Synthetic Biology Industry: Biosafety Risks to Workers

Vladimir Murashov, John Howard, and Paul Schulte

Introduction

Synthetic biology involves two closely related capabilities: (1) the design, assembly, synthesis, or manufacture of new genomes, biological pathways, devices, or organisms not found in nature for use in agriculture, bio-manufacturing, health care, energy, and other industrial sectors and (2) the redesign of existing genes, cells, or organisms for the purpose of drug discovery and gene therapy. Synthetic biology has accelerated the growth of the biotechnology sector of the US economy. This rapid growth has been accompanied by a corresponding increase in the number of workers employed in the synthetic biology industry.

Despite the present and anticipated growth of synthetic biology, workplace health and safety considerations for the synthetic biology workplace have not kept pace with the rapid introduction of this enabling industrial technology. Specifically, biosafety practices for the laboratory need to be adapted to the more complex industrial-scale processes. Therefore, updated health and safety guidance specific to the synthetic biology industry is urgently needed.

Background

Synthetic biology is an emerging interdisciplinary field of biotechnology that applies the principles of engineering and chemical design to biological systems (Ball 2005). The earliest use of the term was by French biologist Stéphane Leduc in 1910. By 1974, synthetic biology was being viewed as the next phase in molecular

V. Murashov (✉) · J. Howard · P. Schulte
National Institute for Occupational Safety and Health, Washington, DC, USA
e-mail: vem8@cdc.gov

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biology by which scientists would "devise new control elements and add these new modules to the existing genomes or build up wholly new genomes" (Szybalski 1974). Such capabilities did not become practical until the turn of the millennium, as illustrated by the sequencing of the first human genome in 2001 (National Research Council 2015). With the emergence of the synthetic biology industry, in 2015 the Ad Hoc *Technical Expert Group on Synthetic Biology* of the United Nations Convention on Biological Diversity proposed defining synthetic biology as "a further development and new dimension of modern biotechnology that combines science, technology, and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems" (Convention on Biological Diversity 2015).

Although it is often difficult to demarcate synthetic biology from other biotechnology research areas, synthetic biology can be understood to involve two closely related capabilities, both of which may have wide utility in commerce and health care and also create unique occupational safety and health risks (Howard et al. 2017). First, while the transfer of already existing genes from one cell to another characterized an earlier phase of the field of biotechnology, synthetic biology involves the design, assembly, synthesis, or manufacture of new genomes, biological pathways, devices, or organisms not found in nature. These operations are made possible by recent advances in DNA synthesis and DNA sequencing, providing standardized DNA "parts," modular protein assemblies, and engineering models (Baker et al. 2006; Eisenstein 2016). Recent milestones in constructing new genomes from DNA sequences include synthesis of a completely new chromosome (Smith et al. 2003); a new bacterial genome (Gibson et al. 2008); the first synthetic life form, a single-celled organism based on an existing bacterium (Gibson et al. 2010); and living protocells assembled entirely from nonliving, individual biological components (Miller and Gulbis 2015; Kurihara et al. 2015). This capability to construct new genomes is the core use of synthetic biology in advanced chemical manufacturing, agriculture, health care, energy, and other industrial sectors (National Research Council 2015). Such capability could also give rise to increased biological hazards for workers in synthetic biology industry.

The second capability of synthetic biology involves the redesign of existing genes, cells, or organisms for the purpose of drug discovery and gene therapy (Scott 2018) and is utilized primarily in the health-care industry (Synthetic Biology Project 2018). Modification of existing genes in animal and human cells is enabled by four major genome editing platforms: (1) meganucleases, (2) zinc-finger nucleases (ZFNs), (3) transcription activator-like effector nucleases (TALENs), and (4) the clustered regularly interspaced short palindromic (CRISPR)-associated system (Cas) (Yin et al. 2017). Progress in this branch of synthetic biology has yielded remarkable therapeutic advances in gene therapy well beyond the achievements of conventional drugs and biologic agents (Naldini 2015) and has led to the first FDA-approved gene therapy (for acute lymphoblastic leukemia) on August 30, 2017 (FDA 2017). As of March 15, 2018, there were 709 gene therapy clinical trials underway according to the NIH Clinical Trials database (https://clinicaltrials.gov/search?term=%22gene+therapy%22). These trials address a broad range of

conditions from cancers to inherited disorders. Gene therapies could also bring harmful genetic changes and infections with replication-competent gene carriers and lead to adverse health effects among health-care workers upon unintentional exposures to gene therapy agents.

Due to these advances in underlying science and technology, synthetic biology is becoming a widespread enabling technology whose range of applications will only increase in the near future (Center for Biosecurity of UPMC 2012). The biotechnology sector of the US economy has grown on average greater than 10% each year over the past 10 years, and the sector is growing much faster than the rest of the economy (Carlson 2016). Workforce development and workforce protection are both critical in driving the national bioeconomy, where economic activity is powered by innovation in the biosciences (White House 2012). Synthetic biology is playing an increasing role in the commercial bioeconomy as providers of biological designs and optimized biological molecules and laboratory suppliers of customer-specified DNA, RNA, enzymes, and cell-cloning services and in drug development (Lokko et al. 2018). A 2015 analysis of the private sector landscape shows that 162 US companies were engaged in substantial activity in the synthetic biology area, drawing about $6 billion in investments from venture capital individuals and firms (Department of Defense 2015). In 2016 alone, over $1 billion was invested globally in synthetic biology companies (SynBioBeta 2017). The United Kingdom expects to achieve a market in synthetic biology products equivalent to $10 billion in British pound sterling by 2030 (Synthetic Biology Leadership Council 2015). To further facilitate venture capital investments in synthetic biology companies, business risks should be assessed and mitigated proactively. These risks include future liabilities stemming from adverse health and environmental effects such as occupational injuries and ill health that can increase insurance premiums and provoke legal actions (Murashov and Howard 2009).

Provided that this nascent technology is demonstrated as safe, synthetic biology is expected to continue expanding into new application domains. It has been touted as an enabling technology to solve problems not only on earth but also in space. For example, remarkable resilience and adaptation of fungi and yeast to space conditions including high levels of radiation and microgravity conditions has led to proposals for using synthetic biology based on these organisms to synthesize useful materials such as essential nutrients, medicine, and polymers for a range of applications during space travel and eventual colonization of other planets (deGrandpre 2017; Phelan 2018).

Workers participate in all phases of synthetic biology, from laboratory research and development through start-up and pilot operations to production, manufacturing, and end-of-product-life activities. There are hundreds of companies and laboratories worldwide engaged in synthetic biology activities (Department of Defense 2015; Carlson 2016). Workers are involved with each activity. The expanding scope of synthetic biology in the new bioeconomy both nationally and internationally marks an opportune time to review existing risk assessment and risk management measures to better protect current and future synthetic biology workers from harm.

Discussion

Industrial Synthetic Biology and Occupational Risks

Synthetic biology promises both tremendous societal benefits in treating human genetic disease (Lander 2015) and huge commercial market potential for technology investors (Hayden 2015). At the same time, synthetic biology has raised concerns about potential biosafety risks to workers and to the society in general (Trump et al. 2018; Howard et al. 2017).

The biosafety concerns about synthetic biology and its gene editing tools are similar to the concerns lodged about recombinant DNA technology when genetic engineering was first introduced in the early 1980s (Kuzma 2016). Those concerns include whether products resulting from the recombinant DNA technology would pose greater risks than those achieved through traditional manipulation techniques. For example, concerns were raised about potential biological hazards to workers in the field of genetic engineering (Berg et al. 1975; OSHA 1985). Ongoing reports of potential exposure incidents to workers at Level 3 and Level 4 containment laboratories only serve to increase biosafety concerns about synthetic biology (Young and Penzenstadler 2015; Young 2016; Grady 2017). A strong perception exists that biosafety rules cannot keep up with practices in the modern biotechnology laboratory (Pollack and Wilson 2010).

To manage the risk of biotechnology, in 1986, the White House Office of Science Technology and Policy (OSTP) developed the US government's *Coordinated Framework for the Regulation of Biotechnology* ("CF") (Office of Science Technology and Policy 1986). As a result of the CF, the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the US Department of Agriculture (USDA), the National Institutes of Health (NIH), and the Occupational Safety and Health Administration (OSHA) outlined their respective roles in ensuring the safety of biotechnology research and products.

OSHA determined that the general duty clause, together with a set of existing occupational safety and health standards, provided an adequate and enforceable basis for protecting biotechnology workers and that no new synthetic biology-specific standards were necessary. OSHA also provided a set of guidelines for biotechnology laboratory worker safety based on existing OSHA standards. The specific OSHA standards that may be applicable to biotechnology laboratories include (1) blood-borne pathogens (OSHA 2010); (2) toxic and hazardous substances (OSHA 2005a); (3) access to employee exposure and medical records (OSHA 2005b); (4) hazard communication (OSHA 2014a); (5) exposure to toxic chemicals in laboratories (OSHA 2014b); (6) respiratory protection (OSHA 2014c); and (7) safety standards of a general nature (e.g., general environmental, walking and working surfaces, fire protection, compressed gases, electrical safety, and material handling and storage contained in 29 CFR Part 1910 Subparts J, D, E and L, H, S and N). As a part of the 1986 CF comment process, the National Institute for Occupational Safety and Health (NIOSH) recommended increased injury and

illness surveillance of biotechnology workers given the gap in information about occupational health and safety risks to such workers (National Archives and Records Administration 1992). That recommendation has become even more salient with the rise of the industrial phase synthetic biology.

The Coordinated Framework was most recently updated in 2017 (OSTP 2017). The update aims to clarify roles of the three main agencies regulating the products of biotechnology: EPA, FDA, and USDA. While it does not reference OSHA explicitly, the update states that some occupational risks are addressed by EPA under the 1976 Toxic Substances Control Act (TSCA) and the 1972 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The update clarifies that under TSCA, new microorganisms utilized by synthetic biology would be considered "new chemicals." Specifically it states that "microorganisms formed by the deliberate combination of genetic material from synthetic genes that are not identical to DNA that would be derived from the same genus as the recipient, are considered 'intergeneric' (i.e., 'new') microorganisms, and so would be subject to the pre-manufacturing review provisions" (OSTP 2017). The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended TSCA in 2016. Under this amendment, "EPA must make an affirmative finding on the safety of new chemical substances, including intergeneric organisms, before they are allowed into the marketplace" (OSTP 2017). The amendment did not change EPA authority to issue significant new use rules (SNURs) under the TSCA Section 5(a)(2) and consent orders under the TSCA Section 5(e). Under these sections, EPA has the authority to require implementation of exposure mitigation measures in the workplace (Murashov et al. 2011).

Under FIFRA, EPA regulated the sale, distribution, and use of all pesticides, including those produced through synthetic biology (OSTP 2017). The FIFRA registration process requires pesticide data submission which includes, among other data, information about worker exposure and a copy of the proposed labeling containing directions for use, storage, and disposal, as well as warnings, restrictions, and other information. Through FIFRA authorities, EPA developed a regulatory standard aimed specifically at worker protection. EPA's 2015 Worker Protection Standard for Agricultural Pesticides (WPS) is a regulation to reduce the risk of pesticide poisonings and injuries among agricultural workers and pesticide handlers (EPA 2015). The WPS contains requirements for pesticide safety training, notification of pesticide applications, use of personal protective equipment, restricted-entry intervals after pesticide application, decontamination supplies, and emergency medical assistance (Murashov et al. 2011).

Separately, OSHA considered the need to support a comprehensive employer-established infection control program and control measures to protect employees from aerosol exposures to infectious disease agents. OSHA published an Infectious Diseases Request for Information (RFI), held stakeholder meetings, conducted site visits, and completed the Small Business Regulatory Enforcement Fairness Act (SBREFA) process in support of rulemaking. However, OSHA froze this rulemaking process in 2017 and placed the Regulatory Agenda for the Infectious Diseases Notice of Proposed Rulemaking under a "long-term action" (OSHA 2018). It remains unclear

whether the scope of the final ruling for such a standard would include industrial processes in synthetic biology.

Private sector groups have also called for improvements in the regulatory infrastructure to address the implications of new synthetic biology products (Ledford 2016; Bergeson et al. 2015; Carter et al. 2014; Lowrie and Tait 2010). Public interest groups have recommended applying the precautionary principle to any further research and commercialization of synthetic products until specific biosafety mechanisms can be developed to keep pace with synthetic biology advances (Friends of the Earth et al. 2010). Other groups have proposed detailed risk governance policies for commercial entities, users, and organizations engaging in synthetic genomics research, including compiling a manual specifically addressing biosafety in synthetic biology laboratories (Garfinkel et al. 2007; Cummings and Kuzma 2017).

Biosafety guidance specific to scientific advances in synthetic biology is necessary to fill the gap in safety oversight. Currently, the World Health Organization's *Laboratory Biosafety Manual* (WHO 2004) and *Biosafety in Microbiological and Biomedical Laboratories* (DHHS 2009), jointly co-authored by the US Centers for Disease Control and Prevention and the National Institutes of Health in the US Department of Health and Human Services, address an earlier phase of biotechnology aimed primarily at prevention of exposure to already existing pathogens in traditional biology laboratories. However, synthetic biology is using newly designed organisms and viral vectors (i.e., tools used to deliver genetic material inside a cell), not unmodified existing pathogens. Furthermore, industrialization of synthetic biology requires translating well-established safety guidelines for pathogenic organisms and recombinant DNA in laboratory research to industrial-scale manufacturing. The laboratory guidance should be also adapted to Do It Yourselfers (DIYers) as synthetic biology often is not being performed solely by "biologists," but by engineers, physical scientists, and others who are not familiar with fundamental biosafety measures such as biocontainment protections.

Health care and occupational risks Gene therapy is one of the most promising applications of synthetic biology in health care. Since the first gene therapy trial in 1990 (Blaese et al. 1995), various non-viral and viral delivery strategies of functional genes have been developed (Yin et al. 2017). In non-viral delivery, physical methods (electroporation and microfluidic technologies) and nanomaterial-based methods (lipid- and polymer-based nanoparticles, cell-penetrating peptides) are utilized (Yin et al. 2017). In viral delivery, viruses are used as gene transfer devices or "vectors," such as retrovirus, adenovirus, adeno-associated virus, and herpes simplex virus (Cross and Burmester 2006; Merten and Al-Rubeai 2011). For example, vectors made from members of the *Retroviridae* (retroviruses) family have gained attention as efficient gene transfer vehicles (Robbins and Ghivizzani 1998; Levine et al. 2006). All retroviruses have the ability to transcribe their single-stranded RNA genome into double-stranded DNA by the reverse transcriptase enzyme. Transcribed RNA-DNA can then be integrated into the host cell genome, producing permanent genetic change in the organism (Maetzig et al. 2011). Among retroviruses, lentiviruses, a subgroup of retroviruses, such as the human immunodeficiency virus (HIV),

found in humans and animals, are most widely used in gene therapy (Schlimgen et al. 2016; Tomas et al. 2013).

To increase the range of cell types that viral vectors can infect, envelope glycoproteins responsible for cellular attachment are modified through "pseudotyping" with glycoproteins from another virus (Cronin et al. 2005). However, this increased tropism, or specificity of a viral vector for a particular host tissue, can also result in the unintended transduction of "off-target" cell types in a worker who becomes occupationally exposed to viral vectors used in genetic therapies. Pseudotyping viral vectors illustrates just one of the hazards that synthetic biology researchers, clinicians, and ancillary workers face when they are occupationally exposed to viral vectors. Other hazards associated with unintentional viral vector worker exposure include the generation of replication-competent viruses (Schambach et al. 2013), insertional mutagenesis, and transactivation of neighboring genome sequences which could lead to cancer and other diseases (Mosier 2004).

Since 1974, the biological safety of federally funded research involving recombinant DNA molecules and targeting medical applications has been addressed through the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH 2016). These guidelines focus on biological hazards only and do not cover other hazards such as physical, mechanical, and chemical hazards. They outline general biosafety requirements and specific requirements for selected biological agents (e.g., influenza viruses) and for large-scale uses and production of organisms. The 2016 update of the NIH Guidelines streamlined the NIH protocol review process in light of decades of safety data, increased experience with recombinant DNA technology, and concurrent oversight from the US FDA, institutional review boards, and institutional biosafety committees. Under the NIH Guidelines, investigators must initially assess the risk of the agent to cause disease in laboratory workers or others if a release occurs. After the disease risk is assessed, a decision must be made as to the level of containment to control potential exposure. In determining the level of containment, factors such as virulence, pathogenicity, infectious dose, environmental stability, transmissibility, quantity, availability of treatment, and gene product effects such as toxicity, physiological activity, and allergenicity should be considered (NIH 2016).

For an organism containing genetic sequences from multiple sources, the 2016 NIH Guidelines require assessing the potential for causing human disease based on the source(s) of the DNA sequences and on the virulence and transmissibility functions encoded by these sequences. Combining sequences in a new biological organism may produce an organism whose risk profile could be higher than that of the contributing organisms or sequences. Using these considerations, the appropriate biosafety level (BSL) containment conditions (Levels 1 through 4) can be selected (NIH 2016). The NIH Guidelines highlight three complementary means of containment: (1) administrative containment, a set of standard practices that are generally used in microbiological laboratories; (2) physical containment, special procedures, equipment, and laboratory installations that provide physical barriers that are applied in varying degrees according to the estimated biohazard; and (3)

biological containment, the application of highly specific biological barriers that limit either the infectivity of a vector or vehicle (plasmid or virus) for specific hosts or its dissemination and survival in the environment.

The 2016 NIH Guidelines require that any significant problems, violations, or any significant research-related accidents and illnesses are reported to the NIH Office of Science Policy within 30 days. Specifically, they prescribe that spills and accidents in BSL2 laboratories resulting in an overt exposure and spills and accidents in high containment (BSL3 or BSL4) laboratories resulting in an overt or potential exposure are immediately reported to the NIH Office of Science Policy.

In addition to the 2016 NIH Guidelines, enforced for federally funded research, private sector research laboratories generate site-specific safety guidance for working around viral vectors (Stanford University 2018; University of Cincinnati 2014; Gray 2011; Byers 2015).

The risks to workers may increase in the future as synthetic biology is commercialized. Proactive steps should be taken now to ensure worker health and safety protection as the new field of synthetic biology advances. Worker safety has been a guiding principle of biotechnology since the risks of recombinant DNA were first considered at the 1974 *Asilomar Conference on Recombinant DNA Molecules* (Berg et al. 1975), which led to the issuance of the first NIH Recombinant DNA Guidelines for federally funded research in 1976 (Fredrickson 1980). The risk control measures identified then—the use of biological and physical barriers to contain potentially hazardous organisms—remain the mainstay of the largely self-regulated, voluntary approach to worker protection in synthetic biology today.

Risk mitigation in synthetic biology The maturation of synthetic biology from laboratory experiments to industrial biofabrication processes requires enhanced risk governance strategies. These strategies, described below, include health surveillance, proactive risk management, prevention-through-design principles, dynamic guidance for synthetic biology processes, and attention and involvement by occupational health professionals and government officials.

Health Surveillance Synthetic biology risk assessment can be enhanced by adding health surveillance capabilities to current efforts, which NIOSH has been raising since its comments in response to OSHA announcement of Guidelines on Biotechnology in 1985 (OSHA 1985). Such surveillance includes recording, collecting, and analyzing injury and disease experience of the populations of workers exposed to synthetic biology laboratory, therapeutic, and industrial processes. Injury and disease surveillance efforts can be used to minimize potential worker harm. A temporal challenge to disease surveillance in synthetic biology is that many of the long-term adverse health effects such as adverse oncogenic effects of viral vectors may not be detectable for years or decades following exposure (Howard et al. 2017). Since workers move from job to job, a long-term exposure registry of synthetic biology workers should be considered. Registries have been successfully used and recommended for other hazardous agents and emerging technologies (Schulte et al. 2011).

Proactive Risk Management As synthetic biology emerges from the research laboratory into the bioeconomy, a greater number of occupational safety and health professionals will be involved in ensuring worker health and safety protections. The use of synthetic biotechnology in advanced manufacturing requires educating occupational safety and health professionals not currently involved in biosafety about risks to workers associated with synthetic biology. More professionals will have to take a role in proactively assessing the potential risks to workers as synthetic biology products become increasingly used in advanced biological manufacture and in routine clinical care delivery settings. Additionally, as the synthetic biology workforce expands, worker training tailored to safe approaches to commercial synthetic biology will be needed.

Proactive risk management approaches developed for other emerging technologies such as nanotechnology could be useful in synthetic biology risk assessment and risk management (Murashov and Howard 2009). Workers must be free to report deviations from high-reliability safety procedures without fear of reprisal, and employers should conduct detailed investigations of near-misses and other potential safety failures (Weick and Sutcliffe 2015; Trevan 2015). As applied to other emerging technologies, the proactive approach in synthetic biotechnology provides an opportunity to address occupational health and safety risks at the design stage of synthetic biotechnology workplaces, processes, and products prior to widespread dissemination in commercial arenas (Schulte et al. 2008).

Other aspects of proactive risk management include identifying industrial scenarios where workers could be exposed to synthetic biological products. Industrial synthetic biology is already a growing field, and several industries anticipate using the commercial applications: energy, chemicals, materials, pharmaceuticals, food, and agriculture as well as in the medical diagnostic and therapeutic areas (Erickson et al. 2011; Schmidt 2012; Rohn 2013). By identifying the processes where synthetic biology can be used in these industries, risk managers can make proactive assessments of possible risks to workers and what controls need to be put in place. Transportation and warehousing workers handling synthetic biological products and first responders to unplanned releases would also have potential exposure and should be included in the proactive risk assessments. Little is known about occupational exposures that could occur when synthetic biological products, vectors, or organisms are used in industrial scenarios. Exposure assessments of synthetic biology will depend on whether the area of interest is in or around containment structures or in the external environment.

Worker hazards that are unique to synthetic biology are not well defined. Some information on potential types of laboratory hazards may be drawn from laboratory-acquired infections (LAIs) that occurred over the last 60 years in clinical, research, and industrial microbiological laboratories (Sewell 1995; Wurtz et al. 2016). The history of LAIs generally has involved organisms (or toxins of these organisms) that have been known to cause disease or reasonably believed to cause diseases in people and animals. The extent to which LAIs have occurred in synthetic biology laboratories is not known because there is no plan for data collection. A recent

global survey of LAIs in biosafety Level 3 and 4 laboratories found infrequent occurrence and identified "human error" as the causal factor in "a very high percentage" of the cases (Wurtz et al. 2016).

There is still uncertainty surrounding the hazards associated with the "construction in organisms that may contain genes or proteins that never existed together in a biological organism or that contain newly designed biological functions that do not exist in nature" (NIH 2016). It is not reasonable to characterize the hazards of synthetic biological organisms, processes, or products with a single overarching descriptor. There are and will be many different hazards. There will be a range of hazard severities. The hazard of a specific synthetic biological organism is a function of its pathogenicity or immunogenicity. Synthetic organisms are designed to reproduce and will evolve. The hazards associated with them may change as well. The nature of a hazard will drive management and control measures.

Prevention-Through-Design Worker protections in synthetic biology may benefit from applying prevention-through-design principles to promote further risk control research on physical and biological containment (NIOSH 2014). The mainstay of risk management for genetic engineering, including for synthetic biology, has been containment. Biosafety containment can be categorized as physical (or extrinsic) and biological (or intrinsic) containment.

Extrinsic containment was developed in the late 1940s and early 1950s chiefly at the US Army Biological Warfare Laboratories at Fort Detrick, Maryland. Extrinsic containment was designed to provide physical containment of highly infectious organisms in secure rooms or cabinets. Biological safety cabinets (BSCs) provide three classes of protection: (1) personal and environmental protection (Class I); (2) personal and environmental protection as well as product protection (Class II); and (3) maximal protection through a gas-tight enclosure where gloves are attached to the front of the BSC to prevent direct contact with hazardous materials (Class III), often referred to as glove boxes (DHHS 2009). BSCs are now the mainstay of extrinsic containment in laboratories around the world. The effectiveness of the personal protective equipment such as gloves and coveralls to reduce potential for exposures to biological agents is under active investigation (Villano et al. 2017). A 2016 systematic review of reported studies used very low quality evidence to conclude that (1) more breathable types of personal protective equipment (PPE) may not lead to more contamination but may have greater user satisfaction and (2) double gloving and protective clothing "doffing" guidance from the Centers for Disease Control and Prevention appear to decrease the risk of contamination and that active training in PPE use may reduce PPE and doffing errors more than passive training (Verbeek et al. 2016).

Intrinsic containment is a more recent type of containment, which leverages the fact that synthetic biology is chiefly an engineering discipline in the life sciences. Organisms live or die through a variety of processes, some of which can be interrupted. Intrinsic containment is still under active development in the field of synthetic biology. The aims of intrinsic containment include (1) controlling growth

of the engineered organism in the research laboratory or after an unintentional environmental release; (2) preventing the horizontal flow of genetic material from a synthetic organism to a natural one (gene flow); (3) preventing the use of engineered microbes as bioterror agents; and (4) protecting the intellectual property of biotechnology companies (Cai et al. 2015). Genetic safeguards intrinsic to the synthetic organism can restrict its viability in defined environments (Schmidt and de Lorenzo 2012). Designing these safeguards into synthesized organisms can protect workers and supports designing out hazards and preventing the occurrence of harmful exposures.

Since the 1980s, the field of intrinsic containment has grown rapidly to encompass a number of different strategies. Control of cell growth by engineered auxotrophy, i.e., the inability of an organism to synthesize a particular organic compound required for its growth, protects against it surviving environmental release (Steidler et al. 2003). Intrinsic containment methods to produce safer viral vectors involve splitting gene vector components into three plasmids; using vectors without viral accessory proteins that are important for a natural virus as a pathogen, but not as a vector (Sakuma et al. 2012); and using self-inactivating (SIN) vectors which can help mitigate the risk of insertional gene activation (Cockrell et al. 2006; Zufferey et al. 1998). Other methods include designing engineered regulators that control the expression of essential genes (Gallagher et al. 2015), transcriptional and recombinational strategies to control essential gene functions (Gallagher et al. 2015), the use of microbial kill switches (Chan et al. 2016) and other vector suicide strategies (Bej et al. 1988). Developing a quantitative assay for insertional mutagenesis can help produce safer viral vectors (Bokhoven et al. 2009). Finally, a largely theoretical intrinsic containment method involves engineering organisms with chromosomes made not from DNA and RNA, but from xeno ("stranger") nucleic acids or XNA (Schmidt 2010). Unrealistic as such "organisms" seem to us today, their utility could prevent "gene flow" with DNA-based organisms, serving as a genetic "firewall."

Rigorous effectiveness studies should assess these intrinsic containment methods and others that emerge as synthetic biotechnology becomes more commercial. Although funding in this area is not customarily a high priority for governmental biomedical funders or for entrepreneurs (Garfinkel 2012), it will likely advance worker protections.

Dynamic Guidance Safety guidance that is specific to synthetic biology should be developed in an electronically updatable format that reflects advances in risk science. NIOSH's *Approaches to Safe Nanotechnology* serves as an example of safety guidance for an emerging technology (NIOSH 2009). This safety guidance should include steps to foster a robust safety culture characterized by employer commitment to and worker involvement in safe synthetic biology. Model guidance could be adopted by national governments as a mandatory standard or used as the basis for a national or international consensus standard (Murashov and Howard 2008; Murashov et al. 2011).

Greater Awareness and Involvement Medical professionals and government agencies contributing to protecting worker safety should have an understanding of the complex risk assessments and risk management issues inherent in synthetic biotechnology. During the research-only phase of synthetic biology, biosafety professionals have worked diligently to keep workers safe. The increases in biosafety research laboratories, the number of workers potentially exposed to synthetic biology products, the use of gene transfer-viral vectors in synthetic biology, and the emerging commercialization of synthetic biology oblige the involvement of the occupational safety and health practice community and governmental occupational safety and health research and regulatory agencies.

Conclusion

As the *Presidential Commission for the Study of Bioethical Issues* recommended in 2010, maximizing synthetic biology's benefits and minimizing its harms will benefit from risk assessment and risk reduction strategies (Presidential Commission for the Study of Biomedical Issues 2010). NIOSH has identified synthetic biology as a possible hazard to workers; however, where and how exposure to these hazards could occur is not well defined. NIOSH is establishing an Emerging Technologies branch that will work to identify where hazards to workers might occur and how to mitigate exposures in emerging technologies such as synthetic biology.

As synthetic biology enters more and more industrial workplaces, engagement from the entire occupational safety and health practice community is needed for the responsible development of commercial synthetic biology while protecting the health and safety of its workers (Moe-Behrens et al. 2013). Proven risk mitigation approaches for emerging technologies including health surveillance, proactive risk management, prevention-through-design principles, and dynamic guidance should be implemented to ensure that no worker suffers adverse health effects in the emerging synthetic biology workplace and that the synthetic biology realizes its full potential in improving quality of life for all.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health, the Centers for Disease Control and Prevention, or the US Department of Health and Human Services.

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