



Dealing with the Dangers

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What You Will Learn in This Chapter

Particular concerns regarding synthetic biology work will be presented in this chapter. What hazards are involved and what threats they pose will be discussed. We will also look at methods to assess these hazards in order to prepare for any mishaps they might cause. Assessment of risk will be defined in terms of the impact such hazards would have on human health and the environment, as well as the likelihood of such mishaps happening. We will discuss some means by which risk assessments can be made more reliable, as well as some strategies for minimizing the impact of certain hazards.

6.1 The Risks of Synthetic Bioarchitectures

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We have seen how different groups in the synthetic biology community have highlighted and addressed safety concerns arising from such work. As with all powerful and fast-moving technologies, synthetic biology—and consequently its toolbox, synthetic bioarchitectures—can have severe and far-reaching impacts on existing life, if not guarded against in time.

Potential of Synthetic Biology

We are about to learn how to manipulate the most basic elements of living systems

‘In near future, synthetic genomics technology should make it possible to recreate any existing virus for which the complete DNA sequence is known.’

<http://www.grid.unep.ch>

This is particularly true in the case of synthetic organisms. Globalization has already produced unintended consequences, such as xenobiotics, which are organisms that (even unintentionally) are transported by travelers or as contaminations on containers or ship surfaces (for example, water ballasts). They are often imported because they are considered attractive, such as many flowers—for example, the beautiful *Kosmee* flower. Another example is the large, sweet, colorful *Pomacea* water snail, which became popular in aquaristics but became a considerable threat to Spanish rice fields; consequently, the importation of *Pomacea* has been prohibited by European Union (EU) law since 2013. Invasive organisms, such as this snail, sometimes present a disturbance to the natural balance in a population, and many examples come to mind, from plants to animals, where this phenomenon has been observed. Over time, many such “intruders” have become integrated into the ecosystem; however, in other cases, the original “wild” form has vanished.

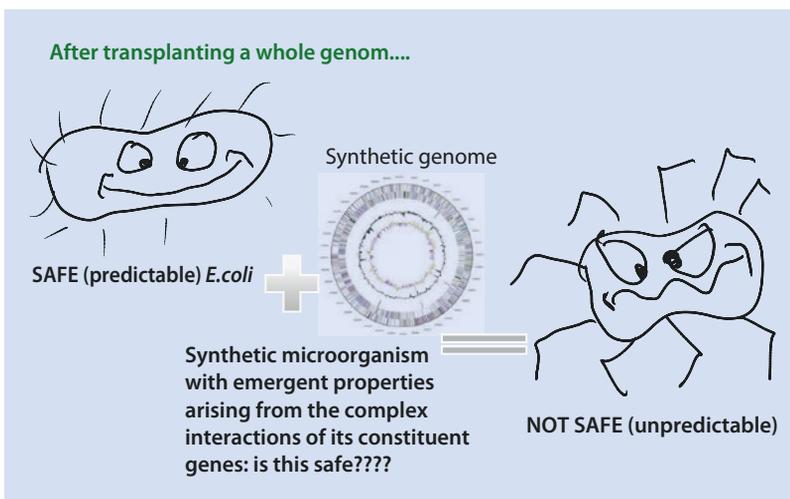
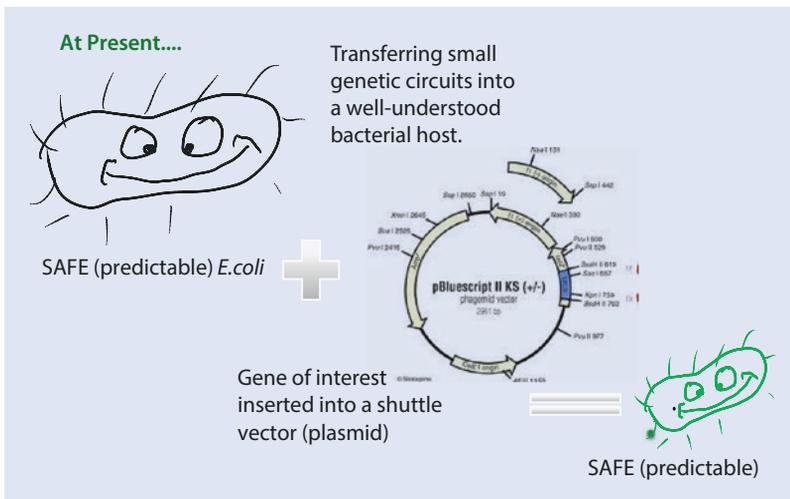
There is deep concern that the toolbox of synthetic bioarchitectures could be harnessed for the development of a new generation of life-forms, which could be considered “intrinsic xenobiotics.” And, not by chance, the term “synthetic biology” has been strongly linked in history to the term “human enhancement.” Humans have already started—sometimes unintentionally—to expose habitats to foreign life-forms that present alien properties to the environment; in some cases such alien properties can lead to an advantage, while some do not. It will constitute an interesting question as to what extent drastic combinations of “nonevolutionary” genetic combinations crossing the natural borders of species will overstretch the Darwinian context.

6.1 • The Risks of Synthetic Bioarchitectures

Synthetic bioarchitectures represents a toolbox for engineering of life—and it would be harder for existing life to adapt to drastically engineered life-forms as they possibly are “outsiders” for the natural inhabitants and additionally they will inherently modify their environment, as any life-form does.

Such contact poses the following hazards: (1) the synthetic organism might out-thrive existing life-forms, leading to depopulation, or even extinction, of the latter; (2) if it survives and spreads, the synthetic organism cannot be removed entirely even if it has escaped from the laboratory environment unintentionally; and (3) the behavior (e.g., feeding habits) of the synthetic organism could be destructive to the environment. Research on ecosystems and modeling of interactions and population dynamics would be of help in order to assess and mitigate potential risks from engineered life-forms, as this is already necessary to understand and protect natural habitats from such xenobiotics.

It is a valid question in synthetic biology as to whether such drastic changes in an organism (such as implanting a foreign genome) can be assessed under the same boundary conditions as those for a “standard” genetically modified organism.



There are three major sources of concern: (1) the ease of access, by improperly informed laypersons, to materials and methods used for synthetic biology; (2) desire on the part of individuals or groups to harness the power of synthetic biology to cause harm; and (3) unforeseen threats to existing life, for example, posed by novel living systems.

HOWEVER...

The “precautionary principle” has to be applied - treating synthetic microorganisms as dangerous until proven harmless.

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Many of the materials and methods used in synthetic biology are readily available to users even if they are not affiliated with any accredited organization. Various projects already exist that encourage amateur or alternative experimentation with synthetic biology. This raises the question of what motivates such groups and why they operate outside the mainstream.

In summary, even if the intentions of researchers are completely benign, there is still uncertainty as to what the impact of synthetic systems would be on existing life. This is true for both amateurs and bona fide scientists and engineers. A means is needed to guard against unforeseen exposure of existing life to the products of synthetic biology.

Synthetic Biology and the Risk of Deliberate Misuse

The Central Intelligence Agency of the US released a short white paper that concludes,

“Growing understanding of the complex biochemical pathways that underlie life processes has the potential to enable a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects.”

6.2 Risk Assessment

To be effective in preparing for a mishap, a rational approach is required. This requires that (1) a threat be clearly defined, so that it can be recognized; (2) precautions be used so that a mishap is prevented from occurring; and (3) plans be put in place for what to do if such a mishap occurs, so that its consequences can be minimized or removed altogether. Risk is not the same as uncertainty—actually, it is quite the opposite: a risk can be considered only once the procedures involved have been identified and, as such, a risk is involved in something we are familiar with. Uncertainty still can be involved, as our expectations and competence in prediction might be insufficient.

This approach treats every potential mishap as a risk. Risks comprise (1) the dangerous material or process in consideration; (2) the impact of exposure to this material, or occurrence of this process; and (3) how frequent such exposure or occurrence would be. These components allow us to categorize risks and prepare, or act, to mitigate them.

To reduce the subjectivity of this process, a method has been devised to quantify risks, by first assigning values to the impact of a hazard (Consequence) and the frequency, or likelihood, of its occurrence (Frequency). Risk is then equated to the product of Consequence and Frequency:

$$\text{Risk} = \text{Consequence} \times \text{Frequency}$$

The resultant value is then used to judge the severity of the risk, and that, in turn, will suggest what precautions and counteractions to take. In summary, as risk never equals zero, if a facility operates for long enough, it is certain—statistically speaking—that it will experience an accident. In other words, we need to assess and (if possible) reduce risks, and mitigate any consequence of the application of synthetic biology, as we can never surely exclude a potential mishap.

So, we can only assess the bona fide risks according to the “most actual” status of research and technology. To make ourselves familiar with the most actual status and the dissemination of the most recent research results, this is where the “responsibility” of a society—and, finally, the individual—kicks in.

6.2.1 The Consequence Term

The matrix below shows how one might grade the Consequence term. Depending on the effects of the mishap, its Consequence can be assigned a value.

For example, a hazard whose effects are to (1) cause a single, disabling injury to the worker; (2) result in hospitalization or serious injury to others; (3) cause irreversible damage to the environment; and (4) cost \$1–10 million in damages annually will be assigned a value of 3, which represents a Consequence described as “severe”. Such matrices are already standard in organizational portfolios in order to assess the risk of certain processes in monetary values.

Consequence Matrix

	Employee Safety	Public Safety	Environmental Impact	Economic value
low	Report	No impact	Limited impact (correctable)	10–100k€
moderate	Hospital	Small impact (smell, etc)	Report to Agencies	100–1M€
severe	Disabling injury	Hospitalization /reports in public	Irreversible Damage	1–10M€
very severe	Letal/multiple severe injuries	Letal/multiple severe injuries Massive negative publicity	Catastrophic consequences	Larger than 10M€

Adapted from: Ian Sutton, Process Risk and Reliability Management, Elsevier, 2015, 2nd Edition

6.2.2 Frequency of Occurrence

A similar matrix can be drafted for Frequency. In this way, Frequency can also be assigned a value.

The Consequence and Frequency matrices can then be combined to give the Risk matrix. In this way, the degree of risk posed by a threat can be determined, and appropriate precautions and actions can be arranged. For instance, a risk that is judged to be low might warrant the placement of equipment or materials, such as first aid kits, which the endangered might use to assist themselves. A risk that is judged to be high might warrant the use of highly specialized protective equipment or perhaps the establishment of a specialized team of helpers who are trained to handle the specific hazard.

Use of the Risk matrix suggests that no hazard can be completely free of consequences or can never occur. This means that any hazard can never be risk free, although one can try to reduce the impact and likelihood of a hazard through planning and preparation.

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6.2.3 Caveats

Not all hazards may be assessed by the same determinants and thresholds. Furthermore, not enough information is available sometimes for Consequence or Frequency matrices to be used objectively.

Facts are never truly objective

A truth ceases to be a truth as soon as two people perceive it.
Oscar Wilde (1854 – 1900)

In such cases, the values chosen might be influenced by assumptions, estimations, beliefs, and other biases. This often exacerbates the subjectivity of risk assessments or, as Ian Sutton stated in his famous book: “We only learn from blood” (see “Further Reading”).

Involvement of Subjectivism into Risk Assessment

Sutton Ian

- The subjective component of risk becomes even more pronounced when the perceptions of non-specialists, particularly members of the public, are considered.
- Hence the successful risk management involves understanding the opinions, emotions, hopes and fears of many people, including managers, workers and members of the public.

6.3 Model Ecosystems

As another means of reducing this element of subjectivity, models might be used to study hazards in miniature. This allows the assessors to observe the impact of a hazard on a particular set of conditions, on a small scale. An example would be to use isolated model ecosystems to study the impact of synthetic life on existing flora and fauna.

Furthermore, one might ask if the risks posed by synthetic organisms are any different from those posed by genetically modified or even nonindigenous organisms. From the perspective of general biosafety, all three groups pose the same risks. Any uncharacterized organism, including synthetic ones, should be handled as a health hazard until proven otherwise.

6.4 Handling Biohazards

Following the precept favoring prevention over a cure, general biosafety stresses containment of hazardous living material. This means to limit or prevent exposure of existing life to the hazard unless proper precautions are in place. This approach would be just as effective when used with synthetic organisms.

Living material is typically handled in biosafety facilities. Experimental cell and tissue materials should be considered capable of causing human disease or environmental damage when released. As such, they should be handled in isolation according to the appropriate biosafety level. A synthetic organism, by virtue of being novel and uncharacterized, should be considered highly suspicious and therefore warrant more stringent biosafety precautions.

In case the synthetic organism manages to escape a biosafety facility, it should be ensured that it would not survive, nor have a selection advantage over native flora and fauna. This can be done by designing a biological response, such as suicide, following specific conditions such as overgrowth or exposure to an introduced environmental signal.

The Risk of Accidental Release

“Despite the fact that no accidental release of a genetically- engineered microorganism (GEM) from a laboratory has been reported, it is possible that such releases have occurred but that the effects were so unremarkable that they remained undetected.”

THE NEW ATLANTIS, JONATHAN B. TUCKER AND RAYMOND A. ZILINSKAS
www.TheNewAtlantis.com

6.5 Orthogonality

Orthogonality is one of the aims in synthetic biology—for example, when it comes to pathway engineering. The adjective “ὀρθός” (*orthós*) comes from Old Greek and means “correct” or “right”; together with the suffix “-gonal” it describes the right angle and is used in the language of mathematics. The right angle is the least interference of a vector with

another—describing the attempt to disturb a system as little as possible. Transferring this term to molecular biology, it means to “reprogram” a gene without any disturbance of the context. Everyone who has ever tried to knock out a single gene knows how “nonorthogonal” this attempt becomes in most cases! The complexity and still unknown regulation factors and intermingled pathways often lead to unexpected consequences of the resulting organism. In plant biology, the multiple genomes add to this problem. So, we can understand the aim “orthogonality” as an aim for the synthetic biologist, which is addressed in systems biology, when the network of pathways is the subject of research and identification of individual “valves” in a respected pathway is the prerequisite for successful pathway engineering, as the mutation in this special place will most likely lead to a controlled change and, thus, can be termed “orthogonal” as only the desired pathway is affected by the change. Still, many side effects happen, as interconnected pathways are regulated by products and educt concentrations are changed. This is an inherent bottleneck in modifying a living organism; however, in so-called cell-free approaches, one can investigate such changes in a cellular lysate and once the regulatory interactions are resolved in such systems, the chances for investigation of isolated gene products become higher.

In another context, such orthogonal changes are valuable tools for mitigating the risk of unintended release of synthetically engineered organisms. One strategy to prevent the survival of such released organisms is so-called biological firewalls—for example, the use of noncanonical amino acids in a modified organism. Several strategies are underway, as such synthetic organisms might be designed to subsist only on synthetic nutrients, such as non-natural DNA and amino acids. This strategy works only if the modified pathway results in an “orthogonal” mutation, leading to a 100% dependent species, which has no work-around strategy in place to bypass the critical pathway, so that essential supplements must be supplied for them to remain viable. Such measures will ensure that these organisms will not survive outside the laboratory. Such special metabolic requirements would also ensure that synthetic organisms would not be able to influence existing life biologically. For example, a synthetic organism designed to use xenonucleic acids (instead of nucleic acids) for genetic material would not be able to affect natural life genetically. Such a strategy was also mentioned in ► Chap. 2, where autopoiesis was discussed. If the synthetic organism is designed to be viable only under non-natural conditions, such as the use of non-natural nutrients, exposure to the natural environment should lead to its death, preserving the natural inhabitants.

6.6 Constant Monitoring

Transparency and careful scrutiny of research work, such as monitoring of the purchase of hazardous material, will allow watchers to determine if suspicious research activity is present. This is particularly useful if such material is being accessed by amateurs or rogue scientists. Mainstream research work, on the other hand, can be easily curbed through control of resources, such as funding and facilities. This is one of the most critical issues in synthetic biology and its toolbox—synthetic bioarchitectures. Here we need to rely, as scientists and members of our respective societies, on transparency of and access to research results, and governance by the laws of the respective country. As a consequence of terrorist attacks, the acquisition and use of critical genetic sequences is monitored by the companies and databases involved. This is one of the attempts to restrict and control research, and the same strategy is in place for stem cell use. Still, the deliberate misuse of genetic material/information is one of the critical threats of today’s societies.

■ Conclusion

Ultimately, it needs to be those who are responsible for the products of synthetic biology who are the most vigilant. However, their concerns and recommendations must reach others, particularly those who might be affected, as well as those involved with regulation of research. This can only be effective when there is constant, open, informed, and rational dialogue across all social strata.

Take-Home Messages

1. Synthetic biology results in materials and living organisms that may turn out to be hazards.
2. The impact that a hazard has on human and environmental health can be mitigated if one is prepared.
3. Preparation requires that hazards be identified before they cause a mishap.
4. Once identified, the risk they pose can be evaluated by considering the severity of the effects of any mishap on human and environmental health, as well as how frequent or likely such mishaps might be.
5. Risk assessments are inherently subjective, since different people might perceive severities or likelihoods differently. Various means are needed to reduce this subjectivity.
6. The impact of a hazard on the environment can be studied in model environments. These models mimic important characteristics of the environment without exposing the environment to the hazard.
7. Synthetic organisms should be handled in the same way as any uncharacterized naturally occurring organisms. In the absence of contrary evidence, both kinds of organisms should be considered dangerous to human health and the environment (the precautionary principle).
8. Constant monitoring and evaluation of research activities, particularly in the area of synthetic biology, would allow potentially hazardous work to be dealt with in time.
9. Public discussion of controversial work in synthetic biology will help to maintain vigilance. This would be necessary in order to prepare for any hazards that may arise.

Further Reading

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