CONTRIBUTIONS to SCIENCE, **6** (1): 99–103 (2010)
Institut d'Estudis Catalans, Barcelona
DOI: 10.2436/20.7010.01.87 ISSN: 1575-6343
www.cat-science.cat

Reflections on biosafety: do we really know what biosafety, biocontainment, and biosecurity mean?

F. Xavier Abad Morejón de Girón, David Solanes Foz, Mariano Domingo Álvarez

Animal Health Research Center (CReSA), Automonous University of Barcelona – Institute for Food and Agricultural Research and Technology (UAB-IRTA), Bellaterra, Spain

Resum. Els temes de bioseguretat, biocontenció i bioprotecció no són sempre completament entesos per molts científics i comparteixen, pel públic en general, alguns significats ominosos. El sentit últim de les paraules prèviament esmentades —però també el disseny, la construcció i el funcionament d'aquests tipus de instal·lacions— seran discutides tenint en compte els significats complementaris. El disseny, la construcció i la posada en marxa d'una unitat de biocontenció, requereixen d'equips complementaris (i de vegades oposats) de persones que juguen els papers d'arquitectes, enginyers, científics però també de funcionaris.

Paraules clau: bioseguritat · bioprotecció · biocontenció · validació · directrius

Abstract. Biosafety, biocontainment, and biosecurity issues are not always fully understood by members of the scientific community and, as for the general public, have in some cases acquired ominous connotations. This review seeks to better define these terms, in addition to discussing the design, construction, and operation of safe and secure biocontainment facilites. These latter tasks require teams made up of architects, engineers, scientists, and public officials with complementary, but sometimes also conflicting interests.

Keywords: biosafety · biosecurity · biocontainment · validation · guidelines

Over the last two decades, there has been increasing concern regarding emerging and reemerging diseases, most of them zoonotic, involving either bacteria or viruses. The outbreak of diseases such SARS, avian influenza, and the new H1N1 influenza has fueled interest in the design, construction, and operation of a plethora of new biosafety-biocontainment facilities and/or laboratories [12,13] in the USA and in Europe but also in Asia and Africa. However, all over the world [13], and particularly in Europe, differences in the terminology and interpretation of the content of legislation on biosafety and laboratory biosecurity have led to conflicting and sometimes inappropriate approaches to biosafety and biosecurity, and, in turn, to difficulties in communication and scientific exchange.

Biosafety, biocontainment, and biosecurity issues are not always fully understood by members of the scientific community, including those working inside such facilities, although usefull and extensive guidelines have been published by several sources and are periodically updated [14–16].

Here, we begin by providing a few definitions, extracted from Webster's Encyclopedic Unabridged Dictionary, 1989, of some key terms closely related to the topic of our discussion.

Correspondence: F. Xavier Abad Morejón de Girón, Biosafety level 3 Laboratory Manager, CReSA (Centre de Recerca en Sanitat Animal), Campus Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain. Tel. +34-935814564. Fax +34-935814490. E-mail: xavier.abad@cresa.uab.es

Safety. The state of being safe; freedom from occurrence or risk of injury, danger, or loss.

Security. Freedom from danger, risk, etc; safety; something that secures or makes safe; protection; defense; precautions taken to guard against theft, sabotage, the stealing of (military) secrets.

Containment. To hold or include within its volume or area; to keep under proper control; restrain.

These three terms, when applied to the management of biological issues, can, however, take on an ominous meaning when extrapolated to biosafety, biosecurity, and biocontainment. Subtle differences arise, however, from the proper definitions listed above. Biosafety (Fig. 1) is closely related to the set-up and execution of procedures for non-risk (or, realistically, very low risk, as zero risk is unattainable) use, manipulation, and handling of pathogenic (for animal, plants, or humans) microorganisms, and it is definitively linked to the internal activities of a given research or production center. Therefore, biosafety practices and procedures depend on factors linked to the microbial agent (its pathogenicity, host range, stability, and transmission route, for instance) and to the activity (volume and infectious titer handled, animal experimentation, etc.). Biosafety focuses on reducing exposure to and the release of biological materials and countering their accidental release. It is currently managed by scientific staff in management positions, with the help of technical and research personnel.

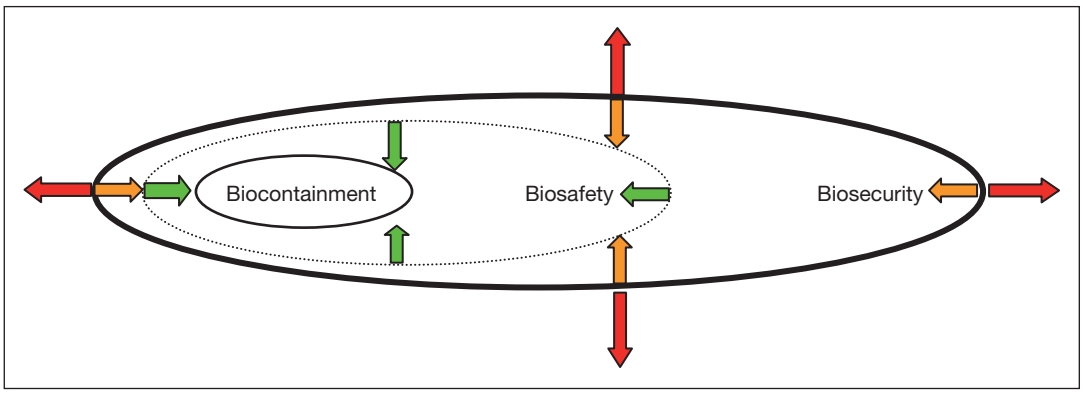

Fig. 1. How biosafety, biocontainment and biosecurity work.

Biocontainment (Fig. 1) is, in our opinion, more closely related to the physical and construction-related factors associated with the design of the facility and thus belongs to the realms of architecs, engineers, and construction teams. Finally, biosecurity (Fig. 1) is strongly related to the enforcement of security measures established for the installation in order to prevent the external (but also internal) activities of some people (luckily, few in number) who may compromise pathogen containment. Biosecurity refers to ensuring the security of biological materials to prevent their theft or illicit use and to counter their deliberate release. Therefore biosecurity tries to prevent the potential proliferation of bioweapons whereas the goal of biosafety is to try and mitigate biohazard [1]. Of course, biosecurity should not be the task of scientists, but rather the responsability of the general management of the facility and of public powers.

During the design and construction of a biosafety level 3 or 4 (BSL-3 or BSL-4) facility, future security and containment considerations must play primary roles. All operational and practical requirements have to be listed in a document that also details the future activities or processes to be conducted within the facility and by its personnel, an assessment of the evolution of the facility and its activities, and how to carry them out appropriately. We cannot expect scientists to be leaders in biosafety but rather to establish the playing-field, as these safety requirements are the responsibility of technical and scientific support staff who will take charge when the facility is up and running. Thus, the implementation of biosafey is initially the responsibility of a given facility's architects, engineers, and construction team. As an example, utilization of the correct materials when the biocontainment facility is being built is an important issue, and an expert team would be aware of the fact that walls made of poured concrete are more durable than concrete masonry unit construction [4]. Furthermore, containment issues become more critical when the facility has to deal with large animals (calves, deer, chamonis, pigs, etc.) as they require boxes or housing units rather than caging systems as containment devices; thus, large-animal containment relies on the hermeticity of the building and all its junctions, doors, and windows [7,8].

The construction phase is also the time to decide on the types and extent of biosecurity tools to be installed in the biosafety facility: closed circuit television (CCTV) systems around the building's perimeter, linked with 24-h sufficient lighting levels; CCTV within animal boxes for surveillance of animals and caretakers; zoned security access design, progressing from less restricted zones to more secure ones, by using card readers, biometrics devices, or personnel security checks [4,6]. These measures are not restricted to BSL-3 and BSL-4 facilities but could also be used in BSL-2 laboratories [6].

The construction of BSL-3 or -4 facilities is highly technical, and there are few universally recognized standards. Many systems have to be installed and connected in order to work in a cooperative manner [9]: heating, ventilating, and air conditioning (HVAC) redundancy, gas tightness, etc.; filtration systems and their control, i.e. high-efficiency particulate air (HEPA) efficiency testing, etc., not only in rooms but also in animal housing devices [2,10]; effluent and water treatment [3]; decontamination devices and measures (air or water shower, fumigation); fire extinguishing and security systems; and, finally, structural and architectural components (e.g., leak-proof doors, windows, and walls, and paints with resistance against chemicals, disinfectants, etc.). Some examples are shown in Fig. 2, which depicts a typical animal experimentation box. However, it must be noted that several containment issues are still under development and can be expected to improve from year to year (waste treatment, fire extinguishing, leak tightness, etc.). Any wrong (or non-right) decision could have significant cost repercussions. And one of the most typical wrong decisions in the design and comissioning of a containment facility is to save money in areas of flexibility and redundancy. In biocontainment animal facilities, it is highly necessary to provide alternative solid-waste (carcass) disposal methods, such as the new developments in thermal and alkaline tissue digestion systems [4], to replace incineration, which has became very controversial due to environmental considerations. If it is economically and spatially feasible, both systems should be included, working together as a commuted system. Redundancy criteria have to be applied also to electric power sources (an independent generator located in the facility is imperative), efluent liquid treatment (thermal but also chemical inactivation) [3], etc. Taking all these considerations into account, it is critical to realize that building costs for a BSL-3 facility will typically exceed by 2- to 4-fold those of a BSL-2, and this difference becomes even larger when operational costs come into play (200–800%). As the running costs of high-containment facilities are extremely high (energy, maintenance, dedicated personnel) and rapidly ex-

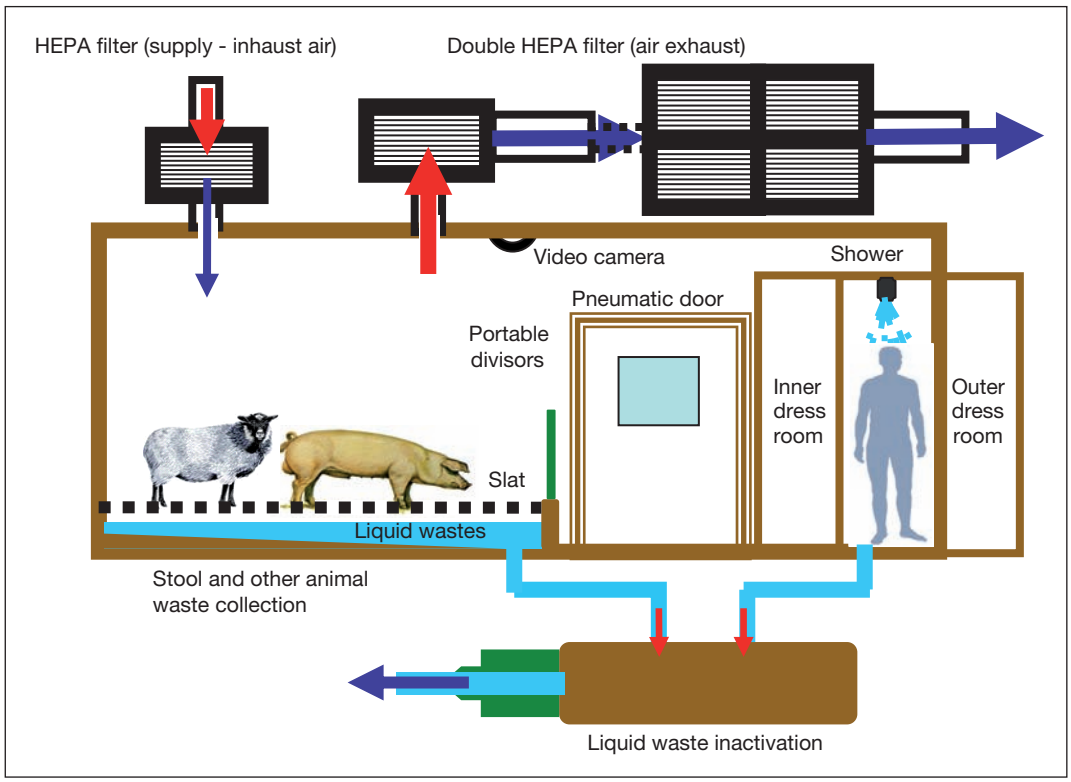

Fig. 2. A diagram of an animal box (published with permission of CReSA).

ceed investment costs, long-term funding for biosafety programs should be guaranteed before the planning of a high-containment facility is initiated.

During this stage of design and construction, two heterogeneous teams are present. On the one side are those who want the project completed on time and with no changes in budget. Quite often, although not always, this side comprises project managers, architectual teams, and engineering and contracting companies, who are also focused on containment and security issues. On the other side are those who want a pleasant, safe, and efficient facility in which to work. Typically, final users and maintenance teams (and in fact they are also users) have converging interests, which often also include those of the planned facility's biosafety officers. All of the aforementioned individuals have as their priority the fulfillment and implementation of biosafety procedures.

When construction of the facility is completed, systematic assessments of its compliance with specifications (electrical system, access control, utilities, critical containment points such as joints and penetrations, mechanics, etc.) and strong validation performances have to be carried out [9]. Validation, which checks and records critical performances according to specific protocols, provides a realistic picture of the capabilities of the biocontainment facility. These tasks must be carried out by specific companies with sufficient expertise, joined by scientists.

During the validation period, personnel must be intensively trained in all the details about the facility's systems, procedures, and maintenance activities. The education of laboratory personnel to ensure compliance with biosafety rules must remain the top priority [11].

Only when validation (of ventilation systems, autoclaves and decontamination air-locks, biosafety cabinets, etc.) has been carried out and confirmed should the facility be used. Periodically thereafter, the facility should be re-validated, albeit to a lesser extent than during the first check. A summary of these activities is provided in Table 1, which also includes a schedule.

Other aspects regarding regulations and guidelines should be discussed. As regulations are minimal in terms of content, the goal should be to surpass their requirements; in fact some official guidelines recommend, but not force, enhanced containment measures. It is undoubtely preferrable to be capable of handling any risk posed by a group 3 pathogen without need for an up-grade (or simply having flexibility in this manner), rather than to be confronted later on with the need to design, implement, and validate new structural elements or procedures to meet a higher-level challenge.

The meanings of biosafety, biocontainment, and biosecurity (Fig. 1) should not be confused with each other. Biosafety (linked to practices, handling, and experimental works) and biocontainment (physical and construction aspects only) are issues that have been around for a long time. Biosecurity (the legal and regulatory issues), in contrast, is a recent concern, at least to the extent that it involves the public and is not strictly a scientific issue.

For instance, it is quite usual that the preparation of highly pathogenic viral or bacterial stocks implies the use of a centrifuge for phase separation [5]. Throughout the centrifugation process of these organisms, biosafety, biocontainment, and biosecurity all come into play, albeit at diferents levels (Fig. 1). Biosafety must answer several questions such as: How can highly pathogenic microorganisms be safely centrifuged (protective equipment, experimental actions, etc.) [5]? Biocontainment is concerned with the implications derived the choice of procedure: What are the characteristics of the centrifuge? Is

Table 1. Timetable for construction and operation of a biocontainment facility

	1	2	3	4	5	6	7	8	9	10	11	12
Users requirements				(*)					(*)			
Basic design												
Detailed design												
Construction												
Validation												
Start of activities												

The overall time for construction and operation of a BSL-3 ranges from 18 months to more than 36 months. The numbers shown correspond to quarters.
(*) It could be interesting that users know the final detailed design and construction jobs in order to allow slight modifications that may make later activities easier, and therefore improving validation.

the whole centrifuge hermeticly sealed to aerosols, or only the rotor? Can the centrifuge be located inside a biological safety cabinet (BSC), or, due its size, can only the rotor be opened in a BSC? Or, more interestingly, could a centrifuge be located inside a BSC without affecting its air-flow? What are the conditions in the laboratory where the centrifuge is set up? How do the air supply and air exhaust systems in the laboratory work? Could the laboratory be sealed and decontaminated? Finally, biosecurity looks for appropritate answers to: Who has permission to enter the facility, and, especially, the laboratory when this work is in progress? Who is responsible for granting permission? Are these processes controlled electronically? Is there a TV system monitoring all laboratories and animal facilities? Are all movements of external personnel in the facility recorded, and are these personnel continuously supervised by internal staff? Is there proper and exhaustive control of pathogenic biological material?

If we are genuinely committed to improving our preparedness in biosafety issues we have to remove not only mental but also procedural barriers to reporting errors and infractions of biosafety and biosecurity. We have to pursue a clearer definition of what constitutes *exposure* to a biologic agent, to demand better safety training of all laboratory personnel, and to be willing to spend money to maintain the physical infrastructure of high-containment labs long after their construction is completed.

We must therefore keep in mind that safety cannot be expressed in absolute terms. It is a relative concept defined in terms of tolerability, acceptability, and feasibility limits; it implies a balance between the cost of biosafety measures and the potential benefits of the work for all of society [11].

Do conflicts arise in achieving the goals of biosafety, biocontainment, and biosecurity? This is not often the case although it must be ensured that narrow biosecurity does not impinge upon or prevent well thought-out biosafety activities and programs. Nonetheless, biosafety, biocontainment, and biosecurity must always be considered as words with complementary meanings to describe a general environment of responsible work in the handling highly pathogenic microorganisms.

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About the authors

F. Xavier Abad Morejón de Girón received his Ph.D. in Biological Sciences in 1994, from the Biology School of the University of Barcelona. Since 2006, he has worked as BSL3 Laboratory Manager of CReSA (Animal Health Research Center), UAB-IRTA, a research center devoted to animal health located at the Bellaterra Campus of the Autonomous University of Barcelona (UAB). His main research interests include: the persistence of animal and human viruses in the environment, with particular attention to water, fomites, and foods; inactivation and removal procedures to assure the viral safety of blood derivatives, cosmetics, and foods; and biocontainment and biosafety issues in microbiological research laboratories. The CReSA has become a reference center in matters of biosafety and biocontainment.

David Solanes Foz studied Veterinary Medicine at the Autonomous University of Barcelona (UAB), and has worked as an associate professor at the UAB's Veterinary School. He begun to work as a BSL3 Biocontaintment Unit Manager of CReSA in 2004 and since 2007 he is acting as a Director of Services. His main research interests include the animal welfare and the use of high standard ethical experimental procedures and biocontainment and biosafety issues in biocontaintment units.

Mariano Domingo Álvarez received his Ph.D. in Veterinary Medicine at the University of Giessen (Germany) in 1982. Since 1984 he has been developing teaching and research activities at the Department of Animal Health of the Autonomous University of Barcelona, and in 1999 he was appointed director of CReSA. His main research topics have been porcine and ruminant diseases, both of bacterial and viral origin, combined with diagnostic pathology. He coordinates a large research project of the Spanish Ministry of Research (CONSOLIDER) on porcine virus diseases and is an expert for the European Food Safety Authority (EFSA) in the Panel of Animal Health and Animal Welfare since 2006.