Review Article

Applied Biosafety:
Journal of ABSA International
2019, Vol. 24(1) 34-45

DOI: 10.1177/1535676018778538
journals.sagepub.com/home/apb

The Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences: A Comprehensive Literature Review

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Abstract

Introduction: Managing biological risks requires an organizational culture that holistically ensures the biosafety, biosecurity, and biocontainment of infectious disease agents and toxins, in addition to conducting science in a responsible manner, complying with relevant laws, regulations, guidelines, and policies, as well as emphasizing norms, values, and beliefs of the entire life sciences profession.
Methods: Drawing upon the Federal Experts Security Advisory Panel's (FESAP's) 2014 recommendation to "strengthen a culture that emphasizes biosafety, laboratory biosecurity, and responsible conduct in the life sciences," we undertook a comprehensive literature review of the culture of biosafety, biosecurity, and responsible conduct in the life sciences, including metrics by which to evaluate interventions at the organizational level.
Results: We identified 4031 unique citations published from January 2001 to January 2017 by searching the MEDLINE/PubMed, Scopus, Web of Science, and Global Health databases. In addition, a subset of 326 articles was reviewed in full.
Discussion: We found that while there were discussions in the literature about specific elements of culture (management systems, leadership and/or personnel behavior, beliefs and attitudes, or principles for guiding decisions and behaviors), there was a general lack of integration of these concepts, as well as limited information about specific indicators or metrics and the effectiveness of training or similar interventions.
Conclusion: We concluded that life scientists seeking to foster a culture of biosafety and biosecurity should learn from the substantial literature in analogous areas such as nuclear safety and security culture, high-reliability organizations, and the responsible conduct of research, among others.

Keywords
biorisk management, biosafety, biosecurity, organizational culture, responsible conduct of research

In 2014, the Federal Experts Security Advisory Panel (FESAP) made a number of recommendations to federal agencies and relevant stakeholders to optimize biosafety and biosecurity in the United States. As part of its recommendation to "create and strengthen a culture that emphasizes biosafety, laboratory biosecurity, and responsible conduct in the life sciences," the FESAP recognized a need for "semi-quantitative methods to evaluate the efficacy of training, education, codes of conduct, and similar interventions to reduce risk and improve safety in domestic research laboratories housing infectious agents and toxins."[1]

Drawing on Edgar Schein's seminal work on organizational culture and the International Atomic Energy Agency (IAEA) guidance on nuclear safety and security culture,[2-5] a FESAP working group is studying culture in the context of the life sciences. The working group defined the culture of biosafety, biosecurity, and responsible conduct in the life sciences as "an assembly of beliefs, attitudes, and patterns of behavior of individuals and organizations that can support, complement or enhance operating procedures, rules, and practices as well as professional standards and ethics, designed to prevent the loss, theft, misuse, and diversion of biological agents, related materials, technology or equipment, and the unintentional or intentional exposure to (or release of) biological agents."[6,7]

As a step in developing the recommended semiquantitative methods, the FESAP working group conducted a comprehensive literature review of existing methods for identifying and evaluating an organizational culture of responsibility in the

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Life Sciences	AND	Biosafety/Biosecurity	AND	Culture	AND	Interventions	AND	Laboratories
("life sciences" OR biotechnology OR genomics OR proteomics OR bioinformatics OR "biomedical research" OR "pharmaceutical research" OR genetics OR "life sciences research" OR "biological science disciplines" OR microbiology OR "molecular biology" OR "synthetic biology" OR synbio OR biopharmaceutical)		(biosafety OR biosecurity OR "security measure" OR "security measures" OR "biorisk management" OR biocontainment OR "biological select agents" OR "biological select agent" OR "biological select agents and toxins" OR "dual use research" OR DURC OR "gain of function" OR biosurety OR "responsible conduct" OR "research integrity")		("organizational culture" OR culture OR "shared beliefs" OR behavior OR behaviour OR "shared values" OR "organizational environment" OR "laboratory culture" OR "culture of responsibility" OR "professional standards" OR "cultural values" OR "cultural attitude" OR "cultural beliefs" OR attitude* OR value* OR belief* OR "guideline adherence" OR "cooperative behavior" OR "social responsibility" OR "organizational policy" OR "social values" OR "ethical responsibility" OR "ethically responsible" OR "moral responsibility" OR "morally responsible" OR "ethical research" OR "professional practice" OR "professional practices" OR "social responsibility" OR "responsible conduct" OR "responsible research" OR "responsible science" OR "decision making")		(training OR education OR "continuing education" OR "statement of values" OR "codes of conduct" OR "code of conduct" OR "codes of ethics" OR "code of ethics" OR "ethical code" OR "ethical principle" OR "ethical principles" OR "good behavior" OR "professional ethics" OR "personnel reliability" OR "organizational policy" OR "personal code of conduct")		(laboratories OR laboratory OR "biosafety level 2 laboratory" OR "biosafety level 3 laboratory" OR "biosafety level 4 laboratory" OR "biosafety level laboratory" OR "BSL laboratory" OR "biosafety level laboratories" OR "BSL laboratories" OR "containment laboratory" OR "containment laboratories" OR "research laboratory" OR "research laboratories" OR "diagnostic laboratory" OR "diagnostic laboratories" OR "biological laboratory" OR "biological laboratories" OR "biomedical facility" OR "biomedical facilities" OR "clinical laboratory" OR "clinical laboratories" OR "pathogen storage" OR "medical laboratory personnel" OR "laboratory personnel" OR "research personnel" OR "clinical laboratory personnel" OR "medical technologist" OR "laboratory technician" OR "laboratory animal technologist" OR "veterinary research laboratory" OR "veterinary diagnostic laboratory" OR "veterinary research laboratories" OR "veterinary diagnostic laboratories")

Figure 1. Keywords used in search strategy.

life sciences. In this article, members of the working group analyzed the existing ways in which life scientists and educators around the world are trying to define characteristics or indicators of a strong culture of responsibility and to measure the impact of specific interventions on that organizational culture.

Early efforts to improve responsibility in the sciences focused on issues of scientific integrity, such as falsification, fabrication, plagiarism, and authorship disputes that are relevant to all scientific disciplines.[8] However, in light of several high-profile biosafety and biosecurity incidents at laboratories in recent years, there has been an effort within the life sciences to develop a culture of responsibility specifically focused on laboratory safety and dual-use issues.

Dual-use ethical dilemmas arise within the life sciences because knowledge, products, or data arising from scientific research may have the potential to be used for malevolent purposes (ie, bioterrorism, biocrime, or biological weapons), as well as for good. Intentionally, or unintentionally, scientists can sometimes make pathogens more virulent or more transmissible. Dual-use research policies require that research be ethical and that the benefits gained from the research outweigh the risks. Well-known examples of dual-use research include an experiment where mousepox virus was altered to evade the immune response,[9] a study describing how botulinum toxin could be used to contaminate the milk supply,[10] and the recent synthesis of horsepox virus.[11] Policies for dual-use research cannot possibly cover every potential and future research scenario. To ensure that scientists adapt, they must be trained in the "relevant skills of critical reflection and acceptance of responsibility for the conduct and outcomes of research rather than merely learning the relevant research ethics rules."[12]

After a series of incidents at the Centers for Disease Control and Prevention (CDC), including potential personnel exposures to anthrax, the CDC released a report that recognizes "the responsibility of people at every level of the organization . . . to strengthen the culture of safety."[13] Many others have echoed this call, including the National Academies of Sciences[14] and the National Science Advisory Board for Biosecurity (NSABB).[15]

It has been noted that "responsible science makes scientists a part of the solution, not part of the problem."[16] This belief resonates with the National Academies of Sciences observation that any effective policy or set of procedures will require ownership by the scientific community.[17] A survey of US life scientists on their awareness of and attitudes toward the dual-use dilemma showed that 15% (260 of 1744) of the respondents made one or more changes in their research behavior or activities in response to dual-use concerns.[18] These results indicate that it is possible to improve responsibility in the life sciences; our challenge is to find the most effective catalysts to promote and nurture a culture of responsibility.

Methods

The MEDLINE/PubMed, Scopus, Web of Science, and Global Health databases were searched by a medical librarian (A.A.L.) in March 2017 for literature published in English from January 2001 to March 2017. A combination of medical subject headings

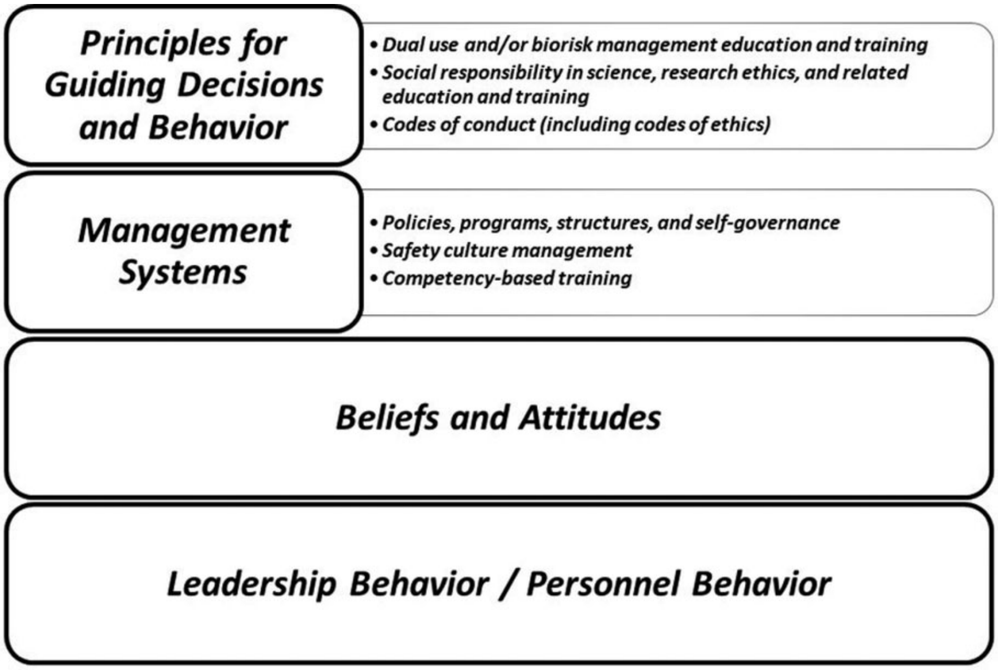

Figure 2. Elements of a culture of biosafety, biosecurity, and responsible conduct in the life sciences.

(MeSH) and keywords representing the main concepts of "life sciences," "biosafety and biosecurity," "organizational culture," "interventions," and "types of laboratories" were searched in each database. See Figure 1 for a list of keywords used.

Three reviewers (D.P., K.D., A.E.R.) screened each publication's title and abstract. If 2 reviewers agreed the publication met the selection criteria, the publication passed to the second-level review of the full text. Publications passed the screening if they were likely to meet 1 or both of the following selection criteria:

- the publication discussed organizational culture (or any of its elements) in research, diagnostic, or production laboratory facility;
- the publication discussed how biosafety, biosecurity, or bioethics training and education, codes of conduct, or other such interventions affect organizational culture, ideally as measured by specific indicators.

Articles in fields such as psychiatry, nursing, or dentistry were excluded, as were all articles that used other concepts of biosafety and biosecurity, including agricultural biosecurity, biosafety in the context of the Cartagena Protocol, and biosecurity as a philosophical concept (often linked to Foucault's biopolitics). Records without full texts in English were also omitted.

In the second-level review, a total of 326 publications were reviewed. In addition, relevant gray literature identified by the authors was included in the review, including reports from the National Academies of Sciences, the InterAcademy Partnership (IAP), and the World Health Organization (WHO).

Results

The searches retrieved 4031 unique citation records in the PubMed/MEDLINE (1433), Scopus (1107), Web of Science (390), and Global Health (1101) databases. Of the 4031 unique citations, 326 publications underwent a second-level review of their full text and key themes were extracted.

These records included articles from Austria, Azerbaijan, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Honduras, Italy, Kenya, The Netherlands, Nigeria, Pakistan, South Africa, Sweden, and the United States. A large number of these articles addressed the National Institutes of Health (NIH) requirement for training in the responsible conduct of research (RCR), defined as "the practice of scientific investigation with integrity. It involves the awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research."[19] The links between a culture of responsibility in the life sciences and the body of literature on RCR are addressed in the Discussion section of this article.

Culture of Biosafety, Biosecurity, and Responsible Conduct in the Life Sciences

The concept of a biosafety and biosecurity culture (as a subset of organizational culture) is multilayered and complex. Using Schein's 3 layers of culture and the IAEA model,[2] the FESAP working group broke this concept down into 4 elements (Figure 2). Of note, while the IAEA addresses nuclear safety culture and nuclear security culture independently, we adopted a definition combining biosafety and biosecurity cultures in recognition of their overlap and synergy in biorisk management. These elements are principles for guiding decisions and behavior (corresponding to what Schein calls "espoused values"), management systems (organizational processes, procedures, and programs that make biosafety and biosecurity a top priority and have an important impact on the biorisk management functions), beliefs and attitudes (corresponding to what Schein calls "underlying assumptions"), and leadership and personnel behavior (specific patterns of behavior and actions that foster effective biosafety and biosecurity practices). Findings for each of the 4 elements are discussed below.

Principles for Guiding Decisions and Behavior

An effective culture of biosafety, biosecurity, and responsible conduct rests on a shared set of principles that life scientists believe in and display through their actions. The IAEA model of nuclear security emphasizes the values of motivation, leadership, commitment and responsibility, professionalism, and competence, all of which are based on the key value of learning and improvement.[2] Indeed, organizations promote the adoption of these principles through initial and ongoing education and training, as well as peer-to-peer socialization processes. In addition, organizations promote the principles through visible demonstration of them in the behavior of scientific leaders (not just by declaratory statements) and through the organization's rules and policies.[20]

Of the articles reviewed, the largest segment addressed principles for guiding decisions and behavior in some way. Three recurrent themes were found: dual-use and/or biorisk management education and training; social responsibility in science, research ethics, and related education and training; and codes of conduct, including codes of ethics.

Dual-Use and/or Biorisk Management Education and Training

The dual-use dilemma is characterized by the difficulty in finding the appropriate balance between national security interests and the traditional openness of science. As Atlas and Reppy[21] noted, "the norm must be that the development of biological weapons is unethical . . . and that scientists will act responsibly to limit the potential misuse of scientific materials and information by potential bioweaponeers." To protect science from misuse, the scientific community must develop "a culture of responsible conduct and real scientific engagement in the process of deciding what should be done."[22] Nixdorff[23] emphasizes that "for nearly a decade civil-academy society as well as States Parties to the Biological and Toxin Weapons Convention have recognized the importance of dual use biosecurity education for life scientists as a means to foster a culture of responsibility and prevent the potential misuse of advances in the life sciences for non-peaceful purposes." She calls for government involvement in implementing biosecurity education for life scientists.

The most comprehensive effort toward dual-use education came from Malcolm Dando and Brian Rappert, who conducted a multiyear project to educate scientists in several countries about dual-use issues.[24] However, few of the national projects contain in-depth evaluation to assess educational impact or learning outcomes. The exception is Minehata et al,[25,26] who used a pre- and post-training questionnaire. Similarly, dual-use issues and related education challenges are described in publications such as *Preventing Biological Threats: What You Can Do*,[27] but there is little information, beyond the anecdotal, about how to evaluate the outcomes of training or outreach efforts.

While education is important, many argue that it is not sufficient. Kuhlau et al[28,29] emphasize the need to go beyond awareness raising to skill development: "Dual use ethical competence therefore entails more than simply knowing ethics; it implies capacities that enable individuals to also develop and apply their knowledge in ethically challenging situations." Similarly, Coughlin et al[12] note that "it is not enough to know what you ought to do, but requires that you do the right thing . . . training involves the development of the relevant skills of critical reflection and acceptance of responsibility for the conduct and outcomes of research rather than merely learning the relevant research ethics rules." Scientists must recognize that a decision-making situation has dual-use ethical implications, assess the impact of an ethical decision on others and society, and understand how ethical decision making is influenced by utilitarianism (focused on outcomes and consequence) vs formalism (relying on rules, norms, and precedents).[30]

Social Responsibility in Science, Research Ethics, and Related Education and Training

Social responsibility in the life sciences can be described as the pursuit of research based on "consensual values, needs, and interests, arrived at through wide societal deliberation . . . and ongoing processes of ELSI [ethical, legal, social implications] examination that balance proaction and precaution and seek ways to mitigate the negative and increase the positive impacts of new and emerging technologies."[31] Specific to bioterrorism, Resnik and Shamoo[32] believe that scientists' responsibilities include the duty not to conduct or publish research that is harmful or dangerous to others or to share dangerous biological materials, to maintain the confidentiality of classified research, to report suspicious activities, to inform the public and to educate researchers and students about bioterrorism, and to help develop policies related to bioterrorism and to advocate for research to respond to bioterrorism.

The literature included several different approaches for integrating social responsibility into life sciences research. Based on controversial gene-editing experiments, Sankar and Cho[33] developed a basic framework for incorporating social responsibility into life sciences research, including basis (factors or values investigators rely on for justifying research), approach (reasoning for weighing risks and benefits), timing, participants, and transparency. To address the challenges of exercising social responsibility in the sciences, Resnik and Elliott[34] recommend interdisciplinary collaborations with ethicists, humanists, and others; disclosure and discussion of scientists' value assumptions when addressing the policy implications of their research; ethical education; and establishing or making use of advisory bodies. Resonating with the recommendation for interdisciplinary engagement, Flipse et al[35] conducted a case study among industry-based microbiologists and found that interaction with an "embedded humanist" changed researchers' decision making over time.

Similar to the dual-use dilemma, approaches to improve social responsibility in the life sciences rely heavily on education[36] and training using relevant vignettes.[37] Evaluation, if any, includes surveys and interviews regarding the usefulness of instruction by soliciting participants' feedback.[38] One literature review of this area found that ethics education "is an essential, although insufficient, measure for promoting a culture of responsible conduct of research."[39]

Ethical decision making regarding dual-use research of concern (DURC) and social responsibility issues should be addressed in a consistent and comprehensive manner internationally.[40] While enactments of social responsibility primarily rely on education and self-regulation by scientists, Taylor[41] warns that a top-down approach by government may become inevitable "if there is no consensus within the research community that effectively matches genuine self-regulation with public views."

Codes of Conduct (Including Codes of Ethics)

Codes of conduct are formal, systematic statements of rules, responsibilities, norms, and expectations of appropriate behavior. In the life sciences, codes of conduct help raise awareness of dual-use issues and social responsibility, promote best practices, and reinforce the norm against the use of biological agents for bioterrorism or biowarfare. Whether a code is aspirational or regulatory depends in part on its enforceability. While many professional organizations have such codes, they vary greatly in breadth, depth, and purpose, as well as in the extent to which they inform or request members' adherence to public laws and regulations.[42]

Professional organizations such as the American Society for Microbiology (ASM) have developed codes of conduct for their members that include prohibitions on the misuse of microbiology.[43] In Europe, a biosecurity code of conduct has been developed as an initiative of the Organization for Economic Cooperation and Development (OECD)[44] and is meant to complement existing legislation on preventing science misuse, as well as raise awareness of scientists' obligations. Past Review Conferences of the Biological Weapons Convention and Meetings of Experts have also entertained the idea of an international code of conduct and have been stage to a lively debate regarding their utility and whether codes should be international, national, or institutional.[45] These codes of conduct address areas such as biorisk management, raising awareness, reporting misuse, internal and external communication, research and sharing knowledge, and accessibility. A similar biosecurity code of conduct has been proposed by Somerville and Atlas.[46] In addition, organizations that represent amateur scientists, such as DIYBio, have developed their own codes of conduct to guide member behavior, and these include many of the same themes.[47] Some have called for instilling codes of conduct in students at the high school and undergraduate levels to reach not just scientists but the general public.[48]

However, codes of conduct can be challenging to implement, and there is little empirical evidence linking them to positive changes in the behavior of scientists. There is some evidence that codes of conduct provide only limited utility,[49] and some argue that "the current burgeoning of codes and guidelines can actually blind people into thinking that ethical awareness can be reduced to a tick-box activity rather than being an element of professional identity, character and responsibility."[50]

The solution may lie in education. Other groups, such as the NSABB, have found that codes of conduct can be effective in raising awareness about dual-use issues and that the process of developing a code leads to opportunities for engagement and education. Novossiolova[51] notes that laws and norms are mutually reinforcing and that "fostering norms via formal codes and regulations is a slow and arduous endeavor which often needs to overcome considerable resistance and, as such, can hardly succeed only by dint of enforcement." Novossiolova views the implementation of a global biosecurity education program, based on the International Nuclear Security Education Network (INSEN), as a critical step in fostering the biosecurity norms that undergird effective codes of conduct.

Management Systems

An organizational culture of biosafety, biosecurity, and responsible conduct in the life sciences includes policies, processes, procedures, and programs in the organization that make biosafety and biosecurity a top priority and have an important impact on the biorisk management functions. In the IAEA model,[2] management systems include visible safety and security policy, clear roles and responsibilities, performance measurement, work environment, training and qualification, work management, information security, operation and maintenance, continual determination of trustworthiness, quality assurance, change management, feedback process, contingency plans and drills, self-assessment, interface with the regulator, coordination with offsite organizations, and recordkeeping.

Similar to the nuclear domain, effectively managing biological risks requires a "combination of technology, culture, and people . . . [and] the more sophisticated security technologies and arrangements are, the more important are the people who design, operate, maintain and improve the technologies."[52] In reviewing the publications on this topic, 3 approaches emerged: policies, programs, structures, and self-governance; safety culture management (as a potential scaffold for building and strengthening biosecurity culture); and competency-based training.

Policies, Programs, Structures, and Self-Governance

Most publications in the management systems category covered biosafety and biosecurity measures as well as relevant rules and regulations in the United States[53] and internationally.[54,55] Some articles in this group focus specifically on biosecurity, emphasizing processes such as risk identification, risk assessment, and risk management (physical security, personnel reliability, materials control and accountability, transfer security, and information security).[56,57]

Many publications describe ongoing biorisk management programs, including personnel reliability,[58-61] behavioral screening,[62] or reporting and tracking incidents and near misses,[63,64] which are vital elements of a culture of biosafety, biosecurity, and responsible conduct in the life sciences. These are examples of the "measures that are taken every day to safeguard the laboratory staff, the community, and the nation."[65] However, there is little systematic analysis of the elements of these programs that are most effective or discussion of how to assess a program or policy to determine its level of effectiveness or improvement.

A few articles focused on risk assessment and governance in new laboratory planning and development.[66,67] Of note, safety culture considerations were raised during the proposal, planning, and construction of the new biosafety level 4 (BSL-4) laboratory at Boston University and elsewhere.[68,69]

In contrast to the nuclear domain, self-governance is an important characteristic of the life sciences, especially in regard to dual-use research.[70] At the national level, "establishing and valuing a culture of ethical and safe behavior and implementing effective biorisk management appear likely to prevent misuse of biological materials and significantly improve control of potential dual-use issues in the life sciences community."[71] At the level of the facility or institution, self-governance of the life sciences is achieved through institutional biosafety committees,[72] institutional ethics committees,[73] or institutional committees established to review dual-use research of concern. This distribution of governance responsibilities represents a challenge because each committee and each organization will have its own subculture and established norms and practices.

Safety Culture Management

The articles in this group generally addressed a governance framework for safety, focused on structures, people, processes, and technologies. A common thread is that many laboratory accidents are caused "not by a lack of physical barriers or regulations, but by the absence of a strong biosafety culture in labs and their oversight bodies,"[74] and by lacking a reliable system for incident reporting, monitoring, analyzing, and sharing lessons learned. A strong safety culture involves "seeing safety as a *culture* (the way to work) rather than as an imposed obligation"[75] and "requires that laboratory safety become an integral and apparent priority to the organization, embraced first and foremost by top management and with the concomitant infrastructure support required to foster safe behaviors among its employees."[76] To achieve this level of integration, it is critical to get buy-in from workers at all levels of the organization.

Although safety culture and reliability have been analyzed in many disparate industries,[77-79] the literature on biological laboratories does not appear to make good use of the wealth of available studies. The literature on high-reliability organizations (HROs), in particular, could be a useful starting point. In his study of HROs, Parker et al[80] described HROs as "those few organizations (e.g. air traffic control, aircraft carriers) with high risk technologies which nevertheless cope well with the associated hazards and have good performance records . . . Compliance is ensured with surveillance, because members of the organization are intrinsically motivated for safe working behavior." Their framework for analyzing safety culture includes 5 levels in an ascending order of maturity: pathological, reactive, calculative, proactive, and generative. In addition, laboratories themselves must look beyond biosafety as they embrace increasingly multidisciplinary research and processes, many of which involve mixed hazards (eg, biological, chemical, radiological). The Association of Public and Land-Grant Universities (APLU) has an extensive guide to implementing safety culture in university laboratories.[81] Many of these general recommendations could be easily adapted to the life sciences context.

Safety culture can also be a catalyst for improving biosecurity. Burnette and Connell[72] note that "a good biosecurity culture will be more easily introduced and maintained at those institutions with a strong biosafety program." Husbands[82] also emphasized that "framing the issue as Responsible Science makes concepts such as biosecurity and dual use relevant and more readily accepted when presented as part of the larger social responsibility of science . . . and provide[s] a basis for discussing additional measures or changes in practices."

Competency-Based Training

While education and training have been discussed above as means to ingrain relevant principles for guiding effective decisions and behaviors, competency-based training is a characteristic of management systems. The CDC and the Association of Public Health Laboratories (APHL) define competencies as observable and measurable action-oriented statements that delineate the essential knowledge, skills, and abilities that are critical to the effective and efficient performance of work. Competencies strengthen the workforce "by providing a guiding framework for producing education and training programs, identifying worker roles and job responsibilities, and assessing individual performance and organizational capacity"[83] and also by bolstering the culture of biosafety, biosecurity, and responsible conduct in the life sciences.

The articles in this group included some focused on training biosafety level 3 (BSL-3)/BSL-4 laboratory workers[84-86] (by a combination of didactic classroom training, supervised practical training and exercises, and mentor-on-the job training) and guidelines for biosafety competencies or general competencies for public health laboratory workers.[87] A survey by Chamberlain et al[88] of biosafety professionals concludes that "variations in biosafety training requirements, incident-reporting practices, and attitudes toward laboratory safety . . . support the development of core competencies in biosafety practices that could lead to more uniform and robust safety culture."

Articles that focus on laboratory quality often include safety as an additional benefit. For example, the CDC/APHL laboratory competencies include measures of safety. While a novice worker "describes the culture, programs, and communication processes regarding quality, safety, and ethical practices," a competent worker "adheres to the culture, programs, and communication processes regarding quality, safety, and ethical practices," a proficient one would "advocate for a culture of quality, safety, and ethics," and an expert would "foster a culture of quality, safety, and ethics."[87] An article by Sanchez et al[89] described an assessment of biosafety practices at several laboratories that included a scoring system and qualitative interpretation of results. In that study, 97% of respondents considered biosafety training part of the overall best practices and quality assurance of their laboratory or workspace. These results indicate that laboratory quality management may be a way to start a discussion about safety and biosecurity. In addition, programs such as Lean Six Sigma that focus on quality improvement and reduction of errors in manufacturing may yield insights than can be adapted to the laboratory context.

Beliefs and Attitudes

Beliefs and attitudes toward biosafety and biosecurity comprise a distinct element of culture that is difficult to assess by tests of competence. They are "complex mental processes that cannot be measured directly, but only inferred through behavioral, cognitive, or affective expression."[90]

This issue is complex because an individual's response to a situation is a result of behavior (eg, actions, intentions to act), cognition (eg, thoughts, opinions), and affect (eg, feelings, emotions, and autonomic nervous system activity).[90] In addition, individuals come to the laboratory with a wide variety of prior beliefs and experiences, which underlie their beliefs and attitudes. As Husbands[16] notes, "Trainees are not empty vessels into which we pour culture."

Few publications address this complex issue directly. One of the few that does is *A Survey of Attitudes and Actions on Dual Use Research in the Life Sciences: A Collaborative Effort of the National Research Council and the American Association for the Advancement of Science* (2009).[91] This report provides baseline data on current levels of awareness and attitudes about dual-use issues and policies among life scientists to inform educational efforts. In general, survey respondents indicated support for mandatory education and training about dual-use issues. Similarly, Schuurbiers et al[49] surveyed attitudes related to the Netherlands Code of Conduct for Scientific Practice, with a discussion on the debatable usefulness of such codes to influence scientific practice. The majority of those surveyed felt that "discussion of the guiding principles of scientific conduct is called for . . . [but] they did not consider the code as such to be a useful instrument."[49]

Using quantitative data and analysis of results of BioQuiz, an online Likert-style questionnaire that assessed students' attitudes toward science and science learning, and qualitative data from student interviews, Tomas et al[92] showed that a write-to-learn strategy improves the cognitive and affective components of students' attitudes toward science. However, this study did not focus on biosafety or biosecurity issues, and it is uncertain if the results would apply to graduate students and mature researchers. It is clear that more research must be done to survey the existing beliefs and attitudes of researchers in the life sciences and also to determine how to effectively foster beliefs and attitudes that are supportive of biosafety and biosecurity goals.

Leadership and Personnel Behavior

The IAEA model of nuclear security culture identifies the following characteristics of leadership and personnel behavior, which can generally be adapted to the life sciences domain[2]:

Leadership behaviors:

- expectations,
- use of authority,
- decision making,
- management oversight,
- involvement of staff,
- effective communications,
- improving performance,
- motivation,
- personnel behaviors:
- professional conduct,
- personal accountability,
- adherence to procedures,
- teamwork and cooperation, and
- vigilance.

Strong leadership is vital to ensuring the success of a high-containment laboratory. James Le Duc et al[93] have observed that without a standard training or certification framework for BSL-4 workers, it falls to the laboratory directors to ensure that personnel are adequately trained. Leadership behavior also has a strong impact on what behaviors laboratory personnel adopt and prioritize.

Johnston et al[94] used social cognitive theory-based variables related to handwashing, self-reported compliance, and demographic factors in a survey and determined that behavioral modeling by supervisors and coworkers had the strongest association with workers' compliance. Based on the social cognitive theory, Johnston et al[94] note that human behavior is influenced by the individual's beliefs, attitudes, values, and cognition, as well as physical and social influences in the environment. This is clearly another area where more research specific to the biosafety and biosecurity context would be of great value.

Discussion

Of the many interventions that might be used to improve the culture of biosafety and biosecurity, educational and training interventions are among the most frequently employed or cited. Unfortunately, there has been little assessment of these interventions specifically directed at improving biosafety and biosecurity in laboratories. However, there is a related body of work regarding the effectiveness of RCR training that may serve as a basis for those seeking to improve responsible conduct in the life sciences.

Since 1985, institutions receiving federal funds under the US Public Health Service Act have been required to have policies addressing research misconduct. On December 6, 2000, the US Office of Science and Technology Policy published the *Federal Research Misconduct Policy*, consisting of a "definition of research misconduct and basic guidelines for the response of Federal agencies and research institutions to allegations of research misconduct."[95] All federal agencies or departments supporting intramural or extramural research were required to implement the policy within one year.[96] The largest agency funding life sciences research, the NIH, requires instruction in RCR as a condition of funding for all trainees, fellows, participants, and scholars receiving support through the NIH. While the federal mandate does not specify the nature or content of RCR education, it generally includes topics such as conflict of interest, human and animal subjects, mentoring, collaboration, peer review, data management, research misconduct, authorship and publication, and scientists and society. This requirement has led to a proliferation of research on the impact and effectiveness of RCR training.

The US National Academies of Science's report, *Fostering Integrity in Research*, includes a comprehensive review of the state of the art in RCR training evaluation.[97] This review lays out the basic education evaluation principles, including the need for standardized instruction and reliable measures of assessment for the effects of RCR instruction, assessing and maintaining change, and whether observed changes transfer to other tasks or performance settings. Of particular importance to the concept of culture assessment, the authors discuss the need to assess change not only in individual behavior (ie, students undergoing RCR training) but also in laboratory practices or organizational climate. Drawing heavily on the work of Michael Mumford, the report also discusses in depth different types of measures that might be used to evaluate ethics training, including those reflecting individual performance, knowledge, mental models and reaction, and organizational climate and outcomes.

While the concept of RCR shares some similarities with the FESAP vision of responsible conduct, topics such as biorisk management, DURC, and international norms against biological weapons and bioterrorism are not usually included in RCR education. However, there is an opportunity to adapt RCR techniques and materials that have been shown to be effective to cover topics relevant to biosafety and biosecurity.

A recent meta-analytic study showed moderate RCR instructional effectiveness (Cohen's $d = .48$),[98] suggesting that such education enhances knowledge and understanding of ethical concepts, norms, and rules; promotes awareness of ethical issues and problems; improves ethical reasoning abilities; and shapes ethical attitudes.[99] However, despite decades of RCR training, there is still a lack of international harmonization of training resources and metrics of success, and it is difficult to say whether training leads to actual changes in behavior, attitudes, or work practices.[100] Many assessments of training effectiveness use self-reporting or feedback conducted after training, but these are based on surveys or interviews, without long-term monitoring. Despite these shortcomings, the research on RCR training effectiveness is still significantly more advanced than efforts specifically targeted to the life sciences. Those seeking to improve the culture of responsibility in the life sciences context should build upon the lessons learned in RCR training.

Conclusion

Rules and procedures have no worth if people do not follow them; a culture of responsibility is essential for ensuring that people follow safety and security procedures and that they act responsibly in new or unfamiliar scenarios. There is a rising interest in organizational culture from governmental and nongovernmental organizations (including professional organizations).[101-104] This comprehensive review of existing literature sought to assess the contribution of biosafety and biosecurity training, education, codes of conduct, and similar interventions to effectively contribute to an improved or strengthened organizational culture in research, diagnostic, and production laboratory facilities. Unfortunately, there are few systematic efforts at evaluating the impact of interventions on specific aspects of organizational culture in life sciences laboratories. However, as Mumford et al[105] noted in the context of RCR education, "The demands of evaluation, systematic evaluation, and meta-analysis of these evaluation efforts, may at first glance appear daunting. Ultimately, however, evaluation provides data, and science is a process of applying data to test procedures and theories."

To improve the culture of biosafety, biosecurity, and responsible conduct, the life sciences will have to pay more attention to lessons learned in other fields and to adapt those tools and frameworks to the life sciences context. While there is still work to do, the RCR field has made a significant start in evaluating the effectiveness of different types and formats of ethical training. The nuclear field, in particular the IAEA, has built a safety culture, many elements of which can be carried over into life sciences laboratories. The body of literature on HROs will yield additional insights on to how to build organizations that consistently meet very high safety and reliability performance standards. Anthropologists such as Ruthanne Huising[106,107] are beginning to take an interest in the organizational culture of laboratories, and there may be additional lessons to learn from Lean Six Sigma–type programs that seek to reduce errors and increase quality in the manufacturing sector. In short, there is a wealth of information about organizational and safety culture, but little of it is being integrated and used by those in the life sciences.

Answering questions on whether biosafety, biosecurity, and bioethics programs work, as well as how well they do, will also provide a basis for progressive improvements of training practices. Developing practical tools and sharing experiences and lessons learned on such self-assessments will provide learning opportunities for organizational growth and development, as well as strengthen the culture of biosafety, biosecurity, and responsible conduct in the life sciences.

Acknowledgments

We thank Captain Theresa Lawrence, HHS/ASPR, for her review and input on the manuscript. Kathleen McGlaughlin and Karen Stakes, NIH Library Writing Center, provided assistance with editing of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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