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Managing Biological Risks in Biomedical Laboratories in Greece

Dionysios Vourtsis

SCHOOL OF HUMANITIES, SOCIAL SCIENCES AND ECONOMICS

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Student Name:	Dionysios Vourtsis
SID:	4402180008
Supervisor:	Dr. Gijsbert van Willigen

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ABSTRACT

This dissertation was written as part of the MSc in Bioeconomy: Biotechnology and Law at the International Hellenic University.

Biomedical laboratories are full of various biological risks. All these risks should be identified, assessed and controlled, in order to prevent accidents, laboratory infections and loss of lives, and improve the overall safety and quality. Controlling the biological risks in the laboratory requires the identification of these risks with a risk assessment, following by the implementation of the hierarchy of controls, which is a combination of engineering and administrative controls, good microbiological practices and procedures and the appropriate personal protective equipment.

A Biorisk Management system must be put in place, in order to sufficiently develop and implement the risk policy, the procedures and the responsibilities in the laboratory, with the objective to eliminate or to minimize to an acceptable level the biological risks for the laboratory professionals, the community and the environment.

Greek Biomedical laboratories still have to introduce a biorisk management approach and a Biosafety culture. This introduction will help to make the Biomedical laboratories in Greece a safer workplace and to improve the quality of diagnostic testing performed in these laboratories, because standard operating procedures contribute both in Biosafety and in Quality. That approach not only needs changes in the organizations themselves and at the national/regional level, but also at the regulatory level in Greece.

Keywords: (Biorisk management, Biomedical laboratories, Biological risk, Biosafety, Biosecurity)

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Dionysios Vourtsis
31/12/2019

CONTENTS

INTRODUCTION

A *Biomedical laboratory* or a clinical laboratory is a facility in a hospital or a health center in which diagnostic tests are performed on patient samples, to obtain information on the patient's health and to help diagnose, treat and prevent a disease (Farr and Shatkin, 2004).

Laboratories play a crucial and key role in the identification, diagnosis, treatment and management of illnesses in all health care systems (Brown et al., 2015). In almost all aspects of health services, laboratory results are crucial for health decision-making, since roughly 60-70% of medical decisions based on laboratory diagnostic test results (Kessel, 2014).

Biomedical laboratories are an example where science is applied for the direct benefit of the patient, unlike to those laboratories such as found in academic or research institutions and the pharmaceutical industry that are focus on basic science.

In hospitals and other healthcare settings, the layouts of Biomedical laboratories vary greatly from one facility to another and are generally divided into the following sections: Anatomic Pathology, Clinical Microbiology, Clinical Chemistry, Hematology, Blood Bank and Molecular Diagnostics.

Biomedical laboratories are full of biological risks due to the nature of the diagnostic samples and the uncertainty of any microbiological agent that could be present in these samples. During the commissioning of such a laboratory, all potential risks of the handled materials and procedures need to be identified, evaluated and controlled. Besides the risk assessments, it is preferable that a risk management system is also implemented to avoid incidents, accidents or fatalities and to continuously develop the total safety and efficiency at the laboratory. Controlling the biological risks in the laboratory is a combination of engineering and administrative controls, good microbiological practices and procedures and personal protection, such as personal protective equipment (PPE) and vaccination, that should all be part of a risk management system. Another important aspect of laboratory safety is the safety culture, which must be adopted, supported and developed by the top management, to eliminate or to minimize the biological hazards to an acceptable level for the laboratory professionals, the community and the environment (Tun, 2017).

One aspect of laboratory safety is the *Biosafety*, which often represented with the symbol of Biohazard (Figure 1). According to WHO, Biosafety is the term to describe the unintentional exposure to pathogens, thus: "*the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release*" (World Health Organization, 2004).

Biological safety management includes defining significant hazards of the biological materials handled in the laboratory and ensuring that adequate precautions are taken, to avoid and to prevent laboratory acquired infections (University of Birmingham, 2014).

Biosafety is a Multi-sectoral area requiring the involvement and cooperation of all interested authorities, professionals and stakeholders and is not only a list of guidelines, but mostly what we do with these guidelines and how to implement them.

Figure 1: Symbol of Biohazard. (Adapted from World Health Organization, 2004)

Besides laboratory Biosafety some laboratories also need laboratory *Biosecurity*, based on the agents processed in the lab. Biosecurity is the term to describe "*institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens and toxins*" (World Health Organization, 2004).

These two concepts (Biosafety and Biosecurity) complement each other, but there is no Biosecurity without a proper Biosafety regime. Biosecurity is only of importance for laboratories handling high-risk materials and highly dangerous pathogens.

CHAPTER 1

Risk agents and Risk groups

Biological agents are Bacteria, Viruses, Parasites, Prions, etc. Although many of these agents are found in nature and they are harmless for humans, some may cause hazards (Occupational Safety and Health Administration, n.d.). The World Health Organization (WHO) divided the biological agents into four risk groups, according to their main biological characteristics and the way that the potential disease could be transmitted (World Health Organization, 2004; Centers for Disease Control and Prevention, 2009). A comparable classification was defined in the NIH Guidelines and 4 hazardous risk groups were designated as human etiology agents (National Institutes of Health, 2016). WHO and NIH classifications are included in Table 1.

Table 1: Risk groups (Modified from World Health Organization, 2004)

RG	Individual Risk	Community Risk	Description	Treatment Prevention
1	No / Very low	No / Very low	Unlikely to cause human or animal disease	–
2	Moderate	Low	Can cause disease	Often Available
3	High	Low	Usually causes serious human disease	May be Available
4	High	High	Usually causes serious human disease	Not usually Available

Laboratory-acquired infections (LAIs)

Laboratory staff handling biological materials in Biomedical laboratories (Table 2) is exposed to biological risk factors, both through direct contact with biological samples that are potentially containing biological agents, or the biological agents isolated from these samples. Incidents when handling these biological samples can lead to LAIs, through one of these transmission routes: aerosol transmission, ingestion, blood-blood contact and contact with the biological agents.

Table 2: LAIs (Modified from Pike, 1976)

Laboratory category	Number	Percentage
Research	2307	58.8
Biomedical Laboratories	**677**	**17.3**
Production	134	3.4
Teaching	106	2.7
Unspecified	697	17.8

LAIs include infections acquired in the laboratory or lab-related activities and they could be either symptomatic or asymptomatic (Figure 2). Because causes are not always known how the infection took place, there are many challenges regarding the prevention of exposure to pathogens and the prevention of infections acquired in the laboratory. Reasons for this are lack of precise data on the actual risk of infection after exposure, lack of uniform and coherent surveillance systems for LAIs, under-reporting of LAIs, incomplete/heterogeneous reporting on incidents and accidents, the type of information required in post-exposure reporting and insufficient evidence and based studies on safe practices in Biomedical Laboratories (Sewell, 1995).

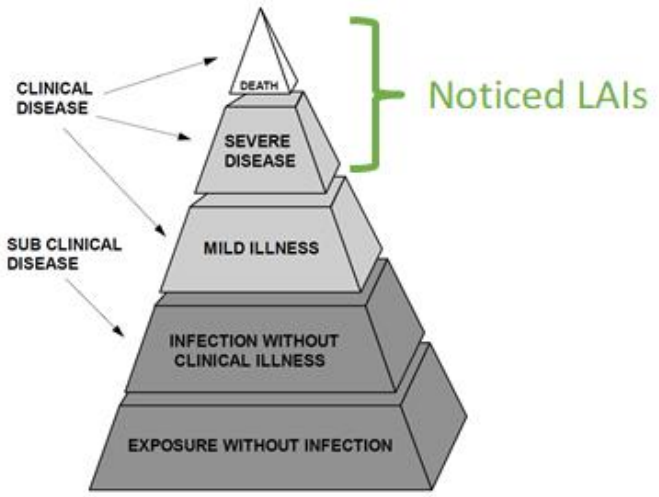

Figure 2: Noticed LAIs (Adapted from Pfeiffer, 2002)

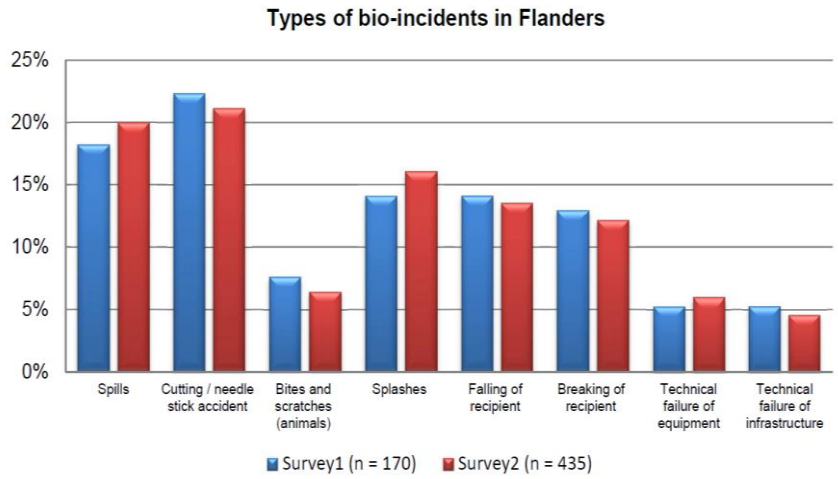

Figure 3: Bio-incidents (Adapted from Willemarck et al., 2012)

Incidents with biological samples that can result in LAIs are diverse. In a recent inquiry in Flanders Belgium, the most frequent laboratory incidents are spills and needle stick incidents (Figure 3). Other frequent incidents are splashes and failing recipients. Technical failures of equipment or containment measure are less frequent, but still occur. It is believed that the incidents that happen in other laboratories in Europe will not differ greatly from those in Belgium and thus will also occur in Biomedical laboratories in Greece and are the main causes of LAIs. Also, in the past, these incidents were considered the main causes of LAIs (Figure 4).

Accident	No. (%) of infections reported by:	
	Pike[a]	NADC[b]
Splashes and sprays	188 (26.7)	2 (5.9)
Needlesticks	177 (25.2)	3 (8.8)
Sharp objects	112 (15.9)	2 (5.9)
Animal or ectoparasite bite/scratch	95 (13.5)	2 (5.9)
Mouth pipetting	92 (13.1)	0
Other, unknown	39 (5.5)	25 (73.5)
Total	703	34

[a] Adapted from reference 110.
[b] NADC, National Animal Disease Center; adapted from reference 93.

Figure 4: Types and accidents associated with LAIs (Adapted from Sewell, 1995)

The main cause of LAIs are infections spread by aerosols. Most of the incidents from the Flanders inquiry and those of Pike can create aerosols and are therefore a great risk for the health of the laboratory staff. To decrease the number of incidents or the effects of the incidents for laboratory staff appropriate Biosafety measures should be in place in Biomedical laboratories.

Despite the increasing use of containment measures supported by safe Laboratory Practices and the increase in the level of training of staff, accidental exposures, incidents and accidents still occur in laboratories (Table 3). This suggests that the procedures of Biosafety and Biosecurity are not always effectively implemented or followed, probably due to a lack of awareness by the management and the laboratory staff.

Table 3: Top Ten LAIs (Modified from Fleming and Hunt, 2006)

Top 10 LAIs 1979-2004	
Organism	**Cases**
Mycobacterium tuberculosis	199
Arboviruses	192
Coxiella burnetii	177
Hantavirus	155
Brucella	143
Hepatitis B	82
Shigella spp.	66
Salmonella spp.	64
Hepatitis C	32
Neisseria meningitidis	31
1.141 Laboratory-associated infections Yellow indicates organism can be transmitted by aerosol formation	

Additionally, this indicates that activities carried out in the Biomedical laboratory require the development of a proper biological risk management and mitigation measures, in order to avoid laboratory acquired infections and diseases and to protect the laboratory staff and thereby the community from biological agents and possible harmful patient samples.

CHAPTER 2: Hierarchy of Controls

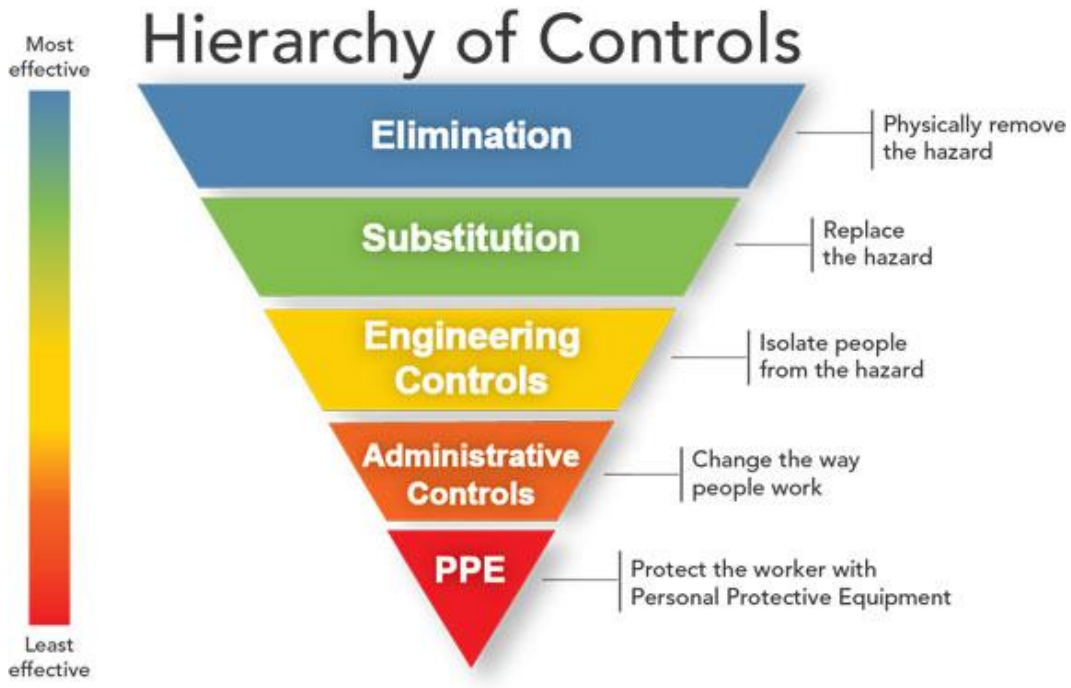

Figure 5: Hierarchy Controls (Adapted from Centers for Disease Control and Prevention, 2015)

An approach for managing biological risks and preventing LAIs is the hierarchy of controls (Figure 5). The conventional hierarchy of controls indicates that when facing hazards in the laboratory there is a correct order to minimize the risk and ensure that laboratory staff is safe and secure. This approach has the following 5 steps to manage risks in the laboratory (Centers for Disease Control and Prevention, 2015):

Elimination

Elimination means not doing the intended examination or deciding not to work with a specific biological agent. Elimination clearly provides the highest level of risk reduction. However, this approach is not feasible working in Biomedical labs, where patients and medical doctors rely on the results of the tests for the diagnosis and treatment.

Substitution

Replace the source with a different, less harmful organism. However, in many situations, the elimination of risk is not always possible. For those cases, it may be necessary to use a substitute, or to replace or exchange the source of the identified risk

with another source that poses less hazard than the original risk. However, also this approach is not an option in the Biomedical laboratories.

Engineering Controls or physical containment

All engineering controls in the hierarchy of controls focus on containment of the materials used in the lab. Containment is a combination of physical changes to workstations, equipment, the laboratory itself, or any other relevant aspect of the work environment that reduces or prevents exposure to hazards.

In Biomedical labs, modern analyzers are most of the time self-contained and provide enhanced safety for the laboratory staff, especially with the new automated systems with intergraded pre-analytical structures; therefore they are considering as closed systems.

The objective of the containment is to minimize or to eliminate hazards from potentially harmful biological agents in the laboratory staff and the environment. Examples of containment of the laboratory itself can vary from the simple method of locking laboratory doors, to large HVAC (Heating, ventilation and air conditioning) systems controlling the directional airflow in a laboratory and filtering the outgoing air via HEPA (High-efficiency particulate air) filters, thereby protecting the environment outside the laboratory itself.

Biological containment could be categorized in 2 levels, Primary and Secondary:

Primary containment provides direct protection to laboratory staff in the Biomedical laboratory and the local laboratory environment itself from biological hazards and exposure to infectious agents. Examples of primary containment include safety equipment such as Biological Safety Cabinets (BSC), sealed containers, safety centrifuge cups and other safety devices, designed to eliminate or reduce exposure to dangerous biological materials (Chesapeake Area Biological Safety Association, n.d.).

The BSC is the main equipment used to achieve isolation from infectious droplets or aerosols formed by a variety of microbiological processes. There are 3 types of Biosafety cabinets. Class I and II cabinets are designed to direct potentially contaminated air away from laboratory staff and through HEPA filters before exiting to the environment, and Class III cabinets are equipped with additional containment and using gas-tight glove

boxes. An idea of another primary obstacle is the security centrifuge cup, a sealed container aimed to prevent the release of aerosols during centrifugation. In order to reduce aerosol risks, containment systems such as BSCs or centrifugal cups must be used while managing infectious agents (Centers for Disease Control and Prevention, 2009).

Secondary containment contains elements of architectural and mechanical design that prevent laboratory staff from contamination and from the escape of infectious materials outside the laboratory, to the environment. Examples of secondary barriers include: Separation of the main laboratory space from the public access, Autoclave facilities, Handwashing and eyewash stations and equipment, advanced Ventilation systems, Directional airflow and limited access areas (Chesapeake Area Biological Safety Association, n.d.).

For instance, secondary barriers for most laboratory work with BSL-2 procedures could include the isolation of the laboratory work area from uncontrolled access, the provision of a decontamination facility (e.g. autoclave) and hand-washing equipment (Centers for Disease Control and Prevention, 2009).

According to the World Health Organization (WHO) guidelines, which have been incorporated into European and Greek legislation, laboratories are classified as Biosafety levels (BSLs) with the aim the effective protection of the laboratory staff. The recommended classification of the Biosafety levels is mentioned with the numeric grade 1 to 4, which are based on the design and construction characteristics of the laboratory, the practices, the operating procedures, the equipment and the isolation capabilities required for safe work with the different risk groups of biological agents in the laboratory (Table 4).

Each level of Biosafety determines the working conditions that ensure laboratory staff is protected from biological factors. The 4 levels of laboratory Biosafety are associated with the 4 risk groups of biological agents, but they are not always identical. Non-airborne biological agents, such as viruses (HBV, HCV, HIV), which belong to the risk group 3 and could be handled at the level of Biosafety 2 (BSL-2), are a good example. The characteristics of each Biosafety level are determined by European and Greek legislation, as well as by the guidelines of international organizations. All Clinical Diagnostic Laboratories must be constructed and function at least for Biosafety Level 2 (BSL-2). However, as no laboratory could have full control over the biological samples it

obtains, the laboratory staff may be exposed to higher risks and therefore a risk assessment should always be performed (World Health Organization, 2004).

Table 4: Biosafety Levels (Modified from World Health Organization, 2004)

Biosafety Level	Laboratory Type	Practices	Safety equipment
Level 1	Basic teaching Research	GMPP*	Open bench work
Level 2	Biomedical Laboratories	GMPP* PPE Biohazard sign	Open bench BSC for potential aerosols
Level 3	Special diagnostic, Research	As Level 2 GMPP* Special PPE Controlled access	BSC and other primary devices for all activities
Level 4	Dangerous pathogens unit	As Level 3 GMPP* Airlock entry Shower at exit Special waste disposal	BSC (class III) Positive pressure suit + BSC II Double door Autoclave Filtered air

*GMPP - Good microbiological practices and procedures

Although the commissioning process gives the laboratory and the surrounding community increased confidence and more trust that structural, electrical, mechanical and decontamination systems will operate as planned to ensure the containment of any possible harmful biological agent working with (Bathula and Rakhimol, 2017), this is not always the case, because it also depends in the working practices and the safety culture of the laboratory staff.

Administrative Controls

Administrative measures are a collection of measures such as controlled and limited entry, SOPs, training of the laboratory staff, but also policies, standards and guidelines to control risks.

More specific, these measures are:

- Standard Microbiological Practices or *Good microbiological practices and procedures (GMPP)*, which are a code of practice, or a collection of standard

operating procedures*, that are relevant to all types of laboratory activities with biological agents.* This includes general behaviour, best practices and scientific procedures, which should always be followed and conducted in a consistent manner in the laboratory. The implementation of the common GMPP could provide protection to the laboratory staff and the community from infections and also avoids environmental contamination. *GMPP are perhaps the most effective control measures,* because human errors, improper laboratory routine examinations and use of laboratory equipment have been found to create the most laboratory damages and laboratory-related infections (World Health Organization, 2019).

- Documenting written *Standard Operating Procedures (SOPs)*. By standardizing the way with which the biological materials are handled, fewer mistakes will be made, and exposure will be minimized. SOPs can also be used to minimize splashes, sprays, and the formation of aerosols, thus minimizing exposure and the risk for laboratory-acquired infections. These SOPs can also help to increase the quality of diagnostic examinations and thereby help to acquire a better level of Quality Assurance (QA) at the diagnostic testing.
- Displaying biohazard or warning signages, markings and labeling, thus controlling patient, visitor and laboratory staff access.
- Simple measures like hand washing before leaving the laboratory can be part of an SOP and reduces greatly the transfer of biological materials from the laboratory staff outside the lab, but also protects the environment and the community.

It should be clear that SOPs are only part of the solution. With the introduction of SOPs, laboratory staff must be trained properly on how to use every SOP and the safety measures described in the SOPs. *If training is not supplied SOPs have no additional benefit.*

Personal Protective Equipment (PPE)

PPE is equipment worn by laboratory staff to protect them against exposure to biological materials and the microorganisms present in these materials. In general, the Personal Protective Equipment includes Gloves, Laboratory Coats (resistant to liquids,

disposable or re-usable), Face protection shields, Face masks, Safety glasses, Goggles, Hoods, Shoe covers, Gowns, Respiratory protection (N95 respirator) and other specific PPE. All these material and safety elements must be provided to the laboratory staff and must be under the legal scope of the managerial aspects of each laboratory (Bathula and Rakhimol, 2017).

PPE is considered the least effective control measure and the last line of defense, because it only protects the person who is wearing it, and only if it is used correctly. For example, a failure (rip in the material or a manufacturing defect) or inappropriate use, would likely result in exposure. Personal protective equipment is also used in combination with BSCs and other protection devices (Centers for Disease Control and Prevention, 2009).

However, *using PPE should be combined with proper training,* especially how to don and doff, otherwise the PPE can be used wrongly, making their effectivity smaller than expected.

Also, vaccination or periodically medical checks are covered by personal protection. In some instances, vaccination is already a prerequisite for working with specific biological materials, for example when working with blood borne viruses, then it is an indication for Hepatitis B vaccination.

"It is essential to control risks usually by elimination or reduction at the source" (Tun, 2017), although in Biomedical laboratories these control measures are no option, as explained above. Using the last 3 steps of the hierarchy of controls, there could be an efficiently blocking of the transmission routes of the biological agents in the Biomedical laboratories ie. aerosol transmission, ingestion, blood-blood contact and contact with biological agents, thereby creating a safe working environment for the laboratory staff. Where danger cannot be managed entirely by the engineering controls, administrative controls or personal protective equipment must be used to protect the laboratory staff. It is worth noting that comprehensive risk assessments must be performed for every situation and/or facility separately. Each laboratory facility has different characteristics, personnel and equipment, and each organization has a different viewpoint on risk mitigation or acceptability. The techniques used in the laboratory and the experience, skills and abilities of the laboratory professionals conducting them are often not the very same.

CHAPTER 3: Laboratory Biorisk Management (LBM)

What is Laboratory Biorisk Management

Risk is the probability that an unfortunate event in connection with a particular hazard or danger will take place and the implications of that incidence (Sandia National Laboratories, 2014). Risk is simply a function of likelihood and consequences. Hazard is anything that has the potential to harm (World Health Organization, 2010). In addition to be at risk, there must be a scenario in which the danger may cause harm. For instance, a sharp needle is a hazard, but if the needle is in an empty laboratory and no one uses it, there will be no risk that someone could be injured by the needle.

Risk management includes a broad spectrum of definitions, which should be mentioned for better clarification of the purposes of Biorisk management and the purpose of this thesis. Risk management is a continuous process for the detection, review, evaluation and monitoring of risk control, and financial resources to minimize various effects of losses (Marquette University, n.d.). Risk management systems are common across many industries, especially those industries in which accidents can cause serious consequences (Salerno and Gaudioso, 2015).

The *Biorisk management system* (Figure 6) is part of the management system of an organization, used to create, enforce and maintain its risk strategy and manage its biorisks. It encompasses organizational structure, risk assessment activities, responsibilities, practices, procedures and resources (European Committee for Standardization, 2011). Biorisk management is a system for the monitoring of safety and security threats, in connection with biological agents handling, storage and disposal in the laboratories (World Health Organization, 2014).

Over the past 30 years Biosafety procedures and later on also Biosecurity procedures are focused on the risks of biological agents based on their risk group classification. With this approach, differences in specific factors of pathogens such as the geographical distribution of the pathogen, increasing or decreasing the risk for the environment and/or the laboratory staff, were normally not taking into account when formulating mitigation measures. Not only in Biosafety practices in the laboratories, but also not in legislation, such as the workers' protection legislation. Other risk factors, such as the

performed work, the geographical location of the laboratory etc. where also considered not significant compared to the risk group (Salerno and Gaudioso, 2015).

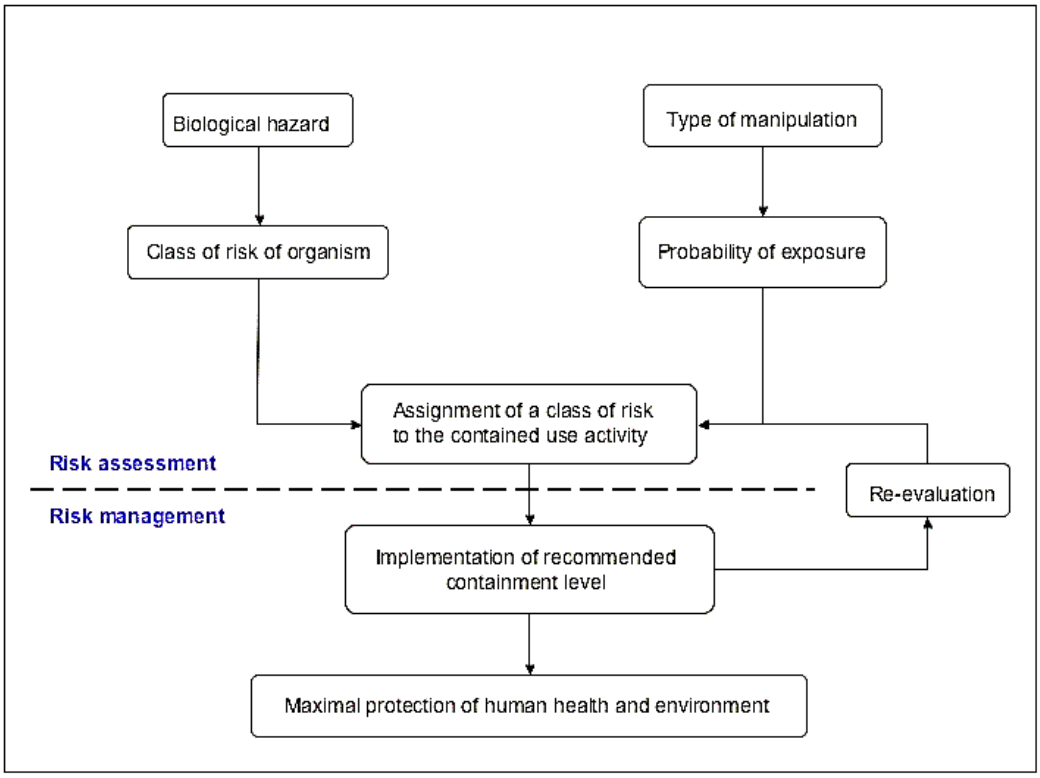

Figure 6: Biological risk assessment and management (Adapted from Willemarck, 2012)

The outcome of this approach suggests that safety and security in laboratories dependents on the resources one can spend on this. Another issue with this approach is that Biosafety and Biosecurity become 2 separate subjects, although they are dependent and should be linked in laboratory environments (Salerno and Gaudioso, 2015).

By using a biorisk management system all subjects involved in Biosafety and Biosecurity are connected to each other on several levels within an organization. It focusses on the roles and responsibilities of the various layers an organization has. These roles and responsibilities are different for the top management and the laboratory staff and all the layers in the hierarchy of an organization. Furthermore, a biorisk management system takes all variables into account when performing a risk assessment and not only the risk group of the biological agent. A management system also ensures that risk assessment is constantly evaluated and adapted when needed, but also the performance of the measures that are in place is been assessed. The advantage of the

biorisk management system approach is that it can be used regardless of the size of an organization and it isn't dependent only on the available resources. This makes a biorisk management system effective in every part of the world regardless of the geographical location of the organization where it is implemented (Salerno and Gaudioso, 2015).

Apparently, the technological development of the biosciences leads to reconsider the conventional methods of preserving Biosafety and Biosecurity. The influence of biotechnology to deal with the threat posed by emerging infectious diseases to the public and economic health and the global accessibility of these technological advances has also led to the rapid expansion of technologically advanced laboratories around the world. The probability of a potentially disastrous Biosafety or Biosecurity incident significantly increases almost daily, notably if the traditional, rule-based Biosafety approach remains intact. Today, the bioscience society needs to establish and embrace a new holistic performance- and risk-based approach to manage the precautions of bioscience, before it is liable for a major disaster (Salerno and Gaudioso, 2015).

Managing risks and risk assessment is a continuous process and needs a commitment of the top management. To manage biological risks the first step is a well-balanced risk assessment.

Risk assessment

As already mentioned above, the risk assessment is the fundamental process of the risk management system and involves steps for the selection of appropriate biological safety and security measures and other facility safeguards, to mitigate risks to an acceptable or manageable level (Sandia National Laboratories, 2014).

Many organizations in the international community acknowledge the importance of risk assessment for the reduction of biological laboratory risks, such as the European Committee for Standardization (CEN), the World Health Organization (WHO) and the US Department of Health and Human Services (HHS).

At the Biomedical Laboratories Risk Management, hygienic and safety conditions are of prime importance, as any risks can arise through the procedures and the tasks performed daily. The common goal is the risk assessment process to be accurate, efficient and reliable (Reid, 1999).

Risk assessments should be performed by a competent team and identified as credible by the various stakeholders. Confidence that hazards and risks have been evaluated methodologically, and that evaluations are accurate, can reduce conflict and confusion from the results of the risk assessments.

There are numerous methods on how to perform a risk assessment. One of these methods is the 5-step method described in the 4th version of the Biosafety manual of WHO, still in a draft version (World Health Organization, 2019). This method described the following steps (Figure 7) for performing a risk assessment:

Figure 7: The risk assessment framework (Adapted from World Health Organization, 2019)

Step 1: “Gather information”

The information is needed to identify the hazard (the materials working with, information from the requesting clinician and from previous tests available) and consider the nature of the work (World Health Organization, 2019).

Questions to be asked in this step are for instance:

- Where is the work carried out?

- Which handlings are performed with the biological materials?
- Which kind of laboratory equipment is used?
- Is there a single test or large volume of examinations?
- Is there any aerosol generation?
- Is there a use of sharps?

Step 2: “Evaluate the risks”

After the collection of all the available information in step 1, we should use them to find out and evaluate any biorisks that exist and calculate the overall risk as shown in Table 5. *Risk = Likelihood x Consequence*, a combination of the probability of an incident and the severity of the damage (Perseus, n.d.).

Table 5: Risk matrix (Modified from World Health Organization, 2019)

Consequences	*Severe*	Moderate	High	Very high
	Minor to Major	Low	Moderate	High
	Negligible	Very low	Low	Moderate
		Unlikely	*Possibly*	*Likely*
		Likelihood		

Step 3: “Develop a risk strategy”

Upon determining the risk level, a risk management system needs to be developed to mitigate the biorisks to an acceptable level and to ensure the work in the laboratory could be done more safely.

Step 4: “Select and implement control measures”

Once the risk strategy has been established, risk control measures must be chosen and implemented, achieving the strategy and controlling the biorisks. In this step, the risks are evaluated and the proper control measures are defined on basis of the hierarchy of controls system, thus the Engineering and administrative Controls, the Personal Protective Equipment, the Vaccination and the medical monitoring of the laboratory staff (World Health Organization, 2019).

Step 5: “Review risks and control measures”

When the risk assessments will be completed, they should be part of a risk management system, in order to make sure that new biological agents’ information, modifications of the laboratory activities or equipment and new controls that may be needed are routinely examined and revisioned, if necessary (World Health Organization, 2019).

It is worth mentioning that every change in an examination, process, SOP, material or technological procedure may lead and should lead to a change in the prevalence of the risk. Before initiating any new work, the laboratory should always conduct and report a risk assessment. A risk assessment should also be performed whenever there is a fundamental change in the laboratory, or a change in the rudimentary nature of the work being carried out. It is also important to initiate a periodic assessment of the laboratory risk, even under stable conditions. Biological risks may still alter even if the procedure or processes do not; thus, *a risk assessment should be carried out and updated at least annually.* Other examples of actions or incidents that alter the risk environment and require a new evaluation typically involve: New biological agents, toxins and reagents, New species of experimental animals, New methods and procedures, New equipment, Improvements in the manufacture or distribution of perishable protection equipment (PPE, containers, waste disposal products, etc.) (Sandia National Laboratories, 2014).

For an effective working LBM system, two different approaches of review and improvements can be used. One is the PDCA cycle and the other one is the AMP system. Both systems will give continuous monitoring and improvement of the LBM, but also have essential differences in their approach.

PDCA Cycle

The PDCA cycle also called the “Deming cycle or Shewhart cycle” (Strotmann et al., 2017), is a lean manufacturing technique developed in 1930 and at the beginning it was used as a tool for quality assurance of the products (Silva et al., 2017). Today is known as a continuous improvement method and is also known as a logic system that can improve operations (Sangpikul, 2017).

In the 1950s, W. Edwards Deming proposed that a simple continuous feedback loop would handle the necessary processes to alter or solve a problem in an organization. This process was illustrated and put into a cyclic and iterative four-step diagram as seen in Figure 8, called the plan-do-check-act (PDCA) model and it is now commonly known as the Deming cycle or the Deming wheel (Deming, 1950).

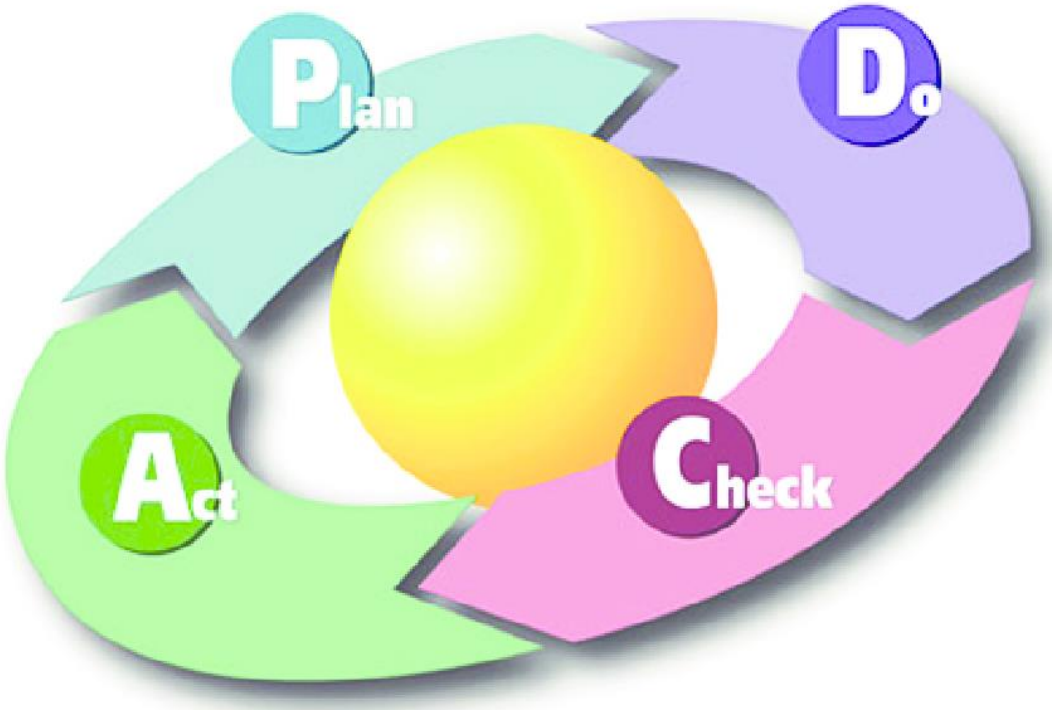

Figure 8: Deming (PDCA) cycle (adapted from Vasić et al, 2015).

Biorisk management systems generally depend upon the PDCA cycle. Even CWA 15793:2011 is built around the PDCA model. Successful implementation of PDCA can lead to measurable improvements in an organization's efficiency, effectiveness and accountability, among other indicators of quality.

When management notices that operations are not running smoothly and laboratory errors are happening too frequently, it is useful to have a process in place to find a solution, with the following steps of the PDCA cycle (Realyvásquez-Vargas et al, 2018):

- "*Plan: Planning, including identification of hazard and risk and establishing goals*"

In this step, a systematic analysis should identify the present status of the process to be studied, evaluate the causes of the problem and propose solutions (European Committee for Standardization, 2011).

- "*Do: Implementing, including training and operational issues*"

The goal of this step is to execute the action plan, collect and record the details, and consider unexpected events, lessons learned and knowledge gained (European Committee for Standardization, 2011).

- "*Check: Checking, including monitoring and corrective action*"

In this step, the outcomes of the actions taken in the previous step are evaluated and what has been learned is established. A comparison is made before and after, performance is measured and improvements are verified, if the objectives have been achieved (European Committee for Standardization, 2011).

- "*Act: Reviewing, make needed changes to the management system*"

This step includes designing methods to standardize the changes, if the goals were met. Furthermore, new data and a progress check are collected only when insufficient data are available, or the conditions have been changed. If the implemented steps have not achieved significant improvements, then the project is stopped and the cycle restarts from the first step (European Committee for Standardization, 2011).

The PDCA cycle is a structured way to ensure continuous improvements in the Laboratory Biorisk Management system. When management recognizes *CHECK* that operations are not running smoothly and laboratory errors are happening too frequently, they can make improvements in the Laboratory Biorisk Management system by *ACTING* on the findings in the *CHECK* phase. In this way, the LBM will be always up to date with the latest improvements, based on the findings in the *CHECK* phase, but also by implementing state-of-the-art laboratory techniques. Also, the quality of the laboratory test will benefit from this PDCA cycle of the LBM.

The AMP Model

Besides the PDCA approach, the World Health Organization uses another management system in its Biorisk Management Advanced Trainer Programme, the AMP model. The AMP model is widely used within the industry.

The AMP model is based on 3 main components: Assessment (A), Mitigation (M) and Performance (P) (see Figure 9 for a schematic representation of the AMP model). The three components do not act separately but closely interact and are dependent on each

other to form the management system. When one of the components is ignored or not resolved the biorisk management system will fail, like a three-legged stool (Gribble, Tria and Wallis, 2015)

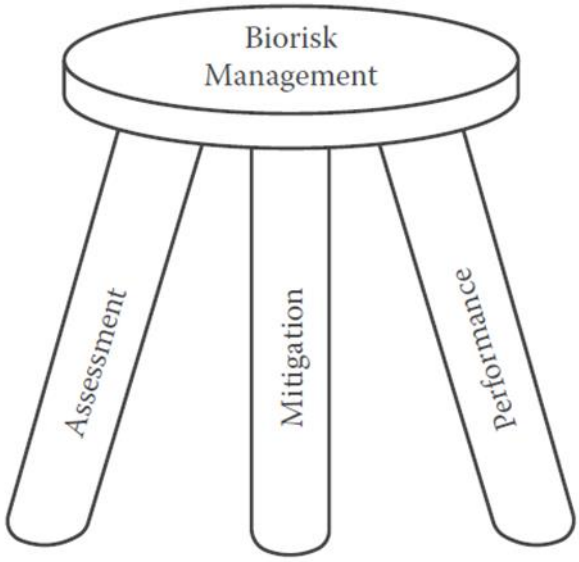

Figure 9: The AMP model (adapted from Gribble, Tria and Wallis, 2015)

In *Assessment* the first essential aspect of the biorisk management system starts with a risk assessment in the laboratory. As mentioned earlier, risk is the "combination of the likelihood of an incident and the severity of the harm" (World Health Organization, (2019). During the risk assessment, risks are identified and mitigation measures are formulated to reduce and handle laboratory risks caused by working with biological materials. The mitigation measures can vary from good microbiological practices and procedures and the use of a variety of adequate safety equipment and may differ depending on the biological agent. Also, security risk and other not biosafety related risks will be identified and measures to mitigate these will be provided (Gribble, Tria and Wallis, 2015).

In the *Mitigation* step of the AMP model, the mitigation measures identified during the risk assessment will be implemented within the working environment and will reduce or eliminate the risk, for the areas identified in the risk assessment, such as the laboratory staff and the environment. Mitigation measures that can be used are numerous and differ greatly, but all play a crucial role in reducing the risk to an acceptable level. Mitigation measures alone, using the hierarchy of control approach,

are not sufficient for an effective biorisk management system, in which continuous improvements are crucial and this needs all the other components of the AMP model (Gribble, Tria and Wallis, 2015).

Performance is the third pillar of the AMP biorisk management model. In this process, the mitigation measures are evaluated by their performance, if they successfully implemented and if they are still functioning adequately in reducing or eliminating the risks. Measures that are no longer efficient or became obsolete can be adapted, replaced or abolished. This helps to make the biorisk management system current and up to date, which is needed to create a safe working environment and helps the organization to achieve its operational goals, such as a high level of quality assurance. (Gribble, Tria and Wallis, 2015).

The connection between Biorisk Management and Quality Assurance (QA)

Most important for management systems is the control and continuous improvement of processes and thus also for the quality of processes and products. A fully developed biorisk management system, or any other management system, will be severely compromised, if a quality evaluation is not or is only partially carried out. Risk management and quality improvement are not systems that are isolated. They are both concentrated on the detection of potential problems and the implementation of corrective measures. Integrating both programmes can enhance the ability of a laboratory to minimize mistakes and improve the efficiency of its services. All laboratory staff needs to work as a team in order to have an integrated organizational risk management and quality improvement program. Regardless of how talented the employees could be, the organization's level of performance is not reached if they cannot function efficiently (Australian Council on Healthcare Standards, 2013).

The ISO 9001:2015 and the ISO 15189:2012 are two examples of this:

ISO 9001:2015 is designed to certify all kinds of organizations and because of that purpose, a generic approach is applied. The core approach is also the PDCA cycle, providing a logical and scientific model of management for a continuous quality improvement. The PDCA could help a laboratory to increase the standard of

performance, e.g. the analytical test results and to guarantee that the patients, but also the State and certification authorities will continue to be satisfied (WESTGARD QC, n.d.).

- In the ISO 15189:2012 standard, in position 4.12, a similar list of actions is described in the WHO Laboratory quality management system, in order to achieve a continual improvement in the laboratory (World Health Organization, 2011). These are listed below:
  - "identify potential sources of any system weakness or error;
  - develop plans to implement improvement;
  - implement the plan;
  - review the effectiveness of the action through the process of focused review and audit;
  - adjust the action plan and modify the system in accordance with the review and audit results." (World Health Organization, 2011)

The quality of laboratory services has an impact not only on the quality of the health care of the individual patients, but it is also essential for the National Health System and the security, thus with the sustainable allocation of resources and the capacity to meet commitments, like the International Health Regulations (World Health Organization, 2005). A comprehensive system of quality management ensures that laboratories could meet their quality requirements and also the Biosafety and Biosecurity regulations and guidelines (World Health Organization, 2016).

Laboratory Biorisk Management standards

In recent years, the concepts and practices of quality assurance programmes, such as the application of International Standard ISO 15189: 2012 to laboratory tests, have been an important strategy of the Laboratories in order to prevent or even reduce risk factors. In addition, other International Standards have been developed and applied.

The CEN Workshop Agreement - Laboratory Biorisk Management CWA 15793:2011 (European Committee for Standardization, 2011) and the most recent ISO 35001:2019 that supersedes the CWA were developed by the global community (for the development of CWA 15793 76 participants from 24 countries have participated) to better minimize biorisk in the laboratory and streamline biorisk management strategies,

by controlling threats related to the process, storage, transfer and removal of biological agents and toxins in laboratories.

Both utilize a management system approach, a structure that incorporates best practices and standards and helps ensure that the organization can successfully meet all of its goals. They raise awareness of Biosafety and Biosecurity risks and strengthens global laboratory cooperation and health harmonization, which may lay the foundation for new or updated laws, or regulations, and may eventually release laboratory certification or accreditation and audits - inspections. The requirements of both CWA 15793:2011 and ISO 35001:2019 are originally meant to be congruent with any established local or national guidelines, as well as with the criteria of other commonly used management system standards, such as ISO 9001:2008, ISO 14001:2004 and BS OHSAS 18001:2007. It is significant for organizations and other users to recognize that these are not only technical requirements. Instead, are performance-oriented reporting systems outlining what needs to be achieved and every laboratory must determine how to fulfill these goals.

Why is it important to have a LBM system?

Risk management systems are prevalent across many industries, especially those in which incidents can have major repercussions. The underlying causes of the high-consequence incidents that are mentioned bibliographically went well beyond technological or human failure and almost always represented underlying deficiencies in security or safety management. High consequence organizations that have established constructive risk management programmes have accomplished a substantial reduction in the number and intensity of incidents (Salerno and Gaudioso, 2015).

Having an established Biorisk Management system in a Biomedical laboratory is very important, because it improves the laboratory processes and manages the risks more efficiently :

- There is a continuous cycle of review and improvement for the laboratory's effectiveness and efficiency, by identifying, understanding and managing the interrelated processes, in which Biosafety plays a big role. That could have as a result:

- strengthening the laboratory's procedures to achieve its Biosafety and Biosecurity objectives
- there is an ongoing analysis and improvement cycle
- there is a successful detection, assessment, monitoring and evaluation of laboratory Biosafety and Biosafety risks, associated with the laboratory activities are carried out

- There is a clear guidance established, by describing the roles and responsibilities for those who work with or have access to biological materials in the laboratory
- The number and the severity of the incidents and the Laboratory infections would be reduced
- The appropriate training to laboratory professionals, supervisors and other personnel of laboratory facilities will have as a result the awareness of the contributing factors to risk, so that they could be mitigated adequately
- The culture of awareness, a shared sense of responsibility and ethics is promoted
- The response and knowledge during an emergency are enhanced (Bathula and Rakhimol, 2017).

The following 2 factors are the most important to create and implement a successful Biosafety management system:

1. *"The Commitment by top management"*, in order to provide adequate resources, to prioritize and communicate Biosafety and Biosecurity policy and to integrate the Biosafety management throughout the laboratory
2. *The "Focus on continual improvement"* by making the continuous improvement a goal for every individual and prosses in the laboratory, identify areas and establish measures and goals for improvement, providing laboratory staff with the appropriate education and training, promote prevention activities and recognize improvement (European Committee for Standardization, 2011).

CHAPTER 4: Biorisk management in Greek Biomedical laboratories, a small survey

Goals of the survey

The first goal of this thesis is to describe the importance of a Laboratory Biorisk Management system. This was described in the first three chapters. The second goal is to review different Biomedical laboratories in Greece, to investigate how they examine the biological materials and get a general view on how Biosafety is handled in these laboratories. Using the results of this review, actions can be formulated to improve Biosafety in the Greek laboratories, with the ultimate goal to create a Biosafety management system and also a Biosafety culture for the Biomedical laboratories and laboratory professionals in Greece.

Method

To achieve the second goal information was needed. To gather this information on the status of Biosafety and biorisk management in Greek Biomedical laboratories, questionnaires (see APPENDIX I) were sent to 25 organizations that have Biomedical laboratories. To avoid any ethical issues that might arise, the first page of the questionnaire stated the purpose of the questionnaire, maintaining the confidentiality of the participants' personal data and information, but also the possibility of withdrawing the questionnaire in a later stage.

The questions asked can be divided into 3 categories:

1. Some general questions to get information on the laboratory
2. Questions regarding the last 2 steps of the hierarchy of controls, ie. Administrative procedures and Personal Protective Equipment
3. Questions regarding good microbiological techniques and practices used

Results, Discussion and Conclusions

General information:

From the 25 send out questionnaires 15 were send back completed. This is 60%. Most of the questionnaires were completed by technologists (11 of 15). The laboratories that

completed the questionnaires cover the entire spectrum of scientific areas of Biomedical laboratories (see Figure 10), whether the laboratories are accredited (Figure 11), which biological materials are handled in these laboratories (see Figure 12) and how the tests are performed on these materials (see Figure 13).

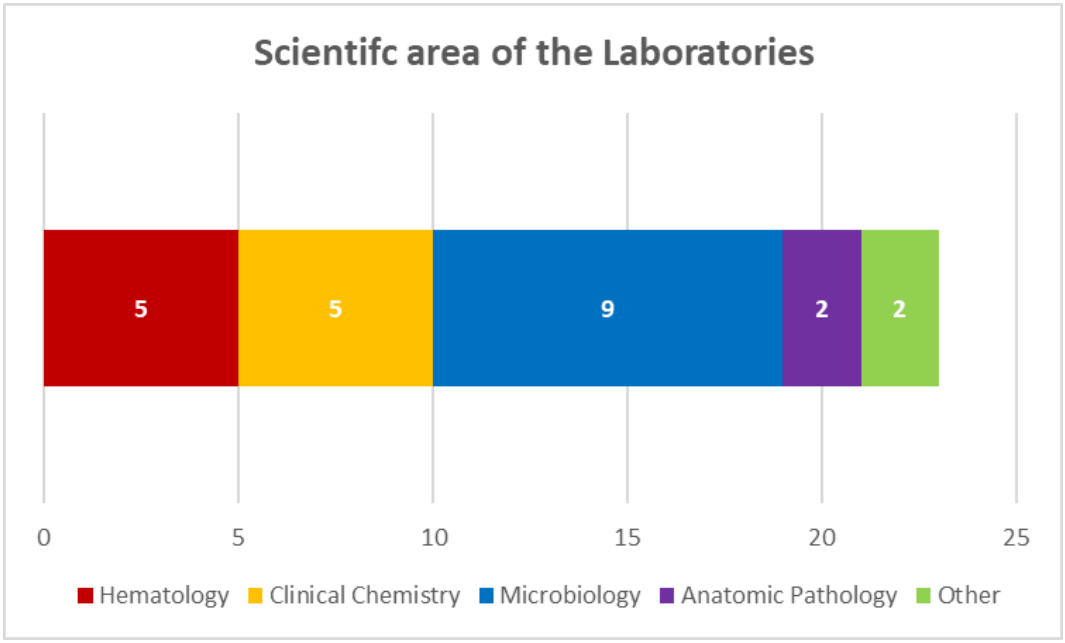

Figure 10: In which scientific area is the laboratory

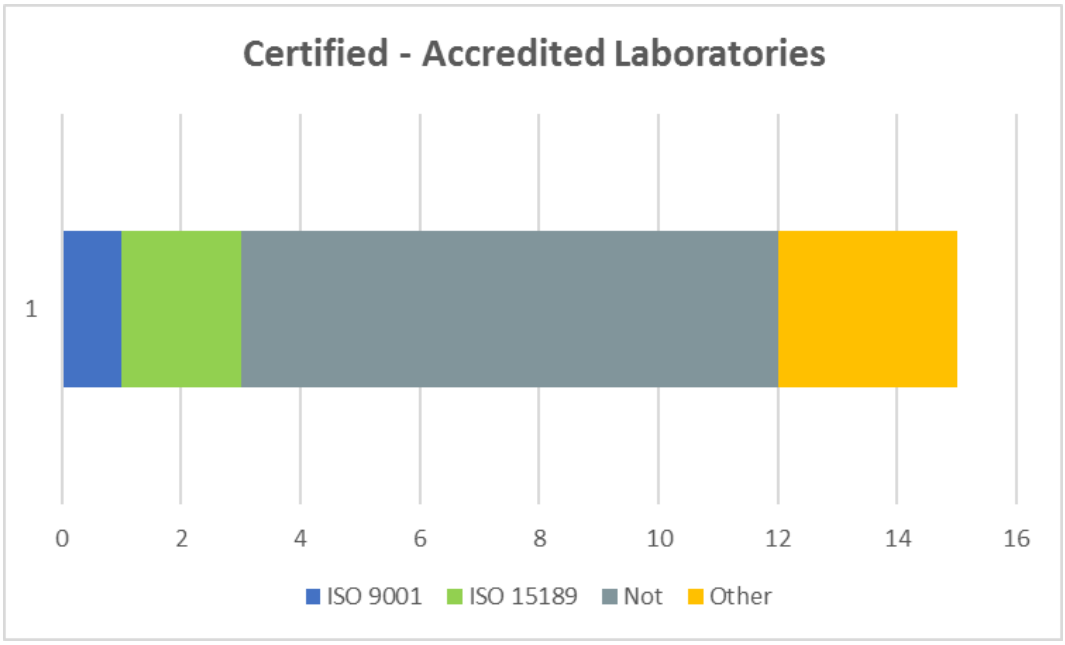

Figure 11: Laboratory is certified or accredited by ISO 9001 or ISO 15189

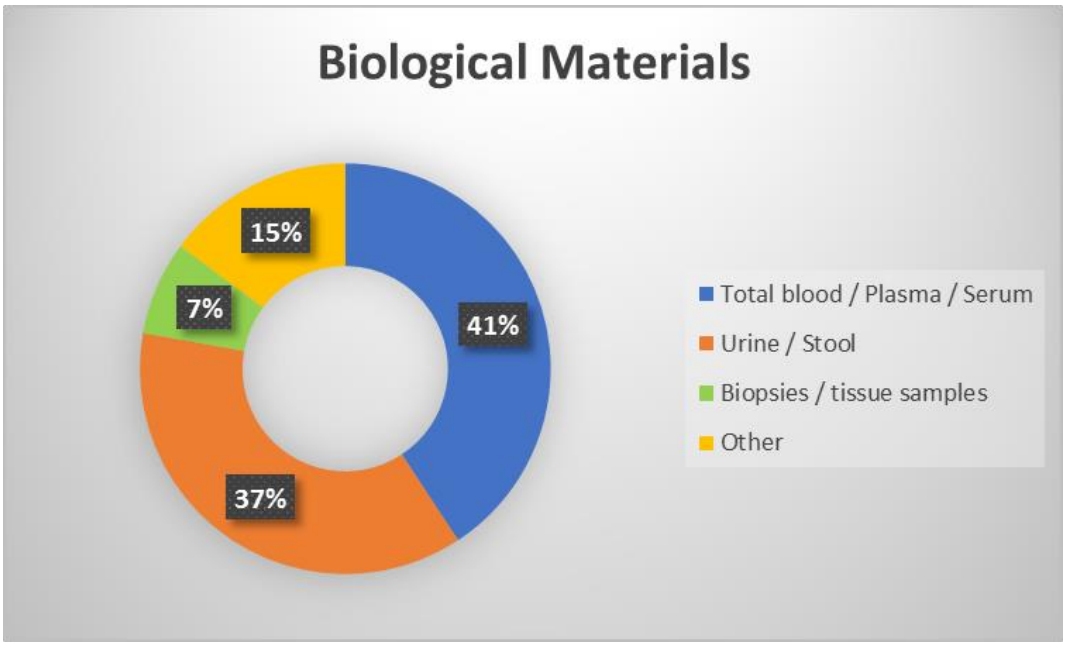

Figure 12: Biological materials handled in the laboratory

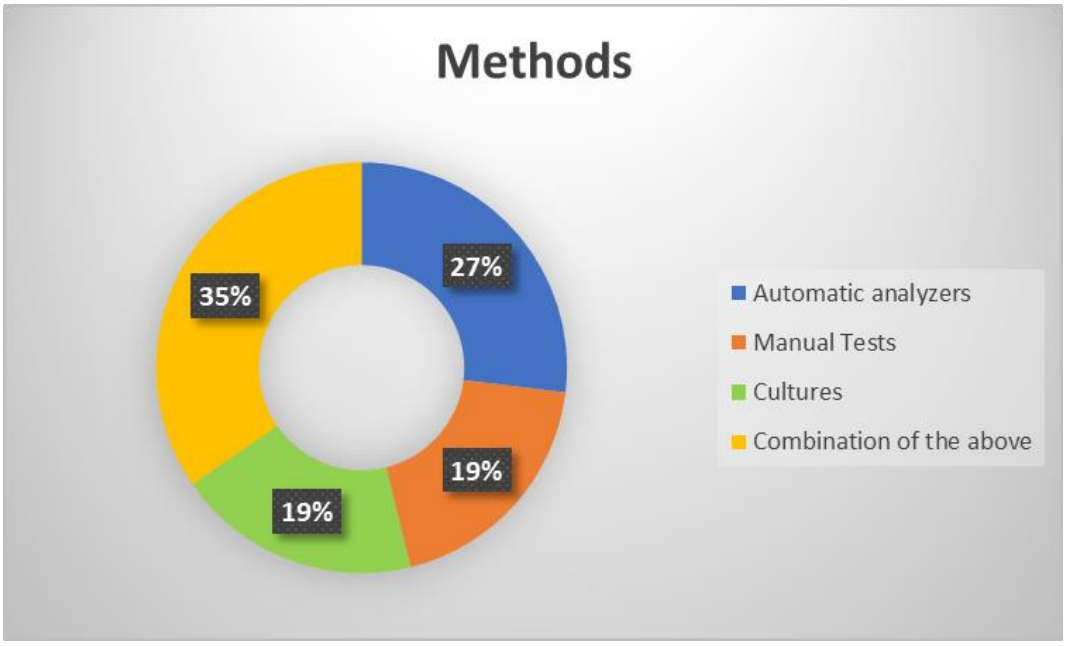

Figure 13: Methods that are used for the examinations

Only 20% of the laboratories have a containment level. These laboratories are all microbiological laboratories handling class 3 pathogens. The main Biomedical laboratories in these institutes are not classified as a Biosafety laboratory (Figure 14).

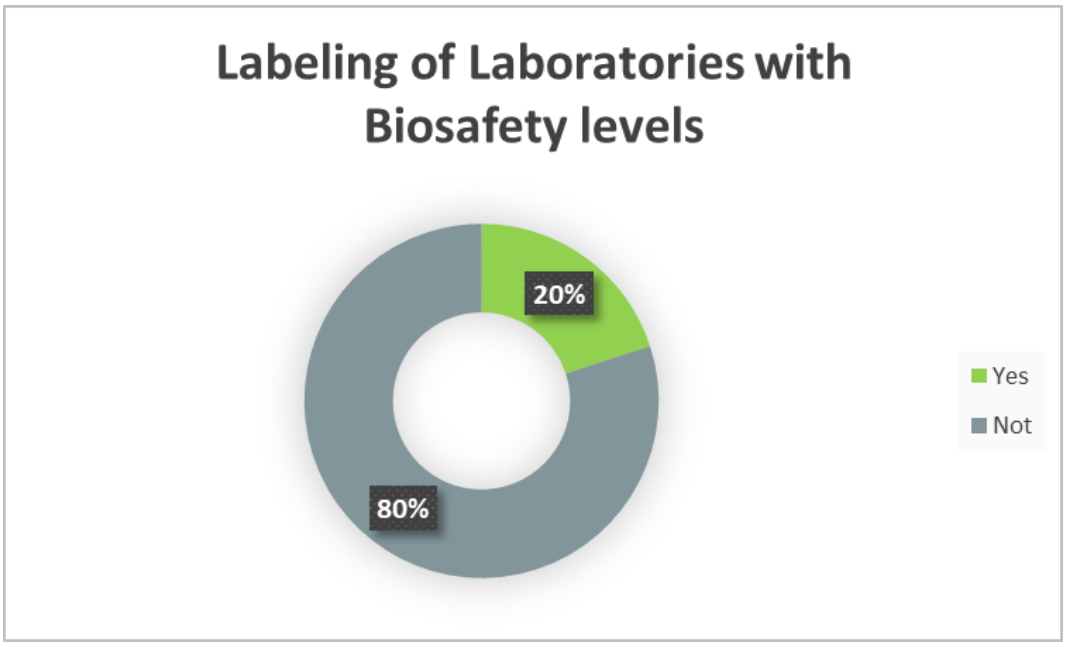

Figure 14: Labelling of laboratories according to the Biosafety levels (BSL 1, 2, 3, 4)

Biosafety approach in the Biomedical labs

Regarding the steps of the hierarchy of controls, the questionnaire was focused on the last 2 steps, Administrative measures and Personal protection equipment. As already mentioned, elimination or substitution is not an option in controlling biological risks in Biomedical laboratories. In the 3rd step, engineering controls have not been taking into account. The reason for this was that modifying laboratories to increase Biosafety would need a budget. Budget is not something that can be easily obtained, especially with the limited fanatical resources in Greece.

Administrative controls

From the results it is clear that only part of the laboratories has a complete set of standard operating procedures for biological materials. Only 4 out of the 15 responders operate fully on SOPs and 7 have partially SOPs for the laboratories (Figure 15).

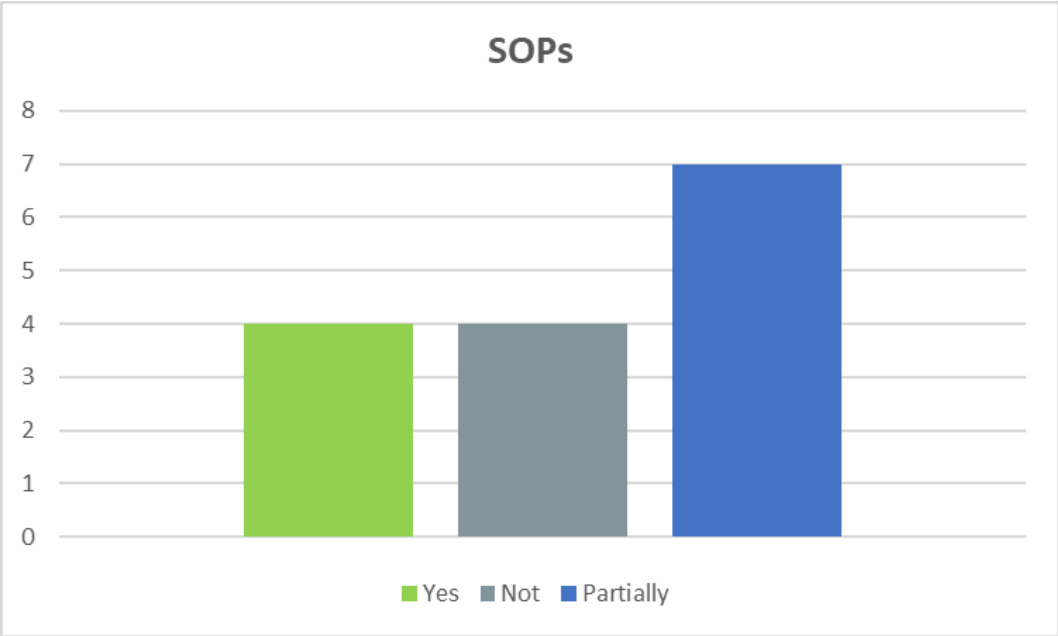

Figure 15: Examinations are performed based on standard operating procedures (SOPs)

From the point of Biosafety, a couple of questions asked, if procedures from good microbiological techniques and procedures were in force in the laboratories. None of the 6 procedures were in force in all the laboratories. The disinfection of workbenches scored the highest with 80%. It was striking that personal hygiene and procedures that prevent contamination during food intake scored low. This is a great risk for the staff to get contaminated during lunch and coffee breaks, but also the community is at risk, because pathogens from the biological samples can leave the laboratories via the laboratory staff. This is unacceptable for reasons of public health in general (Figure 16).

Also striking is that the large majority of laboratory staff do not participate in training courses, indicating that training courses are not offered by the employer, or are not obligatory for laboratory staff. This lack of training (Figure 17) can be the reason why good microbiological techniques are not enforced or even unknown. The lack of training can also be due to the fact that most laboratories have not a Biosafety officer and thus no clear responsible person for Biosafety.

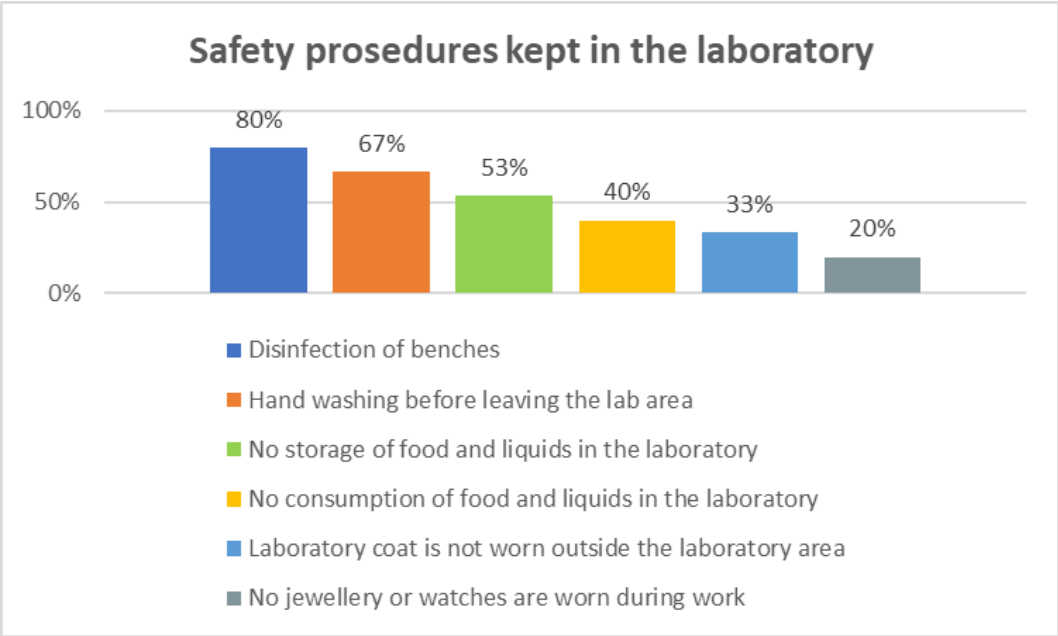

Figure 16: Health and safety procedures are kept in your laboratory

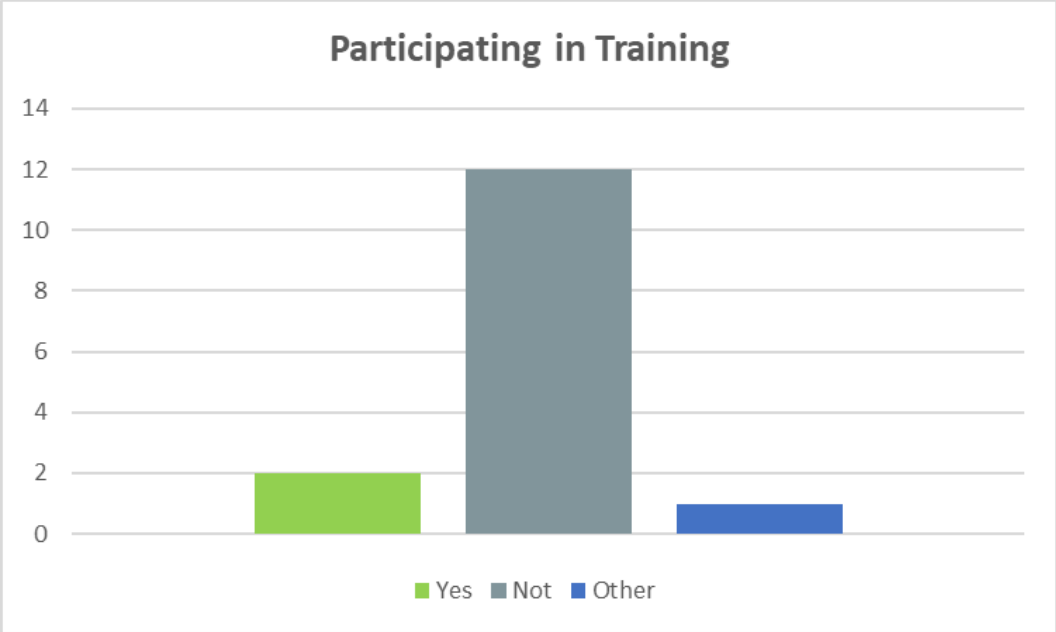

Figure 17: Participating in theoretical or practical training programmes in Biosafety

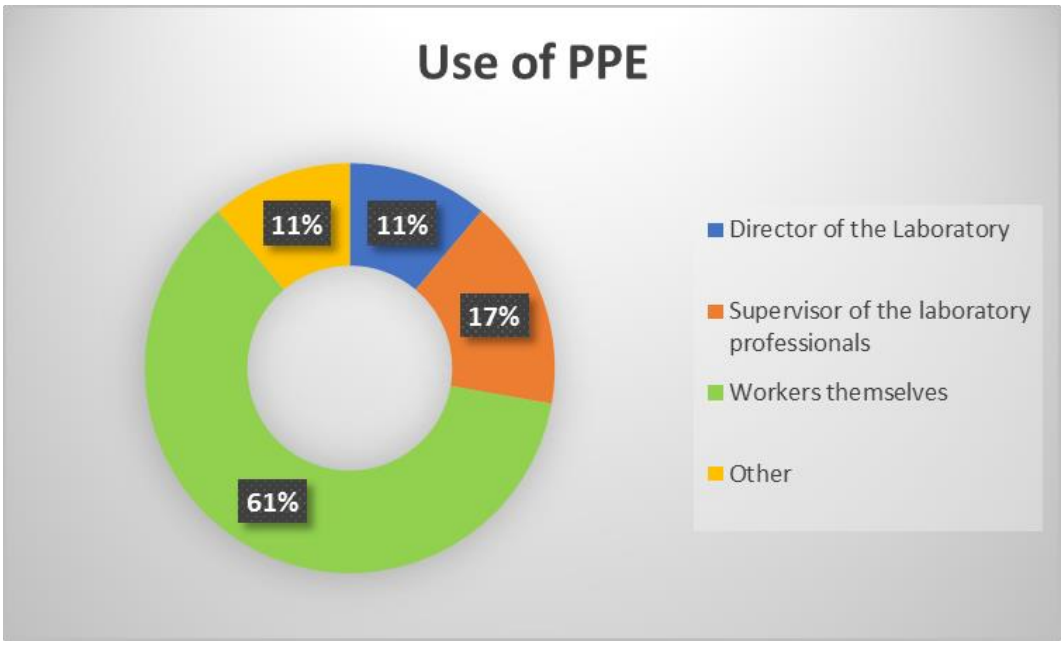

Figure 18: Responsible for the use of PPE by the professionals in the laboratory

Personal protection

From the questionnaires it is clear that the laboratory staff have access to PPE. However, in the most laboratories the staff themselves are responsible for this, although the staff protection law states that the management should be responsible (Figure 18).

Also, here the lack of a Biosafety officer can be due to the fact that this is not properly regulated within the laboratories (Figure 19).

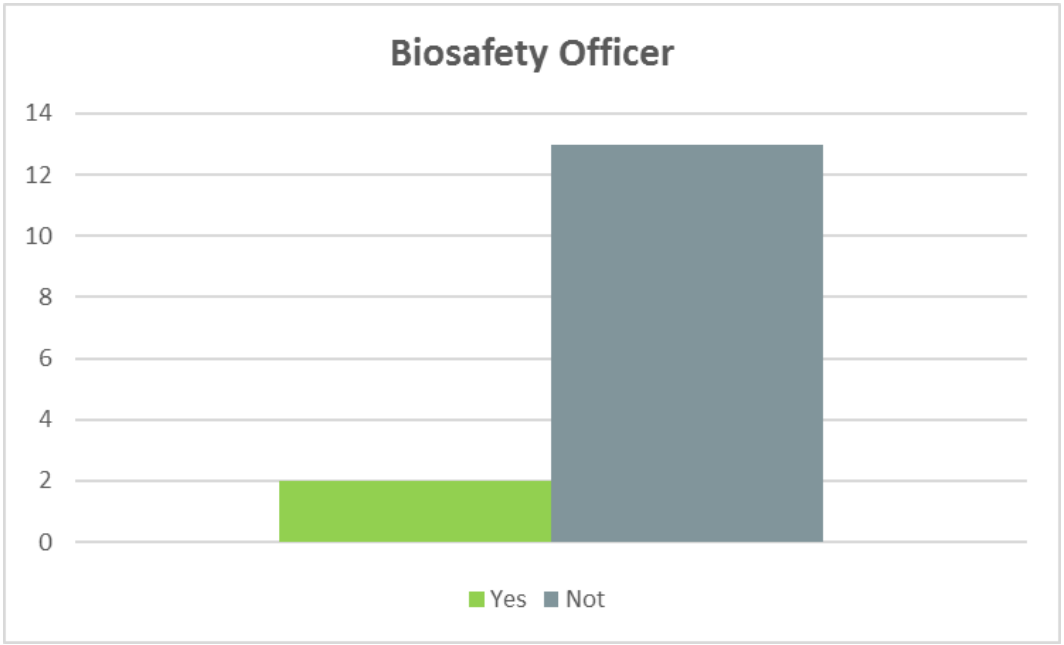

Figure 19: Biosafety officer appointed

Despite the results, most of the laboratory professionals state that they are satisfied with the protection measures. Only a small portion is not satisfied with the protection measures in the laboratory (Figure 20).

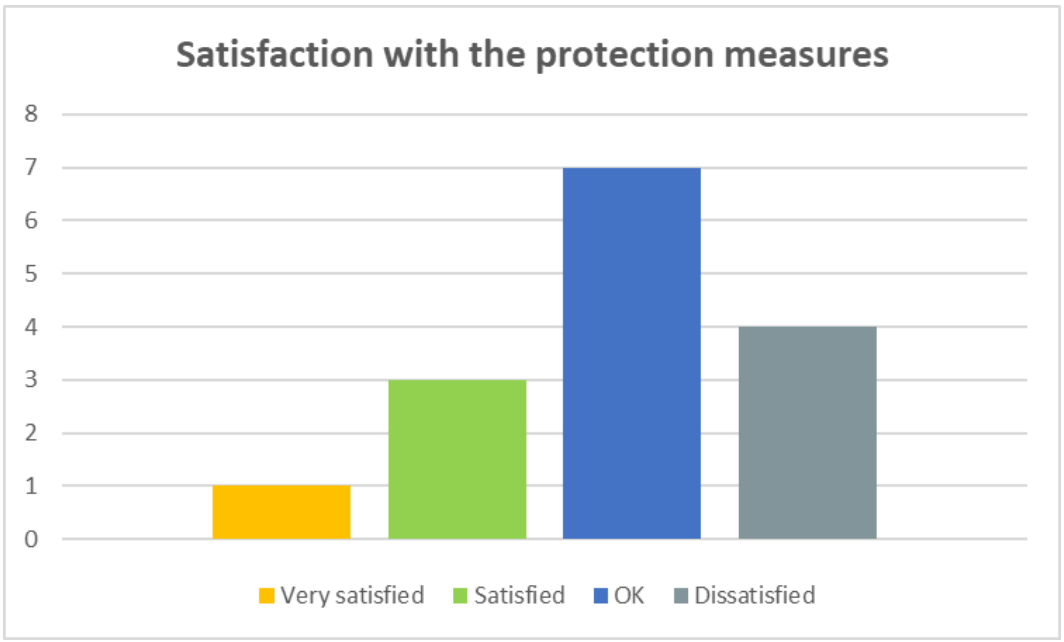

Figure 20: Satisfaction with the protection measures regarding safety and Biosafety

It may be clear from the above presented results that the level of Biosafety in many of the Biomedical laboratories in Greece is not at an appropriate level to prevent LAIs, but also infection of the general public. In general terms it can be concluded that Biomedical laboratories do not comply with the widely accepted BSL-2 standards, such as WHO, ECDC and CDC. Especially the lack of working to protocols and the implementation of BSL-2 principles is problematic for Greek Biomedical laboratories. Not only for Biosafety reasons, but also for QA reasons, and this is important because SOPs contribute both in Biosafety and Quality.

Because most of the laboratory staff is satisfied with the protection measures in the laboratory, the question is if the laboratory professionals are aware of the potential risk not applying general safety and good microbiological techniques and procedures. Especially can be a risk for the laboratory professionals themselves, but also for the general public and the community.

From the results it is clear that none of the laboratories has a proper biorisk management system in place and that there is also no Biosafety culture within the organizations. The management seems not aware of their responsibilities in given

regular training, performing risk assessments, working according to protocols and the use of PPE. Appointing a person with a special interest in Biosafety, such as a Biosafety officer could help the management to set-up and maintain a proper LBM with the mandatory PDCA cycle or the AMP-model.

Recommendations and proposals

What is already in Greek law and legislation

The main Greek Law is the Presidential Decree 186/95 (Government Gazette 97/A/ 30-5-95, as also amended by the P.D 174/97 and P.D 15/99) on "the protection of staff from risks related to exposure to biological agents at work." This law is contacted for the legal enforcement of the European Council Directives 90/679/EEC and 93/88/EEC in Greece, which are also very similar and the origin of the EU Directive 2000/54.

Based on the results of 15 Biomedical laboratories there are issues in the implementation of the national Greek legislation:

- Risk assessments are not performed, although it is referred in the Presidential Decree 186/95, in "*Article 3 - Determination and assessment of risks: In the case of any activity likely to involve a risk of exposure to biological agents, the nature, degree and duration of staff' exposure must be determined with a regularly renewed risk assessment*".
- General precautions and standard Hygiene measures are partially implemented although it is referred to in the Presidential Decree 186/95, in Article 8, "*Hygiene and individual protection: staff do not eat or drink in working areas where there is a risk of contamination by biological agents."*
- Continuous training of laboratory staff by the employer is not carried out although it is referred in the Presidential Decree 186/95, in Article 9 – "Information and training of staff:

  Appropriate measures shall be taken by the employer to ensure that staff and/or any staff' representatives in the undertaking or establishment receive sufficient and appropriate training, on the basis of all available information, in particular in the form of information and instructions, concerning:

  (a) potential risks to health; (b) precautions to be taken to prevent exposure;

(c) hygiene requirements; (d) wearing and use of protective equipment and clothing; steps to be taken by staff in the case of incidents and to prevent incidents.

The training shall be:

- *given at the beginning of work involving contact with biological agents,*
- *adapted to take account of new or changed risks, and*
- *repeated periodically if necessary."*

- Access control in the Biomedical laboratories is not performed although it is referred in the Presidential Decree 186/95, in Article 6 Reduction of risks: "*use of the biohazard sign depicted in Annex II and other relevant warning signs; drawing up plans to deal with accidents involving biological agents*"

From a regulatory standpoint, the conclusion here is that in Greece there is no enforcement of the national Greek legislation. Not only by the competent authorities, but also not by the management of the organizations in the hospitals and in the health centers of the Primary health care sector.

There is hardly any control from the competent authorities on the various EU-regulations that are applicable for Biomedical laboratories and that would ensure adequate control of the biological risks, such as the EU directive 2000/54 and other legislation or directives, on safety and health at work, like that could be found in the European Agency for Safety and Health at Work.

Also, it reveals the lack of protocols, moreover for preventing aerosol formation, and it is very important the development of an efficient biorisk management framework, rigorous laboratory practices, continuous training and growth of the laboratory staff, in compliance with the European and international regulations and standards.

Changes needed on the national/regional level:

1. Update of the main Greek Laws P.D 186/95, P.D 174/97 and P.D 15/99, in order to align with the European EU directive 2000/54, as well as with the resent international regulations and standards
2. Creation of a National Authority for the elaboration of processes, procedures and regulations of Biosafety and Biosecurity aspects for all Laboratories (Biomedical and research laboratories, but also for Animal health laboratories) for the proper

assessment and mitigation of the risks from any biological origin, in order to ensure compliance with the regulations

- The Authority could propose a National Biorisk Management strategy and oversite for the Biomedical Laboratories, irrespective of the ownership type, field of activity, types of microorganisms and toxins with which they operate, and also improvements of the engineering controls (see APPENDIX II)

3. Elaboration of training programmes for the implementation of National and International regulations, guidelines and requirements, in the field of Biosafety and biological risk management
    - Introductory and continuous training of all health professionals (Medical Laboratory Doctors, Biotechnologists, Nurses and other personnel)
    - Biosafety as a subject should be part of the academic training of the above professionals

Improvements that can already start on every institutional level:

Despite appropriate legislation and enforcement of it, also institutions themselves can already start with improving Biosafety and start working on a LBM and the Biosafety culture. In this context and also considering the results of 15 Biomedical laboratories a current biological risk management program, associated with laboratory operations according to the BSL-2 procedures must be enforced, and the following recommendations are the first steps for an acceptable level:

1. Create awareness of the management of the biological risk that laboratory professionals are exposed to and make them aware of their responsibilities, and of the laboratory professionals on biological risks during their work
2. Introduce the hierarchy of controls in Biomedical laboratories
3. Develop SOPs and protocols for all laboratory tests and instrument operating procedures, entering and exiting the laboratory, PPE donning/doffing, emergency response (spills, incidents and accidents with biological materials), hand washing and waste management (see APPENDIX III)
4. Train the laboratory professionals in Biosafety techniques, ie. good microbiological techniques

5. Prepare the Biomedical laboratories for the new standard ISO 35001:2019 (International Organization for Standardization, 2019). In the meanwhile, the 4th edition of WHO Laboratory Biosafety Manual could be used, when it will be published
6. In every Biomedical laboratory a risk assessment should be contacted, with the aim to unveil what could harm the professionals, to determine whether the necessary precautions are in place, or if further actions should be taken, in order to avoid damage
7. Designate an Appointed Biosafety Officer, responsible for Biosafety in the laboratories with a mandate for this purpose from the management
    - The person designated with that function could be biotechnologist-medical laboratory technologist, biologist, microbiologist or a relevant laboratory professional, with the aim to Ensure and Inspect whether Biosafety programmes are complied, to inform the staff for specific hazards and oblige the laboratory with standard operating procedures and practices
    - In every hospital one professional should be appointed as a full time
    - In every health region one professional should be appointed, responsible for the coordination of the health centers in the primary health sector
8. Ensure that general precautions and standard Hygiene measures are taken and overseen, in order to reduce the risk of infection acquired within the laboratory. This includes also the washing and disinfection of the hands
9. Ensure continuous training of laboratory professionals for maintaining the level of safety of the Laboratory, the responsible work with the biological materials and their effective protection. This training should be organized by the management or should be in the mandate of the Biosafety Officer. Training is very important because “It can be argued, therefore, that the best designed and most well engineered laboratory is only as good as its least competent staff” (World Health Organization, 2019)
10. Create levels of access control in all Biomedical laboratories and designate of authorized personnel. There should be a Policy for patients, visitors and non-laboratory staff entering in the lab, entry and departure procedure after completion of work and accident plans.

11. Ensure that all of the above is part of the Biorisk Management. The Biosafety Officer (no. 7) should be responsible for the Biorisk Management System and the connected PDCA cycle or AMP-model.

CONCLUSIONS

The Biorisk Management System is based on a continuous improvement philosophy through a cycle of planning, implementing, reviewing and improving the operations and activities that a Biomedical laboratory undertakes in order to meet its objectives. It could enable the Biomedical laboratories to productively identify, assess, control, monitor and evaluate the Biosafety and Biosecurity risks associated with hazardous biological materials, and additionally could assist to fulfill their legal and quality requirements.

The ultimate benefit and the primary thing to aim from the Biorisk Management is to eliminate or minimize to an acceptable level the risks and the possible Laboratory infections, in order to protect the laboratory professionals, the patients, the community, as well as the environment, from biological agents and toxins that are handled, transferred or stored at the laboratory facilities, by focusing on each individual laboratory professional and inspiring them with a motivation to create a safety culture, thus:

"Biosafety culture is the set of values, beliefs and patterns of behavior instilled and facilitated in an open and trusting environment by individuals throughout the organization who work together to support or enhance best practices for laboratory Biosafety. This culture is crucial for the success of a Biosafety programme and is built from mutual trust and the active engagement of all personnel across the organization, with a clear commitment from the organization's management. Establishing and maintaining a Biosafety culture provides a foundation upon which a successful Biosafety programme can be developed ." (World Health Organization, 2019)

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APPENDIX I Questionnaire

Questionnaire on the status of biosafety in Biomedical Laboratories in Greece

Dear Lady/Sir,

Thank you for your participation.
The purpose of this questionnaire is to research biosafety issues in biomedical laboratories in Greece. It has being conducted for the MSc Program in Bioeconomy, Biotechnology and Law of the International Hellenic University, it consists of 20 questions in multiple choice form and it requires less than 7 minutes to be completed. The questionnaire is anonymous, you could withdraw your answers in a later stage.

General (optional) information

Name of your institution:
Address:

Questions

1. You work in the laboratory as:	
☐	Pathologist (MD)
☐	Medical Laboratory Technologist
☐	Biologist or Biochemist
☐	Nurse
☐	Other, specify:.....

2. Your laboratory is in a:	
☐	Hospital
☐	Health Center
☐	Other, specify:.....

3. In which scientific area is your laboratory:	
☐	Hematology
☐	Clinical Chemistry
☐	Microbiology
☐	Anatomic Pathology
☐	Other, specify:.....

4. Your laboratory is certified or accredited by:	
☐	ISO 9001
☐	ISO 15189
☐	Not
☐	Other, specify:.....

5. With what kind of biological materials do you work in your laboratory:	
	Total blood / Plasma / Serum
	Urine / Stool
	Biopsies / tissue samples
	Other, specify:.....

6. What methods are you using for the examinations you perform:	
	Automatic analyzers
	Manual Tests
	Cultures
	Combination of the above

7. Examinations are performed based on standard operating procedures (SOPs):	
	Yes
	Not
	Partially

8. The use of PPE (Personal Protective equipment) is obligatory in the laboratory:	
	Yes
	Not
	Other, specify:.....

9. Who is responsible for the use of PPE by the professionals in the laboratory:	
	Director of the Laboratory
	Supervisor of the laboratory professionals
	Workers themselves
	Other, specify:.....

10. Which of the following health and safety procedures are kept in your laboratory:	
	Disinfection of benches
	No storage of food and liquids in the laboratory
	No consumption of food and liquids in the laboratory
	Laboratory coat is not worn outside the laboratory area
	No jewellery or watches are worn during work
	Hand washing before leaving the lab area
	None of the above

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11. There is a sharp and waste management program in your laboratory:	
	Yes
	Not
	Other, specify:.....

12. In your laboratory, which of the following are in use: (Answer more than one option when applicable)	
	Limited access-entrance to the laboratory, only by the staff-laboratory professionals
	Special insulation and construction of floors, walls and roof of the laboratory
	Construction material of laboratory bench surfaces is TRESPA or compatible
	Controlled ventilation and air conditioning system
	Autoclaving in the laboratory area
	Biological Safety Cabinets (with HEPA filters)
	None of the above

13. Which of the following is in your opinion more important for the effective protection of workers in laboratories: (Answer more than one option when applicable)	
	Disinfection-sterilization of laboratory benches and containers
	Safety Needles and Blood collection systems
	Waste Management
	Biosafety Manual
	Laboratory professionals and staff Training (introductory)
	Laboratory professionals and staff Training (continued)
	Biological safety Cabinets
	Personal Protective Equipment
	Labelling for potential biological hazard
	Standard operating procedures in each working area
	Other, specify:.....

14. In your workplace, there is a classification and labelling of laboratories according to the biosafety levels (BSL 1, 2, 3, 4):	
	Yes
	Not
	And other, specify:.... .....

15. To what extent do you know what Biosafety is:	
	Very familiar
	Familiar
	OK
	I don't know what Biosafety is

16. In your workplace there is a Biosafety officer appointed:

- [ ] Yes
- [ ] Not
- [ ] Other, specify:.....

17. All staff are participating in theoretical or practical training seminars-biosafety training programs:

- [ ] Yes
- [ ] Not
- [ ] Other, specify:.....

18. Which of the following systems – documents are kept in your laboratory:

- [ ] Biosafety Handbook
- [ ] Anonymous Reporting system for occupational Accidents
- [ ] Accidents - Crisis Plan
- [ ] Biorisk Management System
- [ ] Information of the workers on risks in the laboratory
- [ ] None of the above

19. In your institution medical examinations for the laboratory professionals are carried out, for the preventive control of the occupational diseases:

- [ ] Yes, when hiring new staff
- [ ] Yes, every year
- [ ] Yes, in case of an accident in the lab
- [ ] Not
- [ ] Other, specify:.....

20. To what extent are you satisfied with the protection measures in your institution regarding safety and biosafety:

- [ ] Very satisfied
- [ ] Satisfied
- [ ] OK
- [ ] Dissatisfied
- [ ] Other, specify:.....

Comments, remarks, suggestions:

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APPENDIX II Details on engineering controls

ENGINEERING CONTROLS

- Laboratory design
    - Administration and Secretariat sections should be always constructed separate from the main Laboratory
    - Spaces for personal breaks, feeding and storage of personal belongings and food should be created outside the laboratory area
    - Stocks of consumables and reagents should be stored in separated spaces from the main Laboratory
- The windows should always be closed during performing laboratory tests. This requires the proper operation and maintenance of air conditioning - ventilation, which should be regular checked and logged from the relevant technical department
- Air handling of lab areas should be separate from non-lab areas, such as offices, coffee- and lunchrooms from the lab and should preferably not be recirculating in the lab area as well
- An Annual verification of the Biosafety Cabinets (BSC) should be performed
- All surfaces in the lab should be easy to clean and easy to disinfect and should be nonabsorbent
- The floor in the laboratories should be intact, easy to clean and disinfect and resistant to chemicals and disinfectants
- The surface of benches should be made of HPL (high-pressure laminate) material or other similar type, in order to be resistant to chemicals
- Hands free operable sinks, and soap dispensers, preferably close to the exit of the laboratory

APPENDIX III Details on administrative controls

ADMINISTRATIVE CONTROLS

- In every Biomedical laboratory a risk assessment should be contacted, with the aim to unveil what could harm the professionals, to determine whether the necessary precautions are in place, or if further actions should be taken, in order to avoid damage.
- Designation of an authorized Biosecurity Officer:
  - The person designated with that function could be (biologist, biotechnologist, microbiologist, biochemist), may be a member of the working team and aims to Ensure and Inspect whether Biosafety procedures and programmes are complied. Must be professionally competent to analyse, measure and approve the level of safety, in order to further reduce the potential of infections acquired in the Laboratory.
  - This professional (a better terminology for the officer) shall inform the staff for specific hazards, oblige staff to be aware of the safety manual and the work and comply with the Standard operating procedures and practices.
  - The following responsibilities should attributed to the Biosafety Officer: ensuring that an internal Biosafety system in accordance with the Laboratory / Centre Regulation and Legislative acts in the field; consultations on occupational safety and hygiene; Regular internal inspections of methods, procedures and protocols, biological agents, materials and equipment; Training of the laboratory personnel.
- Access control: designation of authorized personnel. There should be Policy for visitors and non-laboratory staff entering in the lab, entry and departure procedure after completion of work. In Particular:
  - There should be Labels and signs in all areas of the laboratory
  - Access to the Laboratory should only be authorized by authorized personnel, by relevant and clear signages that there are Group 2 or higher microorganisms, that access is only authorized by authorized personnel and the doors of the Laboratory will always remain closed
  - No access should be allowed to young people and pregnant or lactating women, unless Precautionary measures have been taken so that they are not exposed to risk for their health.
  - The central door of the laboratory should have an automatic locking mechanism.
- Continuous training of laboratory staff. It is important that there are certain training activities on biological security for the responsible work and their effective protection. The Training program for Laboratory personnel must include:
  - Good microbiological practices and procedures
  - The characteristic of the biological agents
  - Identifying potential Hazards
  - Appropriate decontamination and disinfection techniques
  - Emergency procedures
  - All SOPs should be a subject in these trainings

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- Standard Microbiological Practices (Good microbiological practices)
    - Work according to the protocol, especially when you think there is no risk
    - Never storing food or drink, or personal items such as coats and bags in the laboratory. Eating and drinking are only to be performed outside the laboratory.
    - Start working with clean hands and nails, without (or by appropriately covering) rings, piercings, bracelets and watches
    - Keep doors and windows closed in the laboratory
    - Prevent hand-mouth contact; do not touch your face, smoke, eat or drink in the lab
    - Prevent aerosol formation
    - Do not pipet by mouth
    - Do not wear a lab coat outside the lab area; Leave lab coat in the lab
    - Thoroughly washing hands, after handling any biological material and before leaving the laboratory
- Develop SOP's and protocols for:
    - Entering/exiting laboratory
    - Instrument operating procedures
    - Use of Biosafety cabinets (BSC)
    - Emergency response
    - Hand washing
    - Waste segregation, management, and disposal
    - Inventory control
    - Experiment-specific activities
    - Spills
    - Sample leakage on receipt
    - Container leakage during analysis
    - Laboratory disinfection
    - Protocols for preventing aerosol formation: When opening the tubes, during centrifugation and during pipetting
    - Detailed Labor and Occupational Safety Protocols that identify known and potential hazards and describe the practices and procedures used to minimize or eliminate these hazards. Work protocols should also include measures to enhance specific safety practices, such as safe waste management, the immediate disposal of used sharp objects in specially designed waste containers, vaccination of staff when an effective vaccine is available, and verification of effective vaccination. and postexposure prophylaxis, based on passive immunization, in collaboration with the Hospital Infectious Diseases Committee.
    - PPE should be prohibited from being used outside the Laboratory, there should be a special storage space for it. Instructions for donning and doffing
    - Signs and equipment for hand washing
    - Rings, bracelets, watches, long hair and beard policy

- In case of Emergensy - Accident:
    - Emergency telephone numbers should be displayed on all spaces of the laboratory
    - In the event of a power failure or other emergency, have a bright exit guide, Danger Exit Signs and an emergency escape plan: site plan, emergency exit signage, first aid kit and Biological spill kit, and especially body and eye showers. There must be alternate power supply for lighting, Biosecurity cabinets, security alarms, etc. to ensure that the laboratory work can be completed safely.
    - Laboratory personnel must immediately report to the laboratory director or the responsible person for health safety any accident/incident associated with the handling of the biological materials
    - There should be no food next to the reagents and analyzers and generally not at all in the laboratory
    - Emergency protocol at sample leakage during transport
    - Emergency protocol for sample leakage within analyzers