in the laboratory, in clinics, and in the environment.

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GLOSSARY OF RELATED TERMS

Antibiotics are substances and/or medications used to treat bacterial infections. Many antibiotics disrupt the bacteria's ability to create a cell wall, prohibiting bacteria replication.

Antifungals function by disrupting the cell walls or membranes of fungi, preventing their growth and survival.

Antivirals work by targeting specific stages of the viral/cell life cycle, such as blocking viral entry into cells or inhibiting viral replication within cells.

Bacteria are microscopic, one-celled organisms that independently divide and replicate.

Bacteriophages are viruses that attack specific bacteria, making them useful when treating bacterial infections. Each bacteriophage is usually specialized to infect a particular bacterium.

Biocontainment refers specifically to the practices, equipment, and facilities used to physically prevent the accidental release of infectious agents into the environment.

Biorisk management refers to the systematic process of identifying, assessing, and mitigating risks associated with biological agents.

Biosafety can be defined as the overall practices, equipment, and facilities used to protect workers, the community, and the environment against biological agents being used in research or other work (e.g., commercial manufacturing).

Biosecurity refers to the practices and systems used to prevent theft, loss, or deliberate misuse of biological agents.

CBRN is an acronym that stands for Chemical, Biological, Radiological, and Nuclear, and usually refers to threats associated with these areas.

Dual Use refers to information, technologies, or research that can be used in a beneficial or harmful way.

Dual Use Research of Concern (DURC), as defined in the U.S. 2024 *DURC-PEPP* Policy, is life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied to do harm with no, or only minor, modification to pose a significant threat with potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security.

Endemic refers to diseases that regularly occur within an area or community.

Epidemic refers to the widespread occurrence of an infectious disease in a community at a particular time.

Fungi are spore-producing, multicellular organisms that feed on organic matter.

Gain of Function (GOF) is an experimental technique that involves modifying an organism’s genome to give it new or enhanced functions.

Gain of Function Research of Concern (GOFROC) refers to studies that involve altering microorganisms to enhance their pathogenic characteristics.

High Efficiency Particulate Air (HEPA) filters are a type of pleated mechanical air filter with a membrane that can remove microorganisms from the air, making them useful to protect individuals against harmful organisms.

Host tropism refers to the range of host organisms (species) a microorganism can infect, as well as the specific cells in those hosts that the infectious agent can enter and replicate within.

Mask types include levels 1, 2, and 3, based on their ability to filter particulates and/or microorganisms before they enter the respiratory system.

Medical Countermeasures (MCMs) are actions, products, or pharmaceuticals that can be used to prevent or treat the spread of disease.

Pandemic refers to the widespread occurrence of an infectious disease across an entire nation or the globe.

Pandemic agent refers to an infectious biological organism (e.g., a virus or bacterium) that has the attributes necessary to cause a pandemic.

Pandemic potential refers to the likelihood that a potential disease outbreak would escalate into a pandemic.

Parasites are organisms that live in or on another species (its host) and benefits by deriving nutrients at the host's expense.

Pathogens are microorganisms (e.g., viruses, bacteria, and fungi) or other infectious agents (e.g., prions and parasites) that may cause illness (morbidity) or death (mortality).

Pathogens with Enhanced Pandemic Potential (PEPPs) or **enhanced Potential Pandemic Pathogens (ePPPs)** are infectious agents that possess characteristics such as high transmissibility, virulence, and a broad host range, which together increase their likelihood of causing widespread outbreaks and pandemics.

Personal Reliability Program (PRP) is a program that enables and supports a culture of responsibility, based on human performance principles, maintains compliance with regulations, and address the risk associated with insider threats.

Powered Air Purifying Respirator (PAPR) refers to a special kind of hooded mask that has a fan and HEPA filter used to filter incoming air and establish positive pressure under the hood. They are typically much more effective than standard, non-powered masks.

Prions are a pathogenic type of protein that cause neurodegenerative diseases and does not contain nucleic acids (DNA or RNA).

Quarantine is defined as a state, period, or place of isolation in which people or animals that may have been exposed to or contracted an infectious disease are placed.

Sequences of Concern (SOCs) are genetic sequences that encode functions, directly contributing to an organism's pathogenicity (ability to spread and cause disease).

Surveillance refers to monitoring and collecting data to determine the presence of infectious agents and/or their resulting diseases.

Transboundary refers to something crossing boundaries or borders.

Tropism refers to the specific cells, tissues, or organisms that microorganisms can infect and replicate within.

Virulence refers to the dose of a pathogen necessary to cause disease.

Viruses are highly specialized pathogens that contain nucleic acids (DNA or RNA), and target specific cell types entering the cells through specific receptors on each cell's surface. They are much smaller than bacteria and are not capable of replicating without infecting a host.

I. EXECUTIVE SUMMARY WITH RECOMMENDATIONS

Biosafety and biosecurity are critical to prevent public health disasters associated with the release of infectious agents either by accident (e.g., University of Chicago 2009, plague release resulting in one fatality) or intentionally (e.g., U.S. 2001 anthrax attacks, resulting in 5 fatalities). The NSABB (National Science Advisory Board for Biosecurity) has recently proposed key recommendations on Dual Use Research of Concern (DURC) and Enhanced Potential Pandemic Pathogen (ePPP) Research, aligning with suggestions from Global Bio Labs, the Bulletin of Atomic Scientists Report, and the Biological Weapons Convention (BWC). In the past year (2023-2024), our group has provided Congressional testimony in both the House (Select Subcommittee on the Coronavirus Pandemic, October 18, 2023, "Strengthening Biosecurity Standards: Protecting Against Future Pandemics") and the Senate (Committee for Homeland Security Government Affairs, July 11, 2024, "Risky Research: Oversight of U.S. Taxpayer Funded High-Risk Virus Research") focusing on biosafety, biosecurity, and the new White House Policy on Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential, released in May 2024.

We recommend:

1) An independent entity for oversight of high-risk pathogen research be established.
- Create an independent biosafety and biosecurity oversight framework that covers all research activities carried out by public institutions (e.g., universities) or private entities (e.g., industry laboratories), irrespective of funding source.

2) Promoting the establishment of strengthened and harmonized global standards for biosafety and biorisk management.
- Promote U.S. biosafety and biorisk management tools, practices, and standards abroad.

3) Enhancing public health measures to improve and protect public safety.
- Strengthen public health surveillance measures around high containment laboratories and implement "no-fault" laboratory accident reporting for safety concerns.
- Foster a culture of safety that values transparency and communication during construction and operation of biocontainment facilities and following breaches in containment.

II. INTRODUCTION

This report is not intended to be exhaustive but is written to provide a clear understanding of the science and policy overseeing work with infectious agents, especially as the United States considers and implements new biosafety and biosecurity oversight policies. Improved literacy on this topic may lead to more informed policy decisions and a better understanding of relevant concepts among the public and policymakers. We strive to define widely used verbiage which may be encountered in news sources, scientific literature, and public debates relevant to guaranteeing public health and safety. Although scientific understanding of pathogens is extensive, genetic engineering tools that allow the creation of new and novel microorganisms is advancing at a rapid pace. Governmental oversight, policies, laws, rules, regulations, and guidelines have not kept pace with the rate of scientific advancements. The ongoing debate on this topic revolves around the intricate balance between promoting scientific progress and minimizing potential harm, a decision ultimately left to human judgment.

III. THREATS FROM INFECTIOUS AGENTS (EXPANDED FROM GLOSSARY)

Pathogens are microorganisms (e.g., viruses, bacteria, and fungi) or other infectious agents (e.g., prions and parasites) that cause illness (morbidity) or cause death (mortality). Generally, infectious agents or microorganisms are grouped into several categories (listed below).

Prions are a pathogenic type of misfolded protein that cause neurodegenerative diseases and do not contain nucleic acids (DNA or RNA). We will consider prions as the smallest infectious agent that can self-perpetuate utilizing the replication mechanisms in an infected host cell. In recent years, the prion disease Bovine Spongiform Encephalopathy (BSE) has manifested itself in cattle and caused the lethal Creutzfeldt-Jakob like disease in humans through the consumption of infected nervous tissue. There is currently no treatment for prion diseases.

Viruses are highly specialized pathogens that contain nucleic acids (DNA or RNA). Viruses target specific cell types and enter the cells through specific surface receptors on each cell. Once inside the cell, the virus integrates into the cell's genomic structure and then utilizes the cell's normal replication mechanisms to reproduce. Diseases associated with viral infections, such as COVID-19, have piqued interest in viral diseases, further encouraged by the re-emergence of diseases such as measles and poliomyelitis. Viruses can naturally mutate or be manipulated to infect hosts in which they would not normally cause disease.

Bacteria are microscopic, single-celled organisms that independently reproduce. Bacterial infections remain problematic although a wide spectrum of antibiotics are now available. Unfortunately, many bacteria have mutated to become resistant to antibiotics. These resistant bacteria may originate from humans who do not complete their prescribed course of antibiotic therapy. When a regimen of antibiotics is not completed, only bacteria with minimal resistance are killed, leaving behind the highly resistant bacteria. Some believe the problem lies with animal feed, which contains antibiotics and perpetuates antibiotic-resistant strains in animals. These strains can be transmitted through proximity to or consumption of animals.

Fungi are spore-producing, multicellular organisms that feed on organic matter. Fungal infections with organisms such as *Candida auris*, have become more prevalent in recent years, particularly in individuals with compromised immune systems. This is problematic, because antifungal agents are not effective. Improved antifungal agents are currently undergoing clinical trials. Because fungi share certain similarities with normal human (mammalian) cells, many antifungal agents also harm normal human cells. Furthermore, fungal vaccines have proven to be incredibly difficult to formulate.

Parasites are organisms that live in or on an organism of another species (its host), and benefits by deriving nutrients at the host's expense. A good example of an intracellular parasite—one that infects cells themselves—is *plasmodium malari*, which causes malaria. An example of an extracellular parasite—one that infects areas outside of cells—are *microfilariae* (small worms), which cause elephantiasis when they lodge in inguinal lymphatics.

CBRN is an acronym that stands for Chemical (e.g., nerve agents), Biological (e.g., infectious agents), Radiological (e.g., medical waste, including dirty bombs and polonium poisoning), and Nuclear (e.g., nuclear weapons), and usually refers to threats associated with these areas. Apart from the byproducts of nuclear weapons (those with exceptionally long

half-lives), many of the hazards associated with chemical, radiological, and nuclear exposures diminish over time. This may result from decay of radioactive particles with relatively short half-lives, or physical removal (e.g., rain) of chemical agents. In any case, each of these factors decreases potential danger over time. This is not true for biological agents, as they can self-perpetuate through the transmission of disease from one person or animal to the next. The ability of microorganisms to expand their scope of distribution makes it more important to contain these diseases in laboratory facilities and necessitates the use of public health measures (such as masking) when there is a breach in containment.

Quarantine is defined as a state, period, or place of isolation in which people or animals that may have been exposed to infectious diseases are placed. Isolation separates people that are sick because they have contracted a contagious infectious disease. Quarantining or isolation of both humans and animals can be a powerful tool in preventing the progression of an infectious agent/disease resulting from close contact with infected patients. There are several significant legal ramifications when dealing with detaining humans and controlling their movement to prevent the spread of disease. There is certainly legal precedent for forced quarantine of infected, or potentially infected, patients. The U.S. Surgeon General and most state health authorities have the authority to isolate patients when issues of public health are involved. There are long standing legal determinations based on the isolation and quarantine of both human and animal patients. If a researcher is exposed to a pathogen, quarantine facilities must exist to isolate patients until a determination can be made as to whether they have acquired an infection.

IV. SOURCES OF INFECTIOUS AGENTS

Naturally occurring diseases may be found in animals and can transmit to humans (zoonotic) or may be found in humans and can transmit to animals (zooanthroponosis, or reverse zoonosis). Infectious agents can be found naturally in a variety of locations. Examples of zoonotic diseases include rabies or parasitic diseases, such as ringworms from cats or tapeworms from dogs. Other naturally occurring diseases include vector-borne diseases (transmitted by mosquitoes, tics, etc.), such as Malaria, Zika, and Rocky Mountain Spotted Fever.

Naturally emerging diseases, such as Bird Flu (H5N1), arise through natural evolutionary processes and manifest as genetic variations of the original disease.

Naturally recurring diseases, such as polio and measles, are diseases that have previously been widespread but are now mostly eliminated, due to vaccine usage. These diseases are recurring, due to the decrease in vaccine usage for a variety of reasons (e.g., vaccine hesitancy).

Unnatural sources of infectious agents include the accidental release of pathogens from research laboratories. Such releases can be due to mistakes by research scientists, or to breaches in containment resulting from equipment failures. The impact of natural disasters, such as earthquakes and floods, are important due to their potential to cause breaches in containment in certain facilities. These public health emergencies may perpetuate disease transmission, including cholera, particularly in conflict zones. An example of a weather-related breach of containment occurred in the Texas Medical Center during Hurricane Ike in 2008. Water levels rose in the soil, which caused the walls in a facility used to store infected samples to collapse, releasing pathogens into the Houston environment. Although COVID-19 was highly disruptive, the virus killed less than 1% of the people infected. The current discussions on biosafety and biocontainment would be much different if the spreading disease had been something like Ebola, with a 60% to 80% death rate.

Agents with pandemic potential exist in nature and represent diseases of concern. The persisting practice of "virus hunting," or intentionally searching for undetected human and animal pathogens in nature, may inadvertently uncover new and potentially dangerous pathogens. Many microorganisms can be used to cause harm when intentionally modified for use as biological weapons. The use of microorganisms as biological weapons by terrorists or disgruntled individuals represents a serious area of concern. The use of microorganisms as a weapon extends far back into history, including the use of catapulted plague-infected corpses into cities, carried out during the Siege of Caffa in 1346. The use of biological weapons has extended into recent history, as the 2001 anthrax attacks in the U.S. demonstrate. The use of biological agents as weapons is impacted by a variety of factors, such as the mode of distribution (e.g., air, water, animals, humans), as well as the type and virulence of the infectious agent being used (e.g., virus, bacteria, fungi). Some microorganisms are inherently more difficult to weaponize, although the danger of such intentional release is no less problematic. Although the U.S. recently destroyed their last chemical weapons, other nation states (e.g., Russia and North Korea) are thought to maintain bioweapons programs, which are not in compliance with the Biological Weapons Convention (BWC).

Workers at the Wuhan Institute of Virology's P4 laboratory
Photo credit: AFP

V. BIOSAFETY AND BIOCONTAINMENT

Biosafety can be defined as the overall practices, equipment, and facilities used to protect workers, the community, and the environment against biological agents being used in research or other work (e.g., commercial manufacturing). Biocontainment refers specifically to the practices, equipment, and facilities used to physically prevent the accidental release of infectious agents into the environment.

Biosafety levels (BSLs) are a set of guidelines and practices designed to ensure the safe handling of biological agents in laboratory settings. BSLs are based on the *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) and the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines). The levels range from BSL-1 to BSL-4, each corresponding to different levels of risk associated with the agents being handled (see Figures 2, 3, 4 and 5 below). The level of risk associated with the agents not only depends on the agent being handled, but also on the type of work being done (e.g., work being done outside of a glovebox, the chance an agent may be aerosolized, or agents that have undergone genetic modification).

Each biosafety level, also known as a biosafety containment level, requires specific infrastructure, training, and protocols to ensure the safety of laboratory personnel and prevent the accidental release of harmful biological materials.

There are a few areas of conflict that arise during the maintenance and operation within high containment labs (at high biosafety levels), particularly as it relates to the use of Powered Air Purifying Respirator's (PAPR), various mask levels, and High Efficiency Particulate Air (HEPA) filters. A PAPR is a special kind of hooded mask that has a fan and HEPA filter in the breathing unit.

Most masks are only able to achieve a rating of PM2.5 (Particulate Matter 2.5) or higher. This means that these masks are only effective at filtering particles that are 2.5 microns (2,500 nanometers) or larger, and only when properly fitted onto the wearer. Mask levels range from level 1 to level 3. Level 1 masks, such as N95s, are rated to filter particles larger than 0.1 micron (100 nanometers) at 95% efficiency. Level 2 masks also filter particles greater than 0.1 micron, but at 98% efficiency. Level 3 masks also function at 0.1-micron level with 98% efficiency, but have improved filtration characteristics when exposed to fluids.

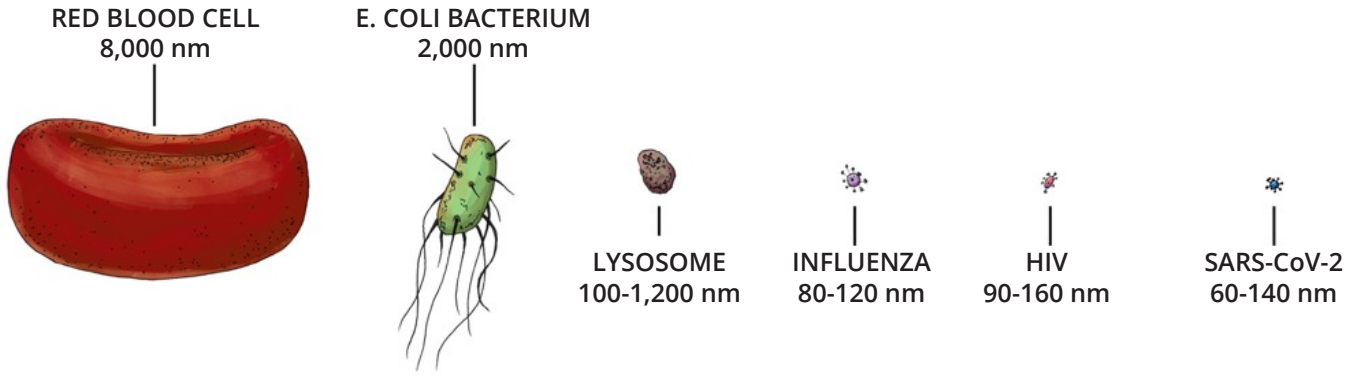


***Figure 1*: Comparison of the relative sizes of several infectious agents compared to the size of a human red blood cell (1 micron = 1000 nanometers)**

A HEPA is a type of pleated mechanical air filter (Environmental Protection Agency, 2024). HEPA filters are used in high containment laboratories and personal ventilation systems (for air purification). This type of air filter can theoretically remove up to 99.97% of dust, pollen, mold, bacteria, and any airborne particles with a size of 0.3 microns (300 nm) or larger (larger particles are trapped with even higher efficiency). It is important to note the virulence of a disease in question, since some pathogens only require a few infectious agents to cause disease, whereas in others, a larger exposure dose is required to cause infection.

When building BSL-3 and BSL-4 labs, qualified engineers must ensure that containment is not breached due to a design, engineering, or construction error. All air entering or exiting a BSL-3 or BSL-4 laboratory must be subject to filtration. This includes the conduit through which electrical wiring is routed to prevent flying insects, such as mosquitos, from entering the building via the tubing. It is also critical to maintain a negative air pressure within facilities utilizing pathogens, as pathogens cannot exit the laboratory against an airflow pressure gradient. Maintaining pressure gradients in high containment laboratories necessitates that air handling equipment can maintain the pressure gradient. To do so, the electricity supplied to these systems must remain constant. If power is disrupted, backup power must be instantly available through emergency generators. In addition, the treatment of all physical and liquid waste must be maintained at a level that precludes pathogens from leaving a biocontainment facility via a waste stream (e.g., garbage and sewage).

BSL-1 laboratories handle agents that are considered low-risk, as they are not known to cause disease in adults who are not immunocompromised. The personal protective equipment (PPE) required in BSL-1's is considered basic, including the use of gloves and lab coats. These labs are typically well-ventilated and are equipped with surfaces that are easy to clean and decontaminate. Examples of agents handled in BSL-1 labs include non-pathogenic strains of bacteria like *E. coli*.

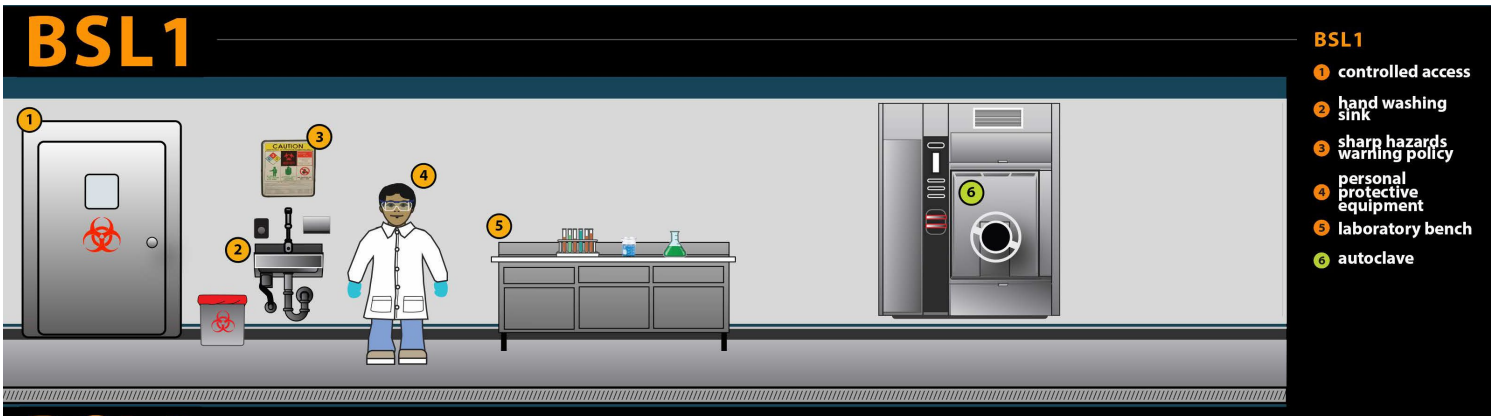


Figure 2: BSL-1 Laboratory and Components.

BSL-2 labs deal with agents that pose a moderate risk to humans and may cause disease. BSL-2 labs require decontamination of waste and have more advanced equipment such as biological safety cabinets and autoclaves for sterilization. Pathogens like *Staphylococcus aureus* and hepatitis B virus fall under this category.

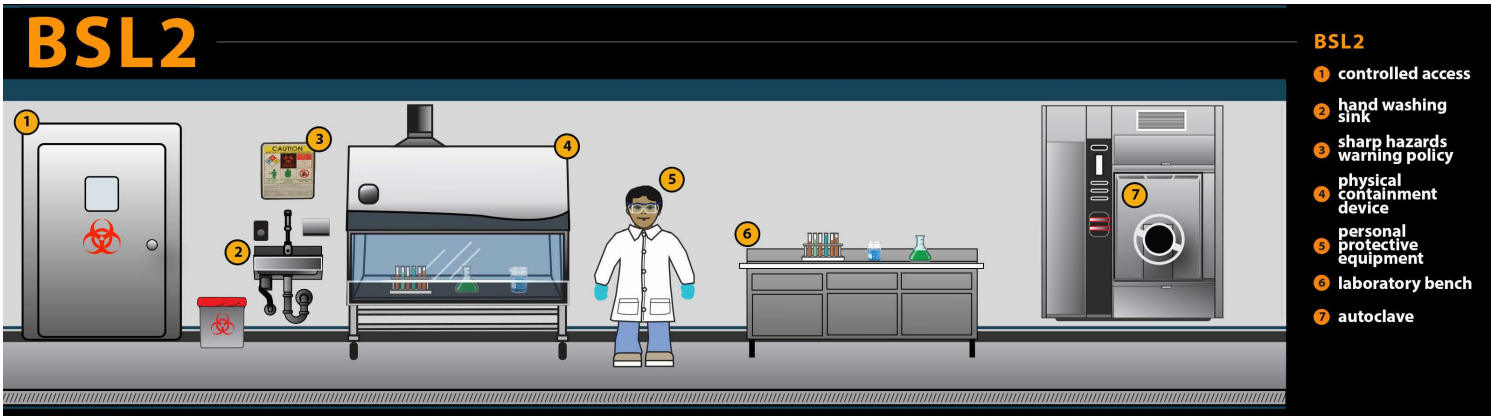


Figure 3: BSL-2 Laboratory and Components.

Moving up, **BSL-3** labs handle indigenous or exotic agents that can cause serious and potentially lethal diseases. These labs require specialized training for personnel, controlled airflow systems, and additional measures such as decontaminating lab clothing before leaving the facility. Examples of pathogens in BSL-3 labs include tuberculosis bacteria and viruses like SARS-CoV-2. The type of experimental procedure is also an important factor when determining whether research should be conducted at the BSL-3 level. For example, if experimental procedures have the potential to create aerosols intentionally or accidentally, then a BSL-3 laboratory may be required.

BSL-3 AG (Biosafety Level 3 Agricultural) laboratories are specialized facilities designed for handling agricultural pathogens that pose risks to animals, plants (as specified in the *NIH Guidelines*), and the environment. These labs implement stringent containment measures to prevent the spread of infectious agents and ensure the safety of researchers, workers, and the surrounding community. BSL-3 AG labs are crucial for studying and addressing agricultural biodefense, food safety, plant diseases, and animal health. They are equipped with advanced ventilation systems, specialized personal protective equipment, and decontamination protocols to minimize the potential for contamination and protection of agricultural resources.

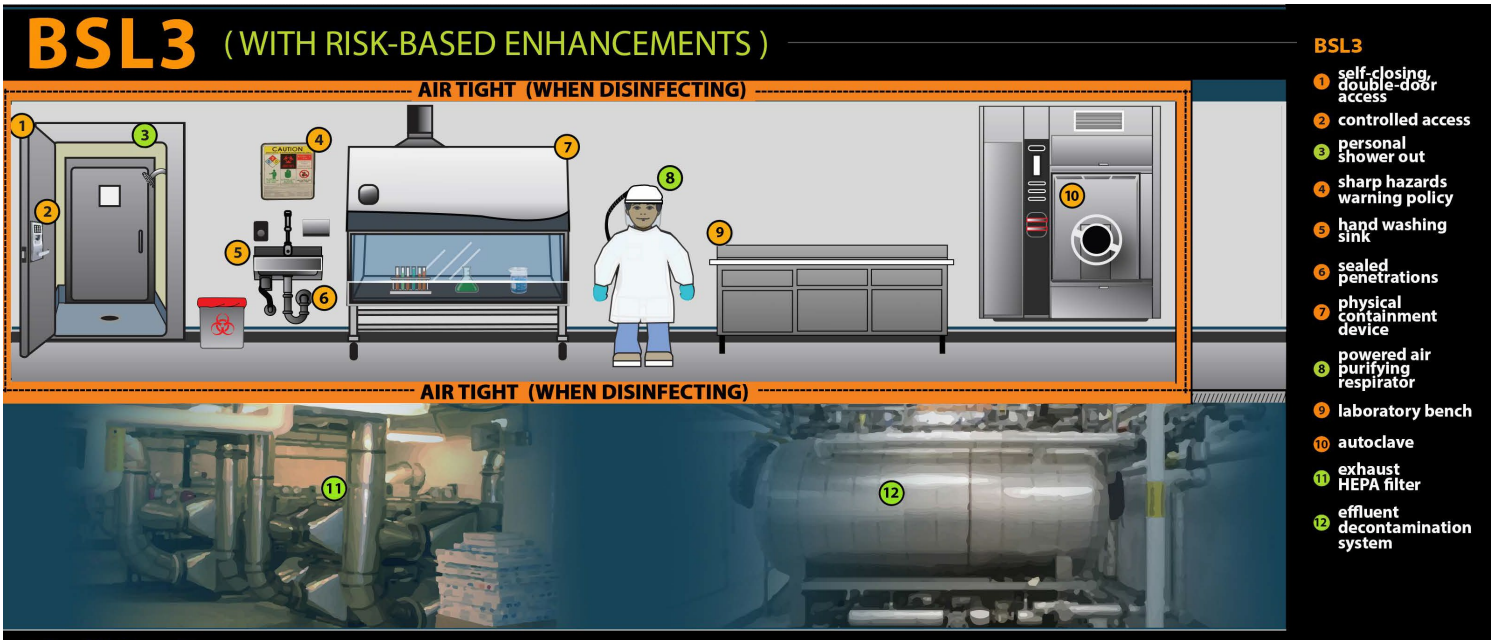


Figure 4: BSL-3 Laboratory and Components.

Finally, **BSL-4** labs are designed for the highest level of containment and safety. They handle dangerous and exotic agents posing a high risk of life-threatening diseases for which no vaccines or treatments are available. BSL-4 labs have stringent procedures for entering and exiting, including full-body suits, airlocks, and multiple layers of security. Examples of agents handled in BSL-4 labs include Ebola and Marburg viruses.

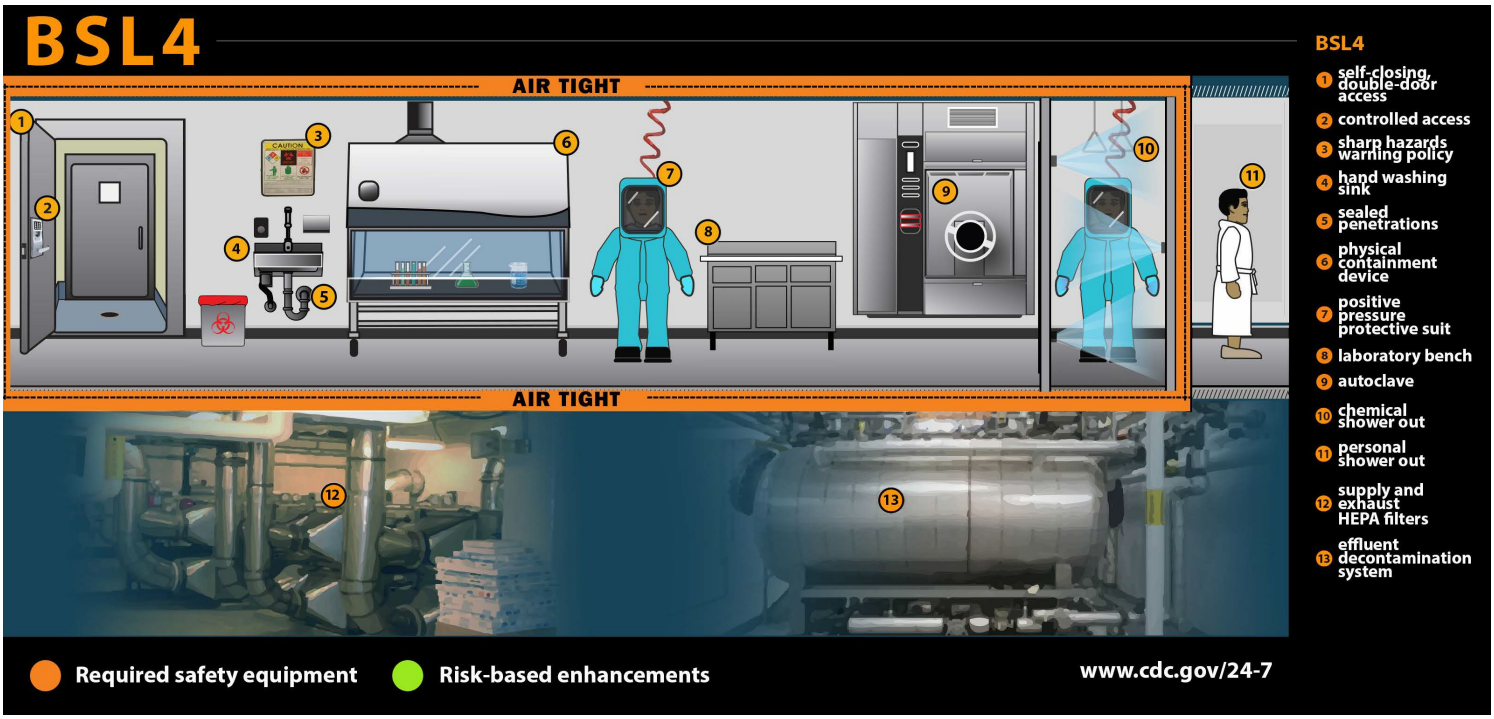


Figure 5: BSL-4 Laboratory and Components.

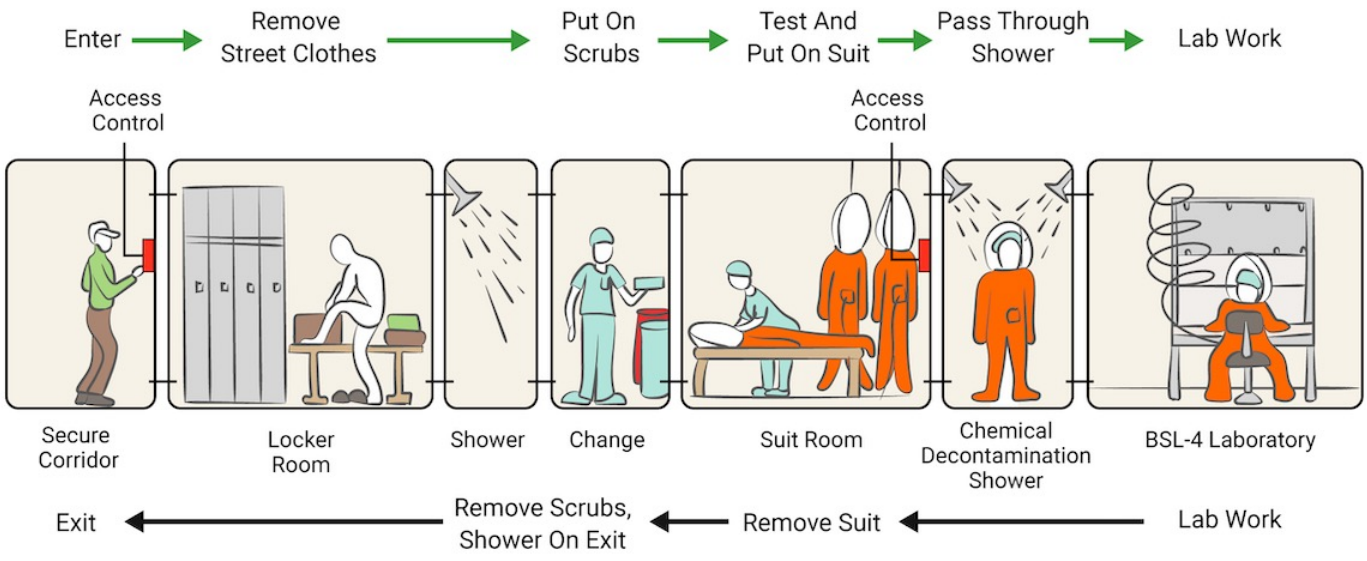


Figure 6: The typical process of entering and exiting a BSL-4 Laboratory.

Medical Countermeasures (MCMs) are actions, products, or pharmaceuticals that can be used to prevent or treat disease. There are few clinical facilities in the United States that can safely provide clinical care to patients infected with particularly hazardous agents. This includes the ability to transport infected patients via aircraft or ambulance. Health systems must also be equipped to store and safely dispose of the remains of infected and deceased patients.

Surveillance refers to monitoring and collecting data to determine the presence of infectious agents or their resulting diseases. This may include physical sampling of the environment, such as air, soil, and wastewater. Sampling of biological systems (e.g., human and animal) includes surveillance of body temperature of humans at ports of entry (such as airports, although this may not always be effective), mosquito sampling for various viral diseases, and testing of both human and animal blood samples to determine if subjects have been exposed to or vaccinated against pathogens (known as "titer testing"). Individuals working with pathogens must participate in blood titer testing to determine if they have been exposed to infectious agents.

High containment laboratories typically employ biosafety officers whose primary responsibility is to ensure the safety of laboratory operations. Biosafety officers are responsible for developing procedures, training staff, providing day-to-day advice, investigating accidents, and ensuring compliance with all relevant policies, guidelines, and regulations. Although there is no standard professional background for occupational health biosafety officers, organizations like the Association for Biosafety and Biosecurity (ABSA International) offer training and certification for the biosafety profession. Best practices dictate that biosafety officers should report directly to senior executive management and receive top-level support for their participation in the research process.

A. ISSUES

Difficulty eliminating accidents

Although major advances in technology, biosafety, and biocontainment practices have dramatically cut accident rates, containment breaches continue to occur, even at the most sophisticated laboratories. A 2023 review identified 309 lab-acquired infections and 16 accidental pathogen escapes between 2000 and 2021, which is certainly an undercount, given that few accidents are reported in the literature (Blacksell et al., 2023). In 2022, the annual Federal Select Agent Program (FSAP) report recorded 143 select agent releases involving occupational exposure, although none of them resulted in illness from or transmission of any pathogen (FSAP, 2022). Laboratories overseen by FSAP are required to follow stringent standards, but the continued prevalence of releases reveals that incidents occur, nonetheless.

Examples of significant breaches of containment:

- In 2019, a failure of inactivation at a Chinese veterinary vaccine plant led to a brucellosis outbreak with over 10,000 cases in Lanzhou (Georgios, 2022).
- A review of Chinese medical databases conducted in early 2020 reveals additional laboratory acquired cases of brucellosis in 2006, 2007, 2011, 2012, 2013, 2016, and 2017 (Song et al., 2021).
- A failure at a military lab in the former Soviet Union at Sverdlovsk (now Yekaterinburg) that infected at least 77 people and killed 66 (Meselson et al., 1994).
- The last death from smallpox (in 1978) resulted from a lab exposure in the United Kingdom, although it remains unknown exactly how the victim, who was on an adjacent floor from the lab, became infected (Manheim and Lewis, 2022).

Limited evidence base

There is a lack of data on rates of human error and historical biosafety incidents. There is no comprehensive record of biosafety and biocontainment incidents in the United States or around the globe. Many standards and practices

used today were initially developed by Arnold Wedum while he was working on the United States Biological Weapons Program. President Nixon terminated the U.S. Biological Weapons Program in 1969. Although standards continue to adapt based on learning from accidents and the experience of biosafety officers, information sharing is usually sparse, and no systematic biosafety research program exists.

Lack of funding

Most of the investigator-initiated research funding in the United States does not include dedicated funding for biosafety training, officials, or routine maintenance, although National Institute of Allergy and Infectious Diseases (NIAID) does award some grants to upgrade facilities and systems at existing BSL-3 and BSL-4 labs (NIAID, 2022). This means that ongoing funding for biosafety education, maintenance, and oversight must be provided from indirect costs at the discretion of individual institutions.

Institutions of higher education that receive grant funding from federal agencies (e.g., NIH, NSF, NASA) receive additional funds referred to as Indirect Costs (IDCs) to pay for the institutional expenses incurred conducting research. These IDCs cover items such as pre- and post-award grants management, utilities, and other research support necessities. Each academic institution determines the percentage of grant funding added to proposals as IDCs in negotiations with the federal government. As an example, an institution that has a 50% IDC rate receives $500,000 in IDCs for each $1,000,000 research grant funded. Historically, the rate of IDC returns has varied significantly between institutions, and some federal agencies, such as the United States Department of Agriculture (USDA), provide IDCs at a much lower rate.

Many institutions utilize their IDC returns to fund research committee work, including those overseeing animal usage, human usage, radiation safety, and biological safety. Institutions operating high containment laboratories incur

significant biocontainment laboratory expenses. A portion of the operational expenses are paid for by user fees in the facilities, but this does not cover all expenses. Funding the replacement of expensive HEPA filters to conduct research with pathogens, for example, is usually supplemented by IDCs. Institutions without these facilities are advantaged by avoiding these operational expenses, however they are not able to carry out high-risk pathogen research. Operating high containment facilities generates a constant conflict between universities, principal investigators, and high containment facilities, since each has pressing needs for IDC dollars.

In addition to the lack of dedicated biosafety funding in research grants, individual laboratories around the world often struggle with sustained funding to maintain and replace systems needed for biosafety and biocontainment. Even the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), the birthplace of biosafety, has not been exempt from this problem. In 2019, USAMRIID's BSL-4 laboratory was temporarily barred from working with select agents after its aging infrastructure, especially its wastewater treatment facility, began to fail (Young, 2023). Experts report that these issues are often worse abroad. International funding has been used to build expensive facilities in low-resource settings without adequate support for the significant maintenance and personnel costs required to ensure continued high biosafety and biocontainment standards (Sharples et al., 2019).

Importance of a safety culture in the biosafety workforce

Researchers studying pathogens generally do so out of a desire to advance human health and human knowledge, and they may take personal risks to achieve these goals. In other fields, this practice may have occurred, however, the threat of community spread of disease from infectious agents means that this behavior also puts others at risk. Generally, biosafety training and operating procedures are only as strong as the culture of safety that prioritizes adherence to rigorous standards and proactive risk mitigation. Biosafety officers can play an important role in developing and upholding this culture.

Proliferation of high-containment labs

BSL-3 and BSL-4 facilities are ground zero for potential public health emergencies. These laboratories house infectious agents that could be released into the public through intentional or accidental means. Containment breaches pose significant public health risks by potentially causing infections that may result in more significant disease outbreaks in communities, especially with contagious agents. According to data collected in 2023 by Global Biolabs, there are approximately 69 BSL-4's and 57 BSL-3's worldwide. Seventy-five percent of the 69 BSL-4's are in, or plan to be under construction in, urban centers, while 80% of the BSL-3 labs in the United States are in urban centers as well. Twelve new BSL-4 labs have been planned since the start of the COVID–19 pandemic. Globally, there are 126 BSL-3 and BSL-4 labs planned for construction. All BSL-4 laboratories working with select agents in America are overseen by the U.S. federal government, however those using an agent that does not appear on the federal select agent list remain a cause for concern. Some U.S. local jurisdictions have adopted prevailing federal guidelines to control the work done in their local high containment facilities. However, this practice is not widely adopted by local governments, and according to Global Biolabs, 2 out of 5 U.S. BSL-4s are not governmentally supervised. Funding for operating biocontainment facilities is constrained, and the construction of additional labs heightens the risk of containment breaches, especially since the number of expanding high containment laboratories are competing for the same pool of experienced staff. As discussed, most BSL-3's and BSL-4's are in or are planned to be in areas with high population density, supporting the need for surveillance around these facilities. Laboratories situated in urban areas present a heightened risk due to the larger population density, which amplifies the potential number of individuals affected by a pathogen leak.

VI. BIOSECURITY, RESEARCH RISKS, AND RESEARCH OVERSIGHT

Biosecurity refers to the practices and systems used to prevent theft, loss, or deliberate misuse of biological agents. The three major aspects of biosecurity are physical security, personnel reliability, and information security.

Access control and physical security

Securing of pathogens in biocontainment laboratories begins with control over movement in and out of high containment facilities. This includes the access and egress of humans, animals, and infectious agents. Movement of these subjects can be controlled through locked doors, keycard access to restricted areas, monitoring of facilities, and keeping records of access and inventory, designed to prevent or deter the removal of pathogens from facilities. The anthrax used in the 2001 Amerithrax attack is an example of a pathogen removed from a laboratory and used for nefarious purposes. Maintaining appropriate utilities to biocontainment facilities, such as continuity of electrical supply and human security oversight, are critical for effective access control and security.

Research oversight

Oversight of research activities is often used to promote biosecurity by proactively identifying security risks, including the potential for misuse of information generated by experiments, and determining appropriate risk mitigation measures. At research institutions, oversight responsibility falls to a variety of compliance committees. These committees are staffed by experienced, knowledgeable faculty members who are tasked with evaluating projects and suggesting constructive pathways to assist investigators. Although research oversight is accomplished mainly through faculty members on compliance committees reviewing research proposals, oversight may be exercised at other choke points, such as by the federal government. Oversight is necessary to maintain control over dangerous materials such as pathogens, radioactive material, chemical precursors, and toxins, as these substances can be used maliciously.

Personnel reliability

Security risk assessments, including rigorous background checks conducted by the FBI on all individuals, ranging from research principal investigators, technical staff, and animal care technicians, is required by the Federal Select Agent Program. To work with a small number of especially high-risk (Tier 1) select agents, further ongoing personnel suitability assessments are required. These personnel reliability assessments are another important tool to support biosecurity efforts, as they reduce the risk that individuals with access to high-risk biological agents will seek to use them for harm. Background screening aims to identify links to criminal organizations, foreign governments, and other signals that may indicate malicious intent or a susceptibility to exploitation by malicious actors. Background screening should be done at various security levels based on the pathogenicity of the microorganism being used. These screenings should include suitability assessments to ensure individuals with access to high-risk biological agents do not show psychological risk factors, such as poor mental health, that may indicate a willingness to engage in harmful behavior. The expense of background screenings must be paid for by universities and research budgets analogous to animal, human, and infectious agent oversight committees. Programs, such as the Personnel Reliability Program, exist to support employees working in high containment laboratories (Higgins et al., 2013).

Restrictions on the movement and transfer of pathogens

Biosecurity dictates that researchers without specific needs for access to high-risk pathogens should not be allowed to order, work with, or possess infectious agents. From movement within a biocontainment facility to transport within a state or across state borders, all appropriate state and federal policies, guidelines, and laws must be strictly enforced. When infectious agents are relocated from one facility to another, it is critical that the identity and purity of the agent is confirmed. In the past, multiple pathogens have inadvertently been moved from one facility to another, due to sample contamination. Additionally, viable pathogens have unintentionally been shipped in place of inactivated or killed pathogens to laboratories that are not equipped to handle live samples.

Information security and cybersecurity

Keeping information relating to the types and quantities of pathogens located in containment facilities confidential reduces the risk that such facilities would be targeted by bad actors. Information about research results can also pose a misuse risk by providing bad actors with methods for more easily creating pathogens, ways to enhance the pathogenicity of agents, or genetic sequences of especially dangerous agents. Information on pathogens, as well as Sequences of Concern (SOCs), should be treated with caution. Although much information already exists about infectious agents in the scientific literature and creating weaponized pathogens requires sophisticated expertise and equipment, technological advances are lowering these barriers, and new discoveries may enable dangerous new capabilities. Laboratories should also take cybersecurity precautions to protect their facilities and any sensitive data they may have from being hacked.

A. ISSUES

Risks versus value of open science and difficulty regulating publication

Scientists place a premium on the open publication of research results, including methodological details, to allow other researchers to replicate and build on earlier research findings. This norm is deeply held and widely regarded as essential to enabling the impressive scientific progress achieved over the last century. Naturally, many in the research community are skeptical of any restrictions on publication, even when national security issues arise. In principle, the scientific community recognizes some limits—most major journals have policies of reviewing manuscripts for dual-use concerns and potentially refusing to publish some information or entire articles—but the bar for what qualifies as sufficiently risky is often quite high. In a 2005 study regarding the reconstruction of the 1918 influenza virus—responsible for a devastating pandemic with a fatality rate at least five times that of COVID-19—the National Science

Advisory Board on Biosecurity (NSABB), which advises the National Institutes of Health (NIH), voted to publish the study. However, Science Magazine stated that it would proceed with publication even if the NSABB had voted against publication (Science, 2005).

The U.S. Government has also embraced the principles of scientific openness; in 1985, the Reagan administration formalized this in National Security Decision Directive 189 (NSDD-189), which made it U.S. policy that "to the maximum extent possible, the products of fundamental research remain unrestricted" where "'fundamental research' means basic and applied research in science and engineering, the results of which ordinarily are published and shared broadly within the scientific community, as distinguished from proprietary research and from industrial development, design, production, and product utilization, the results of which ordinarily are restricted for proprietary or national security reasons" (NSDD-189: National Policy on the Transfer of Scientific, Technical and Engineering Information, 1985). The administration reasoned that an open scientific enterprise was one of the greatest strengths of the West in its competition with the Soviet Union, and that preserving this openness was worth the cost of Soviet spies and scientists having equal access to research produced in the United States and its allies. As a result, federal agencies generally do not act to restrict the publication of research unless it has been classified from the start, meaning that it was conducted in a classified setting.

With the practice of posting papers on preprint servers before publication becoming increasingly widespread, the difficulty of stopping dangerous research information from being published has greatly increased. Even if governments, publishers, and preprint servers were to agree to some restrictions, many scientists have other platforms to share their findings, including social media, blogs, and news outlets. Controlling access to research at the publication stage is likely impossible without cooperation from the researchers themselves. This suggests that top-down governance is most effective at an earlier point when research funding decisions are made or while research is underway.

Published information cannot be retracted

Once information is made available on the internet, the knowledge can no longer be withdrawn. Users from across the world can download the information, store it on their local devices, and re-upload it on any number of forums. Even if the original source deletes the information, these additional copies will persist. Actors with a range of motivations, including a belief in transparency or a malicious desire to spread harmful information, will likely act to preserve controversial and dangerous research findings. At best, governments can make finding published dual-use information more difficult.

Outsourcing with gene synthesis and contract research

Historically, synthetic biology techniques like creating a laboratory culture of viruses based on genetic sequence data have required specialized equipment, knowledge, and experience. However, the options to outsource or automate biological research are rapidly expanding. Many laboratories now order genetic material shipped to them from specialized gene synthesis companies. Other firms are now beginning to offer services that allow users to conduct entire experiments in highly automated cloud laboratories or contract research facilities. New equipment such as benchtop gene synthesis devices are also automating parts of the research process, and this trend looks likely to continue as computing advances.

These changes introduce new security challenges as they are decreasing the cost and knowledge requirements to access advanced synthetic biology techniques. If not secured, these systems could enable inexperienced or malicious actors to create dangerous biological agents. Efforts to oversee research biosecurity should consider how to account for automated and outsourced laboratory work.

VII. SCIENCE THAT DRIVES POLICY

A. Sequences of Concern (SOCs)

Rapidly advancing technology may be lowering barriers and making list-based approaches ineffective

The current Select Agent list is insufficient in identifying all dangerous pathogens and toxins and requires modernization to better serve its purpose. However, it provides a foundational starting point for this effort. There are many unlisted infectious agents that are as virulent as those currently listed, such as Middle Eastern Respiratory Virus (MERS). More fundamentally, a system must be implemented to account for the capability to genetically manipulate microorganisms, making benign pathogens more dangerous, or creating new pathogens. A growing number of individuals from the scientific and political communities are now considering the oversight of infectious diseases in terms of high-risk genetic sequences rather than high-risk organisms. This approach is developing out of scientific successes in recognizing the function of pathogens' genes. Many of a pathogen's genes deal with basic or non-pathogenic functions, such as replicating or building its structure. While these functions are needed for the pathogen to exist, they do not directly contribute to its ability to evade the immune system, attack cells, or disrupt the host's biological processes. The sequences that encode these and other functions that directly contribute to an organism's pathogenicity (or ability to spread and cause disease) are known as Sequences of Concern (SOCs). Since enhancements to a pathogen or the development of a novel pathogen will almost certainly require modifying or transferring SOCs from known organisms, controlling SOCs could provide a more comprehensive and adaptable approach (Godbold et al., 2023). SOCs could be used to replace or supplement existing list-based approaches, but in the future, they could also be used to train Artificial Intelligence (AI) models to recognize entirely novel high-risk sequences. This may become necessary if future AI capabilities enable bad actors to design and create such novel sequences.

Genetic material can be purchased from commercial vendors. Although many vendors, such as those in the International Gene Synthesis Consortium, already screen their orders for similarity to the genetic material of dangerous pathogens, this screening is neither universal nor entirely comprehensive. To prevent the sale of potentially dangerous SOCs, one company, SecureDNA, screens sequences against an existing SOCs database that identifies the potential for increased pathogenicity of a microorganism. This company has structured their screening service to maintain confidentiality and protect potential patents and commercialization of a user's intellectual property. This approach would cover existing select agent pathogens, newly constructed pathogens, and the genetic sequences used to create new pathogens.

B. Gain of Function Research

There is disagreement regarding the definition of Gain of Function (GOF), however for our purposes we define GOF as a change in an organism's genetic makeup, which leads to the organism gaining new or enhanced functions. Research involving GOF aims to intentionally modify an organism so that it may gain new phenotypic characteristics or functional capabilities. This type of research is common and valuable, as it allows researchers to engineer organisms to produce useful compounds, make organisms easier to work with the in the laboratory, or answer basic science questions about evolution and how organisms function. The vast majority of GOF does not occur with pathogens and poses minimal risk. For example, creating a strain of E. coli to produce human insulin or fluorescently labeling an organism both technically constitute GOF. Some GOF work with pathogens also poses a low or moderate level of risk and can be helpful to explore host susceptibility (ability of a host to contract an infection), as well as vaccine development and enhancement.

When policymakers talk about "gain of function" research, they are typically referring to high-risk research that is designed to enhance the pathogenicity of organisms. This paper will refer to this research as Gain of Function Research of Concern (GOFROC). GOFROC makes up an exceedingly small subset of life sciences research with serious risks and should not be conflated with the vast majority of low- to moderate-risk gain of function research.

An even smaller subsection of GOFROC research deals with pathogens capable of producing a pandemic. As of May 2024, in a new White House policy, these pathogens are referred to as Pathogens with Enhanced Pandemic Potential (PEPPs)—defined as pathogens capable of causing a pandemic that have been created in the laboratory by enhancing a pathogen's transmissibility, changing its tropism or host range, enhancing its virulence, disrupting existing immunity, or reconstituting an extinct pathogen.[1]

An example of GOFROC is the now widely controversial research grant that allowed chimeras to be created regarding MERS- and SARS-related coronaviruses. A chimera is a virus that contains genetic material derived from two or more distinct viruses. This research was supported by federal funds through the non-profit Eco Health Alliance (EHA) at the Wuhan Institute of Virology (WIV). While this work may have been well intentioned, it certainly became high risk.

One aim of EHA's research was to find natural and create novel, non-natural coronaviruses with high potential for interspecies transmission to study molecular mechanisms related to changes in host tropism. Changes in host tropism can have significant implications for the transmission and virulence of a virus. When a virus jumps from one species to another, such as from animals to humans, it undergoes changes in its tropism, allowing it to infect and replicate within the cells of the new host species.

[1] So long as they are also assessed to pose a significant threat to public health, the ability of health systems to function, or national security. Before May 2024, a related but slightly different term was used: enhanced Pandemic Potential Pathogen (ePPP).

The WIV was the first to discover bat Severe Acute Respiratory Syndrome (SARS)-related Coronaviruses (CoVs) collected from the Yunnan region in southern China that can bind and infect human cells. After this discovery, molecular components from receptor binding domains from viral spike proteins, were studied extensively to characterize receptor binding affinity to human cells, and those with the highest affinity were studied further. Simply stated, WIV scientists mixed and matched pieces of different coronaviruses to generate novel viruses that they thought might show the ability to better infect human cells. Their research intentionally sought the optimal genomic combinations needed to enhance interspecies transmission and then tested those chimeras using human cells, humanized animal models, and other animal models to estimate zoonotic pandemic risk (at least in surrogate in vitro and in vivo models in the laboratory), with potential to cause human infection and human disease via the respiratory system.

Whether or not this work caused the COVID-19 pandemic remains contested. Regardless, it posed a significant risk of creating a pandemic-capable virus. To justify the risks to society, this kind of research should be assessed to make sure it has commensurate benefits, and that adequate biosafety and biosecurity measures are in place. Some experts have disputed that these experiments have the immediate public health benefits their proponents often claim.

C. Dual Use

Dual use refers to information, technologies, or research that can be used in both a beneficial and harmful way. Most life sciences research is inherently dual use, which necessitates a focus on defining and overseeing the highest risk work. As an example of relatively low-risk dual use research, developing a more efficient bioreactor would allow companies to manufacture valuable biological drugs, such as synthetic insulin, but it could also allow bad actors to more efficiently produce biological weapons.

Dual Use Research of Concern (DURC) is the term used in federal policies to refer to high-risk dual-use research. As of 2024, the latest policies define DURC as research reasonably anticipated to provide knowledge, information, products, or technologies that could be misapplied with no or little modification to pose a significant threat to public health and safety, agricultural crops and other plants, animals, the environment, or national security.

Dual use can also be applied to facilities. In 1979, what the Soviet Union claimed was a laboratory experienced a breach in containment, exposing the fact that it was a bioweapons facility and killing at least 66 people. Without this leak or a human source inside the plant, it would be nearly impossible to determine whether the plant was producing vaccines or biological weapons.

Figure 7 below illustrates the relationship between GOF and dual use research. The figure does not reflect quantitative estimates of risk or volume, but it shows the general points that GOF can be considered a subset of dual use research and that the vast majority of both types of research poses little risk.

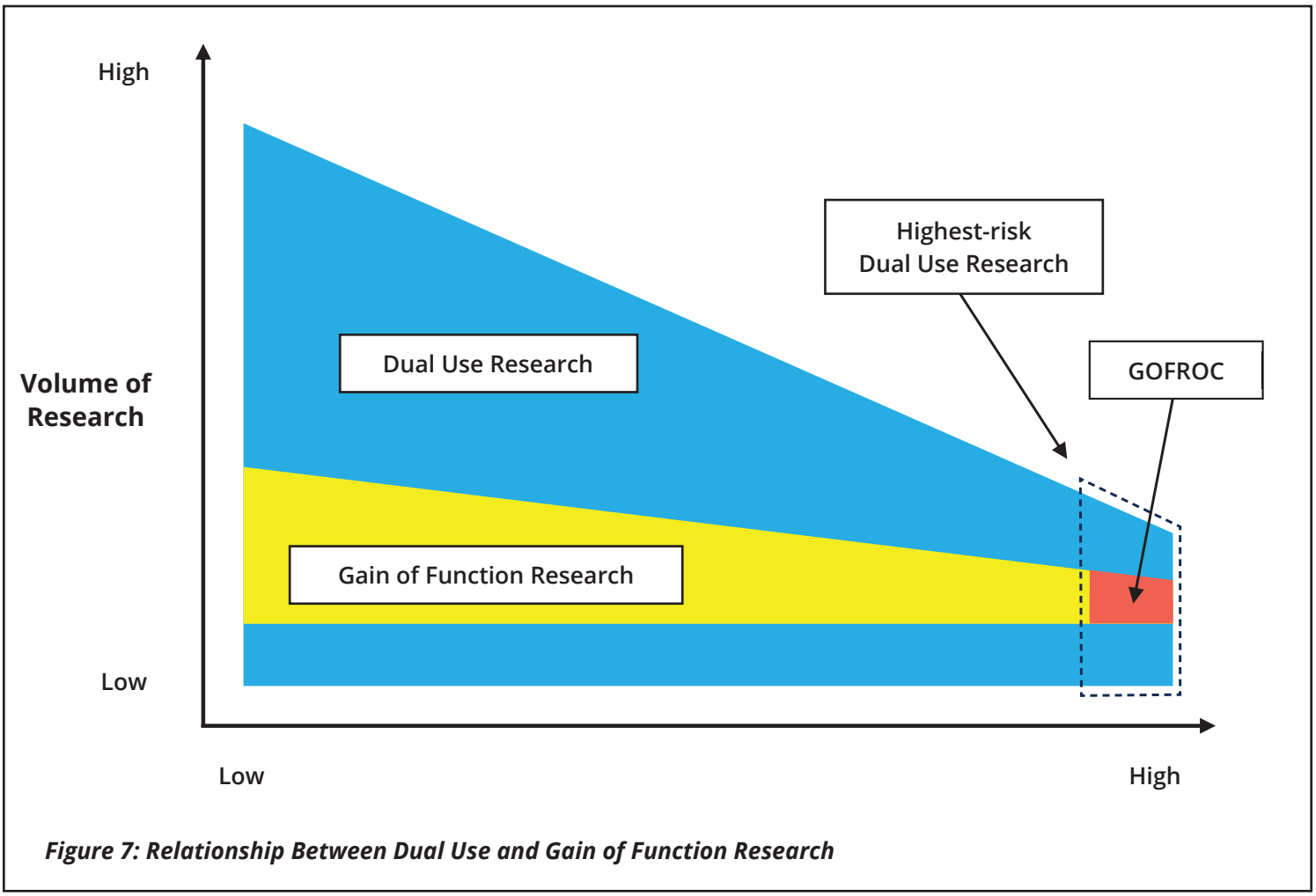


Figure 7: Relationship Between Dual Use and Gain of Function Research

POLICY LANDSCAPE

Regulations

There are only two sets of regulations—meaning legally binding policies (as opposed to guidance or policies tied to funding decisions)—related to biosafety and biosecurity in the United States.

The Federal Select Agent Program

The first of these is the Federal Select Agent Program (FSAP), which regulates the possession, use, and transfer of pathogens and toxins on the select agent list, maintained by the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS), and the Animal and Plant Health Inspection Service (APHIS), within the Department of Agriculture. For biological agents or toxins to be included on the list, they must be assessed by APHIS (the APHIS Administrator has this authority) or HHS (the HHS Secretary has this authority) to have the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal or plant products. The list currently contains 68 pathogens and toxins, including *Yersinia pestis*, the agent that causes plague, ricin, a deadly toxin, and foot-and-mouth disease virus, a pathogen that infects cows and threatens the cattle industry. Examples of pathogens not on the list include MERS-CoV, the virus responsible for a disease with low transmissibility but a fatality rate of 35% called Middle Eastern Respiratory Syndrome, and HIV, the virus responsible for AIDS.

The list is separated into tiers, with Tier 1 containing the most dangerous agents and the strictest requirements. Attenuated, or weakened, strains of many select agents can be exempted from the select agent regulations; FSAP maintains a list of these exemptions as well.

Individuals and institutions that possess, use, or transfer any select agent must register with the select agent program; undergo periodic inspections; follow appropriate biosafety and biosecurity procedures; report the loss, release, or theft

of agents; undergo training; maintain careful records of select agent samples; conduct certain types of experiments only with prior approval;[2] and receive a periodic security assessment by the Federal Bureau of Investigation (FBI).

The FSAP has its legislative roots in the Antiterrorism and Effective Death Penalty Act of 1996, which created a "Select Agent Rule" that regulated the transfer of a short list of biological agents and toxins. This was expanded into the current program by the Public Health Security and Bioterrorism Act of 2002, following the 2001 Amerithrax attacks.

FSAP only regulates physical research materials, such as pathogen samples, and does not have any controls for research information, such as pathogen genetic sequences stored on a computer.

Export controls

The United States has two export control programs: the International Traffic in Arms Regulations (ITAR), overseen by the U.S. Department of State, and the Export Administration Regulations (EAR), overseen by the U.S. Department of Commerce. ITAR and EAR include lists of physical items, software, and information that could be misused by adversaries and cannot be exported to certain countries without first receiving a license.[3] Transfers of knowledge, like providing technical training or posting information on the internet, can be considered exports under these policies. Transfer of items, software, or information to foreign nationals within the United States are known as "deemed exports" and are regulated by these policies.

Fundamental research, defined as research typically published and shared broadly in the scientific community and which is not restricted for proprietary or national security reasons, is exempt from controls on knowledge or deemed exports. This means that results from fundamental research can be published broadly and that foreign nationals can participate in fundamental research in the United States, even if the work involves controlled pathogens, so long as all the technology used is already or is made publicly available. United States biosecurity export controls are harmonized with the Australia Group, an informal group of 42 countries and the European Union that voluntarily share intelligence and coordinate export controls to prevent biological and chemical weapons proliferation.

ITAR controls are stricter and are intended to cover technologies intended for military use. Biosecurity controls include certain biological agents and their genetic components, modified to be more easily weaponized to cause human casualties, damage agriculture, or degrade equipment.[4] It also includes military equipment and components for the use of and defense against biological weapons. Unlike EAR, licensing requirements are based on the nature of the item rather than the end-user (military or civilian) and licenses are required for export to every country, with some limited exceptions. Twenty countries are proscribed or prohibited from nearly all ITAR controlled exports.

EAR covers dual-use technologies that could have both military and civilian uses, and its controls are less strict. The list of controlled substances includes human, animal, and plant pathogens and toxins and goes beyond the select agents list. EAR also controls nucleic acids (and organisms containing them) coding for genes specific to controlled viruses or toxins. The genes of controlled bacteria or fungi are also controlled so long as the genes represent a significant threat to human, animal, or plant health, or could enhance pathogenicity. Technology for the development, production, and disposal of controlled agents is also controlled; so is equipment for handling biological materials, including containment

[2] There are only three specific and uncommon types of experiments on this list.

[3] ITAR's list is known as the U.S. Munitions List, and EAR's list is known as the Commerce Control List.

[4] This includes effects such as overcoming acquired or natural immunity, evading standard detection methods, overcoming personnel protection, and increased stability in the field, but it does not explicitly specify properties like increased transmissibility or virulence.

facilities, fermenters, and centrifuges, among others. With a few exceptions, all of these may be exported to other Australia Group members without a license.[5] Vaccines, immunotoxins, and toxin-based products containing or designed to treat controlled agents are also controlled, although they may be exported without a license to many countries. Four countries, considered state sponsors of terrorism, are prohibited from nearly all EAR controlled exports. In deciding whether to issue a license, the Department of Commerce considers the nature of the item itself, the country it is going to, who the end-user is, and what its intended use is. In practice, partly because exporters know what is likely to be granted or denied, the vast majority of licenses are approved; in 2020, just over 1% were denied (U.S. Department of Commerce, 2021).

Crucial to understanding the U.S. biosecurity enterprise is an understanding of the structure of the U.S. Department of Health and Human Services (HHS). HHS is organized into Operating Divisions (OpDivs) and Staff Divisions under the Office of the Secretary (StaffDivs). Operating Divisions include well-known agencies such as the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and Administration for Strategic Preparedness and Response (ASPR) alongside many other OpDivs. StaffDivs are smaller divisions of HHS and operate as part of the Office of the Secretary (OS) with responsibilities that span the entire Department, for example on issues such as legislation, financial resources, and information technology. Both StaffDivs and OpDivs report to the Secretary of HHS, but many OpDivs are much larger organizations with significant resources for intramural and extramural research. The distinction between OpDivs and StaffDivs is internal to HHS and is neither replicated in other federal departments or agencies nor reflected in statute – it is simply an organizational practice of HHS.

Importantly, this means that several federal agencies that fund research with potential pandemic pathogens, such as the National Institute for Allergy and Infectious Diseases within NIH, or which have partial oversight responsibility for select agents, such as CDC, are within and subordinate to HHS.

Guidance & other policies

No other policy governing biosafety, biocontainment, and biosecurity carries force of law. Some, like the Biosafety in Microbiological and Biomedical Laboratories (BMBL) are guidance documents that suggest best practices. Others, like the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential and NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, make compliance a condition of receiving federal research funding.

While these policies and guidance documents are not legally binding, it should be noted that they are significantly easier to update than regulations or laws, which require consulting with more stakeholders or decision makers and/or navigating time-consuming bureaucratic processes such as public comment periods.

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* specify biosafety and biocontainment standards for working with recombinant—meaning made up of pieces from different sources—or synthetic nucleic acids (DNA or RNA). Compliance with these standards is required for all NIH-funded work with recombinant or synthetic nucleic acids. For institutions within the United States that receive any NIH funding of

[5] Ricin and Saxitoxin are more tightly controlled under the Chemical Weapons Convention, to which the United States is a party, and both require a license regardless of destination.

this type, it applies to all their work with recombinant or synthetic nucleic acids regardless of funding source.[6] If an institution fails to comply, funding from NIH covered by the policy may be restricted or terminated.

The *NIH Guidelines* were originally published in 1976, as genetic engineering techniques were becoming widely used, and have been updated every few years by the NIH Office of Science Policy with the most recent update taking effect in September 2024. The *NIH Guidelines* were originally written following the Asilomar Conference on Recombinant DNA in 1975, where scientists gathered to discuss the risks and benefits of genetic engineering and agreed research using these techniques should continue under stringent guidelines.

NIH Guidelines key contents:

- Instructs institutions to create an Institutional Biosafety Committee (IBC) to oversee biosafety and biocontainment standards and ensure compliance with the *NIH Guidelines*.
  - Generally, institutions must appoint a biological safety officer who serves on this committee and conducts inspections, advises principal investigators, and develops emergency plans.
- Classifies biological agents into four risk groups based on their threat to human health.

Risk Group	Definition	Examples
1.	Not known to cause disease in healthy adults.	Many *E. coli* strains, the most common bacterium used in laboratories; *Saccharomyces cerevisiae*, baker's yeast
2.	Associated with human disease which is rarely serious and for which vaccines and treatments are *often* available.	*Salmonella*; Measles virus
3.	Associated with serious or lethal human disease for which vaccines and treatments *may* be available.	*Yersinia pestis*, the bacteria that causes plague; Monkeypox virus
4.	Likely to cause serious or lethal human disease for which vaccines and treatments are *not usually* available.	Ebola virus

- Specifies the facilities, equipment, and practices required for the biosafety and biosecurity of research. There are four containment levels, or biosafety levels, that roughly correspond to the four risk groups, but the decision about what containment level to use ultimately rests with the risk assessment of the principal investigator and IBC, which takes into account other factors like the nature of the activities involved. There are different sets of containment levels for work that involves plants, involves animals, or occurs at a large (industrial) scale.
- Lists types of experiments that require approval or notification of IBCs, the NIH Office of Science Policy, or the NIH Director before they can begin.
- Instructs institutions to report illnesses, accidents, or violations within 30 days to NIH Office of Science Policy.

[6] The actual policy is slightly more complicated. It also applies to any research that involves testing in humans of materials containing recombinant or synthetic nucleic acids developed with NIH funds, so long as the institution that developed them is sponsoring or participating in the research (merely providing the materials does not count).

Principal investigators (PIs) are responsible for following and supervising the guidelines in their own labs with oversight from institutions and some limited oversight from NIH.

The *NIH Guidelines* are widely considered best practice, and many institutions not required to follow them set their own policies based on the NIH's recommendations.

Biosafety in Microbiological and Biomedical Laboratories

A collaboration between NIH and CDC that is published by the CDC, *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), is a document with detailed best practices for biosafety, biosecurity, and containment when working with biological agents in a laboratory.[7] Since its initial publication in 1984, the BMBL has been updated several times, and the 6th edition was released in 2020. While the BMBL describes general principles that apply to all laboratories, the document is focused on the practices, equipment, and facilities recommended for Biosafety Levels (BSLs) 1-4, which correspond to the same levels in the *NIH Guidelines*, and describes how to work safely with particular agents, including what BSLs should be used.

Unlike the *NIH Guidelines*, the BMBL is a purely advisory document and compliance is entirely voluntary. Like the *NIH Guidelines*, the BMBL is widely regarded as the gold standard, and many researchers and institutions around the world follow its recommendations. Funding organizations, including federal agencies, companies, and philanthropies may also make compliance with the BMBL (or the *NIH Guidelines*, for that matter) a condition for receiving a grant. Some local jurisdictions, such as the City of Boston, also mandate compliance with the BMBL for some laboratories (See Boston's Biological Laboratory Regulations).

United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential

On May 6, 2024, the White House issued a new policy intended to harmonize and modernize the U.S. Government's oversight of life sciences research as a major research funder. The new policy, *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential* (DURC-PEPP policy), replaces previous research oversight policies from 2012, 2014, and 2017.

Two types of research are covered by this policy.

1. The first is research with particular pathogens or toxins that could make them more dangerous—through at least one of nine experimental outcomes listed (outlined below)—and whose products or results could be easily misused to pose a significant threat to human health, agriculture, the environment, military equipment, or national security. This roughly corresponds with previous definitions of Dual Use Research of Concern (DURC).

2. The second type of research is work with or that is reasonably anticipated to create a Pathogen with Pandemic Potential (PPP), defined as a pathogen likely capable of wide and uncontrollable spread in a human population and that would likely cause at least moderate disease and/or death in humans (through one of four types of experiments outlined below), and that poses a significant threat to public health or national security. The policy refers to this as work with Pathogens with Enhanced Pandemic Potential (PEPPs).

[7] It includes both biomedical and clinical laboratories.

The first type of research is known as Category 1 research (or DURC) and the second is Category 2 research (or PEPP research). For both categories, researchers are responsible for notifying their research institution if their work falls into one of these categories. For ongoing research, they must pause their work until the review process is complete. The policy requires research institutions to have a review body that assesses these cases, shares their determination with the federal agency funding the research, and if the research is Category 1 or Category 2, works with the researcher to conduct a risk-benefit analysis and create a risk mitigation plan (all shared with the federal funding agency).

For Category 1 research, the federal agency must review the information submitted by the institution before deciding whether or not to fund it, or for ongoing research, allow it to continue. For Category 2 research, this review must be elevated to the department level. Both reviews must involve committees with a range of scientific and national security expertise and the department-level committee should be designed to avoid conflicts of interest. The policy also instructs the federal government to create an aggregate annual report about the types of Category 2 Research funded, the anticipated risks and benefits, and the risk mitigation measures in place.

As defined in the DURC-PEPP policy, research within the scope of Category 1 are those experimental outcomes with a biological agent or toxin (with some examples) that are reasonably anticipated to:

i. Increase transmissibility of a pathogen within or between host species; (Example: Wuhan laboratory modified the transmissibility of COVID–19 to a respiratory mechanism from bats to humans, increasing transmissibility of the virus)
ii. Increase the virulence of a pathogen or convey virulence to a non-pathogen; (Example: manipulating the genome of a microorganism by insertion of genetic sequences of concern)
iii. Increase the toxicity of a known toxin or produce a novel toxin;
iv. Increase the stability of a pathogen or toxin in the environment, or increase the ability to disseminate a pathogen or toxin; (Example: manipulation of Anthrax to allow more efficient distribution of spores)
v. Alter the host range or tropism of a pathogen or toxin; (Example: Wuhan laboratory increased host range of Covid from bats to humans, as well as making the pathogen airborne)
vi. Decrease the ability for a human or veterinary pathogen or toxin to be detected using standard diagnostic or analytical methods;
vii. Increase resistance of a pathogen or toxin to clinical and/or veterinary prophylactic or therapeutic interventions; (Example: conferring resistance to pathogens in human patients occurs in nature under various circumstances including the overuse or underuse of antibiotics)
viii. Alter a human or veterinary pathogen or toxin to disrupt the effectiveness of preexisting immunity, via immunization or natural infection, against the pathogen or toxin; or
ix. Enhance the susceptibility of a host population to a pathogen or toxin. (Example: susceptibility of a pathogen can be increased by immunosuppression in individuals undergoing bone marrow transplants or pharmacologically, as in AIDS patients)

Research within the scope of Category 2 produces experimental outcomes or actions with a pathogen that are reasonably anticipated to:

i. Enhance transmissibility of the pathogen in humans;
ii. Enhance the virulence of the pathogen in humans;
iii. Enhance the immune evasion of the pathogen in humans such as by modifying the pathogen to disrupt the effectiveness of pre-existing immunity via immunization or natural infection; or
iv. Generate, use, reconstitute, or transfer an eradicated or extinct PPP, or a previously identified PEPP.

Institutions and researchers share the responsibility to comply with this policy and any risk mitigation plans, although federal agencies are instructed to support or review evidence from laboratory inspections (although no additional funding or authorities are provided) to ensure compliance. Compliance is a condition of receiving federal research funds, and if researchers or institutions fail to follow this policy, agencies can restrict or withdraw research funding. The policy applies to all federally funded research; while federally funded institutions in the United States are required to attest that they are reviewing non-federally funded research to the same standards, this policy provides no federal oversight for this work.

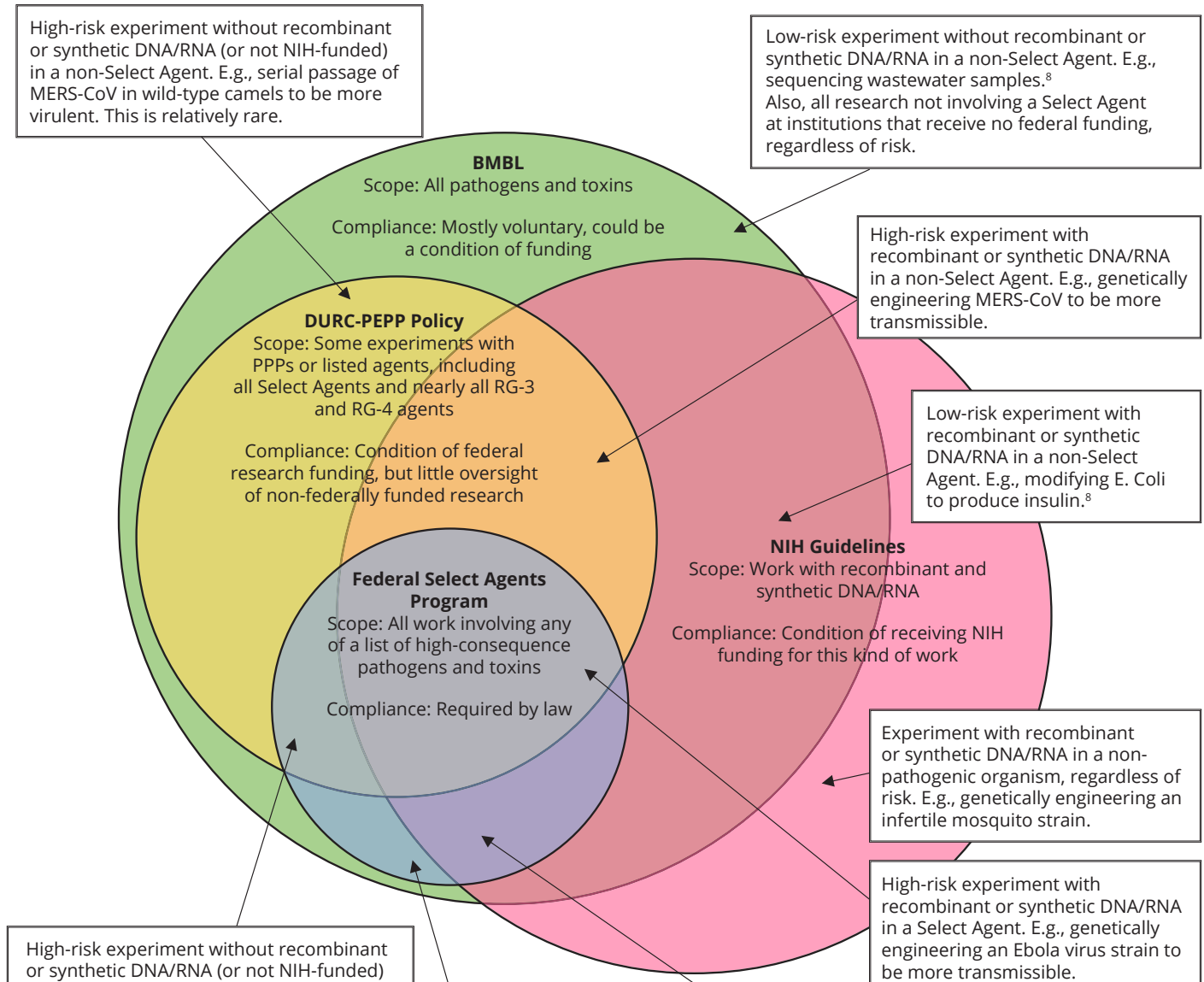
The United States Governments Office of Science and Technology Policy (OSTP) is tasked with updating this policy at least every four years, and the policy will take effect on May 6, 2025. The policy is also accompanied by an 85-page implementation guide with examples, flow-charts, and further clarification of definitions to guide the agencies, researchers, and institutions in implementing the new policy.

For an overview of the overlapping federal policies governing U.S. life sciences research, including examples of experiments that would be covered under different combinations of policies, see Figure 8 on the next page. The sizes of the different circles do not precisely show the expected scope of the different policies, but they do roughly correspond to the number of agents they cover. The BMBL covers all work with pathogens and toxins, so it includes all work in scope of the DURC-PEPP policy and FSAP. The *NIH Guidelines*, on the other hand, covers all work with synthetic and recombinant DNA or RNA, so it is the only policy governing work that does not involve pathogens. The DURC-PEPP policy covers experiments that involve modifying organisms, which typically involves working with synthetic or recombinant DNA/RNA; although not reflected in the diagram, implies that most work covered by DURC-PEPP is also covered by the *NIH Guidelines* (unless funded by a federal agency other than NIH).

The National Science Advisory Board on Biosecurity

The National Science Advisory Board for Biosecurity (NSABB) was established by the White House in the 2005 and authorized by Congress in the 2005—2006 timeframe as a Federal Advisory Committee that operates in compliance with the Federal Advisory Committee Act. The NSABB is managed by the NIH. Since 2006, the NSABB has produced twelve reports, including recommendations in 2023 that informed the 2024 White House DURC-PEPP policy. The board,

Figure 8: Overview of U.S. Federal Policies Governing Life Sciences Research[8]



[8] Research not initially in the scope of the DURC-PEPP policy could fall under it if unexpected results covered by the policy occur. In that case, the researcher must pause their work until a review can be completed.

comprising up to 25 experts from various fields, is tasked with making recommendations—it is not a policymaking body—in response to taskings from NIH. In the past, although not officially a part of its mandate, the NSABB has been called to consult on how the federal government should react to particular dual-use research manuscripts that were about to be published, such as two experiments in 2012 that created a strain of H5N1 bird flu capable of spreading between ferrets (widely used as a model of the human respiratory system). The NSABB has not been used in that capacity since 2012.

Issues with Current Policies

Lack of independent oversight with effective verification and compliance incentives

Current policies rely heavily on bottom-up leadership of safety and security by the scientists conducting research and the institutions that house them. This bottom-up approach to responsibility is an essential feature of a strong risk management framework, but it must be united with prudent top-down governance that includes legal incentives to curtail bad or irresponsible actors and provides independent oversight to avoid potential conflicts of interest.

Other than FSAP, no biosafety or biosecurity policies have legal requirements. While, in many cases, compliance is tied to research funding, federal agencies have historically been hesitant to use punitive measures. Without legal requirements, agencies, institutions, and researchers may fail to fully comply with or implement federal risk-management policies.

All policies are managed and enforced by agencies that also fund and/or conduct life sciences research. This includes the CDC and USDA APHIS, which jointly manage FSAP. This may offer an advantage by ensuring that policies are developed and maintained by individuals with technical expertise, but it also creates the potential for conflicts of interest. Employees or divisions in charge of these policies may worry that criticizing or penalizing their colleagues could jeopardize their careers, influence, or prestige.

Finally, limited funding and authority hinder the U.S. Government's ability to verify that institutions and researchers are following these policies. The DURC-PEPP policy, *NIH Guidelines*, and BMBL all place the burden of ensuring compliance on institutions, with few avenues for verification. Only the Federal Select Agent Program conducts inspections of facilities.

Minimal oversight for work without government funding unless it is a select agent

Unless working with a select agent, oversight of non-federally funded research, especially at institutions that receive no federal funds, remains minimal. Outside of FSAP, all other biosafety and biosecurity policies are tied to federal life sciences research funding. While the *NIH Guidelines* apply to some non-federally funded research at federally funded research institutions, the new DURC-PEPP policy reduces oversight of work not directly funded by the U.S. Government (compared to the 2014 policy it replaces), now requiring institutions merely to certify that they are applying the same internal controls to all their research. Although the federal government is the largest funder of life sciences research, broadly exempting private sector research leaves a major gap. This will likely require Congressional action to address.

Lack of dedicated funding for institutions and oversight bodies

The process for monitoring compliance with various policies, guidelines, and regulations for those doing research at the university level includes the animal use committee, human use committee, recombinant DNA committee, pathogens committee, and other focused committees overseeing the use of dangerous agents at research institutions. These committees are comprised of faculty members that have other jobs (serving on committees is not their main goal, it is the result of academic responsibility).

Compliance with federal regulations and policies is expensive for institutions; to comply, they must construct and maintain advanced facilities with expensive features such as HEPA filters, create training resources, and pay for staff time spent on internal oversight and compliance. In theory, institutions are provided with generous indirect cost rates on federal research grants to pay for these kinds of expenses, but biosafety and biosecurity must compete with other priorities for this funding.[9] No federal policy provides dedicated financial resources to defray the cost of compliance with biosafety and biosecurity related guidelines and regulations.

Oversight and regulatory bodies are also poorly resourced. The new DURC-PEPP policy instructs federal funding agencies to convene new oversight bodies and spend staff time on additional research review, but no additional resources are provided. Among researchers, FSAP is known as being notoriously slow to approve registration and have staff cleared and approved to work with select agents under a personnel reliability program. These problems are symptoms of insufficient staffing. The *NIH Guidelines*, the policy with the broadest reach, is overseen by a team with at most four full-time members.

Burdensome to researchers & some requirements ineffective or outdated

In addition to slow processes as a result of understaffing, some requirements have not been updated to reflect evidence that they offer little safety or security benefit, pose a disproportionate burden on researchers, or have been made obsolete by advances in biology.

For example, export controls (ECCN 1C351 and ECCM 1C353) include controls on the genomes of two fungi responsible for valley fever even though there is no known procedure to create living fungi from a synthetic genome. Some researchers also argue that FSAP's focus on tracking inventory adds little benefit given that imperceptible quantities of select agents may be secretly retrieved and grown into larger volumes.

Outdated requirements may slow down valuable research, costing time and money and harming innovation. It may also create a false sense of security for requirements that seem stringent but provide little benefit.

Limits of list-based approaches in the age of synthetic biology

Biosafety and biosecurity policies typically apply only to the organisms or toxins on a particular list. The assumption behind this approach is that pathogens and toxins can be separated into high- and low-risk groups based on their danger to health, agriculture, the environment, etc. This is attractive because it could allow targeted oversight that mitigates severe risks without burdening the vast majority of life sciences activities. This is how the Federal Select Agent Program works: its regulations apply only to the transfer, possession, and use of organisms on the select agent list.

Advances in synthetic biology are increasingly challenging this model of oversight as organisms can be genetically engineered, including inserting synthetic genes or creating chimeras using components from multiple organisms. There are a vast number of potential combinations and modifications, and while our scientific understanding is not advanced enough to reliably predict the result of all these changes, it is certain that some modifications can make pathogens more dangerous. This makes it nearly impossible to specify all the dangerous possibilities in a list. Perhaps, inserting a particular gene from the MERS virus into a coronavirus that usually causes the common cold would result in a deadly superbug capable of causing a pandemic. Although this work only involves an organism that causes the common cold, the result would clearly pose a serious safety and security threat.

[9] Indirect costs average around 50% of a grant's value, but it may be as high as 80%.

This has led some experts to suggest a risk-based approach that applies regulations to organisms and toxins based on an assessment of the risks they pose. This approach has its own issues: it may expand the scope of oversight to a burdensomely large set of life sciences work. It also requires expert judgment to make uncertain predictions about threats—there are no clear-cut empirical tests to determine risk level—leaving room for different interpretations to emerge.

Fragmented, overlapping, and confusing guidelines

As shown in the Figure 8, federal research oversight remains divided between the new DURC-PEPP policy, the Federal Select Agent Program, the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, the CDC's Biosafety in Microbiological and Biomedical Laboratories, and the U.S. export control regime, which overlap in scope and rely on different compliance mechanisms managed by nearly a dozen government agencies and departments. This includes NIH, CDC, the Department of Agriculture, the National Science Foundation, the Department of Defense, the Department of Homeland Security, the Department of Health and Human Services, the Department of State, the Department of Commerce, and the Executive Office of the President.

The complexity of the overall oversight framework increases uncertainty for researchers and institutions and makes compliance more costly. The proliferation of definitions and policies generates misunderstandings and makes assessing the effectiveness of the framework more difficult.

Lack of reporting on accidents and information on laboratories

There is no government body that maintains a comprehensive list of high containment laboratories or laboratories working with pathogens in the United States. If a laboratory is working with a select agent, they must register with the Federal Select Agent Program. Otherwise, there is no requirement that the U.S. government to know of a facility's existence (although most facilities receive federal research funding). The surprise discovery of twenty pathogen samples—with labels including HIV, hepatitis, and SARS-CoV-2—after a code officer noticed an illegally occupied warehouse in Reedley, California in 2023 illustrates this gap. Whether operating legally or illegally, without the code violations, local and national authorities would not have known about this operation. In this particular case, the risk was likely low, but the facility could have been legally storing or working with more dangerous pathogens, putting the local community at risk without the knowledge to prepare for the case of a lab accident or a natural disaster damaging the facility.

Additionally, there is a patchwork of reporting requirements that are neither comprehensive nor optimized to improve safety and security processes. Both the FSAP and *NIH Guidelines* include reporting requirements; they mandate reporting of accidental releases/exposures and rule violations to ensure compliance with policies and proper incident response. The data from these reports are not combined into a comprehensive system, and little is currently done to analyze these data for trends to update practices. Voluntary, no-fault reporting of near misses, considered best practice in aviation and hospital safety, could also provide more evidence about what works and what challenge areas remain.[10]

[10] The Federal Aviation Administration's extensive reporting system, which includes both voluntary, no-fault reporting and mandatory incident reporting, has contributed to the safety of the U.S. airline industry.

VIII. RECOMMENDATIONS

The National Science Advisory Board for Biosecurity has recently proposed key recommendations on Dual Use Research of Concern and enhanced potential pandemic pathogen research oversight, aligning with suggestions from Global Biolabs, the Bulletin of Atomic Scientists Report, and the Biological Weapons Committee. Our recommendations build upon previous reports and emphasize the need to establish an independent oversight authority for high-risk pathogen research.

1. Establish Independent Oversight of High-Risk Pathogen Research

- Create a harmonized, comprehensive regulatory framework for all high-risk pathogen research activities, irrespective of funding source. This framework should encompass:
    a. Review of Dual Use Research of Concern (Category 1) and Pathogens with Enhanced Pandemic Potential research (Category 2) based on the existing DURC-PEPP Policy.
    b. Specific safety and security standards, based on the Biosafety in Microbiological and Biomedical Laboratories and *NIH Guidelines*, for work with high-risk biological agents or toxins, beginning with Select Agents but expanding to all agents that require high-containment (at least BSL-3).
    c. Screening for synthesis of nucleic acids (DNA and RNA) in line with HHS Guidelines and the existing White House Framework.
    d. A roadmap for moving from definitions based on lists of agents and toxins to definitions based on Sequences of Concern and flexible risk assessments, including using artificial intelligence tools to assess risk where appropriate.

- Establish an independent regulatory entity (e.g., like the Nuclear Regulatory Commission but appropriate for high-risk pathogen research) tasked with overseeing the nation's regulatory and oversight frameworks for high-risk pathogen research. This entity should also perform the following functions:
    a. Review research that could threaten global health and security, such as work involving Pathogens with Enhanced Pandemic Potential.
    b. Provide timely advice to institutions and investigators in response to questions about safety, security, or compliance, and offer biosafety training and education resources.
- Develop a comprehensive registry of BSL-3, BSL-3 enhanced, and BSL-4 laboratories that includes a list of pathogens in use in those locations; where security allows, this should be made available to local officials, law enforcement, and first responders.

2. Strengthen Global Standards for Biosafety and Biorisk Management

- Provide U.S. biosafety and biorisk management as a model for nations committed to improving their own standards, including sharing learnings and implementation resources (e.g., training curricula) with other nations.
- Fund research on biosafety and biocontainment in low-resource settings to provide evidence for low-cost ways to improve sustainability and safety.
- Promote biosafety and biorisk management tools, practices, and standards abroad—such as the International Biosecurity and Biosafety Initiative for Science (IBBIS) or SecureDNA and their DNA synthesis screening services.

3. Enhance Public Health Measures for Public Safety

- Surveillance
    a. Strengthen public health surveillance measures around high containment laboratory facilities (e.g., conduct site inspections, employee titer testing, as well as soil, air, water, and sewage sampling).
    b. Encourage employee reporting of incidents and safety concerns in a legal safe harbor, "no-fault" system that reports to the independent oversight agency.
    c. Conduct after-action reviews of incidents to identify trends, evaluate the effectiveness of existing measures, and address gaps.
- Transparency
    a. Establish public fora input into new biosafety and biosecurity facilities/initiatives so the public can remain fully informed.
    b. Clearly define protocols for public notification in cases of containment breaches and during the construction of new facilities.
    c. Foster a safety culture that values transparency, communication, and continuous improvement.

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Biosafety and biosecurity are paramount when working with deadly pathogens in the laboratory, in clinics, and in the environment.

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