Safe, Secure and Ethical?
Assessing and Regulating Risks Associated with Synthetic Biology

by

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Submitted to the Engineering Systems Division in Partial
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Safe, Secure and Ethical?
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ABSTRACT

Synthetic biology is an emerging field, with a rapidly developing academic-industrial base and the promise of extensive product launches over the next few years. An intense debate over the risks and benefits of synthetic biology has developed even before commercialization. Nongovernmental organizations and official commissions have published over a dozen reports on the potential pitfalls and promise of synthetic biology, with widely varying analytic assumptions, assessment methods, definitions of values, and policy recommendations. How should governments go about developing regulatory policies to govern synthetic biology?

This thesis begins by outlining the synthetic biology academic-industrial base, and then describes and critiques official and unofficial assessments of synthetic biology risks and the regulatory policies now in place to regulate risks. It differentiates among risks to security, safety and environment, and ethics, and finds that regulations in each of these areas suffer from significant deficits. Regulations are not well grounded on technical understanding of synthetic biology, lack methodologies for risk assessment of organisms without close natural counterparts, frame risk assessment as a technocratic process without substantial input from stakeholders, and emphasize physical risks to safety and security over non-physical threats to ethics and values. The thesis suggests that the US government and European Union modify existing regulations governing risks associated with synthetic biology and, more fundamentally, processes for developing such regulations to mitigate some of the deficits identified above.

Thesis Supervisor: Kenneth A. Oye

Title: Associate Professor of Political Science and Engineering Systems
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CHAPTER 1 Introduction

Synthetic biology is an emerging field, inspired by systems biology and enabled by technological advances in DNA sequencing and synthesis. The academic-industrial base is developing rapidly and product launches are promised within the next few years. Despite its newness and the fact that products are yet to be launched, an intense debate over the risks and benefits of synthetic biology has already developed.

Nongovernmental organizations and official commissions have published over a dozen reports on the potential pitfalls and promise of synthetic biology, with widely varying analytic assumptions, assessment methods, definitions of values, and policy recommendations. For example, NGOs encourage a moratorium on the further development of synthetic biology until risks have been assessed, while many actors from the academic-industrial complex promote self-regulation and minimal government oversight.

Governments are thus attempting to make decisions about the regulation of a new technology under pressures from diametrically opposed actors with different framings and definitions of risks. Coupling this to uncertainty in the assessment of risks, doubt about whether established regulatory frameworks are applicable and adequate for synthetic biology, and a risk framing that undermines traditional, technocratic governmental approaches to risk management, amounts to quite a challenge for governments. This thesis is an attempt to clarify the situation through systematic analysis.

1.1 Research Questions and Goals

Because of the differences in definitions, procedures and approaches between individual reports and news articles, the picture of synthetic biology that has been transmitted to the general public and governmental regulators is fragmented, polarized and sometimes even incorrect. This is of course a problem as individuals and government officials try to understand synthetic biology, analyze it and design individual or regulatory responses. The first contribution of this thesis is to perform a detailed analysis of synthetic biology and its academic-industrial complex, to provide a better picture of the field and its applications than what has previously been available. As such, this first part answers to principal questions:

- What is synthetic biology?
- What is synthetic biology as an academic-industrial complex?

The answer to these two questions provides the foundational understanding upon which the remainder of the analysis rests. The study continues by analyzing a handful of the most influential reports that have been published so far, and identifies and evaluates their perception of what the risks of synthetic biology are. In so doing, this part answers the third question:

- What are the perceptions of risks of synthetic biology?

A systematic evaluation and analysis of risks supplies the foundation to the final part of the thesis, which evaluates how current regulatory frameworks assess and manage the identified risks. This section represents the most significant part of the study and is also the part in
which the most conclusions are drawn. It also answers the fourth, and final, research question:

- How do current regulations govern the management of risks of synthetic biology?

The final goal of this study is to analyze and assess the applicability of current regulatory frameworks to synthetic biology, to identify weaknesses and make recommendations on how to address them. By conducting a more comprehensive background review of synthetic biology and its perceived risks, the regulatory analysis will be an improvement over most other evaluations of synthetic biology, its risks, and regulations. The objective is to provide all interested actors, and especially governments, with information and analysis that improves their capability to evaluate and assesses risks and the regulatory framework, and to balance pressures from stakeholders.

1.2 Scope

This thesis defines synthetic biology as scientific discipline and academic-industrial complex, identifies social actors responding to its development, evaluates the risks that they raise and the international, European and American regulations that address and manage identified risks. It is limited to analyzing regulations that govern risks to security, safety and the environment, and ethical values, and does not consider other governmental policies that could also affect the development of synthetic biology, such as taxation systems and innovation policy. Furthermore, it is limited to analysis of scientific developments and regulatory frameworks that are applicable in the EU and US.

1.3 Structure

The thesis is divided into four distinct parts, all corresponding to the research questions defined above. Part I: Synthetic Biology and the Academic-Industrial Complex, composed of Chapters 2 and 3, answers research questions one and two. Part II: Risk and Perception of Synthetic Biology, composed of Chapters 4, 5, and 6, provides both a framework for analyzing risks and regulations and an answer to research question number three. Part III: Policies and Regulatory Frameworks Governing the Risks of Synthetic Biology, composed of Chapters 7, 8, and 9, answers the fourth research question. Finally, Part IV: Conclusions and Recommendations, composed of Chapter 10, combines the answers to the four research questions and conclusions from those answers into a holistic analysis of the regulatory framework. This analysis results in an identification of main weaknesses in regulatory frameworks and recommendations for how to address and improve them.

1.4 Approach

The first part of the study is aimed at understanding synthetic biology and its academic-industrial complex, a goal that is achieved by conducting interviews with members of the synthetic biology community, taking coursework in synthetic biology, and reading books and recent publications in the field.

The second part of the thesis analyzes the risk perceptions that societal actors reacting on synthetic biology have expressed in various reports and communications. This part begins with a theoretical chapter composed of a literature review of the most relevant publications on risk framing, perception, and assessment, which serves as the foundation upon which
synthetic biology risks and regulations are analyzed. The second chapter is a review of the perceptions of risks present amongst social actors reacting to synthetic biology, and provides the foundation upon which the third chapter’s description and analysis of risks is based. These two chapters are arrived at by conducting document and argument analysis of reports and communications published by the studied organizations.

The third part of thesis is composed of three chapters describing and analyzing the regulatory frameworks governing risks to safety, security and ethics posed by synthetic biology. These chapters are achieved through document analysis of key regulations and extraction of the most important elements of regulations as well as their underlying foundation and ideological base. The fourth and final part connects all findings of the previous chapters into a holistic analysis of synthetic biology, its perceived risks, and regulatory context, finishing by identifying weakness in regulatory systems and recommendations for addressing them.
PART I:

Synthetic Biology and its Academic-Industrial Complex
CHAPTER 2  Synthetic Biology

Synthetic biology represents a new paradigm and conceptual framework to biological engineering, and is enabled by recent transformations in DNA sequencing, synthesis and computing. It emerged as scientific discipline during the late 1900s and early 2000s, with the first International Conference on Synthetic Biology (SynBio 1.0) being held at Massachusetts Institute of Technology (MIT) in June 2004 (Heinemann and Panke 2006). Since then, synthetic biology has gained momentum, grown and developed considerably, and it is now possible to discern some of the key characteristics of the field.

This chapter does just this by providing a definition and detailed description of synthetic biology. First, a brief definition of synthetic biology is provided, followed by a description of the technical foundation that enables its development: Finally, a description of the two branches and six sub-fields that were defined as belonging to synthetic biology is provided, before some concluding remarks that transition into the next chapter.

2.1 Defining Synthetic Biology

As is the case for many new disciplines, it is difficult to provide a single definition of synthetic biology. Despite visionary unity to establish foundations that enable deeper understanding of biological systems and their efficient design, synthetic biologists come from a wide range of backgrounds and work many different organisms, techniques and tools. To increase clarity, it is useful to divide synthetic biology into two broad approaches: the “standardization” and “define and alter” branches. The “standardization” branch is associated with the engineering paradigm and “turning biology into a true engineering discipline” (Endy 2005), while the “define and alter” approach attempts to define the minimal characteristics of life and modify its biochemical foundation.

Each of the two approaches can be divided into distinct sub-fields depending on the more specific nature of the research. Table 2.1 provides an overview of the two approaches, their scientific background, subfields, and vision. Specific research within each of the sub-fields is described further in Table 2.2, which is intended as an introductory overview of synthetic biology and key areas of research. The next section provides a brief discussion of the technical foundations underlying the developments in synthetic biology, followed by a description of each of the six sub-fields defined in Table 2.1 and Table 2.2.

Table 2.1 Background, vision and sub-fields of the two branches of synthetic biology.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Scientific background</th>
<th>Sub-fields</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Standardization&quot; synthetic biology</td>
<td>Engineering, biotechnology</td>
<td>Bioengineering Genome engineering</td>
<td>Making biology an engineering discipline</td>
</tr>
<tr>
<td>&quot;Define and alter&quot; synthetic biology</td>
<td>Molecular biology, chemistry, biochemistry</td>
<td>Synthetic genomics Design of minimal genomes Design of protocells Xenobiology</td>
<td>Defining the minimal characteristics for life (genetic and metabolic), constructing novel and &quot;parallel&quot; life forms</td>
</tr>
</tbody>
</table>
Table 2.2 Research within the six sub-fields of synthetic biology at varying levels of the biological hierarchy. Adopted from (Schmidt and Pei 2010).

<table>
<thead>
<tr>
<th>Bio- engineering</th>
<th>Biochemistry</th>
<th>Genes/ parts</th>
<th>Biological systems</th>
<th>Organelles/ organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome engineering</td>
<td>-</td>
<td>Genes and bioparts</td>
<td>Metabolic engineering, bioparts and devices</td>
<td>-</td>
</tr>
<tr>
<td>Synthetic genomics</td>
<td>-</td>
<td>Synthetic genes</td>
<td>Artificial chromosomes</td>
<td>Whole-genome synthesis</td>
</tr>
<tr>
<td>Minimal genomes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Top-down, reducing existing genomes</td>
</tr>
<tr>
<td>Protocells</td>
<td>Standard or alternative biochemistry</td>
<td>Engineered phospholipids</td>
<td>Vesicles lacking key features of life</td>
<td>Bottom-up, designing whole synthetic cells</td>
</tr>
<tr>
<td>Xenobiology</td>
<td>Alternative biochemistry</td>
<td>Changing codon assignment of genes</td>
<td>Novel polymerase and ribosomes</td>
<td>Xeno-organisms, chemically modified</td>
</tr>
</tbody>
</table>

2.1.1 Scientific and Technical Foundations of Synthetic Biology

The development of synthetic biology is dependent on technical breakthroughs in genome sequencing and synthesis coupled to increased activity in systems biology, the discipline upon which synthetic biology is most dependent (Mukunda, Oye and Mohr, What rough beast? Synthetic biology, uncertainty and the future of biosecurity 2009, Deplazes 2009). Advances in systems and synthetic biology are both supported by improvements in whole-genome sequencing and synthesis over the past decades. Since the 1970s, the amount of base pairs that can be sequenced or synthesized per dollar has increased at exponential rate, resembling Moore’s Law for the improvement of integrated circuit density, as is shown in Figure 2.1 (Carr and Church 2009, Carlson 2003).

![Figure 2.1 Efficiency trends in sequencing and synthesis over the past 30 years (Carr and Church 2009).](image-url)
In 1995 the prokaryote *Haemophilus influenza* became the first living organism to have its entire genome sequenced. Today, 974 prokaryotic genomes have been sequenced completely, 656 are in draft assembly, and 576 are in progress. Sequenced genomes are available in public databases in the EU (EMBL), Japan (DDJB) and the US (GenBank), providing researchers with huge amounts of genetic information to explore and exploit (Mukunda, Oye and Mohr, What rough beast? Synthetic biology, uncertainty and the future of biosecurity 2009). Figure 2.2 shows the exponential increase in the number of publicly available sequences in the US.

![Growth of GenBank](image)

**Figure 2.2 Growth of data in GenBank since its inception in 1982 to 2008 (NCBI 2008).**

Obtaining the complete genome of an organism allows for far more detailed studies and deeper understanding of biological systems. Synthetic biology effectively couples the increase in biological understanding with the decrease in price of DNA sequencing and synthesis into a new approach to biological engineering, some of the most prominent features of which are presented below.

### 2.1.2 “Standardization” Synthetic Biology

The standardization branch of synthetic biology is driven by the idea of turning biology into a true engineering discipline. The inspiration from engineering, especially electrical and mechanical engineering, and the desire to create novel organisms with predictable characteristics based on the rational combination of standardized biological parts decoupled from their natural context distinguishes the approach from other disciplines in biological engineering. The branch can be divided into two sub-fields; bioengineering and genome engineering, each of which is described in more detail below.
Bioengineering

Bioengineering uses knowledge developed in systems biology to modify organisms and metabolic pathways much more profoundly than traditional genetic engineering, which is limited to transferring single genes. For example, addition of the gene for insulin represents a classical genetic engineering experiment, whereas bioengineering uses multiple genes and regulatory elements to either create novel metabolic pathways or greatly modify existing ones. Further, bioengineering tries to design novel biological systems by using abstract, standardized and decoupled metabolic and regulatory modules that can be combined freely, ultimately making bioengineering more controllable and predictable than genetic engineering (Deplazes 2009, Schmidt and Pei 2010).

In turning biology into an engineering discipline, synthetic biologists attempt to develop principles and methods for standardization, decoupling and abstraction. Standardization relates to the development of standards that support the definition and characterization of basic biological parts and conditions that support the use of parts in functioning biological systems. Decoupling aims to separate complex problems into smaller tasks that can be executed individually and then assembled into a complete, functioning whole. Abstraction refers to modularizing and managing the complexity of biological networks by creating hierarchies of biological parts, devices and systems (see Figure 2.3), the ultimate goal of which is to enable combination of parts and devices into functioning and predictable biological systems (Endy 2005).

Figure 2.3 The abstraction hierarchy for biological systems as envisioned within the bioengineering branch of synthetic biology. Adopted from (Baker, et al. 2006).

BIOFAB: International Open Facility Advancing Biotechnology

The Biofab vision was presented in 2006, and represents a natural extension of research efforts already underway in bioengineering. Biofab is based on the notion that previous techniques in genetic engineering have been surprisingly void of actual engineering and that
this inhibits the field. Tom Knight at MIT, a key player in this field of synthetic biology, argues that “the lack of standardization in assembly techniques for DNA sequences forced each DNA assembly reaction to be both an experimental tool for addressing the current research topic, and an experiment in and of itself” (Baker, et al. 2006).

Parallels are drawn to early developments in the semiconductor industry, in which the standardization of transistor and circuit manufacturing was paramount to developing the field and its applications. The Biofab group argues that a similar standardization of methods and components in biological engineering will lead to a similar decoupling of design and manufacturing and serve to free biological engineers from many time consuming steps in biological engineering; ultimately allowing them to focus more effectively on understanding and designing biological systems.

In December 2009 the BIOFAB initiative was founded by a two year seed-grant from the National Science Foundation. BIOFAB is operated in partnership with Lawrence Berkeley National Laboratory, the BioBricks Foundation, and the Synthetic Biology Engineering Research Center (SynBERC). The goal, which is in line with the vision presented in 2006, is to produce thousands of free, standardized DNA parts to shorten the development time and lower the costs of doing synthetic biology for academic or commercial biotechnology laboratories (BIOFAB 2010).

**Genome engineering**

Genome engineering, as part of the “standardization” branch of synthetic biology, uses different techniques than the genome-wide engineering efforts found within the “define and alter” approach. Rather than attempting to synthesize, recreate and define the minimal genetic elements of life, genome engineering attempts to develop tools for efficient large-scale alteration in genomes. A number of new technologies and methods for large-scale genome engineering have been developed over the past years, of which the multiplex genome engineering and accelerated evolution (MAGE) technology, developed in 2009 (Wang, et al. 2009) is one of the most powerful.

![Figure 2.4 Illustration of the MAGE technology and its creation of genetic diversity (Wang, et al. 2009).](image)

MAGE enables rapid and continuous generation of sequence diversity at many targeted chromosomal locations in large populations of cells through repeated introduction of synthetic DNA. First, scientists create short strands of synthetic DNA with sequences that
are similar to a gene or regulatory sequence of the target genome but with specific changes to improve an enzyme or a metabolic pathway, for example. The synthetic DNA is then mixed with the target organisms, and the mixture is transferred to the MAGE machine that, through a series of heating and cooling reactions, inserts the synthetic DNA into chromosomal sites in target organisms. The degree of generated genetic diversity is determined by the degree of sequence variation in the synthetic DNA, the number of gene insertions sites that are targeted, and the number of MAGE cycles performed.

Application of the MAGE technology to optimization of metabolic flux through the DXP biosynthetic pathway for the production of the isoprenoid lycopene led to a fivefold increase in production volumes in just three days, a significant improvement over current metabolic engineering techniques (Wang, et al. 2009). It is perceived that application of MAGE to other genetic elements, metabolic pathways and target organisms can lead to similar improvements.

2.1.3 “Define and Alter” Synthetic Biology

The “define and alter” branch of synthetic biology aims to define the minimal characteristics of life, both on the genome and whole organism level. The underlying idea is that knowledge about the essence and bare requirements for life is both scientifically interesting in and of itself and useful in applied settings. The “define and alter” branch consists of four main subfields: synthetic genomics, design of minimal genomes, protocells and xenobiology, all of which are described below.

Minimal Genomes

Research in minimal genomes attempts to define and characterize the minimal set of essential cellular genes. As such, the approach seeks to define the minimal form of life and reduce the enormous complexity found in biological systems. The goal is to produce a platform or “chassis” with the minimal number of genes to survive under certain highly controlled, typically laboratory, conditions. Such an organism could potentially serve as the base upon which additional genetic elements are added to induce production of interesting molecules, such as chemicals and biofuels, or to produce other desirable phenotypes. At the very least, the minimal genome approach provides interesting findings about the fundamentals of life, which in and of itself is relevant to synthetic biology (Schmidt and Pei 2010).

Creation of a minimal Mycoplasma genome

Mycoplasma genitalium has the smallest known genome of any independently replicating organism, consisting of only 580 kilo base pairs and 517 genes, of which 480 constitute protein-coding regions. In 1999 scientists at the J. Craig Venter Institute showed that 265 to 350 of those coding regions are essential under laboratory growth conditions. These results were obtained by inserting 2209 transposons (which disrupt gene function of the genes into which they are inserted) into the completely sequenced genomes of M. genitalium and its close relative M. pneumonia cells. Presence of a transposon in a gene of a viable organism indicated that the gene was disrupted and therefore nonessential. The positions of the transposons were determined by sequencing across the junction between transposons and genomic DNA in viable cells (Hutchison, et al. 1999).
In 2006, the group presented the results from an expanded study in which pure clonal populations of *M. genitalium* Tn4001 mutants were isolated and characterized. The more precise results of this study indicate that 382 of the 482 protein-coding regions are essential (Glass, et al. 2006). However, since the essential gene set is not the same as the minimal genome (genes that are individually dispensable may not be simultaneously dispensable), more research is required until the minimal genetic requirements for life are defined (Hutchison, et al. 1999).

**Synthetic Genomics**

The vision of synthetic genomics is to chemically synthesize and assemble complete genomes that, upon insertion into a host cell, reprogram cells to perform new, predictable tasks. Organisms with synthetic genomes could provide important information about the minimal set of genes required for life and serve as a “chassi” genome to which other genes with specific functionality could be added (Deplazes 2009, Schmidt and Pei 2010).

**Mycoplasma mycoides genome reconstruction**

The J. Craig Venter Institute recently published a paper on the full chemical synthesis and transplantation of the 1.08 mega base pair *Mycoplasma mycoides* genome (Gibson, et al. 2010). This is the first time that a living organism has been assembled from entirely synthetic sequences of DNA and is seen as a breakthrough in synthetic biology. The genome was assembled in yeast from 1,078 individual pieces of 1,080 base pair long DNA sequences ordered from Blue Heron and then transferred to an empty *Mycoplasma genitalium* cell. After incorporation of the synthesized and assembled *Mycoplasma mycoides* genome, the *Mycoplasma genitalium* cells showed a phenotype identical to that of *Mycoplasma mycoides* (Gibson, et al. 2010).

![Figure 2.5 Synthesis of the Mycoplasma mycoides genome from 1,078 individual pieces of 1,080 base pair long DNA sequences (Gibson, et al. 2010).](image-url)
**Protocells**

The protocell sub-field takes a bottom-up approach to identifying the minimal components of life, as contrasted by the top-down approach of minimal genomes. Protocell design is based on the notion that life is composed of two fundamentally different replicating systems: the genetic information and the structure within which it resides. Protocells are hence constructed as the simplest forms of replicating structures, with membranes separating the inside environment from the outside, a rudimentary metabolism and limited genetic material. They generally consist of lipid vesicles containing the genome and essential macromolecules such as enzymes, ribosomes and nucleic acids (Schmidt and Pei 2010, Szostak, Bartel and Luisi 2001).

Attempts at constructing metabolically active protocells have traditionally been focused on establishing and monitoring metabolism rather than genetics. However, recent work attempts to create artificial cell-like devices with ability to maintain a metabolism and propagate genetic material (Szostak, Bartel and Luisi 2001). A self-replicating vesicle surrounding an RNA replicase represents the simplest type of protocell. An RNA replicase is an RNA molecule that is able to act as a template for both the storage and transmission of genetic information through its ability to replicate its own sequence. Simply having a self-replicating replicase in a self-replicating vesicle does not quite constitute life, however. For the protocell to resemble what we consider as life, the growth of the cell must be coupled to the genome. For example, a lipid ribozyme that synthesizes lipids for membrane growth connects the expression of genetic information to the behavior of the cell and constitutes a very simple living, self-replicating entity controlled by its genome.

**Xenobiology**

The vision of xenobiology is to create forms of life that run parallel to those naturally occurring on Earth. The idea is to introduce a certain degree of orthogonality in the genetic elements and/or metabolism of synthetic organisms, and hence to enable uncoupling of synthetic and natural life. In creating metabolically orthogonal systems, researchers attempt to disentangle the metabolic network of the cell into modular components that do not interact with each other, hence allowing for alterations to proceed without disruptions in other components (Schmidt 2010, Sismour and Benner 2005).

When creating biochemically orthogonal systems, scientists seek to alter the chemical composition of amino acids, proteins and DNA. The creation of novel or altered nucleic bases that can be combined to completely new types of nucleic acids and storage systems for genetic information is an example of this approach. Such xeno-nucleic acids would be unable to interact with the genetic material of natural organisms (Schmidt and Pei 2010). The creation of new amino acids is another example, as is the creation of tRNA that can selectively incorporate an unnatural amino acid into proteins is response to the quadruplet codon AGGA. Development of more tRNAs that can decode quadruple codons could allow for expansion of the current 64 ($4^3$) to 256 variations ($4^4$) (Anderson, et al. 2004).
Design of orthogonal biochemical building blocks has been presented as a tool for increasing biosafety. Orthogonal synthetic life forms would supposedly be unable to interact with natural life forms on the genetic level and hence limit the transfer of synthetic genes to wild populations. Furthermore, the dependency of xeno-biological organisms on unnatural compounds for metabolism, XNA synthesis and survival increases human control over their fate in the environment. But, there are also concerns that orthogonal organisms could have a selective advantage over wild species because of resistance to viruses and other predatory life forms, and that their release could lead to unintended consequences (Deplazes 2009, Schmidt and Pei 2010, Schmidt 2010).

### 2.2 Conclusion

The review of synthetic biology leads to three relevant conclusions. First of all, synthetic biology, while characterized by a common vision to establish the foundations for deeper understanding of biological systems and their efficient design, is composed of scientists from a wide range of backgrounds, using different organisms, techniques and tools. To increase clarity, it is useful to divide synthetic biology into two branches: the “standardization” and “define and alter” branches. The “standardization” branch is associated with the engineering paradigm, while the “define and alter” approach attempts to define the minimal characteristics of life.

Second, research within each of the two branches use modern technologies, such as DNA sequencing and synthesis, to develop novel approaches and tools for biological engineering. In their respective ways, they both seek to establish a paradigm shift in biological knowledge and design through systems thinking, inspiration from engineering and radicalism. Finally, synthetic biology has truly emerged and established itself as scientific discipline over the past couple of years. The next chapter explores how these scientific achievements are carried over to the marketplace by exploring the academic-industrial complex and applications of synthetic biology.
CHAPTER 3 The Academic-Industrial Complex

Many of the leading researchers in synthetic biology are also involved in start-ups and the industrial development of synthetic biology, including many of the companies that are reviewed at the end of this chapter. At this point, synthetic biology is thus best characterized as an academic-industrial complex, rather than two distinct areas of science and industry.

The academic-industrial complex of synthetic biology relies heavily on the biotechnology industry and its existing infrastructure. However, synthetic biology is a revolutionary force to the biotechnology industry and provides the foundation for expansion into multiple new markets. Today, the biotechnology industry is mainly concerned with health and agricultural applications; a biotechnology industry transformed by synthetic biology could expand to include environmental services and production of industrial chemicals, pharmaceuticals, biofuels, fine chemicals and enzymes for biological catalysis (Otero and Nielsen 2010).

The first objective of this chapter is to describe the academic-industrial complex of synthetic biology, starting with an overview of the research infrastructure and then to present an overview of potential applications within industry, health, energy, agriculture and the environment, and finally examples of products that are being developed for commercialization. The chapter concludes with a short description of what drives the commercial development of synthetic biology and a review of important companies.

3.1 Research Infrastructure

Research activities in synthetic biology are centered in the United States and Europe, and this is also where the most funding is available. This section provides an overview of the research landscape of synthetic biology, focusing on research in the US and EU.

3.1.1 Sources of Funding

Synthetic biology research is funded by various sources, from governmental agencies to venture capitalists. Since synthetic biology research is still performed at a foundational level, most funding comes from government agencies or foundations that are funded by the government, but interest from venture capitalists is increasing, especially within biofuels (Rodemeyer, New Life, Old Bottles 2009). Table 3.1 is an overview of some agencies, foundations and companies that have either provided funding to projects in synthetic biology before or are active today.

Table 3.1 Sample of institutions funding synthetic biology research.

<table>
<thead>
<tr>
<th>Government agencies &amp; foundations</th>
<th>Private foundations</th>
<th>Venture capitalists</th>
<th>Private companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>European Commission Framework Programme, UK BBSRC, German Research Foundation.</td>
<td></td>
<td>Microsoft Research, Exxon Mobil, British Petroleum</td>
</tr>
</tbody>
</table>
The US government has been more active and spent significantly more money on research in synthetic biology than the European Union and individual member states, as is shown in Figure 3.1.

![Figure 3.1 Annual spending on synthetic biology research by the US government, the European Commission and individual European countries (The Woodrow Wilson Center for International Scholars 2010).](image)

Of the total amount of money spent on synthetic biology research, approximately three percent is devoted to studies of ethical, social and legal implications. Furthermore, the Synthetic Biology Project at the Wilson Center has found that there are virtually no funds specifically dedicated to risk research (as separate from ethics) (The Woodrow Wilson Center for International Scholars 2010). This is a crucial finding to the purpose of this report, and one that will be discussed again in subsequent chapters.

3.1.2 Universities and Institutions Engaged in Research

Research in synthetic biology is the strongest in the US, followed by the EU, as is demonstrated by the number of scientific publications in the field provided in Figure 3.2. The Wilson Center has estimated that more than 180 entities in the United States and 50 in Europe are involved in synthetic biology research (The Woodrow Wilson Center for International Scholars 2010).

Strong research institutions in the US include the University of California Berkeley, Stanford University, Harvard University, the University of California San Francisco, Massachusetts Institute of Technology, and the J. Craig Venter Institute. The Synthetic Biology Engineering Research Center (SynBERC) is a multi-institutional effort to lay the foundation to synthetic biology in which many of the leading US researchers in synthetic biology are engaged. Involved institutions include the University of California Berkeley, Stanford University, Harvard University, and MIT, amongst others.
In Europe, the European Molecular Biology Laboratory (EMBL) in Germany, the French National Center for Scientific Research, Denmark Technical University, Delft University of Technology, and the Swiss Federal Institute of Technology have major research projects in synthetic biology (European Commission, NEST 2006).

### 3.2 Application Areas

There are numerous potential applications of synthetic biology, ranging from human medicine to environmental clean-up, as is shown in Table 3.2.

#### Table 3.2 Examples of applications of synthetic biology in industry, health, agriculture, energy and the environment and their respective levels of containment.

<table>
<thead>
<tr>
<th>Application area</th>
<th>Example</th>
<th>Containment level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>Production of biofuels, fine and bulk chemicals through fermentation</td>
<td>Contained – industrial vats</td>
</tr>
<tr>
<td>Health</td>
<td>Production of pharmaceuticals</td>
<td>Contained – industrial vats</td>
</tr>
<tr>
<td>Health</td>
<td>Bacteria engineered to localize and deliver drugs to cancer tumors</td>
<td>Uncontained – injection into patient</td>
</tr>
<tr>
<td>Agriculture</td>
<td>Crops engineered for increased nutritional value, composition or production of pharmaceuticals</td>
<td>Uncontained – open fields</td>
</tr>
<tr>
<td>Energy</td>
<td>Photosynthetic microalgae engineered for biofuel production</td>
<td>Varies – closed photosynthetic reactors, semi-open or fully open ponds</td>
</tr>
<tr>
<td>Environment</td>
<td>Bacteria engineered for sensing and/or degrading hazardous chemicals</td>
<td>Uncontained – dispersion in soil</td>
</tr>
</tbody>
</table>
Many first-generation applications of synthetic biology will take place in fermentors or other structures that provide containment. Such applications include the industrial production of chemicals, certain biofuels, pharmaceuticals, enzymes and vaccines (Rodemeyer, New Life, Old Bottles 2009, European Commision 2010, Tucker and Zilinskas 2006, Schmidt and Pei 2010, Ducat, Way and Silver 2011, Jones Prather and Martin 2008). On the other hand, many applications of synthetic biology in agriculture, energy and the environment require more or less uncontained use, either for the actual function or for economic viability.

3.2.1 Industrial Applications

Production of fine chemicals, bulk chemicals and enzymes are all potential industrial applications of synthetic biology. The suggestion is to replace chemical synthesis of chemicals with biological synthesis, a transformation that is considered to lead to both more economically viable and environmentally friendly production methods that require less energy and raw materials. Furthermore, replacing chemical synthesis with biological synthesis can significantly reduce the complexity and number of steps in the production process, as is shown in the examples given later in the chapter.

Biosynthesis using synthetic biology is considered especially important to the production of fine and specialty chemicals, many of which are very difficult to produce through organic chemical synthesis. Novel carotenoids and polyketides are two examples of highly complex and interesting chemicals that have been synthesized biologically using synthetic biology approaches to metabolic engineering and pathway design. Likewise, the biological production of commodity and fine chemicals such as PHA, PHB, propanediol, aromatics and amino acids, has also been improved greatly by using synthetic biology (Jones Prather and Martin 2008, Rohlin, Oh and Liao 2001).

Production of enzymes is another major industrial area in which synthetic biology approaches are applicable. Enzymes are used as biological catalysts in a wide array of industries and products, ranging from agriculture to energy to pharmaceuticals. The production of biofuels, chemicals, beer and textiles all employ enzymes, as do products such as laundry detergents, dishwashers and certain animal feeds (van Beilen and Li 2002). Synthetic biology applied to protein design and strain development can lead to more powerful techniques for optimizing enzymes for various industrial and household settings as well as increasing the enzyme yields of production strains (Otero and Nielsen 2010).

3.2.2 Health Applications

Health applications of synthetic biology are similar to those described above, only that microorganisms are designed to produce pharmaceutically active molecules (small molecules or proteins) instead of chemicals. Just like the production of chemicals, biological synthesis of pharmaceuticals has benefitted to a great extent from applying synthetic biology methods, as demonstrated by the production of the anti-malarial drug artemisinin, which is described later.

Another potential health application of synthetic biology involves the use of live bacteria, such as tumor killing bacteria, as targeted delivery systems of pharmaceutically active ingredients. Tumor killing bacteria are engineered to respond to environmental signals
secreted by cancer cells, migrate towards the cancer cells, invade them and finally to over-produce active pharmaceutical ingredients such as toxins, angiogenesis inhibitors and cytokines. The tumor killing bacteria, which are currently in clinical trials, would be injected into patients and complement or even replace chemotherapy and radiation treatment (Pawelek, Low and Bermudes 2003, Anderson, et al. 2006).

3.2.3 Agricultural Applications

Agricultural applications of synthetic biology are an extension of genetic engineering of plant varieties and include wide-scale manipulation and creation of genomes. Genetically modified crops are often classified into one of three generations; first-generation crops include those engineered for enhanced input traits, second-generation crops include those with added-value output traits, and third-generation includes crops that improve the processing of bio-based fuels or produce pharmaceuticals. The move to higher generations of crops increases the complexity of genetic engineering. Currently, only first-generation GM crops are grown commercially; second- and third-generation GM crops are in various stages of research and development (Femandez-Cornejo and Caswell 2006).

Desirable properties include higher crop yields, pesticide and herbicide resistance, enhanced taste, composition or nutritional value, increased stress and draught resistance, and production of pharmaceuticals, fine-chemicals and recombinant proteins (Presidential Commission for the Study of Bioethical Issues 2010, European Commission 2008, Wang and Shi 2009). Since plants require large areas of land for growth they are typically grown in uncontained fields.

3.2.4 Energy Applications

The application of synthetic biology to energy production is currently the most active and commercially developed application area, having experienced a surge of interest and funding over the past years. One of the envisioned, biology-based paths from sunlight to biofuels, as shown in Figure 3.3, involves cultivation of plants that convert solar energy to chemical energy, transformation of biomass to sugars through enzymatic processes, and conversion of sugars into fuels through microbial fermentation. All three conversion steps can be engineered for increased efficiency, yield and tolerance. A second approach aims to engineer photosynthetic organisms to convert sunlight into biofuels in a consolidated process.

Figure 3.3 Route from sunlight, via cellulose and sugar, to fuels, illustrating the organisms that are involved in each step.
Biological systems can be used for production of all four fuel categories (alcohols, esters, ethers and hydrocarbons) and replace current modes of production that mainly rely on chemical processes. Currently, bioalcohols are the only biofuels that are produced on a commercial scale by the procedure outlined above. All other biofuels are produced chemically from biomass, rather than petroleum sources, hence the name.

Biodiesel is produced through transesterification, in which vegetable oil from algae, soy beans or other plants is mixed with either ethanol or methanol and a catalytic base. Proposed biological biodiesel production involve microbial conversion of either triglycerides or sugars into biodiesel (Fukuda, Kondo and Noda 2001, Kalscheuer, Stölting and Steinbüchel 2006). Dimethyl ether is produced chemically by mixing of methanol and water in the presence of a catalyst, a process known as methanol dehydration. Just like for biodiesel, dimethyl ethers can also be synthesized biologically by employing metabolic pathways in microorganisms. Finally, hydrocarbons can be produced either chemically, by dehydration or hydrogenation, or biologically by engineering metabolic pathways.

Using synthetic biology to engineer microorganisms for enhanced or novel biofuel production can significantly increase efficiency and decrease costs. While synthetic biology approaches are useful for increasing tolerance, growth and yields of desirable polymers in plants such as corn, sugarcane, soy and grasses, the major impact will be felt for microorganisms that are easier to engineer than plants and do not require direct land-use for growth (Savage, Way and Silver 2008). A number of companies in energy and synthetic biology are currently developing microorganisms for production of biofuels, as is described in the section on industrial actors later in the chapter.

The level of containment for biofuel production depends on the type of organism that is being used. In general, bacteria are cultivated in closed bioreactors, algae in photosynthetic reactors or semi-open ponds, and plants in open fields. Due to the early stage of most synthetic biology developments in this field, large-scale production and strategic choices regarding containment facilities and measures to limit environmental release have not been implemented yet.

### 3.2.5 Environmental Applications

Biological clean-up of hazardous chemicals (bioremediation) and organisms that are able to sense the presence and concentration of certain chemicals (biosensors) are two potential applications of synthetic biology within the environmental area (European Commision 2010, Presidential Commission for the Study of Bioethical Issues 2010, Tucker and Zilinskas 2006, Schmidt and Pei 2010). Biosensors derived from synthetic biology can detect toxic substances on-site with very short analysis times, a vast improvement over previous environmental monitoring methods (Schmidt and Pei 2010).

*In situ* bioremediation requires the release of genetically modified and synthetic microorganisms into the environment, and so does biosensing typically also. Bioremediation using naturally existing organisms that have been bred selectively has been used for several decades, but genetically modified bacteria have never been used in actual projects, as opposed to field testing, in the US or EU (Employee EPA 2010). One reason for this is that genetically engineered microorganisms tend to be weaker than those found in nature and
thus have a hard time surviving in the open environment. Furthermore, bioremediation is a complex process that involves multiple genes and biological networks and is therefore not amenable to the reductionist approach of one compound, one strain, one pathway found in traditional genetic engineering with rDNA (de Lorenzo 2008).

Systems and synthetic biology are seen as very promising approaches to reaching a solution to the many problems of in situ bioremediation. The ability to perform large-scale studies of genomes, metabolites and even whole microbial ecosystems increases both the understanding of biodegradation and the ability to predict, design and construct individual microorganisms or whole communities to efficiently degrade pollutants and toxic chemicals (de Lorenzo 2008). Engineered microorganisms are especially important for biological degradation of unnatural, xenobiotic compounds such as TNT, certain herbicides and industrial chemicals since natural systems have been exposed to xenobiotic compounds for a very short time and hence not evolved corresponding degrading capabilities (Rylott and Bruce 2008, Mattozzi, et al. 2006).

3.3 Application Examples

3.3.1 Health: Biological Synthesis of Artemisinin

Microbial synthesis of a precursor to the anti-malarial drug artemisinin, known as amorphadiene, is the first health-related application of synthetic biology. Artemisinin is traditionally extracted in small quantities from the wormwood plant, a process that requires large areas of land. Even though there are no naturally existing biosynthetic pathways for the microbial production of amorphadiene from which to start, the Keasling lab at the University of California Berkeley produced an E.coli strain capable of synthesizing amorphadiene by inserting and engineering a total of eight genes in 2003 (Martin, et al. 2003). For example, the genes coding for the entire mevalonate pathway found in the yeast Saccharomyces cerevisiae was transferred into the E.coli strain. Microbial production of artemisinin is considerably cheaper than previous production methods (Martin, et al. 2003). In later stages of development, the pathway was reengineered in yeast as this was seen as a more superior production organism than E.coli (Ro, et al. 2006).

3.3.2 Energy: Photosynthetic Microalgae

Photosynthetic algae have, due to their relatively high photosynthetic conversion efficiencies, diverse metabolic capabilities, superior growth rates, and ability to store or secrete energy-rich hydrocarbons, attracted significant interest as platforms for biofuel production. Microalgae operate close to the theoretical maximum of photosynthesis and experiments suggest a several-fold increase in biomass production per area of the best energy crops. Algae are also able to produce biomass with very high lipid content, which makes extraction easier (Savage, Way and Silver 2008). Finally, algae can be grown using waste or salt water on marginal land and do not compete with resources directly necessary for food production, unlike corn and soy (Radakovits, et al. 2010).

Technical problems to be overcome before microalgae are an economically viable platform for biofuel production include low light penetration in dense microagal cultures, the presence of invasive species in large-scale ponds, and the development of efficient
techniques for harvest of microalgal cells and extraction of bioenergy carriers. To overcome these issues and increase the productivity of microalgal systems, synthetic biology is used to engineer major biosynthetic pathways (illustrated in Figure 3.4). Biological engineering targets lipid metabolism and biosynthesis, direct pathways for biofuel synthesis, secretion systems, carbohydrate metabolism, and stress tolerance. Systems and synthetic biology are valuable tools because of the complexity and integration of networks, the multiple steps involved, and the need for lowering production costs (Radakovits, et al. 2010).

![Figure 3.4 Microalgal biosynthetic pathways (Radakovits, et al. 2010).](image)

3.3.3 Environment: Paraoxon Remediation

Paraoxon belongs to the toxic organophosphate class of molecules that have been used as pesticides and nerve gas agents. Paraoxon, which has been used as an insecticide, is much less toxic than the types of organophosphates that have been used as chemical weapons, but its persistence in the environment is a problem nonetheless. Paraoxon is, like all organophosphates, produced synthetically and therefore resists degradation by naturally existing microorganisms.

In 2006 a team at the University of California Berkeley reported on the engineering of a Pseudomonas putida strain which could efficiently degrade paraoxon and use it as a carbon, energy and phosphorous source through a completely novel biodegradative pathway. The strain was engineered by addition of multiple natural and synthetic operons, single genes and promoters from a wide range of different organisms. The complexity and large number of...
genes involved in this project distinguishes it from traditional genetic engineering, and is what enabled the design of a completely novel metabolic pathway.

### 3.4 Drivers for Commercial Development

The development of bio-based production methods through application of synthetic biology is dependent on a number of factors that are summarized in Figure 3.5. The application of synthetic biology to sectors such as industry, agriculture, health and the environment is dependent on factors that are related to both technological developments, economic constraints and societal context.

![Figure 3.5 Drivers of the adoption of synthetic biology to industrial production. Adopted from (Otero and Nielsen 2010).](image)

For example, when engineering a microorganism for production of biofuels or chemicals, several different feedstocks can be used; the choice of which is as much a question of technical feasibility as it is of economic constraints. Further, the choice of application areas and organisms has been shown to influence public perception, and this also needs to be considered. Finally, political actions, such as whether or not biofuels are subsidised, also have a large influence on the commercial development of synthetic biology. It is worth keeping these factors, the complexity of their interactions and their influence on synthetic biology in mind when discussing potential application areas and products.

### 3.5 Industrial Actors

Companies within synthetic biology can be divided into two categories: those that provide synthetic DNA (oligonucleotides, genes or genomes) and those that consume synthetic DNA to construct novel biological systems. Providers of synthetic DNA include ATG:biosynthesis, Blue Heron Biotechnology, DNA 2.0, Geneart and Genomatica. Consumers of synthetic DNA include Amyris, Codexis, Modular Genetics, DSM and LS9.
A number of the leading companies engaging in synthetic biology are described briefly, focusing on those that consume synthetic DNA.

### 3.5.1 Synthetic Genomics Inc.

Synthetic Genomics was founded in 2005 and is based in La Jolla, California. They use an array of genome engineering techniques to develop microorganisms and plants that can transform biomass into chemicals and fuels. Their most well-known project involves engineering photosynthetic algae for production of biofuels, a project in which they have partnered with ExxonMobil. In July 2010 they opened a greenhouse facility for testing of various algae, both natural and engineered strains, in different growth systems such as open ponds and closed photobioreactors, under a wide range of conditions with varying temperatures, light levels and nutrient concentrations. An outdoor testing facility is scheduled for opening in mid-2011 (ExxonMobil 2010).

Synthetic Genomics have also partnered with BP for the development of microbial-enhanced solutions to improve hydrocarbon recovery and conversion solutions for production of fuels and chemicals from subsurface hydrocarbon reserves. Additionally, they collaborate with the Asiatic Centre for Genome Technology in a project to engineer and improve plants for biomass or fuel production. The plants, mainly oil palm and jatropha, have been engineered for increased yield, disease resistance and economic viability (Synthetic Genomics Inc. 2011, Rodemeyer, New Life, Old Bottles 2009).

### 3.5.2 Amyris

Amyris was founded in 2003 and is based in Emeryville, California. They have raised capital from a number of venture capitalists and foundations including the Bill & Melinda Gates Foundation, Khosla Ventures, TPG Biotechnology, Advanced Equities Inc, DAG Ventures, and the Westly Group. Amyris first developed its platform technology for non-profit production of the previously discussed anti-malarial drug artemisinin but are currently using this platform for production of a broad range of renewable fuels and chemicals in yeast. The engineered yeast convert sugar into a class of compounds called isoprenoids, which include pharmaceuticals, industrial chemicals and fuels. Their initial focus lies on the 15-carbon isoprenoid beta-farnesene, which can be chemically derivatized into a variety of products. Amyris uses sugarcane as feedstock and will place production in Brazil, launching their first production facility during the second quarter of 2012 (Amyris 2011).

### 3.5.3 Joule Unlimited

Joule was founded in 2007 by Flagship VentureLabs and is based in Cambridge, Massachusetts. The business model relies on applying advanced genome engineering to develop a library of engineered photosynthetic microorganisms that use solar energy to convert carbon dioxide and water directly into ethanol or hydrocarbon fuels. Waste carbon dioxide is the only feedstock that is required apart from water. The process offers an advantage over making biofuels from corn or cellulose since it does not require large amounts of arable land. Further, since organisms are engineered to directly synthesize and secrete fuels, a number of production steps, such as biomass harvesting and downstream
refinement, are eliminated. Joule completed its first pilot plant in Leander, Texas, and will begin commercial production in 2012 (Joule Unlimited 2011).

Figure 3.6 Joule’s proposed production system for chemicals and fuels (Joule Unlimited 2011).

3.5.4 LS9, Inc.

LS9 was founded in 2005 by Flagship VentureLabs and is based in South San Francisco, California. Their overall business model is to develop biological, fermentation-based processes for production of traditional petroleum products such as chemicals and fuels starting from renewable raw materials. To achieve this they use synthetic biology approaches to engineer a wide range of so-called DesignerMicrobes™ for use in fermentation processes. The technology platform and production methods are the same for production of fuels and chemicals, but with changes in metabolic pathways of employed microorganisms. LS9 is in the process of starting a demonstration plant, called the LS9 Renewable Petroleum Facility, in Florida for scale-up and demonstration of their technologies and paving the way towards full commercialization (LS9, Inc. 2010).

Synthetic biology has been essential in engineering the LS9 microbial catalysts. The biosynthetic pathways to produce finished fuel products do not exist in native E. coli and the genes for alkane biosynthetic were largely unknown. In engineering its microbial catalysts, LS9 designed the pathways, synthesized the genes encoding each enzyme in the pathway and constructed biosynthetic operons for insertion into the E. coli production strains. Yield and productivity were improved through genetic optimization of biosynthetic pathways and production strains by synthetic biology approaches such as computational design and automated parallel construction of gene, operon and recombinant cell libraries for rapid construction and evaluation of thousands of engineered microorganisms (Biotechnology Industry Organization 2010).
3.5.5 Genencor

Genencor, which is a division of the Danish company Danisco, was founded in 1982 and is based in Palo Alto, California. They are a leading producer of industrial enzymes and proteins (Genencor 2011). In 2008 they entered a collaboration with Goodyear Tire & Rubber Company to develop a reliable, high-efficiency fermentation-based process for the BioIsoprene™ monomer, which is used in the production of synthetic rubber. Microorganisms are engineered using synthetic biology approaches to optimize the microbial expression of genes for isoprene synthesis originally derived from plants (Biotechnology Industry Organization 2010).

3.5.6 Codexis, Inc.

Codexis was founded in 2002 and is headquartered in Redwood City, California. They develop customized enzymes for use in energy production, household care, foods and industry. Their technology platform Codexis CodeEvolver™ uses gene shuffling and other whole-genome techniques to engineer enzymes and microbial production strains (Codexis, Inc. 2011). Codexis and Merck are collaborating to develop a new transaminase capable of catalyzing the biocatalytic route for synthesis of the type II diabetes treatment Sitagliptin, a dipeptidyl peptidase-4 inhibitor that was previously synthesized chemically. Codexis identified a new enzyme that provided some initial activity and improved its activity greater than 25,000-fold. The enzymatic production method is currently in scale-up towards commercial manufacture (Biotechnology Industry Organization 2010).

3.5.7 Royal DSM

Royal DSM was founded in 1902 and is headquartered in Heerlen, the Netherlands. They have used synthetic biology approaches to improve an existing process for production of the antibiotic Cephalexin. They introduced and optimized two genes for fermentation of the precursor, which was subsequently converted into Cephalexin in two enzymatic steps. This microbial production method replaced the previous process that required thirteen chemical steps. DSM has also used synthetic biology to develop yeast strains that are capable of co-fermenting hexoses and pentoses, and new production methods for succinic acid, which is traditionally made from petroleum based feedstocks (Biotechnology Industry Organization 2010).

3.6 Conclusion

These two chapters have shown that synthetic biology has the potential to transform production methods and process in a number of sectors, ranging from healthcare to energy, and that these developments are, in fact, already well underway. Currently, the focus lies on the development of biofuels and chemicals, with extensive product launches within the next few years. This rapid development of the academic-industrial base of synthetic biology and corresponding product launches has led to a lively societal discussion about its benefits, risks and regulations; an overview of which is provided in the next part of the thesis.
PART II:
Risk and Perception of Synthetic Biology
CHAPTER 4 Framework for Risk and Regulatory Analysis

Before heading into a discussion and evaluation of risks and concerns expressed about synthetic biology, a framework for analyzing risk, risk perception, assessment and regulation is developed. This framework will be used in subsequent chapters and their evaluation of risks, perceptions and applicability of regulations. Developing a framework to apply while evaluating risks and regulations will give a more structured analysis and clearer results.

The chapter begins with a brief introduction to the concept of risk in modern societies, followed by a review and comparison of two disparate frameworks for risk assessment. Third is a discussion of the specific challenges that scientific uncertainty adds to risk assessment and management, with an overview of the two main approaches by which governments can design policies and regulations in areas with uncertain scientific estimates of risk. The chapter then moves to discuss the difference between physical and non-physical risks and the problems that modern societies have had in addressing non-physical risks historically. Finally, the notion of risk perception and factors that have been shown to influence it are introduced.

4.1 Post-Industrial Risks

It is only quite lately that risk has emerged as a central topic in society and governmental activity. Risk materializes as a side-effect in the industrial production of wealth and material goods, and the logic of risk distribution becomes a key concept alongside the traditional logic of wealth distribution as industrial societies transition into late modernity. In Europe and the United States, this transition begun during the 1970s, during which governments started responding to a range of risks by designing new statutes, regulations and administrative agencies (Beck 1992).

It is important to differentiate between traditional risks and those that emerge as a result of industrial production (also known as post-industrial risks). Traditional risks include those that individuals are able to sense and respond to, examples of which include a speeding car or burning house. Post-industrial risk, such as nuclear radiation and toxic chemicals, are of a different nature because we are limited in our ability to detect and react to them. Since post-industrial risks are indiscernible to human senses, they exist only in our scientific knowledge about them and are thus open to social definition and construction. Finally, they are also of a more far-reaching and global character than traditional risks and typically lack connection to their place of origin (Beck 1992).

Beck’s analysis of the concept of risk in post-industrial societies appears highly relevant to synthetic biology. Because of the inability of our senses to perceive risks of synthetic biology we have to rely on the scientific method for their assessment and evaluation. The conceptual framework of risk assessment is the principal method by which post-industrial risks are evaluated. Methodologies for risk assessment have evolved alongside the increasing awareness of post-industrial risks; today, there are a number of perspectives on the proper approach and content of an adequate risk assessment, two of which are presented below.

4.2 Risk Assessment

Risk in its most mathematical, abstract sense corresponds to the probability of an adverse event multiplied by the impact of the adverse event (Kasperson, et al. 1988).
Assessing the probability and impact of an adverse event involves multiple steps, such as hazard identification and evaluation, risk characterization, and vulnerability analysis, all of which combine into the final risk assessment. Two main methodologies for risk assessment, the compartmentalized and the integrated, are described.

4.2.1 The Compartmentalized Approach

The compartmentalized approach to risk assessment is presented in the National Research Council’s publication *Risk Assessment in the Federal Government*, and quickly became very influential. It has subsequently been broadened and adapted to assess not only human health risks of carcinogens, but a range of risks to both human health and the environment (EPA 2011). Risk assessment is defined as “the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations”, a process which is largely science-based and removed from political, social and emotive factors. As illustrated in Figure 4.1, a risk assessment under this paradigm consists of four major steps:

1. Hazard identification – determining whether an agent presents a risk and the nature and strength of the causation;
2. Dose-response assessment – characterizing the relation between the dose of an agent and the biological response in humans;
3. Exposure assessment – measuring or estimating the intensity, frequency and duration of human exposure to the agent;
4. Risk characterization – estimating the incidence of health effects under the various conditions by combining data from the dose-response and exposure assessments.

![Figure 4.1 The compartmentalized risk assessment paradigm, with the distinction between risk assessment and risk management clearly illustrated (National Research Council 1983).](image)

The distinction and separation outlined above between science, driving risk characterization, and policy, driving risk management, is one of the main points of the compartmentalized approach. Policy choices are only allowed to enter the assessment process when scientific knowledge is uncertain, and are thus viewed as a consequence of scientific uncertainty; not
as inherent in the process of risk assessment. Furthermore, political and economic considerations are viewed as fundamentally alien to risk assessment.

4.2.2 The Integrated Approach

The notion that it is possible and desirable to maintain a stable demarcation between science and policy throughout the regulatory process that permeated Risk Assessment in the Federal Government was criticized in a later publication by the National Research Council called Understanding Risk: Informing Decisions in a Democratic Society. This book argues that risk characterization must be seen as an integral part of the entire process of risk decision-making rather than a summary of the scientific finding of risk. Risk characterization is viewed as an analytical-deliberative process whereby the analytical assessment of risk and uncertainty is coupled to an ongoing deliberation among stakeholders to determine future steps and methods to reduce uncertainty.

Risk characterization is defined as "a synthesis and summary of information about a potentially hazardous situation that addresses the needs and interests of decision makers and of interested and affected parties." The process by which risks are characterized, as illustrated in Figure 4.2, is set-up to be recursive, rather than linear, where analysis adds new information while deliberation brings new insights, questions and problem formulations.

![Figure 4.2 The integrative approach to risk assessment (National Research Council 1996).](image)

In order to fulfill its integrative objective, risk characterization must include a scientific estimation of risks that is guided by the decision and directed to issues most pertinent to it, rather than one that progresses in isolation. If the estimation of risk is not decision driven, the resulting risk characterization could become irrelevant to the decision-making process in which it is ultimately to be used and result in inability to proceed. Furthermore, recognition that risks to social, ethical, or ecological values are equally important factors to consider as risks to safety and human health leads to an emphasis on recognizing all significant concerns. Finally, iteration between analysis, which produces answers to factual questions, and deliberation, which increases understanding and reaches concrete conclusions, is considered vital to the process (National Research Council 1996).
4.2.3 Conclusion

Review of, and comparison between, the compartmentalized and integrated risk assessment methodologies shows that the assessment of risks can be viewed either as a strictly scientific activity whose purpose it is to produce a risk estimate that lies as close as possible to the real risk, or as a process of societal discussion whose purpose it is to produce a risk estimate that is acceptable to all relevant stakeholders and is appropriate to the decision-making process. These two perspectives are fundamentally different, both with respect to their philosophical basis and to the procedural requirements of recommended methodologies. In a later stage of this thesis, regulations and governmental methods for risk assessment are evaluated to discern which of the two perspectives they ascribe to.

4.3 The Challenge of Uncertainty

Risk situations can be specified according to their position on a certainty-consensus continuum. At one extreme, we find risk cases that are characterized by high certainty in the available scientific knowledge and analytical models to apply, as well as high consensus with respect to the framing of scientific issues and important values to protect through public policy. At the other extreme, risk cases are characterized by low certainty and low consensus, with low availability and certainty of scientific evidence and disagreement about what potential harms consist their framing (Winickoff, et al. 2005).

The lack of conclusive evidence in areas of low scientific certainty and consensus leads to a situation where the government and regulators are exposed to, and ultimately have to choose from, different knowledge claims from various stakeholders without having an agreed upon body of scientific knowledge upon which to rely (Nielsen and Myhr 2007). This does, of course, create a problem to governmental and regulatory officials, who tend to respond to the dilemma by employing either a precautionary or reactive approach. Key characteristics of the two approaches are described below.

4.3.1 The Precautionary Approach

The precautionary approach emerged as a method for addressing environmental and human health risks during the 1970s, although there are a few earlier examples of its use (Gee and Guedes Vaz 2002). The main element of the precautionary principle is the notion that situations of conceivably serious or irreversible harm to health or the environment potentially require action before strong scientific proof of harm has been developed. The precautionary principle is applicable when the potential harm is either significant or irreversible, scientific knowledge is uncertain, and system interactions are too complex to enable prediction of the impact of a single activity (Ashford and Miller 1998, Gee and Guedes Vaz 2002). Characteristics of a precautionary regulatory system include:

1. Action to reduce risks before full proof of harm is available if impacts are potentially serious or irreversible;
2. Research and monitoring for the early detection of hazards;
3. A general reduction of environmental burdens;
4. The proportionality principle, where the costs of actions to prevent hazards should not be disproportionate to the likely benefits;
5. A cooperative approach between stakeholders to solving common problems and addressing safety issues via integrated policy measures that aim to improve the environment, competitiveness and employment;

The precautionary approach has become controversial during the past decade, much because of the controversies between the US and EU concerning the need for precaution in regulation of genetically modified crops, hormones in beef, global warming and other contentious issues. The precautionary approach is frequently, and incorrectly, argued to be a European phenomenon; the US has implemented precaution in a number of policy areas, examples of which are shown in Table 4.1.

Table 4.1 Some examples of precautionary prevention in the United States (Gee and Guedes Vaz 2002).

<table>
<thead>
<tr>
<th>Issue</th>
<th>Precautionary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food safety (carcinogenic additives)</td>
<td>The Delaney Clause in the Food, Drug and Cosmetics Act, 1957–96 that banned animal carcinogens from the human food chain.</td>
</tr>
<tr>
<td>Food safety (BSE)</td>
<td>A ban on the use of scrapie-infected sheep and goat meat in the animal and human food chain in the early 1970s may have helped the US to avoid BSE.</td>
</tr>
<tr>
<td>Environmental safety</td>
<td>A ban on the use of chlorofluorocarbons (CFCs) in aerosols in 1977, several years before similar action in most of Europe.</td>
</tr>
</tbody>
</table>

4.3.2 The Reactive Approach

The reactive approach manages uncertainty through the proof-before-action principle, arguing that empirical proof of harm is a prerequisite for governmental risk regulation and action to limit marketing of a product. Uncertainty is seen to lead to politicization of risk and the potential for irrational policies that remain locked-in despite evidence of safety, and the regulatory system is designed to reduce unnecessary regulatory lock-ins that limit economic development (Sapolsky 1990). Products are placed on the market without prior individual assessment of risks to humans or the environment; they are only screened to ensure that they do not produce similar hazards as those that have been scientifically established for earlier generations of products. The reactive approach thus creates a regulatory system that reacts to hazards after they have been shown empirically, and is characterized by the following features (Tait 2001):

1. A statistically convincing standard of proof is demanded before any claimed or suspected hazard is given official credence;
2. The industry concerned and/or its products are controlled by a system set up in response to such scientifically proven impacts;
3. New products and processes are screened to make sure that they do not give rise to any similar hazards;
4. The regulatory system is built up slowly in a piecemeal fashion as new generations of product or process exhibit different hazards;
5. Decisions about the need for regulation and the level of regulation required are based on an analysis of relevant costs and benefits.
4.3.3 Conclusion

The review of the specific challenges that scientific uncertainty pose to regulatory decision making has revealed two different approaches by which governments can manage uncertainty: the reactive approach and the precautionary. In subsequent chapters, risks of synthetic biology are evaluated to determine their potential for reaching scientific certainty and consensus as an indication of the degree to which uncertainty will be a challenge to risk regulation of synthetic biology. If it is found that scientific uncertainty appears likely, regulations governing synthetic biology will be analyzed to establish which of the two approaches that appears most dominant.

4.4 Physical and Non-Physical Risks

It is also worth discussing the distinction between physical and non-physical risks. Physical risks have the potential to cause physical damage and harm to individuals or the environment, whereas non-physical risks have the potential to cause emotional distress, harm the well-being of individuals or communities, and go counter to moral values and ethical beliefs. They include deeply held views and values about fairness, equity, and the proper relationship between humans and the natural world.

Typically, physical risks lend themselves to being framed in technical and scientific terms, whereas non-physical risks are best framed in social and ethical terms. In part because of framing, and in part because of the difficulty in reaching agreement over values, modern societies have a track record of framing risks as a scientific matter and tuning regulatory systems to dealing with physical harm. Consequently, open discussion and governmental treatment of non-physical risks and concerns is more or less eliminated (Beck 1992, Kaebnick 2009, Stermerding and Brom 2010, Parens, Johnston and Moses 2009).

Again, the identified risks of synthetic biology will be evaluated to determine whether they are of a physical or non-physical character and regulatory frameworks will be analyzed to conclude the degree to which physical and non-physical risks are addressed.

4.5 Risk Perception

Finally, risk perception is important to investigate for two primary reasons. First of all, the societal perception of risk has been shown to be influenced by more than its mathematic, probabilistic representation (Slovic 1987, Slovic 1991, Wolt and Peterson 2000, Winickoff, et al. 2005, Sjöberg, Perceived Risk and Tampering with Nature 2000, Kaspersen, et al. 1988, Slovic 2002). Second, because governments are responsible not only to the technocrats performing risks assessments but also to the wider public, they must be sensitive to public images of risk. It is therefore important to understand and evaluate factors that influence the perception of risk alongside traditional risk assessment methodologies.

Risky events interact with social and cultural processes, such as economic biases and cultural values, in ways that can either increase or reduce their perceived riskiness (Kaspersen, et al. 1988, Tait 2001). A number of attributes of a potentially harmful event have been shown to influence both its perceived riskiness and the desire for governmental regulation to manage it. A list of influential factors is provided in Figure 4.3, with Figure 4.4 illustrating societal perceptions of potentially harmful events categorized according to the factors in Figure 4.3.
Figure 4.3 Characterization of factors included in the definition of dread and unknown (Slovic 2002).

Figure 4.4 Location of hazards based on the degree to which they are judged as dreadful and known, with DNA technology in the far upper-right corner (Slovic 2002).

As is shown in Figure 4.4, DNA technology is judged as having the potential to produce risks that are highly dreadful, unobservable and uncontrollable. DNA technologies have been shown to score particularly high on factors related to “unfamiliarity”, defined as hazards judged to be unobservable, unknown, new, and delayed in their manifestation of harm (Slovic 1987, Slovic 1991, Slovic 1993, Slovic 2002). Such technologies are generally subject to higher demands for government regulation than other types of technologies. The inability of humans to perceive and influence dreadful and unknown risks coupled to their perceived potential for great harm leads to calls for scientific investigation and government regulation, whereas decisions about undreadful and well-known risks are generally seen as an individual matter. This finding goes in line with Beck’s analysis of post-industrial risks,
especially upon finding that hazards positioned in the upper-right quadrant of Figure 4.4 are related to industrial and technologically advanced activity to a higher degree than risks in the other three quadrants.

Furthermore, trust has been shown to have a central role in risk assessment, management and regulation. Lack of trust underlies the controversies of industrial risks management and technological decision-making in contentious areas such as nuclear waste management and GM crops (Andersson 2008, Bernauer 2003, Slovic 1991, Slovic 1993). The traditional paradigm for risk assessment driven by science and experts, as described in the next chapter, requires high levels of trust amongst the public for it to operate. In general, European citizens have expressed higher levels of trust in their government than their US equivalents. Consequently, the European system relies on expert judgment and governmental administration of risks, while this US system relies on litigation, questioning of expert judgments and citizen intervention in administrative proceedings (Slovic 1993).

Finally, extreme events and moral factors have also been shown to influence risk perception. The 2001 terrorist attack in the US is an example of an extreme event that has led to a strong governmental response to limit similar risks. This is in part due to the perception of risks of terrorism as poorly understood and catastrophic, which leads to the view that terrorist attacks anywhere in the world are indicators of increased risk everywhere, a process which does not occur for familiar and well-understood systems (such as a train-wreck). Furthermore, moral factors, such as “unnatural” and “immoral”, related to the notion of interfering with nature and the proper role of humanity, are also important to shaping risk perception (Sjöberg 2000). Table 4.2 provides a summary of influential factors in risk perception.


<table>
<thead>
<tr>
<th>Emotive attribute</th>
<th>Basis of risk perception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involuntary</td>
<td>A risk one is forced to take</td>
</tr>
<tr>
<td>Uncontrollable</td>
<td>The inability to personally influence an event</td>
</tr>
<tr>
<td>Immoral</td>
<td>Something that is viewed as evil</td>
</tr>
<tr>
<td>Unfamiliar</td>
<td>A new and unnatural (manufactured) risk</td>
</tr>
<tr>
<td>Dreadful</td>
<td>A risk that relates to a fearful consequence</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Scientists are unable to exactly define the hazard and its associated risk</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>Large-scale disastrous events</td>
</tr>
<tr>
<td>Unfair</td>
<td>Exposure to risk without clear benefit</td>
</tr>
<tr>
<td>Untrustworthy</td>
<td>No confidence in the source of risk analysis</td>
</tr>
</tbody>
</table>
4.6 Summary

The purpose of this chapter has been to develop a framework by which risks and regulations of synthetic biology can be systematically evaluated, focusing on four relevant factors, as summarized in Table 4.3. In subsequent chapters, risks and regulations will be evaluated with respect to these areas, approaches and factors, starting with the next two chapters that provide an overview of the risk perceptions of societal actors and an evaluation of the risks that are brought up in their reports.

Table 4.3 Summary of areas that are included in the framework for risk and regulatory analysis.

<table>
<thead>
<tr>
<th>Area</th>
<th>Significance</th>
<th>Approaches or factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment</td>
<td>Methods and processes by which risks are evaluated and estimated are central to the design of a regulatory system</td>
<td>Compartmentalized or integrated</td>
</tr>
<tr>
<td>Scientific uncertainty</td>
<td>Low scientific certainty and consensus creates specific problems in risk assessment and management</td>
<td>Precautionary or reactive</td>
</tr>
<tr>
<td>Physical and non-</td>
<td>Regulatory frameworks are generally geared towards dealing with physical risks, and have trouble with addressing non-physical risks</td>
<td>Potential for harm to health and property or values and well-being</td>
</tr>
<tr>
<td>physical risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk perception</td>
<td>Societal perception of risk is dependent on more than its mathematical, probabilistic representation</td>
<td>Familiarity, controllability, morality, trust etc.</td>
</tr>
</tbody>
</table>


CHAPTER 5 Risk Perceptions of Societal Actors

The societal discussion about risk of synthetic biology is already well underway, as is illustrated by the numerous reports on the subject that have been published so far. A number of organizations – European, American, governmental, non-governmental and industrial – have published reports outlining their view of synthetic biology; its benefits, risks, and regulatory requirements. Reports have been analyzed with regards to the risks and concerns of synthetic biology that they mention and how they recommend regulations to be developed. The purpose of the review is to describe the framing of synthetic biology, which types of risks that are emphasized and where conflicts are being played out. Furthermore, the review will form the basis for the risk evaluation provided in the next chapter.

A total of eleven reports from nine organizations have been reviewed. The organizations are presented in chronological order, based on the date of their first publication on synthetic biology. An evaluation of the Asilomar conferences on recombinant DNA (rDNA) is provided first, as an historical account and introduction to biotechnology regulation. The chapter concludes with a conclusion about contrasting views between actors, and is followed by a more formal evaluation of risks in the next chapter.

5.1 The Asilomar Conferences

When rDNA technologies, which enable the insertion of specific genes into host organisms through a type of “cut and paste” technique using restriction enzymes, were developed in the early 1970s (Cohen, et al. 1973, Lobban and Kaiser 1973), concerns about potential biohazards emerged more or less in parallel with the technological developments. The two Asilomar conferences were set-up as a response to these concerns, with the first, preliminary conference being held as early as 1973. Furthermore, the National Academy of Sciences (NAS) put together an eleven-member committee under the chairmanship of Paul Berg, to do a preliminary study of potential biohazards of rDNA. The committee published their report in 1974, and called for a temporary moratorium on certain types of rDNA research until the risks were better understood and precautionary measures had been implemented (Jasanoff 2005).

The committee also proposed an international scientific meeting to review scientific progress in the field and discuss appropriate ways to deal with biohazards of rDNA. Therefore, a follow-up conference to the first Asilomar conference was held in 1975, attended mainly by scientists (140 biologists and physicians) and a small group of lawyers and journalists (Berg, et al. 1975, Jasanoff 2005). This conference established the foundation of current frameworks for assessing and managing biosafety risks of biotechnology, and still reverberates through the policy discourse on biotechnology (Jasanoff 2005) – suggestions have even been made to perform an Asilomar-style conference to address risks of synthetic biology (Ferber 2004, Kahn 2007).

The risks that preoccupied scientists at Asilomar were biological; broader ethical, socio-economic and political implications of rDNA were put aside (Jasanoff 2005). The goal was to establish guidelines and best practices for how the scientific work could be undertaken with minimal risks to laboratory workers, the public at large, and to animal and plant species sharing our ecosystems. Biological and physical containment of newly created organisms constituted the principal methods for minimization of risks (Berg, et al. 1975). Risks were
seen as emerging on the molecular level through manipulation of genes and through the unchecked spreading of those genes into the environment, and policy measures were designed to control both genetic, molecular manipulation and containment (Jasanoff 2005).

This view on where and how risks of rDNA emerged was in part a result of the dominance of the scientific community in framing and specifying risks. The restricted participation at the Asilomar conferences together with their emphasis on regulation of scientists by and for scientists strikes us as most noteworthy today (Jasanoff 2005). As such, Asilomar represents a science-driven process limited to assessing technical health and safety issues. Society has evolved a great deal in the 35 years since Asilomar, and today we see a much broader discussion over risks and concerns of modern biotechnologies (Capron and Schapiro 2001). It is thus unlikely that enacting an Asilomar-style conference to address risks of synthetic biology will form a sufficient base for government regulation. The remainder of this chapter provides an overview of the current opinions about risk and regulation of synthetic biology.

5.2 National Science Advisory Board for National Security

NSABB is an independent federal advisory committee charged with advising the US government on biosecurity issues and dual-use research and technologies. Biological dual-use research is defined as “biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security” (Office of Science Policy (NIH) 2010). NSABB has published two reports relating to the security concerns of synthetic biology, Addressing Biosecurity Concerns Related to the Synthesis of Select Agents in 2006 and Addressing Biosecurity Concerns Related to Synthetic Biology in 2010.

The 2006 report identifies four specific biosecurity concerns: ease of acquisition of synthetic select agent nucleic acids, increased capabilities for constructing new pathogens, the need for additional regulatory clarity in specific areas, and difficulty in developing a suitable regulatory framework due to the lack of consensus among scientists regarding preferred methods for defining select agents and for screening sequences. They recommend that HHS and USDA collectively develop guidelines for providers of synthetic DNA concerning select agents and the select agent regulations with respect to synthetically derived DNA. Further, they propose the development of a screening framework to be used by providers of synthetic DNA. Finally, they recommend attempts to reach a scientific consensus about the definition and identification of select agents, since merely sequence homology is seen as becoming more and more problematic in light of new developments (National Science Advisory Board for Biosecurity 2006).

The 2010 report discusses many of the same issues as the 2006 report, but also emphasizes that the interdisciplinary nature of synthetic biology and the diversity of those conducting research in the field is an additional risk and challenge to effective government oversight. Specific recommendations include strengthened oversight of synthetic biology, both within and outside of academia and the life sciences, the need for education in biosecurity issues to the synthetic biology research community, and increased monitoring of developments in synthetic biology and understanding of virulence/pathogenicity by the US government (National Science Advisory Board for Biosecurity 2010).
5.3 J. Craig Venter Institute

The J. Craig Venter Institute has been the most active actor from the academic-industrial complex engaging in the debate about synthetic biology. It is a not-for-profit research institute dedicated to the advancement of the science of genomics, formed in October 2006 through the merging of several affiliated organizations. Today, the J. Craig Venter Institute employs 400 scientists, all engaged in genomic related research (J.C. Venter Institute 2011).

In 2007, the J. Craig Venter Institute, the Center for Strategic and International Studies and MIT published the report Synthetic Genomics: Options for Governance, made possible by funding from the Alfred P. Sloan Foundation. The report focuses on three risks; the risk of its use in bioterrorism, risks to the health of laboratory workers and to the public, and possible harm to the environment and communities close to laboratories due to accidental release of microbes with synthetic genomes. A number of policy options are presented and evaluated for their effectiveness in reducing biosecurity risks, health risks and risks of accidental release, as well as their overall costs to the government and industry, whether additional research is needed, whether they impede biological research and progress and whether they promote constructive applications of the technology (Garfinkel, et al. 2007).

5.4 ETC Group

The ETC Group (Action Group on Erosion, Technology and Concentration) is “dedicated to the conservation and sustainable advancement of cultural and ecological diversity and human rights” (The ETC Group 2011). ETC have been deeply engaged in issues relating to the development of biotechnology since the 1980s, and published their first report on synthetic biology in 2007 Extreme Genetic Engineering: An Introduction to Synthetic Biology, and a second in 2010 The New Biomasters: Synthetic Biology and the Next Assault on Biodiversity and Livelihoods.

As the names of the reports imply, ETC views synthetic biology as a threat to biodiversity, global justice and human rights. The 2007 report focuses on six areas of concern; bioweapons, increased biofuel production and its impact on land use and food production, the development of monopolies due to the current patent policies, effects on biodiversity, implications on trade and global justice, and the effects of releasing synthetic organisms into the environment. The report concludes by recommending the initiation of a broad societal debate about synthetic biology’s wider socio-economic and ethical implications, to move away from a situation in which scientists control public discourse and regulatory frameworks, that environmental release of de novo synthetic organisms should be prohibited until wide societal debate and strong governance systems are in place, that international bodies review synthetic biology, that intellectual property rights be heavily restricted on “the basic building blocks of life” and that an international body should be established to monitor and assess societal impacts of emerging technologies, including synthetic biology (ETC Group 2007).

5.5 International Association for Synthetic Biology

The International Association Synthetic Biology (IASB) was founded by a group of biotech companies whose products and services relate to synthetic biology, and is based in
Heidelberg. The main focus of the association is the advancement and future development of synthetic biology (The International Association Synthetic Biology 2011).

The IASB published their report *Technical solutions for biosecurity in synthetic biology* in 2008. As the name implies, the IASB only considers risks to security caused by synthetic biology, and promotes a self-regulatory regime including best practices and codes of conduct. They do, however, mention biosafety concerns as well, and indicate the possibility for a second report on that topic. Sequencing of DNA and customers by gene synthesis companies are recommended as technical solutions to limit biosecurity risks (International Association for Synthetic Biology 2011).

### 5.6 Woodrow Wilson International Center for Scholars

The Wilson Center was established in memory of President Wilson in 1968 and has since sought to connect the world of learning with the world of politics. It has an extensive program on synthetic biology that has published several reports, including *Ethical Issues in Synthetic Biology and New Life, Old Bottles*, both published in 2009.

*Ethical Issues in Synthetic Biology* provides an overview of the debates about ethics and synthetic biology. The report highlights how most discussions about synthetic biology have focused on physical harms and more or less overlooked non-physical harms. Non-physical concerns that are brought up by the report include concerns that developments in which lower life forms are viewed as “artifacts” could lead to less respect for higher forms of life, and that human adoption of an attitude of creators is a mistake about our role and purpose as beings and species.

The relative ease of agreeing that physical harm is undesired compared to the difficulty in agreeing about the extent to which an activity threatens moral values is seen as the main reason for the relatively weak discussion about non-physical harms. Fairness, equity and justice are contested values with multiple interpretations and it is hence hard to reach a similar consensus as for physical harm. The authors argue that non-physical harms should be discussed and addressed in much more detail than has been the case previously and recommend that those who fund and lead research in synthetic biology should also seek to evaluate physical and non-physical harms. It would be a mistake to discontinue discussions about competing conceptions of well-being and synthetic biology simply because of the problems in reaching a consensus (Parens, Johnston and Moses 2009).

The second report, *New Life, Old Bottles*, was published in October 2009. This report is focused on assessing the applicability and adequacy of the current US regulatory system designed for assessing the safety of genetically modified organisms with regards to synthetic biology. The report focuses on potential risks to the public and environment of accidental and intentional release of synthetic microorganisms. For intentional release, the report identifies three risks: the risk that synthetic microorganisms interact with naturally occurring organisms and adversely affect the environment, that synthetic genetic material could be spread to other species, and the instability posed by the ability of living organisms to mutate and evolve.

The report argues that the current regulatory and risk assessment frameworks will most likely be insufficient to handle synthetic biology since they all rest on the comparison...
between engineered organisms and their natural counterparts. With synthetic biology it is, however, possible to produce increasingly complex organisms with genetic elements from a large number of other organisms, or even completely synthetic genomes without natural precedent; hence making comparison obsolete as risk assessment strategy. New frameworks for assessing risks should therefore be developed. Uncertainty is also mentioned as an even more prevalent element that must be handled by risk assessment frameworks. Therefore, the report recommends increasing research about risks of synthetic microorganisms to provide agencies with an informed basis upon which to base risk assessments and regulatory decisions (Rodemeyer, New Life, Old Bottles 2009).

5.7 European Group on Ethics in Science and New Technologies

The EGE is an independent body advising the European Commission on ethics in science and new technologies in connection with EU legislation or policies, and published their opinion Ethics of Synthetic Biology in November 2009 (European Group on Ethics in Science and New Technologies 2009). The report focuses on four ethical aspects of synthetic biology; biosafety, biosecurity, justice, and intellectual property. Within biosafety, the report emphasizes the risk for unexpected interactions between synthetic organisms and the environment or other organisms that could lead to both horizontal gene transfer and effects on the biotic balance and disruption on other species in the ecosystem. With regard to environmental protection, the precautionary principle is mentioned as especially central. Biosecurity is discussed as being threatened by both state and non-state actors, although the cost of technologies for producing novel pathogens and/or other bioweapons is seen as limiting risks from bioterrorism.

With regards to justice, the report cites Rawls theory of distributive justice and argues that principles of justice are central to the development of synthetic biology. Specific elements of justice that are mentioned include the role of the state in protecting its citizens and favoring human rights, global justice, inter-generational justice, and the social contract affecting the actions of leaders against the desires of citizens. Finally, intellectual property is discussed extensively with emphasis on the different roles and effects of the patent system. Three types of inventions are discussed: those that are common to all humankind and should not be patentable, those which should be placed in the public domain for more practical reasons, and those that are patentable.

In terms of specific recommendations, the report finds that biosafety regulation and risk assessment should be adjusted to organisms in which the genome is either entirely synthetic or made up of DNA from several different organisms. The uncertainty in determining the effects on the environment and ecosystems when releasing synthetic organisms and the need to reduce this uncertainty is also discussed in detail. Specifically, the deliberate release of genetically modified or synthetic organisms into the environment has to be balanced against protection of workers and citizens, responsibility towards nature and animals, and the freedom of consumers, and not be done before a long-term ecological risk assessment has been performed.

For biosecurity, the group recommends that the Biological Weapons Convention should incorporate guidelines for synthetic biology, that licensing of researchers is one possible way forward, and that special attention should be paid to the ethical dilemma of balancing security and the need for transparency. Further, the report recommends that an integrated
impact assessment including considerations of social and economic factors should be performed before synthetic biology is introduced in the EU.

The incorporation and implementation of moral reasoning in the intellectual property rights system is viewed as too weak, and patent examiners often complain that the morality clauses in the EU Patent Law are too vague to be effectively implemented, and that instruments to strengthen the input of morals in the IP system be developed. The report also recommends that measures be taken to reduce gaps between the EU and developing countries through bilateral and multilateral trade agreements, such as those discussed in the Doha rounds. Finally, the need for dialogue between society and science is highlighted along with the need for promoting debate and engagement amongst stakeholders.

5.8 Friends of the Earth

Friends of the Earth is a civil society organization based in the United Kingdom and is engaged in issues relating to the environment, climate change and fairness of distribution of global resources. They have not been quite as active as ETC within synthetic biology, but have started paying more attention to the new technology recently. In 2010 they published the paper Synthetic Solutions to the Climate Crisis: The Dangers of Synthetic Biology for Biofuels Production (Friends of the Earth 2010).

The paper criticizes the notion that fuel created though synthetic biology will provide a solution to the climate crisis, arguments for why this is the case and an overview of risks. The report specifically mentions four biosafety risks: gene transfer, damage to ecosystems and other species, mutation and evolution, and effects on biodiversity. Biosecurity risks of spread to state and non-state actors, as well as the potential to make new, or enhanced, biological agents are also discussed.

The paper also examines the potential effects of large scale fuel production using synthetic biology, and criticizes this approach because of its detrimental effects on the livelihood of small-scale farmers, indigenous people and ecosystems. They are skeptical towards the notion that massive quantities of biomass can be harvested sustainably without eroding/degrading soils, destroying biodiversity, increasing food insecurity and displacing marginalized populations. They also express caution over the predictability, controllability and safety of synthetic microbes. Finally, intellectual property right regimes and their creation of monopolies and concentration of wealth are criticized.

The report concludes by claiming that current regulations of synthetic biology as well as industry’s proposals of self-regulation are insufficient to handle its risks and concerns. Instead, they call for a broad debate in society about the risks and benefits of synthetic biology and its impact on the environment, human health, human rights, security, and social justice. They specifically mention the precautionary principle to guide regulations and policies and that the burden of proof should be with scientists and industry to show that new organisms are safe. They propose a moratorium on the release of synthetic organisms until their impacts on the environment, biodiversity, human health, and socio-economic situations are examined. Further, they want Congress to direct the NAS to conduct a study on the full environmental, public health, safety, and societal impacts of synthetic biology and to create a federal regulatory body to oversee and have authority over all synthetic biology research, including the ability to make sure that money is used to study environmental, public health, and socio-economic risks as well.
5.9 Presidential Commission for the Study of Bioethical Issues

The PCSBI was created by executive order on November 24, 2009, replacing the disbanded President’s Council on Bioethics, with the purpose of advising the President on bioethical issues that emerge from advances in biomedicine and related areas of science and technology. The report on synthetic biology called *New Directions: the Ethics of Synthetic Biology and Emerging Technologies* is the group’s first report, published in December 2010 (Presidential Commission for the Study of Bioethical Issues 2010).

The report starts by defining five ethical principles for assessing emerging technologies; public beneficence, responsible stewardship, intellectual freedom and responsibility, democratic deliberation, and justice and fairness. In terms of risks, the report points to environmental risks that may occur when synthetic organisms are released into the environment, such as cross-breeding, uncontrolled proliferation, threats to biodiversity and crowding out of existing species. Other mentioned risks include new and sturdier pests, increased pesticide resistance, and overarching effects on ecosystems and biodiversity. In relation to biosecurity, the report points to risks of spreading of skills and technology to malevolent actors, but notices that few individuals or organizations today have the financial means or skills to employ the new technologies.

Specific recommendations are given under the heading of each of the five ethical principles. A total of eighteen recommendations are provided, some more precise than others. Recommendation four argues that there is no need to create additional agencies for oversight of synthetic biology, but that measures should be taken to ensure that regulatory requirements between agencies are consistent and non-contradictory. Further, recommendations five, six and seven all focus on deliberate environmental release and the need to look over risk assessment paradigms, especially in the face of uncertainty, and to identify reliable strategies for containment, control and monitoring of engineered organisms. The report frequently mentions “suicide genes”, “kill switches” and extreme nutrient dependencies as examples of genetic tools that limit the risks of environmental release.

Further, it is recommended that moral objections to synthetic biology, although not described in the report, be evaluated and debated continuously as the field advances. Engagement from religious groups, civil society and the broader public is encouraged, alongside the need for better education in synthetic biology for these groups, as this is seen as central to fostering a fruitful debate. Finally, the report argues that risks to communities and the environment should be distributed equally and that measures should be taken to develop guidance material and voluntary recommendations to assist manufacturers in limiting uneven distribution of benefits and risks.

5.9.1 Critique and Controversy

The same day that the PCSBI published their report, 58 organizations from 22 countries, including the US and many European countries, wrote a letter of critique to the chairman of the commission. The letter argues that the commission’s recommendations are inadequate responses to the risks of synthetic biology because they ignore the precautionary principle, do not express adequate concern over the environmental risks of synthetic biology, rely too heavily on the use of technologies of self destruction to limit environmental risks (such as suicide genes), and rely on self-regulation.
The organizations emphasize that the precautionary principle should guide regulation of synthetic biology and that a moratorium on the release and commercial use of synthetic organisms is required until a review of all its environmental and socio-economic effects has been performed. They also criticize the report for ignoring effects that increased consumption of biomass will have on ecosystems and communities in the global south and for paying too little attention to ecological risks. Self destruction technologies to limit ecological risks in case of environmental release is seen as an insufficient example of safety engineering since living systems are unreliable and able to evolve.

5.10 Conclusion

This review illustrates some of the problems in the debate about synthetic biology that were outlined in the introduction. First of all, the reports have very different understandings of what the actual risks of synthetic biology are and how regulations should be set-up to assess and manage them. In general, actors from the academic-industrial complex emphasize risks to security, and most notably risks of bioterrorism, while NGOs are more concerned with risks to the environment and moral values, focusing on effects on sensitive ecosystems and marginalized communities. These two types of risk framings are fundamentally different and the resulting debate is often of poor quality.

Second, many reports provide too shallow definitions and analysis of synthetic biology and fail to distinguish between its two branches or at least discuss the heterogeneity of research within the field. As such, they often commit the principal error of evaluating ethical implications of the “standardization” branch, when, as is shown in the next chapter, ethical concerns mainly arise out of the “define and alter” branch. Confusions such as these impair the quality of the analysis and resulting recommendations. This is discussed in more detail in the next chapter’s evaluation of the risks mentioned in the reports.
CHAPTER 6  Evaluating Risk Perceptions

This chapter provides an identification and evaluation of the risks that were brought up in the previous chapter’s review of reports on synthetic biology. In addition to being interesting in and of itself, a more structured evaluation of risks is valuable when analyzing the extent to which regulatory frameworks address certain types of risks and whether some risk categories, such as physical risks, are addressed more directly and explicitly than others, such as non-physical risks.

Risks and concerns of synthetic biology can be divided into three broad categories, as is shown in Table 6.1. A number of specific risks manifest themselves under each category, all of which are described in detail below and analyzed at the end of the chapter.

Table 6.1 Risk categories.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Safety &amp; Environment</th>
<th>Security</th>
<th>Ethics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of risk</td>
<td>Unintentional physical harm to humans, animals or the environment.</td>
<td>Intentional misuse to cause physical harm to humans, animals or the environment.</td>
<td>Non-physical harm to the well-being of humans or communities.</td>
</tr>
</tbody>
</table>

The chapter starts by an overview of safety and environmental risks, followed by a review of security risks and finalized by an assessment of ethical concerns. The purpose is to provide a description of the types of concerns that have been expressed under each category and to elucidate certain factors that impact the level of risk. At the end of the chapter, all risks are analyzed jointly using the framework that was presented in Chapter 4.

6.1  Safety and Environmental Risks

Safety concerns relate to the unintentional exposure of humans and the environment to pathogens, toxins and otherwise harmful or potentially harmful biological material (Schmidt, Ganguli-Mitra, et al. 2009). The overview of risks starts with those that threaten human health, followed by those that threaten the environment.

6.1.1  Human Health Risks

Synthetic biology is seen as producing three types of human health risks: consumption of food composed of or derived from engineered crops, risks to laboratory workers and accidental release of modified organisms from laboratories and other containment facilities into the surrounding environment.

Consumption Risks

Consumption of genetically modified or synthetic organisms is potentially able to cause a number of human health risks. First of all, there are concerns that introduction of a new gene into a plant may create a new allergen or cause an allergic reaction in susceptible individuals. Second, the effects of using and consuming antibiotic resistance markers on individuals and the development of are potential concerns. Changes in the composition, nutritional value and important substances such as antioxidants and toxins are also seen as potential risks. Finally, there are concerns that introduction of foreign genes into food plants may have an unexpected and negative impact on human health (Chassy 2002).
**Risks to Laboratory Workers**

Laboratory workers performing research in microbiology, the life sciences and synthetic biology are exposed to a range of risks. For example, a world-wide literature review conducted in 2000 revealed that 1,267 laboratory-associated infections resulting in 22 deaths had occurred in the 20 years between 1980 and 2000. The main risks do, of course, arise from handling of infectious microorganisms and hazardous biological materials; the pathogenicity of the microorganism is the most important determinant of risk level. Other factors include the type of manipulations or activities performed with the biological agent the experience level of the laboratory worker. The causative event for most laboratory-associated incidents is generally unknown, but risks are the greatest when using a syringe and needle, followed by aerosols, pipetting, and centrifuging (Sewell 1995, Department of Health and Human Services 2009).

**Accidental Release**

Accidental release refers to the escape of engineered and synthetic organisms from their containment structure, such as a laboratory or industrial bioreactor, into the broader environment. If the escaped organism is pathogenic, infectious, toxic or capable of reproduction it could pose a risk to laboratory workers, the environment and the health of individuals in adjacent communities. The ability of living organisms to proliferate means that the risks of accidental release are different and generally seen as greater than those of conventional chemicals. If an engineered organisms escapes into the environment and is able to survive and reproduce there, they can multiply and spread in a way that released chemicals are never capable of (Rodemeyer, New Life, Old Bottles 2009, Tucker and Zilinskas 2006).

6.1.2 Environmental Risks

The release of synthetic organisms into the environment is an area of much debate and concern, drawing on the discussion and disputes surrounding genetically modified crops. Environmental risks are a much greater concern for applications that require uncontained use, such as *in situ* bioremediation, because organisms have to be designed to survive in the free environment in order to perform their intended tasks, and traditional methods for limiting environmental risks by decreasing the survivability of laboratory strains are therefore obsolete. Four types of environmental risks are frequently mentioned in association to synthetic biology: transfer of synthetic genes, effects on the ecosystem and other species, the ability of living organisms to mutate and evolve, and effects on biodiversity.

**Transfer of Synthetic Genes**

Gene transfer from synthetic to natural organisms is one of the most intensely debated environmental risks of synthetic biology. Gene transfer within and between species is an important natural mechanism for transferring functionalities between organisms, especially for prokaryotes. Transfer of genes from synthetic to natural organisms disseminate artificial genes into natural populations, which could lead to unexpected and unpredictable changes in population dynamics and disruptions in ecosystems (Balmer and Martin 2008, Parekh 2004, Bhutkar 2005, van Est, de Vriend and Walhout 2007).
For example, the transfer of genes for improved pesticide resistance from genetically modified crops to weedy wild-type species could create more persistent weeds. Even though the probability of gene flow from any individual synthetic organism is very low, problems when such events do occur can be severe and hard to control. The difficulty in tracking the movement of transgenes is especially problematic with regards to third-generation GM crops that are engineered to produce industrial chemicals or pharmaceuticals; molecules whose appearance in the food supply is most undesired (Ellstrand 2001).

**Effects on the Ecosystem and Other Species**

The introduction of plants and microorganisms that are produced using synthetic biology could have disruptive effects on the balance of ecosystems and on other species. For example, while crops engineered for increased pesticide resistance are designed for tolerance towards a certain pesticide, they could also be harmful to non-target organisms. Further, gene products could have damaging effects to soil organisms and allergenic or toxic side-effects on other mammals. Our knowledge about the interaction of microorganisms, their movements and ecosystem dynamics are still very limited (Steinbrecher 2001).

**Mutations and Evolution**

Mutations and evolution introduce instability and uncertainty even for the safest synthetic organisms. Random mutations or transfers of plasmids from natural organisms could either disrupt genes inserted for safety or introduce undesired genetic traits such as virulence (ETC Group 2007). Further, synthetic organisms will be engineered for superiority in the particular site in which they will be placed and since this could lead to advantages over natural populations, synthetic organisms could take over an ecological niche and reproduce with uncontrolled intensity; outcompeting natural organisms and causing unknown effects on the environment and ecosystems (Balmer and Martin 2008).

**Effects on Biodiversity**

The ETC Group and Friends of the Earth (ETC Group 2010, Friends of the Earth 2010) argue that the release of synthetic organisms could threaten biodiversity in three ways. First of all, deliberate environmental release of synthetic organisms could alter the ecosystem and harm other species. Secondly, accidental release of organisms designed for contained use could have serious effects on the environment both close to and further away from the containment facility. Finally, increased demand for land, water and biomass to be used in the biological transformation of cellulose and sugars to fuels, chemicals or pharmaceuticals will negative affect biodiversity, food security, and livelihoods and stretch the capacity of already pressured ecosystems.

**6.2 Security Risks**

As distinct from safety concerns, security concerns relate to the intentional misuse of synthetic biology to cause harm. The scientific synthetic biology community has chosen to focus mainly on security concerns, especially in the US (Torgersen 2009). The very idea of synthetic biology of being able to design and construct biological systems more efficiently by using standardization, modularization and decoupling results in deskillng, diffusion and general capacity increases. Synthetic biology thus decreases acquisition barriers to required technologies and increases the effectiveness of biological engineering; effectively creating

Risks arising from deskillings of biological engineering and the increased capacity to alter living systems using modular design are two of the most central features of biosecurity threats posed by synthetic biology. (Garfinkel, et al. 2007, Central Intelligence Agency 2003, Mukunda, Oye and Mohr 2009): Deskilling and dissemination increase as the technological advances that underpin synthetic biology make biological engineering more accessible to the general public and malevolent actors with limited resources than has been the case before. Capacity is increased since synthetic biology allows for more sophisticated design of organisms, enabling engineering for increased virulence, attack on distinct biochemical processes, and resistance to treatments. Synthetic biology thus enables the production of more dangerous organisms than are found in nature or have been engineered previously.

6.2.1 Dissemination and Deskilling Risks

One of the goals of synthetic biology is to “make biology easier to engineer” (Endy 2005), an approach which, by necessity, removes a lot of the implicit knowledge currently present in biological engineering and thus removes a major barrier to the production of biological agents. The creation of standardized modules of DNA enables cheaper and faster synthesis of biological systems, a development that lowers the amount of resources, training and time to engage in biological engineering. Such a diffusion of capacity allows deeper engagement by non-state actors without large resources, and thus increases the risk of bioterrorism (Mukunda, Oye and Mohr 2009, National Science Advisory Board for Biosecurity 2010).

Further, the integrative, cross-disciplinary nature of synthetic biology could imply greater security risks since some practitioners might not view their work as biological, but rather as engineering or synthetic chemistry, and hence fail to consider biological and health implications of their work. Practitioners from other backgrounds than the life sciences might also lack sufficient training in biological risk assessment and containment. This is slightly different than diffusion to malevolent actors since these risks are raised through unawareness rather than intention, but it does nevertheless represent a biosecurity risk (National Science Advisory Board for Biosecurity 2010).

Acquisition of a suitable biological agent is the first step in the production of a biological weapon. Most harmful agents, such as the smallpox virus variola and the anthrax bacterium Bacillus anthracis, are very difficult to obtain. However, the increasing rate of DNA synthesis allows for de novo synthesis of potentially harmful agents, with viruses being the easiest to synthesize. Looking further into the future, synthetic biology could also allow easier modification of natural agents and the creation of completely new organisms with novel properties (Mukunda, Oye and Mohr 2009, Tucker and Zilinskas 2006).

Spread to State Actors

A number of reports express concern that the development towards increased deskillings and dissemination of biological engineering present in synthetic biology will increase the ability of malevolent states able to engineer, produce and spread biological agents (Garfinkel, et al. 2007, International Risk Governance Council 2010, European Group on Ethics in Science and New Technologies 2009, ETC Group 2007). States have far greater capacity and
resources to engage in research and development of biological weapons than non-state actors, and in the short term the threat of dissemination to state actors appears more real.

**Spread to Non-State Actors**

Especially the deskilling component of synthetic biology increases the risks of dissemination of capacities to resource restrained non-state actors. Increasing ability to engineer biological systems for less money and lower costs makes biological engineering accessible to actors that have been excluded before because of their limited resources. The threat of spread to terrorists is seen as low in the short-term but significantly higher in longer time perspectives, and is considered a very real risk by several analyses (Garfinkel, et al. 2007, International Association for Synthetic Biology 2011, International Risk Governance Council 2010, National Science Advisory Board for Biosecurity 2010, van Est, de Vriend and Walhout 2007, De Vriend 2006).

6.2.2 **Capacity Risks**

The ability to provide malevolent actors with a much broader variety of novel effects is viewed as the most important, albeit long-term, effect of synthetic biology on biosecurity. These can be grouped into three categories; enhanced lethality, infectiousness and “wild card” applications. The large scale and eventually automated assembly of DNA coupled to an overall reduction in uncertainty about biological systems enables large-scale production and testing of modifications for desired characteristics.

Combining advances in divergent areas of synthetic biology, such as the tumor-seeking bacteria that are designed to be invisible to the immune system and pathways for production of toxins or strong pharmaceuticals, could provide actors with very powerful and carefully designed agents. Agents could be designed to change the behavior of those infected, cause chronic diseases or even to interact only with certain genetic subsets of the population (Mukunda, Oye and Mohr 2009, Garfinkel, et al. 2007, National Science Advisory Board for Biosecurity 2010).

6.3 **Ethical Concerns**

Ethical concerns related to synthetic biology fall into three broad categories; intrinsic (the very nature of the technology used), consequential (effects of applying the technology), and integrated (the process and values used to address biosafety and biosecurity risks). Intrinsic concerns arise regardless of the consequences of the application; they are tied to the very nature of the technology and its effects on human self-conception, morality, and nature. Consequential concerns are, on the other hand, related to the application of the technology and its effects (Kaebnick 2009).

Integrated ethical concerns relate to how biosafety and biosecurity risks should be addressed in an ethical manner. The management of biosafety and biosecurity risks involves a number of policy choices that are of a more ethical character, such as the degree to which humans have an obligation to protect ecosystems and other species, the necessity of weighing benefits and costs of regulations and the need for precaution. Instead of listing them as a separate area of ethical concerns, which would be artificial, they will instead be discussed continuously as integrated elements in the debate about safety and security regulations. The
remainder of this section will thus be spent on the two other categories of ethical concerns: intrinsic and consequential.

6.3.1 Intrinsic Concerns

There are three types of intrinsic concerns expressed in association to synthetic biology: the notion that it is interfering with life, reducing life, or inflicting on nature. All of them stem from the belief that synthetic biology interferes with nature and that humans are somehow crossing a border by developing and using this technology.

Interfering with Life

Human activity in synthetic biology can be seen as conflicting with our metaphysical state of being and our role in the cosmos. The metaphor of ‘playing God’ is a typical example of this line of critique (Kaebnick 2009). When the human race assumes the role of creator, as some see synthetic biology as doing, humans are not only acting immorally correct, but are also inflating our understanding of ourselves and our place in the universe (Boldt and Muller 2008).

Reducing Life

Second, synthetic biology can be seen as interfering with the moral value of life by creating organisms for one specific, predefined purpose and by reducing life to chemical formulas and synthesis (Kaebnick 2009). The ability to create an organism for a specific purpose, and not just modify it, implies a more instrumentalist view of life. Synthetic biologists tend to describe organisms by using a vocabulary that is similar to that used for artifacts; often referring to organisms as ‘living machines’. Such language can be seen as a reduction of the created organism into something that is only valuable in regard to its instrumental value, a perspective that is fundamentally different from views in which life and living organisms have intrinsic values that are unique to life (Boldt and Muller 2008).

Inflicting on Nature

Finally, from an environmentalist perspective, synthetic biology can be seen as inflicting on nature and other species. A creator can engineer ‘nature’ without shortcomings instead of having to start with imperfect nature. In this regard, the world can be seen as a blank space to be filled by various novel life forms for different purposes (Boldt and Muller 2008). This position is changed as applications transition from the contained to the uncontained and synthetic organisms are released into the environment (Kaebnick 2009). The environmental effects of the release of synthetic organisms can be viewed with either a consequential or intrinsic perspective, whereby the disruption of ecosystems and extinction of species is viewed as immoral regardless of the consequences for humans.

6.3.2 Consequential Concerns

There are also concerns that the benefits and risks of synthetic biology applications will be distributed unequally, where certain individuals or social groups systematically obtain the benefits of synthetic biology and other systematically bear the risks. Uneven distribution occurs both within and between nations and concerns about the distributional effects of
synthetic biology are thus played out both within the realm of intellectual property rights and trade and global justice.

**Distributional Concerns**

The distribution of benefits and risks of synthetic biology is influenced by a number of policies, of which the intellectual property rights system is one of the more influential. The patent system is a tool by which research institutions and corporations can seek return on their investments by claiming exclusive rights to new discoveries and is an important mechanism for incentivizing R&D and innovation. But, by providing exclusive rights, the patent system also creates concentration of wealth and limits to the spread and use of new knowledge (Wilson 2001).

Since the seminal case Diamond vs. Chakrabarty in the 1980s, the US Courts of Appeals for the Federal Circuit has established an unusually low non-obviousness threshold for biotechnology, allowing patents on genes and gene alterations. A number of individuals and organizations argue that preservation of this low threshold for synthetic biology could create extensive property rights that stifle the free exchange of information, limit the use of novel knowledge and products, and produce social and economic inequalities (Rai and Boyle 2007, Bhutkar 2005, ETC Group 2007).

There are concerns that problems with intellectual property in both software and biotechnology will combine into a perfect storm for synthetic biology that is highly dependent on both areas (Rai and Boyle 2007). The modular approach of synthetic biology, in which well defined DNA parts are assembled into devices and systems for incorporation into defined chassis organisms, makes it even more susceptible to the anticommons, in which new inventions and products are limited by a myriad set of patent claims on upstream research (Heller and Eisenberg 1998, Rai and Boyle 2007). Synthetic biology thus appears to provide additional challenges for the design of an intellectual property system that will promote investment and innovation while simultaneously allowing diffusion and use of existing knowledge (Oye and Wellhausen 2009).

**Trade and Global Justice**

Bioprospecting and biopiracy, involving both resource piracy in which biological resources of developing countries are freely taken and used to build global economies and intellectual piracy in which the intellectual and cultural heritage of developing countries are freely taken and used for asserting intellectual property rights, are two central concerns over the effects of synthetic biology on trade and global justice. Biopiracy involves false claims of creativity enabled by a perspective in which only scientific knowledge is taken as truth. Western intellectual property systems are biased towards Western style knowledge systems that reduce biodiversity to genes and chemistry; indigenous knowledge thus goes unprotected while piracy of this knowledge obtains protection (Shiva 2001, Dorsey 2001). Since it involves a transfer of ownership of knowledge and resources from developing to developed countries, biopiracy increases global inequality.

The ETC Group (ETC Group 2010) argue that synthetic biology increases the risk of biopiracy since it enables digital biopiracy, whereby the DNA of an organism is sequenced in situ, uploaded and then synthesized elsewhere. This type of piracy does not require any movement of material; only information is transferred. Nevertheless, individuals,
corporations and governments can extract genetic information, use it to create synthetic organisms that can then be patented as inventions.

The displacement of existing commodities is a second effect that synthetic biology could have on poor economies and communities. ETC has focused especially on synthetic production of artemisinin, an anti-malarial drug that is traditionally produced by farming and harvesting the medicinal plant *Artemisia annua*. However, as was described in Chapter 3, Amyris has recently developed a synthetic metabolic pathway that produces a precursor to artemisinin in yeast and ETC is concerned that microbial production of artemisinin will displace current production methods and damage the rural communities currently farming the plant (ETC Group 2010).

### 6.4 Evaluation of Risks

This section provides a summary of the total of fifteen risks and concerns that have been identified, followed by an analysis of the identified risks based on the framework developed in Chapter 4. Risks are analyzed to determine the degree to which scientific uncertainty in their assessment appears likely, whether they are of a physical or non-physical nature and whether synthetic biology as a whole displays characteristics that tend to increase the perception of risks.

Before going into a summary and assessment of risks, it is worthwhile revisiting the definition of synthetic biology provided in Chapter 2. There, it was argued that synthetic biology can be divided into two approaches: the “standardization” branch and the “define and alter” branch. Because of the different nature of the two approaches, they give rise to distinct types of risks. The “standardization” branch, and its focus on standardization and modularity, creates new types of risks to security and safety, whereas the “define and alter” branch, and its focus on defining and creating life, produces risks and concerns of a mainly ethical character. These findings are summarized in Table 6.2 and will be discussed again in the concluding chapter.

<table>
<thead>
<tr>
<th>Branch</th>
<th>Safety &amp; Environment</th>
<th>Security</th>
<th>Ethics</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Standardization”</td>
<td><strong>Secondary impact</strong></td>
<td><strong>Primary impact</strong></td>
<td></td>
</tr>
<tr>
<td>synthetic biology</td>
<td>Standardization and modularization</td>
<td>Standardization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>leads to increased capacity to</td>
<td>and modularity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>engineer synthetic organisms for</td>
<td>leads to</td>
<td></td>
</tr>
<tr>
<td></td>
<td>uncontained use</td>
<td>dissemination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and deskilling</td>
<td></td>
</tr>
<tr>
<td>“Define and alter”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>synthetic biology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Primary impact</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defining and creating life</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>leads to intrinsic ethical concerns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.4.1 Summary of Risks and Concerns

As was mentioned above, a total of fifteen risks and concerns related to synthetic biology have been identified, seven of which fall under the category safety and environment, three under security and five under ethics. Figure 6.1 presents an overview of the fifteen risks and their respective categorization.

![Figure 6.1 Risks and concerns expressed for synthetic biology.](image)

The remainder of the chapter will be spent on analyzing risks, starting with the degree to which their assessment is likely to include scientific uncertainty and continuing with an analysis of whether risks are of a physical and/or non-physical nature.

6.4.2 Scientific Uncertainty

Many of the risks of synthetic biology are similar to those of rDNA technology, especially for first generation products. However, the degree of risk and uncertainty is likely to increase as synthetic biology develops (Rodemeyer 2010). Table 6.3 provides a comparison of the differences between rDNA technology and synthetic biology that have been identified as most central to the assessment of risk, and is especially relevant because, as we shall see in the next few chapters, all current regulations were designed for assessing and managing risks of biological engineering that utilizes rDNA technologies.

The differences between rDNA technology and synthetic biology that are outlined in Table 6.3 indicate that uncertainty is likely to increase as synthetic biology develops. Furthermore, uncertainty about the environmental, human health and socio-economic effects of genetically
modified organisms is already persistent, with substantial controversies within the scientific community about their health and environmental safety (Winickoff, et al. 2005), thus indicating the difficulty in producing conclusive scientific evidence about risks of biological systems and living organisms.

Table 6.3 Differences in risk characteristics between rDNA technology and synthetic biology (van Est, de Vriend and Wallhout 2007).

<table>
<thead>
<tr>
<th>Concern</th>
<th>rDNA technology</th>
<th>Synthetic biology</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Original host organism as reference</td>
<td>No natural reference</td>
<td>New questions and uncertainties about risk analysis</td>
</tr>
<tr>
<td>Security</td>
<td>Known, risky viruses and bacteria</td>
<td>Difficult to determine use of short DNA fragments</td>
<td>Difficult to monitor risky research and potential misuse</td>
</tr>
<tr>
<td>Ethics – Intrinsic</td>
<td>Alteration of existing organisms</td>
<td>Creation of (partially) new life</td>
<td>Morality of creating life, human self-conception, life-machine implications</td>
</tr>
<tr>
<td>Ethics – Distributional</td>
<td>Limited number of genes and production capability</td>
<td>Almost unlimited number of genes and production capability</td>
<td>Impediment on research and innovation, effects on third world.</td>
</tr>
</tbody>
</table>

The differences between rDNA technology and synthetic biology outlined in Table 6.3 translates into several novel uncertainties in assessing risks of synthetic biology, shown in Table 6.4. The table shows that the assessment of risks in synthetic biology is permeated by uncertainty and is likely to be characterized by low scientific certainty and consensus (Tucker and Zilinskas 2006).

Table 6.4 Uncertainties in the risk assessment of synthetic biology within security, safety and ethics.

<table>
<thead>
<tr>
<th>Area</th>
<th>Main uncertainties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>• Assessing the interactions between synthetic and natural organisms</td>
</tr>
<tr>
<td></td>
<td>• Assessing the broader environmental effects of releasing synthetic organisms</td>
</tr>
<tr>
<td></td>
<td>• Assessing the human health effects of consuming organisms with novel properties, especially for novel building blocks (such as new amino acids and XDNA)</td>
</tr>
<tr>
<td></td>
<td>• Assessing the potential (if any) interactions between XDNA and DNA</td>
</tr>
<tr>
<td>Security</td>
<td>• Assessing the capacity (both resources and knowledge) of malevolent actors (state and non-state) to engage in the construction and redesign of biological agents</td>
</tr>
<tr>
<td></td>
<td>• Deriving biological function and potential pathogenicity from short strands of DNA</td>
</tr>
<tr>
<td>Ethics</td>
<td>• Distribution of benefits and risks of synthetic biology</td>
</tr>
<tr>
<td></td>
<td>• Effects of synthetic biology on trade patterns and marginalized communities</td>
</tr>
<tr>
<td></td>
<td>• Understanding which ethical concerns that are most central to the public</td>
</tr>
</tbody>
</table>

6.4.3 Physical and Non-Physical Risks

The broad framing of synthetic biology risks leads to a risk characterization that is marked by a mixing of physical risks (threaten human survival) and non-physical risks (threaten human well-being). As was mentioned previously, modern societies and regulatory frameworks have a track-record of addressing physical risks while neglecting non-physical
risks (Beck 1992, Kaebnick 2009, Stermerding and Brom 2010, Parens, Johnston and Moses 2009). Before analyzing the extent to which this appears to be true for regulations governing biotechnology also, it is useful to characterize risks and concerns of synthetic biology based on their ability to cause physical harm.

Biosecurity risks, if realized, have the ability to cause major physical harm to humans, the environment and economic assets. Biosafety risks also have the capacity to cause physical harms, but also harms that are of a more non-physical type related to our relationship with the environment and other species. Finally, ethical concerns cause non-physical harms to the well-being of individuals or communities. Figure 6.2 is an illustration of the described spectrum of risks of synthetic biology based on their potential to cause physical or non-physical harm.

![Figure 6.2 Characterization of the ability of risks of synthetic biology to cause physical harm, with decreasing ability from left to right.](image)

### 6.4.4 Risk Perception

The degree to which synthetic biology is perceived as risky depends on a number of factors that were identified in Chapter 4. As is shown in Table 6.5, a number of attributes of synthetic biology appear to increase its perceived riskiness. Some of the most important include inconsistency with moral values, inability for individuals to choose whether or not to be exposed, and the limits to human control caused by the ability of living organisms to propagate and evolve.

**Table 6.5 Attributes of synthetic biology that are likely to influence risk perception.**

<table>
<thead>
<tr>
<th>Emotive attribute</th>
<th>Relevance to synthetic biology</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involuntary</td>
<td>Inability to detect and distinguish synthetic from natural organisms and hence to avoid risk</td>
<td>Very important</td>
</tr>
<tr>
<td>Uncontrollable</td>
<td>Ability of living organisms to propagate, mutate and evolve</td>
<td>Very important</td>
</tr>
<tr>
<td>Immoral</td>
<td>Defining minimal requirements of life, creating new life and often for specific purposes</td>
<td>Very important</td>
</tr>
<tr>
<td>Unfamiliar</td>
<td>Creation of new life and new building blocks for life (XDNA)</td>
<td>Very important</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Uncertainty in assessing the safety, security and ethical risks of synthetic biology</td>
<td>Important</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>Relation to September 11 and anthrax attacks</td>
<td>Somewhat important (more in US)</td>
</tr>
<tr>
<td>Unfair</td>
<td>Strong IP rights to discoveries in synthetic biology</td>
<td>Somewhat important</td>
</tr>
<tr>
<td>Untrustworthy</td>
<td>Strong ties between scientists and industry could undermine public trust in scientists</td>
<td>Somewhat important</td>
</tr>
</tbody>
</table>
6.4.5 Conclusion

A number of conclusions can be drawn from the evaluation and analysis of risks. First of all, since the development of synthetic biology is piecemeal, risks are likely to be similar to those of rDNA technology for first generation products, but with the emergence of novel risk scenarios as synthetic biology matures (Rodemeyer, New Life, Old Bottles 2009). As this happens and the first products are launched, more attention will be directed towards issues of risks. Besides from providing a description of those most outstanding risks and concerns, this chapter has also pointed to the following three characteristics of synthetic biology risks:

1. Low scientific certainty and consensus in assessing the degree of risks;
2. Multidimensional character with mixing of physical and non-physical risks;
3. Characteristics that tend to increase the perception of risk.

Together, these three characteristics could make synthetic biology an unusually difficult area to regulate. First of all, low scientific certainty and consensus in assessing the degree of risk has been proved to be a difficult issue for regulatory frameworks. Second, a risk space that is characterized by a mixing of physical and non-physical risks challenges traditional, technocratic approaches to risk assessment and regulation. Finally, the embodiment of several attributes that increase the degree to which a technology is perceived as risky increases both the likelihood for public debate and demands for governmental regulation.

The next three chapters analyze the current regulatory frameworks that govern risks of synthetic biology within safety and the environment, security, and ethics. Regulations are examined both with regard to which of the fifteen identified risks and concerns that they address, and with regard to the framework developed in Chapter 4.
PART III:

Policies and Regulatory Frameworks
Controlling Risks of Synthetic Biology
The previous chapter found identified seven risks of synthetic biology that have the potential to threaten human and/or environmental safety: consumption risks, risks to laboratory workers, risks of accidental release of organisms from the laboratory, transfer of synthetic genes, mutations, evolution and proliferation, effects on the ecosystem and other species, and effects on biodiversity. This chapter aims to describe the most significant regulations set up to control these biosafety risks and to discuss their general applicability to synthetic biology, approaches to risk assessment, methods for dealing with uncertainty and incorporation of ethical and socio-economic values.

The chapter begins with a case study of the regulation and assessment of genetically modified (GM) crops and the conflict between the EU and US in this field, the purpose of which is to provide a historical background and deeper understanding of the evolution of current regulatory frameworks controlling the safety of biotechnology. After this historical background, international, American and European regulatory frameworks are presented. The Convention on Biological Diversity and especially the Cartagena Protocol on Biosafety constitute the international framework for biosafety, with a focus on limiting environmental risks. In the US, the NIH Guidelines govern human health risks of research with rDNA molecules, while the Coordinated Framework governs risks to humans and the environment caused by the commercialization of biotechnological products.

The EU employs a far-reaching and complex legal system for regulation of biosafety risks of biotechnology, with three statutes providing the foundation: Directive 2001/18/EC covers deliberate release of genetically modified organisms (GMOs), Regulation 1829/2003 covers GM food and feed, and Directive 2009/41/EC regulates the contained use of GMOs. Finally, Directive 2000/54/EC covers risks to health and safety of workers exposed to biological agents, genetically modified as well as natural.

Each of these individual regulations are reviewed in detail, with special attention to their definition of covered organisms and genetic material, methods for evaluating risk, approaches to uncertainty, and overall scope. Finally, this information is analyzed as a whole in the concluding section of the chapter that provides a synopsis of the general applicability of current biosafety regulations to synthetic biology, the risks that they address, their approach to risk assessment, uncertainty and incorporation of moral principles.

7.1 Case Study: Regulating Genetically Modified Crops

GM crops have had specific changes in their DNA, generally involving insertion of desirable genes either by a gene gun or by Agrobacterium tumefaciens mediated transformation. Genetic modification is an extension of other, conventional techniques for plant optimization, such as selective breeding and methods to increase the rate of mutation. The most common characteristics introduced in currently grown GM crops include insect and pest resistance, herbicide resistance, bacterial, fungal and viral resistance, abiotic stress resistance (drought and temperature), and nutrient enrichment (Weale 2010).

Introduction of insect resistance and other desirable traits is meant to lead to economic, environmental and health benefits, such as less use of pesticides, better yields, less crop disease, more robust crops and better nutritional value, but some argue that the cultivation of...
GM crops also involves a number of environmental, health, economic and social risks. The debate about potential benefits and risks of GM crops and the weighing between them is intense, with the WTO dispute between the EU and US as the prime example. The differences and conflict between the US and EU concerning risk assessment and regulation of GM crops, as illustrated by the stark difference in rate of adoption of GM crops shown in Figure 7.1 (where all of Europe is represented in the “other” category) is an excellent example of the complexity and intensity of debates involving a mixture of scientific/technical and ethical/social/political issues.

![Figure 7.1 Growth of GM crops globally between 1996 and 2008 (Rodriguez-Cerezo 2010).](image)

7.1.1 Scientific and Technical Issues

A number of issues related to the use of GM crops are of a scientific and technical character and thus addressable through scientific inquiry. Regulatory risk assessments generally consider two types of risks: human health risks and ecological risks. Examples of human health and ecological risks associated with GM crops include (Peterson, et al. 2000):

1. The safety of food and feed consisting of or produced by GM crops;
2. Reduced biodiversity, that may reduce the ecological services provided by agricultural ecosystems;
3. Promoting the development of resistance to the pesticide produced by the GM crop thus eliminating the use of that particular pesticide;
4. Killing non-target species such as caterpillars and butterflies;
5. Movement of genes into nonagricultural ecosystems where the resulting increase in fitness of weedy species could eliminate endangered species;
6. Facilitating the creation of new viruses.
In evaluating the human health effects of food and feed composed of GM crops, risk assessors evaluate the safety of the inserted DNA and the resulting protein products, whether an antibiotic resistance marker is used, whether potential allergens have been introduced, and potential changes in composition or nutritional value (Chassy 2002).

Ecological risk assessments for GM crops are more complex and uncertain because of the complexity of ecological networks and the almost infinite variety of conditions possible in natural ecosystems. Evaluation of potential ecological risks of GM crops is divided into two categories: the modified crop and the introduced trait. To measure the factors presented in Table 7.1, field tests are performed for experimental results that provide the foundation for models of ecological impact. Comparison between the conventional counterpart and the GM crop, based on the concept of familiarity and substantial equivalence, is also done to aid the risk assessment (Nickson och McKee 2002).

Table 7.1 Considerations in the ecological assessment of GM crops (Nickson och McKee 2002).

<table>
<thead>
<tr>
<th>Modified plant</th>
<th>Introduced trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>To determine the ecological impact of the plant, measure:</td>
<td>To determine the ecological impact of the trait, measure:</td>
</tr>
<tr>
<td>• Similarity to the recipient plant</td>
<td>• Potential toxicity</td>
</tr>
<tr>
<td>• Potential altered weediness</td>
<td>• Potential non-target effects</td>
</tr>
<tr>
<td>• Potential for gene flow (outcrossing)</td>
<td>• Consequence of outcrossing</td>
</tr>
<tr>
<td>• Potential altered ecological effects</td>
<td>• Environmental fate</td>
</tr>
<tr>
<td>• Expression profile</td>
<td>• Potential for resistance to develop</td>
</tr>
</tbody>
</table>

In assessing the extent to which an individual GM crop will pose human health and/or ecological risks, risk managers consider a number of characteristics of the organism and environment that are seen as influencing the level of risk. These factors are also typical considerations in the regulatory review process and risk assessment for approval of GM crops and included in the material that regulatory agencies necessitate producers to supply in order to acquire approval. Relevant characteristics include (Peterson, et al. 2000):

1. The environmental conditions in which the GM crop is to be introduced;
2. Closeness to sensitive ecosystems and other crops;
3. The specific genetic modification and its products;
4. Characteristics of the receiving organism;
5. Characteristics of the donor organism;
6. Effects on non-target species.

7.1.2 Ethical, Social and Political Issues

Simply addressing the scientific and technical issues stated above is generally insufficient for addressing the concerns that people express over GM crops; their utilization also threatens certain moral and social values, including (Johnson, et al. 2006, Rigby 2004, Tait 2001):

1. Intellectual property rights and/or technological approaches (such as terminator technology) designed to prevent farmers from saving seed and developing their own seed supplies;
2. Uneven distribution of benefits and risks, with main benefits to seed producers and few directly observable benefits to consumers;
3. Unnaturalness of the technologies used to create the GM plants;
4. Unacceptability of introducing organisms without complete, or at least significant, knowledge of their environmental effects;
5. Unacceptability of limiting the development of an industry and realization of benefits without evidence of risks;
6. Increasing power to agricultural companies and effects on marginalized countries and farmers.

The extent to which the ethical, social and political issues related to the use of GM crops are discussed varies significantly between the US and EU, partly because of cultural and political differences. In general, the EU has, in part through its application of the precautionary principle, allowed greater incorporation of moral and social values into its regulatory process (Tait 2001). The next section offers a review of, and comparison between, risk assessment and regulation of GM crops in the US and EU. Since many of the regulations applicable to GM crops are described in detail later in this chapter, this section will only provide an overarching picture and historical background.

7.1.3 The United States

The United States was the first country to produce and grow GM crops, and is also the country with the current largest share of global GM growth (Clive 2010). The first GM crops, including Bt corn, cotton and potato, where introduced commercially in 1996 (Fernandez-Cornejo and Caswell 2006). Currently, corn, cotton and soybean are the most commonly grown GM crops, and the share of GM crops to traditional crops has increased significantly in the past decade. In 2000, 25 percent of all corn grown in the US was genetically modified, in 2010 that number was 86 percent. Similarly, the percentage of GM cotton has increased from 26 to 86 percent between 2000 and 2010 (ERS/USDA 2010).

In the US, regulation of GM crops has been framed mainly in terms of food safety, with the FDA deciding early on that GM foods and feeds do not require more regulatory oversight or safety testing than traditional foods (FDA 1992). This product-based approach, in which the methods of biotechnology are not considered to lead to increased risks and need for safety testing in and of themselves, is prevalent within US regulation (Jasanoff, Biotechnology and Empire - The Global Power of Seeds and Science 2006). In response to this product based approach, the USDA, FDA and EPA have approved most industry requests for field testing and commercialization of GM seeds, crops, foods and feeds (Bernauer 2003).

While US consumers express various concerns over the cultivation and consumption of GM crops, these concerns have not been translated into regulatory action or changes in the marketplace. This gap between consumer concerns and regulation could be explained by the strong, well organized and influential US seed and agricultural industries (Fernandez-Cornejo and Caswell 2006), who tend to enjoy the most directly observable benefits of first-generation GM crops. Additionally, environmental NGO opposed to GM crops, that drove the debate for stronger regulations in Europe, have had little political influence on biosafety regulations in the US (Bernauer 2003).
7.1.4 The European Union

The EU has been far more conservative than the US in adopting GM crops, and adopts a process based approach to regulation. Risks of GM crops have been framed considerably wider than in the US, especially with respect to environmental and socio-economic concerns. The process-based approach of the EU argues that the very methods of modern biotechnology could lead to additional risks and hence that new laws, regulations and safety testing regimes should be developed specifically for biotechnological products such as GM crops (Rigby 2004).

Regulation of GM crops begun in 1990 with Directive 90/219 (contained use) and Directive 90/220 (deliberate release), subsequently replaced by Directive 2001/18 and Directive 2009/41, respectively. The labeling regime was initiated in 1997 through Directive 258/97, which was replaced by Regulation 1829/2003 in 2004. Fourteen GM plant varieties were authorized for release under directive 90/220 prior to the 1998 de facto moratorium (Bernauer 2003).

In 1996, Monsanto’s glyphosate tolerant GM soybeans began to enter the EU without labeling or segregation. In part because of these imports, the issue of GM crops became an important political issue in the EU, with increasing demand to ban further GM imports. In 1997, Austria and Luxemburg banned number of GM varieties despite their having been authorized under Directive 90/220, with additional bans following in Greece, Italy and Germany. In 1998 a number of member states agreed to block further authorizations in the absence of a labeling regime, a blocking that accounted for sufficient votes to prevent the qualified majority in the Council of Ministers required for approval of new GM products. Hence, in 1998 a de facto moratorium for GM plant varieties came into effect (Rigby 2004). The moratorium lasted six years and was effectively lifted in May 2004 when the GM corn variety (MON810) was approved (Hanrahan 2010).

A number of food safety related events, such as the BSE and foot-and-mouth disease, took place across Europe in the 1990s, and are generally considered as contributing to the negative stance of European consumers towards GM foods and the governments’ rapid response to those public concerns (Tait 2001). The BSE disease, which started in the UK and spread to other parts of Europe, is probably the most prominent. UK food safety authorities initially insisted that BSE could not be transmitted to humans eating BSE infected meat, but in 1996 evidence showed that this was indeed possible, a finding that greatly undermined public confidence in food safety authorities in particular and governmental regulation in general (Hanrahan 2010).

Furthermore, NGOs opposed to agricultural biotechnology became increasingly influential in European politics at this time. The coalitions included consumer groups, farmers, environmental organizations, food processors and retailers. This combination of public sensitivity, fragmentation of producers’ interests caused by NGO campaigns and low concentration of producers in the agricultural and grain handling sectors, explains the regulatory developments in the EU and differences in relation to the US that had a very different political situation.

Finally, since the European system has traditionally relied on expert judgments and governmental administration of risks (Slovic 1993), the breakdown of public trust in the
regulation of GM crops represented a major break in the European model. In order to restore public trust in the European governance model, politicians and regulators were more or less forced to respond by designing an unusually strong, precautionary regulatory system for GM crops.

7.1.5 Conflict between the US and EU


The SPS Agreement is an international agreement that aims for regulatory harmonization in food safety standards by requiring that WTO members either adopt international standards or justify deviant measures with risk assessments and scientific evidence. Hence, a higher level of protection than achievable under international standards is only valid as long as the WTO panel finds that the justification therefore is based on a sufficiently “scientific” risk assessment. Only if the relevant scientific evidence is insufficient can members maintain higher standards without legitimating them through risk assessment (Winickoff, et al. 2005).

In essence, the US argued that the EU had failed to adhere to established principles of scientific risk assessment in its blocking of GM products, that the moratorium constituted unreasonable delay under the SPS Agreement and that the moratorium therefore amounted to illegal protectionism (Jasanoff, Biotechnology and Empire - The Global Power of Seeds and Science 2006). The EU, on the other hand, argued that scientific evidence was insufficient to perform an adequate risk assessment at the time of the regulatory decision and hence that the safe harbor provision of the SPS Agreement, which permits members to impose precautionary measures under certain circumstances, was applicable (Winickoff, et al. 2005).

As has become clear at this point, the interpretation of “sound science”, “risk assessment” and which type of scientific evidence that justifies a precautionary approach to food regulation, lie at the core of the conflict. On November 21, 2006 the WTO’s Dispute Settlement Body handed down its ruling. The panel agreed with the US in that the EU had maintained a moratorium on approvals of GM crops between June 1999 and August 2003, that the blocking of GM crops in Austria, France, Germany, Greece, Italy and Luxemburg violated the SPS Agreement and that the unwillingness to approve 24 out of the 27 GM crops in the approval pipeline constituted undue delay under that agreement. However, the panel dismissed US claims that the EU approval procedures were not based on appropriate risk assessment and that the application of different risk assessment standards for GM products and traditional crops was inappropriate (Hanrahan 2010).

Both Canada and Argentina have settled their disputes with the EU, and agreements involve bilateral, biannual meetings between competent authorities of the European Commission and Canada and Argentina regarding issues relevant to trade of GM crops. The EU and the US have, however, not settled their dispute and continue technical discussions on market access for GM products. Current conflicts involve the EU labeling and traceability regime that
requires that all foods, feeds and ingredients containing more than 0.9 percent GM content be labeled and traceable. Compliance with this regime requires segregation of GM crops and non-GM crops from the time of planting all the way through the processing and marketing chain, and procedures to prevent pollen drift from GM crops to non-GM crops. US interests argue that these problems discriminate against US shipments, restrict trade and that food companies that are forced to label GM products could face huge liabilities (Hanrahan 2010).

7.1.6 Conclusion

The examination of regulatory developments and conflicts over GM crops leads to four conclusions. First of all, it was found that ethical, social and political concerns were very important in shaping public understanding and governmental regulation. Second, differences in the political climate of the US and EU led to differences in regulatory approaches. Third, in the EU, technocratic risk assessment strategies failed to inform the choices that had to be made in the decision-making process, ultimately leading to conflict and polarization. Fourth, failure to design risk assessment and decision-making strategies that were sensitive to the social, economic, and political context in Europe greatly decreased public trust in the process and blocked constructive developments.

These lessons are valuable insights in analyzing the regulatory frameworks for safety and environment of biotechnology, and in drawing conclusions about their applicability and weaknesses. The remainder of this chapter provides a description of international, American and European regulations, and concludes with a holistic analysis.

7.2 The International Policy Framework

The Convention on Biological Diversity and the Cartagena Protocol on Biosafety are the two major international regulations governing the safety of biotechnology products, both of which are reviewed below.

7.2.1 The Convention on Biological Diversity

The Convention on Biological Diversity is a legally binding international treaty that was opened for signature in the Earth Summit in Rio de Janeiro in June 1992 and entered into force on December 29, 1993. The United States has signed, but not ratified the Convention. The three main goals of the Convention on Biological Diversity are stated in Article 1:

- Conservation of biological diversity;
- Sustainable use of biological resources and diversity;
- Fair and equitable sharing of the benefits arising from genetic resources.

In order to achieve this, Contracting Parties are required to, amongst other things, develop and implement national strategies for the conservation and sustainable use of biological diversity, identify and monitor components of biological diversity important for its conservation and sustainable use, regulate or manage biological resources, establish a system of protected areas, promote the protection of ecosystems, and encourage the equitable sharing of benefits arising out of utilization of traditional knowledge. Further, developed countries are encouraged to cooperate with and share technical and scientific knowledge.
relevant to biological diversity with developing countries, and provide financial support for
the implementation of the Convention by developing countries.

The Convention also discusses the development and use of biotechnology and genetic
resources. It specifically requires Contracting Parties to “[e]stablish or maintain means to
regulate, manage or control the risks associated with the use and release of living modified
organisms resulting from biotechnology which are likely to have adverse environmental
impacts that could affect the conservation and sustainable use of biological diversity, taking
into account the risks to human health.”

In relation to access to genetic resources, the Convention establishes that the authority to
determine access to genetic resources rests with national governments and hence that access
must rest on mutually agreed terms and subject to prior informed consent. Contracting
Parties are also required to take legislative, administrative or policy measures to provide for
participation in biotechnological research, the fair and equitable sharing of results and
benefits arising out of biotechnologies, especially with regard to developing countries who
contribute with the genetic resources for such research. Parties also have to develop a
protocol for the safe handling, transfer and use of living modified organisms.

7.2.2 The Cartagena Protocol on Biosafety

The Cartagena Protocol provides a biosafety extension to the Convention of Biological
Diversity and was finalized and adopted in Montreal on January 29, 2000. To date, 159
countries and the European Union have ratified or acceded to it (United Nations 2010). Its
objectives are stated in Article 1 as “to contribute to ensuring an adequate level of protection
in the field of the safe transfer, handling and use of living modified organisms resulting from
modern biotechnology that may have adverse effects on the conservation and sustainable use
of biological diversity, taking also into account risks to human health, and specifically
focusing on transboundary movements.” As such, it is intended to create a uniform
international procedure for regulating the safe transfer of living modified organisms.

The Cartagena Protocol only applies to international transboundary movement of living
modified organisms for the intentional introduction into the environment of the importing
Party; food, feed, and organisms designed for contained use are partially covered by the
Protocol, but not as thoroughly as organisms for intentional release. Living modified
organisms are defined as any living organism that possesses a novel combination of genetic
material obtained either through application of in vitro nucleic acid techniques (rDNA and
direct injection of nucleic acids) or by fusion of cells beyond the taxonomic family.

Before exporting living modified organisms for intentional release into the environment
exporters must notify the competent authority of the importing party in writing and submit
specific information. The importer must perform a scientifically sound risk assessment
based on the information submitted by the exporter, identify and evaluate the possible
adverse effects of the modified organisms on the conservation and sustainable use of
biological diversity, and make its decision based on this assessment.
Annex II specifies the information required to perform an adequate risk assessment of the biological safety of a GMO:

1. **Recipient organism**: relevant biological characteristics of the recipient organism or parental organisms;
2. **Donor organism or organisms**: relevant biological characteristics of the recipient organism or parental organisms;
3. **Vector**: characteristics of the vector;
4. **Characteristics of modification**: genetic characteristics of the inserted nucleic acid and the function it specifies;
5. **Living modified organism**: identity of the living modified organism, and differences between the living modified organism and the recipient organism;
6. **Detection and identification of the living modified organism**: suggested detection and identification methods and their specificity, sensitivity and reliability;
7. **Information about the intended use**: information relating to the intended use of the living modified organism, including new or changed use compared to the recipient organism;
8. **Receiving environment**: information about the location, geographical, climatic and ecological characteristics, including relevant information on biological diversity.

The tension within the text regarding the grounds upon which parties may make decisions on the import of GMOs is interesting, especially since there were serious disagreements about the proper scope of the Protocol during the negotiations. The discussions about scope were centered on whether human health risks should be included, whether parties should be allowed to make decisions based on socio-economic factors and whether the precautionary principle should be allowed as a basis for decision-making (Street 2007).

The issue of whether socio-economic considerations should be allowed as basis for decision making is unclear in the final text, where Article 26 allows for consideration of socio-economic factors while Article 10 requires decisions to be based on scientifically sound risk assessments. Furthermore, the phrase ‘in consistence with their international obligations’ included in Article 26 is a reference to their responsibilities under WTO agreements and thus an attempt to limit the ability of states to justify their decisions based on Article 26. Likewise, the precautionary principle is severely limited and may only be implemented if the scientific risk assessment is indecisive.

### 7.3 The US Policy Framework

US regulation of biotechnology was initiated after the second Asilomar Conference in 1975, after which the NIH established a Recombinant DNA Advisory Committee and published its Guidelines for Research Involving Recombinant DNA Molecules (Levin and Strauss 1991). Since the NIH Guidelines only deal with safety within the lab and for laboratory workers, and do not consider release into the broader environment they were complemented by the Coordinated Framework in 1986 to assess and control the safety of biotechnological products that were transferred from the laboratory to the marketplace (Harlow 1986).
7.3.1 NIH Guidelines for Research Involving Recombinant Molecules

The NIH Guidelines, which are managed and implemented by the Recombinant DNA Advisory Committee (RAC), were implemented in 1976 as a result of the call for development of safety guidelines and mechanisms to assess the safety of research using rDNA that grew out of Asilomar. The NIH Guidelines apply to all federally funded research involving rDNA molecules (Tucker and Zilinskas 2006). In line with the ethos of the Asilomar conference, the NIH Guidelines are designed to manage risks of accidental release and the safety of laboratory workers, whereby the risk of the experiment is based on the risk to the laboratory worker, the public and the environment.

All research involving rDNA is categorized into one of four risk levels (minimal risk, low, moderate and high) based on the characteristics of the host and/or donor organisms, with containment measures that are proportionate to the risk level. Organisms known to be extremely dangerous must be handled in the highest-level biosafety containment facilities, whereas those that pose minimal risks experience much lower containment requirements. Scientists are also required to engineer safeguards into the host organisms to reduce the probability that they survive and proliferate outside the containment facility. Typically, researchers have used extreme nutrient dependency and metabolic deficiency to limit the survival of strains outside of the controlled environment of the laboratory (Tucker and Zilinskas 2006).

In March 2009 NIH published a proposal to update the NIH Guidelines to also cover research using synthetic DNA. Their action was a result of the NSABB recommendation that the US Government examine the language and implementation of current biosafety guidelines to ensure that they cover research with chemically synthesized DNA. The proposed amendments would broaden the scope of the Guidelines, which currently cover DNA molecules that are created via recombinant techniques (joining of DNA), to encompass nucleic acids that are synthesized chemically without the use of recombinant techniques. The name of the Guidelines would also be changed to NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules. As of May 2011, the changes had not been implemented.

7.3.2 The Coordinated Framework

*The Coordinated Framework for Regulation of Biotechnology* was published by the White House Office of Science and Technology Policy in 1986 as a response to growing demands for a regulatory system to control risks connected to the commercialization of biotechnology products (Marchant 1988, Kingsbury 1990, Levin and Strauss 1991, Wrubel and Krimsky 1997, Office of Science and Technology Policy 1986, Rodemeyer, New Life, Old Bottles 2009, Bernauer 2003). The Coordinated Framework did not seek to develop new statutes or agencies for the regulation of biotechnology and instead created a patchy system with significant overlap between the three responsible agencies EPA, FDA and USDA (Rodemeyer, New Life, Old Bottles 2009).

In essence, the EPA regulates all types and uses of genetically engineered microorganisms under the Toxic Substances Control Act and transgenically inserted PIPs (plant incorporated protectants) under the Federal Insecticide, Fungicide, and Rodenticide Act, the USDA
regulates all genetically modified plants, animals and animal biologics under their authority to regulate introductions of agricultural pests and noxious weeds in Federal Plant Protection Act, while the FDA regulates genetically modified foods and drugs under the Food, Drug, and Cosmetics Act (Office of Science and Technology Policy 1986). An overview of the regulatory system is provided in Table 7.2.

Table 7.2 Agency responsibilities in approval of biotechnology products. Adopted from (Office of Science and Technology Policy 1986).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Responsible agency(ies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods and food additives</td>
<td>FDA</td>
</tr>
<tr>
<td>Human drugs, medical devices and biologies</td>
<td>FDA</td>
</tr>
<tr>
<td>Animal drugs</td>
<td>FDA</td>
</tr>
<tr>
<td>Animal biologies</td>
<td>APHIS</td>
</tr>
<tr>
<td>Other contained uses (closed systems)</td>
<td>EPA</td>
</tr>
<tr>
<td>Plants and animals</td>
<td>APHIS (lead), FDA</td>
</tr>
<tr>
<td>Intergeneric microorganisms, agricultural use</td>
<td>APHIS</td>
</tr>
<tr>
<td>Intergeneric microorganisms, non-agricultural use</td>
<td>EPA</td>
</tr>
</tbody>
</table>

7.3.3 The Environmental Protection Agency (EPA)

The EPA regulates all types and uses of genetically engineered microorganisms under the Toxic Substances Control Act (TSCA) and genetically engineered pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under the TSCA and FIFRA, the EPA has favored a more process-based regulatory approach to genetically modified organisms than the USDA and FDA (Bernauer 2003).

The Toxic Substances Control Act (15 U.S.C. §2601 – 2692) was enacted in 1976 to allow the EPA to conduct testing, evaluation, approval and monitoring of chemicals not covered by other statutes. The TSCA grants EPA authority to control the import and export of covered chemicals, to maintain a directory of chemicals, and to test chemicals if new concerns arise. Asbestos, PCBs, and inter-generic microorganisms are all covered under the TSCA, whereas chemicals used in food, drugs, and medical devices are uncovered.

One weakness of the TSCA is its inability to require the provision of relevant information from producers. Section 5(e) of TSCA provides that the EPA may only delay or prohibit the manufacture of a chemical (or recombinant organism) if it can show that the chemical may present and unreasonable risk in cases where information to make a reasoned evaluation of the health and environmental effects is insufficient. In essence, this means that the EPA has the obligation to prove harm to prohibit the manufacture of a chemical. Such an approach is typical to the reactive approach to uncertainty, as opposed to the precautionary approach where the producer can be obliged to prove safety before manufacturing. Because of these limitations of TSCA, concerns have been expressed over its limited adequacy to managing the risks of new technologies such as synthetic biology (Rodemeyer, New Life, Old Bottles 2009).
FIFRA was passed by Congress in 1947 and amended in 1964. The 1964 amendments broadened the scope of the FIFRA and shifted its focus from controlling the efficacy of pesticides to controlling their safety, a shift that has been emphasized further since the EPA was given the task of implementing the legislation in 1970 and further amendments were made in 1972. §408 of the FFDCA mandates the EPA to issue tolerances or tolerance exemptions for the allowable residues in of pesticides that are applied in food or feed (Mendelsohn, Kough, et al. 2003, EPA 2003).

Regulation by the EPA under the TSCA

The EPA regulates the deliberate environmental release of genetically modified microorganisms under *Microbial Products of Biotechnology; Final Regulation under the Toxic Substances Control Act* (EPA 1997), which is designed for identification and assessment of risks of inter-generic microorganisms but does not cover intra-generic or naturally occurring microorganisms. In order to cover microorganisms under the TSCA, the EPA defines DNA as a chemical and asserts that recombinant DNA is new since the new genome is not found in nature (Marchant 1988). An intergeneric microorganism is defined as one that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.

A manufacturer or importer of an inter-generic microorganism is required to submit a microbial commercial activity notice (MCAN) to the EPA at least 90 days before initiation of manufacturing. For field tests, a TSCA experimental release application (TERA) is required instead of the MCAN. The information that is required in a MCAN includes taxonomic data of the donor and recipient microorganism, a description of the introduced genetic material and how this is intended to affect the microorganism, the ecological habitat of the microorganism, and health and environmental data. Necessary information in a TERA includes part of the information required for an MCAN and additional data about the research activity, duration of the field trial and procedures for monitoring (EPA 1997).

Certain types of inter-generic microorganisms are exempted from review under the Tier I and Tier II exemptions. The criteria for exemption are listed in §725.420 and §725.421, which specify certain species of microorganisms in which well-characterized and safe genetic material have been inserted.

Regulation and Overview by the EPA under the FIFRA and FFDCA

The EPA regulates pesticides under 40 CFR Parts 152 and 174: *Pesticide Registration and Classification Procedures* and Part 172: *Experimental Use Permits*. No one may sell or use a pesticide unless it is registered by the EPA. A pesticide will be registered for use only if the EPA finds that the pesticide will not pose unreasonable risks to humans or the environment.

Genetically modified crops with PIPs (plant-incorporated protectants) are regulated under specific rules in 40 CFR Parts 152 and 174: *Plant-Incorporated Protectants: Final Rules* (EPA 2001). It is important to note that the EPA only claims authority over GM crops with PIPs. Plants engineered for better nutritional value or brighter colors will not be reviewed by the EPA, nor will crops in which plant-incorporated protectants have been obtained through conventional plant breeding. In regulating plant-incorporated protectants, the EPA focuses on the characteristics of the pesticidal proteins, and less on issues related to risks of
increased weediness and dissemination of transgenes, as this does not lie within its statutory framework.

Before issuing permits for pesticidal GM crops, the EPA conducts a review and assessment of human health and environmental risks and benefits. The assessments consider factors such as the identity of the new genetic material and all new proteins (pesticidal and non-pesticidal), comparison of new proteins to known toxins and allergens, length of time required for the new proteins to degrade in the environment, and toxicity testing on mammals, birds, fish, earthworms, and certain insects (EPA 2003). In determining the pesticide tolerance limit, the EPA reviews information about the toxicity of the pesticide, how much of the pesticide is applied and how often and how much of the pesticide that remains in the food by the time it is marketed (EPA 2009).

7.3.4 The Department of Agriculture (USDA)

The USDA regulates all genetically modified plants, animals and animal biologics under the Federal Plant Protection Act (FPPA). The FPPA was passed by Congress in 2000, through a consolidation of ten previous USDA plant laws into a comprehensive statute. The authority to implement the FPPA has been delegated from the Secretary of Agriculture to the USDA's Animal and Plant Health Inspection Service (APHIS). APHIS has the mandate to control and restrict introduction, distribution and use of plant pests, with an overarching task to protect US agriculture from plant pests (Mendelsohn, Kough, et al. 2003).

Regulation and Overview by the USDA under the FPPA

APHIS regulates the introduction (importation, interstate movement, and release into the environment) of genetically engineered organisms (including plants, insects, or microbes) that may pose a risk to plant or animal health under 7 CFR Part 340: Introduction of Organisms and Products Altered or Produced through Genetic Engineering Which are Plant Pests or Which There is Reason to Believe are Plant Pest. Depending on the organism, introduction may require an APHIS permit or APHIS notification. The permit process is similar to the notification process but requires more detailed information about field tests and movements of the organism. All genetically modified crops with pesticidal traits are considered plant pests until the USDA concludes that they are not and give crops a non-regulated status. Until non-regulated status is achieved, crops are subject to the standard USDA oversight for environmental release.

Genetically modified organisms are defined as those whose genetic material has been altered or produced through genetic modifications using rDNA techniques. Plant pests are defined as the living state of an organism that can injure or cause disease or damage to plants, parts thereof or any products derived from plants. Certain microorganisms are exempt from review. In general, only recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only non-coding regulatory regions are excluded.

Material required in an application for non-regulated status is includes studies and data that demonstrate that the release of the genetically modified organism will not yield significant plant pest risks. This must be supported by a description of the inserted genetic material and its products, experimental data and publications, description of the differences in genotype
and phenotype between the regulated article and the non-modified recipient, and field test reports. There are no specific test requirements; data from field experiments on the lack of toxicity and a nutritional comparison are considered sufficient (Spök, et al. 2004).

When determining whether or not to grant non-regulated status to a genetically modified organism, the USDA conducts an environmental risk assessment. APHIS is mainly concerned about harms to other organisms (especially agriculturally beneficial and non-target organisms), increase in weediness in another species after crossing, adverse effects on handling, processing or storage of commodities, threats to biodiversity (Spök, et al. 2004).

### 7.3.5 The Food and Drug Administration

The mission of the FDA is to protect public health by assuring the safety, efficacy and security of products such as drugs, cosmetics and foods. This is done through development and enforcement of regulations and by helping to speed innovations that make medicines more effective, safer, and more affordable (FDA 2010). The FDA regulates genetically engineered foods under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §301 – 399), which was enacted in 1938 and has been amended several times since. The FDCA grants authority to the FDA to assure the safety of foods, drugs, cosmetics. The FDCA requires pre-market approval for food colorings and food additives but not for whole-foods.

**Regulation and Overview by the FDA under the FDCA**

The two main sections of the FDCA that apply to genetically engineered foods are 402(a)(1) and 409 (Parisian 2001). 402(a)(1) imposes a legal duty on those that produce and sell foods to assure that the food satisfies the applicable safety standard. Section 409 deals with food additives and requires producers of a new food additive to demonstrate safety to the FDA prior to marketing. However, for additives that are generally recognized as safe (GRAS), this is not necessary. Genetically modified food additives are not automatically on the GRAS list, and a pre-market demonstration of safety might thus be necessary. However, most foods from new plant varieties are whole foods, rather than food additives, and are hence covered under 402(a)(1) rather than 409.

In 1992 the FDA published its *Statement of Policy: Foods Derived from New Plant Varieties* (FDA 1992), which establishes a voluntary consultation process under the FDCA for food from bioengineered plants. The policy does not apply to other foods derived through biotechnology, such as enzymes, sweeteners and colors. The FDA has chosen not to promulgate a regulation specific to biotechnological products or require premarket approval of such products. This is because the FDA believes that the characteristics of the food product is the key issue in determining the safety of a food, rather than the method by which it was produced (FDA 1992).

As mentioned, the FDA employs a voluntary review process for foods derived from genetically engineered plants; risk assessments are hence not required. Under the voluntary consultation process manufacturers can however submit a safety and nutritional assessment containing information about toxicity, allergicity, the introduced genetic material, comparisons with the original plant, and so forth (FDA 2010).
7.4 The EU Policy Framework

The European Union has implemented an encompassing regulatory framework governing risks to human and environmental safety of biotechnology. This study reviews four of the most central statutes in this framework: Directive 2009/41/EC regulates the contained use of GMOs, Directive 2000/54/EC governs risks to health and safety of workers exposed to biological agents (genetically modified as well as natural), Directive 2001/18/EC controls deliberate release of genetically modified organisms (GMOs), and Regulation 1829/2003 regulates GM food and feed.

7.4.1 Directive 2009/41/EC on the Contained Use of GM Microorganisms

Directive 2009/41/EC governs risks related to contained use of genetically modified microorganisms and was entered into force in late 2009. Contained use is defined as any activity in which specific containment measures are used to limit the release of GM microorganisms and assure a high level of safety for the environment and general public. An assessment of the risks to human health and the environment according to procedures set out in Annex III is required prior to initiation of use, the result of which is a classification of the contained use into one of the four risk levels (negligible risk, low, moderate and high).

Criteria used for establishing the safety of GM microorganisms for health and the environment include the identity of the strain, evidence of safety, genetic stability, non-pathogenicity, non-toxicity, non-allergenic, absence of harm due to transfer of genetic material and safety for the environment in case of an accidental release. The assessment of safety must consider the potential for harm to humans, animals, plants and the environment using information about the donor, recipient, introduced genetic material, vector and resulting GM microorganism. Finally, the minimal requirements and measures necessary for each level of containment are presented.

7.4.2 Directive 2000/54/EC on Protection of Workers Exposed to Biological Agents

The objective of Directive 2000/54/EC is to protect the health and safety of workers exposed to biological agents. Biological agents are defined as any microorganisms (genetically modified or not) that are able to provoke infection, allergy or toxicity, and are classified in four risk groups based on the hazard they pose to workers and the community. The classification of risk group for several common microorganisms is provided Annex III of the Directive. Employers are obliged to reduce the risk of exposure to as low as necessary to protect adequately the health and safety of workers, to provide information and training to workers and to keep lists of those exposed.

7.4.3 Directive 2001/18/EC on the Deliberate Release of GM Organisms

Directive 2001/18/EC was put into force in October 2002, repealing Council Directive 90/220/EEC that had been in place since 1990. Largely because of the public pressures with respect to GM crops described earlier, the new Directive has a considerably tighter permission process for the release of GM organisms into the environment, including limiting the life of permits and requiring monitoring of the impact of the organisms on the environment. The directive regulates approvals for field trials, GM crop cultivation and import of crops that can propagate (European Union 2001, Bernauer 2003). A GMO is
defined as an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Specifically, techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism are covered. The same definition of a GMO is used in all EU directives applicable to GMOs.

The main differences between Directive 90/220 and Directive 2001/18 includes a maximum time limit of approvals of 10 years, with the possibility for renewals, out-phasing of antibiotic resistance markers between 2005 and 2008, intensification of monitoring of field trials and environmental effects, and increasing transparency of the approval process, field trials and cultivation sites. However, the legal instruments and authorities remain the same as for the previous directive, with national authorities evaluating the applications, performing the risk assessments and sending their recommendations to the European Commission. Judicially, the Commission has the authority to grant authorization to the release of GMOs even if individual member states disagree, but in practice the Commission has been reluctant to do so (Bernauer 2003).

The possibility for dead-lock is thus apparent, and has been an issue lately. To decrease the tension and dead-lock the Commission agreed on an amendment to Directive 2001/18/EC that will give member states full responsibility over cultivation within their territory. The European Commission describes it as a proposal for combination of the EU science-based authorization system with freedom for member states to decide on the cultivation of GMOs. In effect, member states are allowed to block authorization on grounds other than those based on a scientific assessment of health and environmental risks, such as effects for local agricultural systems and other social and economic impacts. The amendments must be approved by the European Parliament and the Council before entering into force (European Commission 2010), and this was not done as of May 2011.

GMOs are not to be imported or grown in the EU without first obtaining authorization under Directive 2001/18/EC, which provides a step by step approval process based on case by case assessments of risks to humans and the environment. Specific information and procedures for the assessment of human and environmental risks are provided in Annexes II and III. Information required in notifications concerning releases of GM organisms other than higher plants includes:

1. **Characteristics of the donor and recipient** – taxonomy, phenotypic and genetic markers, identification and detection techniques, description of natural habitat, organisms to which transfer of genetic material is known to occur, pathological, ecological, and physiological traits, etc;
2. **Characteristics of the vector** – nature and source, sequence of non-coding genetic elements used to construct vector, etc;
3. **Characteristics of the modified organism** – information about the genetic modification (methods for modification, vector construction etc) and about the final GMO (description of genetic traits, genetic stability, history of previous releases etc);
4. **Information on the release** – description of the release, size of site, quantities of GMOs to be used, worker protection measures etc;
5. **Information on the environment** – geographical location, physical or biological proximity to humans, other significant biota, biotopes or protected areas, description of target and non-target eco-systems likely to be affected, etc;

6. **Characteristics affecting survival, multiplication and dissemination**

7. **Interactions with the environment** – predicted habitat of GMOs and description of ecosystems in which GMOs will be dispersed, studies of GMO behavior and their ecological impact, genetic transfer capability, measures taken to ensure genetic stability, identification of adverse effects on non-target organisms, etc;

8. **Monitoring techniques** – methods for tracing and monitoring the effects of GMOs;

9. **Control of release** – methods to avoid spread of GMO beyond site of release;

10. **Waste treatment**;

11. **Emergency response plans.**

The information required in notifications concerning releases of GM plants is significantly less than that required for other organisms:

1. **Information relating to the recipient** – complete name, reproduction, survivability, dissemination, geographical distribution and other potential interactions of the GM plant with the ecosystem, including toxic effects on humans or other organisms;

2. **Information relating to the genetic modification** – methods used, name and source of vector, donor organism;

3. **Information relating to the release** – purpose, date and duration, method for release and cultivation of GMO, approximate number of plants.

Annex II provides the principles for conducting the environmental risk assessment, the objective of which is to “on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have.” An environmental risk assessment needs to consider the recipient organism, the genetic modification including the vector and donor, the GMO, intended release, the potential receiving environment and the interaction between these. Six separate steps are proposed to determine environmental risks:

1. Identification of the characteristics which may cause adverse effects (including the changes in agricultural practices);

2. Evaluation of potential consequences of each adverse effect;

3. Evaluation of the likelihood of the occurrence of each identified adverse effect;

4. Estimation of the risk posed by each identified characteristic of the GMO;

5. Application of management strategies for risks from the deliberate release or marketing of the GMO;

6. Determination of the overall risk of the GMO.

Finally, the Directive explicitly states that the precautionary principle must be considered when implementing it and that respect for ethical principles recognized in member states is particularly important. Member states may take ethical considerations into account when conducting their risk assessment and recommendation for the authorization of the deliberate release or marketing of GMOs (European Union 2001).
Regulation No 1829/2003 was implemented in 2004 and was crucial in ending the de facto moratorium on authorization of GM crops discussed previously. Regulations, as opposed to directives, become immediately enforceable as binding law in all member states simultaneously and constitute one of the most powerful forms of law in the European Union. The choice to make EU decisions on GM food and feed into regulations, rather than directives, illustrates the political significance that the issue has gained in Europe. The objective of the regulation is "to provide the basis for ensuring a high level of protection of human life and health, animal health and welfare, environment and consumer interests in relation to genetically modified food and feed, whilst ensuring the effective functioning of the internal market." The scope is thus considerably larger than that of comparable US regulations.

Regulation No 1829/2003 is applicable to GMOs for food use, food containing or consisting of GMOs, and food containing from or containing ingredients produced from GMOs. Covered foods may not be marketed in the EU without first obtaining authorization. Authorization is only granted if producers demonstrate that the GM food does not:

1. Have adverse effects on human health, animal health or the environment;
2. Mislead the consumer;
3. Differ from the food which it is intended to replace to such an extent that its normal consumption would be nutritionally disadvantageous to the consumer.

The application for authorization is filed to individual member states, but the European Food Safety Authority (EFSA) is the principal body conducting the GMO risk assessment upon which the decision on whether to grant authorization is based. The GMO applicant has the responsibility to demonstrate safety of the GM product (EFSA 2011), and submit the following information:

1. All information specified in Annex II of the Cartagena Protocol;
2. The designation of the food and the transformations used;
3. A detailed description of methods of production and manufacturing;
4. Copies of studies showing that the food complies with the criteria for authorization specified above;
5. An analysis showing that the characteristics of the food do not differ from its conventional counterpart or a proposal for labeling of changes in composition, nutritional value or health effects for certain parts of the population;
6. A reasoned statement that the food does not give rise to ethical or religious concerns or a proposal for labeling of ethical or religious concerns;
7. Where appropriate, conditions for placing the food on the market, including use and handling conditions;
8. Methods for detection, sampling and identification of the food;
9. Where appropriate, a proposal for post-market monitoring.

For applications regarding GMOs for food use, the application must be supplemented with the information specified in Annexes III and IV of Directive 2001/18/EC, information and conclusions of the risk assessment carried out in accordance with Annex II of the directive, and a monitoring plan of environmental effects conforming to Annex VII.
Section 2 of the regulation sets forth the principles and requirements for labeling. Labeling is only required for GMOs food that has a GMO content higher than 0.9 percent. Any foods containing more than 0.9 percent GMOs the list of ingredients must contain the words 'genetically modified' or 'produced from genetically modified (name of ingredient)', as applicable. Foods with changed composition, nutritional value or nutritional effects, intended use or implications for health of certain parts of the population must have a label of this describing the differences. Finally, foods that may give rise to ethical or religious concerns must also carry a label that describes the nature of the concerns.

*The European Food Safety Authority*

EFSA was created through Regulation (EC) No 178/2002 as a way for the EU to respond to a series of food crises during the late 1990s, such as the management of GM crops and BSE. EFSA performs all risk assessments for GMOs to be used in food or feed. EFSA describes its role as being an “independent source of scientific advice and communication on risks associated with the food chain” and that their most critical commitment is to “provide objective and independent science-based advice and clear communication grounded in the most up-to-date scientific information and knowledge.” (EFSA 2003).

### 7.5 Analysis of the Policy Framework for Safety & Environment

As was mentioned in the beginning of the chapter, regulations for biosafety are analyzed with respect to their general applicability to synthetic biology, which risks of synthetic biology that they address, their approach to risk assessment, methods for dealing with uncertainty and incorporation of values. The analysis begins with an overview of which of the seven identified biosafety risks that are addressed by the current biosafety regulations (see Table 7.3), and continues with some general remarks of the international, US and EU regulatory frameworks before going into the specific sections devoted to the applicability of regulations and their respective approaches to scientific uncertainty and risk assessment.

**Table 7.3 Analysis of regulatory coverage of safety and environmental risks of synthetic biology.**

<table>
<thead>
<tr>
<th>Risk</th>
<th>International Regulation</th>
<th>US Regulation</th>
<th>EU Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations, evolution and proliferation</td>
<td></td>
<td>Coordinated Framework – EPA</td>
<td>Directive 2001/18/EC</td>
</tr>
<tr>
<td>Consumption risks</td>
<td>Coordinated Framework – EPA (only for plant incorporated pesticides)</td>
<td></td>
<td>Regulation 1829/2003</td>
</tr>
</tbody>
</table>
Table 7.3 shows that the international framework mainly addresses environmental risks of genetically engineered organisms. In fact, a major conflict during the drafting of the Cartagena Protocol on Biosafety was exactly the question of whether it should address human health risks in addition to environmental risks (Street 2007). The current protocol contains references to human health and a specific section on GM food and feed, but these parts are weaker than those that address environmental risks. This is probably caused by the fact that governments view citizens and their well-being as more relevant constituents than the environment and are hence more reluctant to give up sovereignty in the politically more relevant area of human and public health than in environment.

The regulatory framework of the European Union is by far the most encompassing and addresses all identified biosafety risks through statutory law. As such, it has been critiqued for being cumbersome and requiring unnecessarily high standards of proof of health and environmental safety before approval biotechnological products for marketing or direct environmental release. The force of the EU regulatory framework is a direct result of the controversy over GM crops in Europe and the political and public pressures for stronger regulation that emerged during that controversy.

The fragmentation of the Coordinated Framework is the most striking feature of the US regulatory system for biotechnology. A conviction that biotechnology regulation should focus not on the process of biotechnology but on the inherent properties of its products, led the US government to promote a system in which biotechnology was to be handled under already existing statutes. Consequently, biotechnological products are currently covered by three different agencies operating under four separate statutes, and the result is a regulatory system marked by fragmentation, lack of coordination and different standards for different types of products.

For example, review of genetically modified animals that will not be used directly as food is more or less unregulated under the current framework, while genetically modified crops with plant incorporated protectants are reviewed by all three agencies. Further, the difference in statutory mandate, risk assessment methodologies and agency cultures between the EPA, APHIS and USDA creates a system whereby the stringency of the risk assessment and approval process is more dependent on the specific product category than on the risk of the product. Furthermore, the very rationale of the US government to not enact a separate, specific statute for biotechnology has effectively been undermined by the specific regulations promulgated by the responsible agencies; the US has, in effect, adopted a regulatory system that has separate review mechanisms for most biotechnological products, just like the European one. Finally, the degree to which current statutes, such as the TSCA, can be stretched to include and effectively handle technologies and products of synthetic biology remains unclear at this point.

For these reasons, it would be beneficial to replace the Coordinated Framework with a single statute for biotechnological products. Such a statute could still divide responsibility between the three agencies but could, in its holistic approach, make sure that all relevant types of products are covered, that the required information, risk assessment methodologies and risk levels for approval are similar, and develop frameworks for more systematic cooperation and coordination between agencies. This would increase the clarity, cooperation, and
effectiveness of the overall regulatory system and lead to a similar approval process for all products.

7.5.1 Applicability to Synthetic Biology

Biosafety regulations governing risks of rDNA technology will probably be sufficient to cover most first generation products of synthetic biology but as synthetic biology matures scientists will be able to create increasingly complex organisms with genomes composed of genetic material from multiple organisms or completely lacking natural counterparts. This increase in complexity presents a challenge to current regulatory frameworks, which will have to evolve both their definitions of covered organisms and/or genetic material and risk assessment methodologies. Analysis of the definitions of covered organisms and/or genetic materials (see Table 7.4) provides an initial indication of regulatory applicability.

Table 7.4 Analysis of the applicability of the definitions of covered organisms and/or genetic material in current regulations to synthetic biology.

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Definition of covered organisms and/or DNA molecules</th>
<th>Applicable to synthetic biology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartagena Protocol on Biosafety</td>
<td>Living organisms with a novel combination of genetic material obtained by in vitro nucleic acid techniques (rDNA and direct injection of nucleic acids) or by fusion of cells beyond the taxonomic family.</td>
<td>Probably not. Only covers rDNA techniques and direct injection of nucleic acids. Does not mention synthetic nucleic acids.</td>
</tr>
<tr>
<td>NIH Guidelines</td>
<td>DNA molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell.</td>
<td>Only in part. Does not apply to complete genetic constructs of chemically synthesized nucleic acids.</td>
</tr>
<tr>
<td>Coordinated Framework – EPA</td>
<td>Organisms formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.</td>
<td>No. Does not cover chemically synthesized nucleic acids, nor DNA of unnatural origin.</td>
</tr>
<tr>
<td>Coordinated Framework – APHIS</td>
<td>Organism that have been altered or produced through genetic modification by recombinant DNA techniques.</td>
<td>No. Only covers modifications produced by rDNA techniques.</td>
</tr>
<tr>
<td>Directive 2001/18/EC</td>
<td>Organisms in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination, by techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism.</td>
<td>Probably. Specifically mentions that the introduced nucleic acids can be produced by any type of technology.</td>
</tr>
</tbody>
</table>

The evaluation shows that most regulations are not applicable to organisms with genetic material that is either composed of chemically synthesized nucleic acids or nucleic acids without natural counterpart. This is especially true for regulations under the US Coordinated Framework; EPA and APHIS regulations only cover organisms that have had naturally
existing DNA inserted by rDNA technologies and not chemically synthesized DNA or DNA lacking natural origin. The broader definition of genetic modification in European regulations will most likely cover genetic elements and organisms of synthetic biology.

The material that the international, American and European regulations require for their risk assessment and approval process typically relates to the donor organism, the recipient organism and the inserted DNA. Focus on donor and recipient organisms indicates that the main method of establishing risk is by comparison with natural equivalents. This approach is most obvious in the APHIS regulations and somewhat less evident, but nonetheless dominant, in European regulations.

Developments in synthetic biology that enable the construction of organisms with chemically synthesized DNA and introduction of multiple and complex genetic elements render risk assessment by comparison fundamentally obsolete. It is thus crucial that risk assessment methodologies develop the ability to assess risk based solely on the inherent properties of genes, proteins and organisms and move away from the current comparative frameworks. This task is much more challenging than the need to expand the scope of regulations to cover chemically synthesized DNA and DNA without natural origin.

### 7.5.2 Approaches to Risk Assessment and Uncertainty

Analysis of approaches to risk assessment and uncertainty constitutes the final evaluation of this chapter, and is presented in Table 7.5.

**Table 7.5 Approaches to risk assessment and uncertainty in current biosafety regulations.**

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Level</th>
<th>Year</th>
<th>Risk assessment approach</th>
<th>Dealing with uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convention on Biological Diversity</td>
<td>UN</td>
<td>1993</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cartagena Protocol on Biosafety</td>
<td>UN</td>
<td>2000</td>
<td>Scientifically based with (little) incorporation socio-economic factors</td>
<td>Unclear (mentions the precautionary principle but text is indecisive)</td>
</tr>
<tr>
<td>NIH Guidelines</td>
<td>US</td>
<td>1976</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coordinated Framework – EPA</td>
<td>US</td>
<td>1986/1997</td>
<td>Scientifically based</td>
<td>Reactive (but more precautionary than APHIS and FDA)</td>
</tr>
<tr>
<td>Directive 2000/54/EC</td>
<td>EU</td>
<td>2000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Directive 2001/18/EC</td>
<td>EU</td>
<td>2002</td>
<td>Scientifically based with incorporation of ethics and socio-economic factors</td>
<td>Precautionary</td>
</tr>
<tr>
<td>Regulation 1829/2003</td>
<td>EU</td>
<td>2004</td>
<td>Scientifically based with incorporation of ethics and socio-economic factors</td>
<td>Precautionary</td>
</tr>
</tbody>
</table>
Here, the differences between the EU and US, and the problems in reaching an international consensus, become very clear. The US regulatory system is reactive and based on scientifically-based assessments of risk without inclusion of ethical and socio-economic factors, while the EU regulatory system is precautionary and allows at least rudimentary inclusion of ethical and socio-economic factors. The ambiguity of the international framework with regard to the need for precaution and incorporation of ethical and socio-economic factors is a direct result of this disparity between the EU and US, whom are both influential in internationally and in negotiations.

Problems created by the discrepancy between the EU and US is thus not only limited to the two countries and their trade relations, but reverberate throughout the UN system and hence globally. Furthermore, problems of persistent conflict and divergence between the EU and US within biosafety regulation are likely to increase as biological engineering and synthetic biology develop more capacity to deliver novel products and processes and thus increase the importance of biological production methods and biotechnology. For these reasons, it appears crucial that the EU and the US settle their dispute at the WTO and at least attempt to converge their regulatory systems.

Finally, it is interesting to discuss the way in which the EU has responded to the GM crop debate by including ethical and socio-economic factors as valid points of regulatory intervention in the marketing of biotechnology products. Despite this somewhat broader framing of risks compared to that of US regulation, the EU risk assessment approach is nonetheless based on the compartmentalized approach outlined in *Risk Assessment in the Federal Government*. Ethical and socio-economic values are only allowed to enter *fait accompli*, after the scientific assessment of risk, and not as integrated elements in the process for characterizing and assessing risk, as presented in the later book *Understanding Risk: Informing Decisions in a Democratic Society*.

The conclusion from this finding is that the EU, despite its problems and political pressures in designing a regulatory framework for genetically modified organisms, did not seek to fundamentally alter or broaden the process by which biosafety risks are evaluated and assessed. Instead, they employ the same principal approach as before when evaluating and characterizing risks, albeit involving more data and a deeper analysis. Socio-economic and ethical concerns are not viewed as belonging in the risk assessment framework but as unique intervention points after the completion of the risk assessment. Maybe this is a result of the WTO trade dispute over GM crops between the EU and US, where the EU was forced to argue that their risk assessment approach adhered to the WTO definition and was sufficiently scientific, or maybe European leaders, just as their American equivalents, see risk assessment as a strictly scientific method whose sole purpose it is to achieve an assessment of risk that corresponds as close as possible to the real risk.

The European approach is, however, unlikely to satisfy few, if any, of its stakeholders. Those that see risk assessment as a strictly scientific process will be disappointed by the mere inclusion of ethical and socio-economic values, while those that see it as a broader process will be disappointed by the minor role played by values. The approach taken by the EU is thus unlikely to resolve neither the social conflict in Europe, nor the trade dispute with the US about GM crops and biosafety. I think the EU would have been better off implementing a broader, more integrated risk assessment methodology in line with the one
presented in *Understanding Risk: Informing Decisions in a Democratic Society* that incorporates stakeholders and their perspectives directly in the process. This approach would be clearer, distinguish the EU from the US, and challenge the US model rather than, as is the case today, attempt to provide a compromise between two fundamentally incompatible perspectives on the role and process of risk assessment.

### 7.6 Conclusion

The analysis of international, US and EU regulatory frameworks for biosafety has produced four principal conclusions. First of all, the case study of the regulation of GM crops showed that perceptions of risk and their assessment are not only dependent on technical and scientific issues, but also on ethical, social and political concerns. Because of this, technocratic framing and assessment of risks proved insufficient to dealing with the concerns that the public expressed over GM crops, and finally led to an undermining of trust and subsequent governmental responses and design of more stringent regulations to regain the confidence of its citizens and limit social conflict.

Second, the US Coordinated Framework is highly fragmented and would benefit from being replaced by a single statute for biotechnological products. Currently, some products are unregulated while others are reviewed by all three agencies. Further, the difference in statutory mandate, risk assessment methodologies and agency cultures between the EPA, APHIS and USDA creates a system whereby the stringency of the risk assessment and approval process is more dependent on the specific product category, which determines agency responsibility, than on the risk of the product. Finally, the degree to which current statutes can be stretched to include and effectively handle technologies and products of synthetic biology remains unclear at this point. A single statute would reduce overlap, increase clarity, cooperation and overall effectiveness of the regulatory system and lead to a similar approval process for all product types.

Third, current regulations in both the EU and US were developed for rDNA technology and are inadequately equipped to deal with synthetic biology. In many cases, the very definition of covered organisms and/or genetic material is not even applicable to synthetic biology, and, more severely, all regulations rely on risk assessment through comparison with natural equivalents. Comparative methodologies to risk assessment are rendered obsolete by capacities to construct organisms with multiple and complex genetic elements composed of chemically synthesized DNA, and governments should develop risk assessment methodologies that are able to assess risk based solely on the inherent properties of genes, proteins and organisms.

Finally, the US and EU both adhere to the compartmentalized model for risk assessment presented in *Risk Assessment in the Federal Government*. In part as a result of the controversies over GM crop regulation, the EU has allowed inclusion of ethical and socio-economic factors, but only after the risk assessment is completed and not as integrated elements during the analysis. The compartmentalized approach thus appears to continue to dominate risk assessment, despite its problems in producing risk assessments that are relevant to the decision-making process and social context for a range of technologies, of which GM crops are but one example.
Chapter 6 showed that synthetic biology gives rise to three types of security concerns: spread of biological weapons to state and non-state actors and increased capacity to engineer more active biological agents. This chapter describes and analyzes the policy and regulatory frameworks that address these risks.

The review begins with the international policy framework, which consists of the Biological Weapons Convention, the Australia Group Guidelines, and the UN Security Council Resolution 1540. Description of the US framework is initiated by an overview of the 2001 Anthrax attacks that were extremely influential in shaping the US response to and regulation of biosecurity risks; all reviewed American policies on biosecurity except the Export Administration Regulations were implemented after 2001 and address threats from bioterrorism. These policies and regulations include the National Strategy for Countering Biological Threats, the Select Agent Regulations and the Guidance for Providers of Synthetic Double-Stranded DNA. European regulations are less encompassing, and limited to the EU Strategy against Proliferation of Weapons of Mass Destruction and Regulation 428/2009 on export controls.

Like in the previous chapter on biosafety, each individual regulation is reviewed in detail, with special attention to the definition of covered organisms and/or genetic material, approaches to uncertainty, and overall scope. Finally, this information is analyzed as a whole in the concluding section of the chapter that provides a synopsis of the general applicability of current biosecurity regulations to synthetic biology, the risks that they address, and their methods for dealing with uncertainty.

8.1 The International Policy Framework

The international policy framework governing security risks is stronger and more encompassing than that governing safety risks. The Biological Weapons Convention forms the foundation of international efforts aimed at limiting the dissemination and use of biological weapons and is supported by the Australia Group Guidelines and UN Security Council Resolution 1540.

8.1.1 The Biological Weapons Convention

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and Their Destruction was opened for signature on April 10 1972 and entered into force on 26 March 1975. As of June 2005, 171 states had signed the convention, of which 16 still needed to ratify it, while 23 states had not signed (The Biological and Toxin Weapons Convention Wepage 2005). It supplements the Geneva Protocol of 1925, which only prohibits the use of chemical and biological weapons during warfare (League of Nations 1925) and is currently signed by 173 states.

Article I of The Biological Weapons Convention prohibits signatory states from developing, producing, stockpiling or otherwise acquiring or retaining “Microbial or other biological agents, or toxins whatever the origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes (and) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purpose or
in armed conflict.” Subsequent articles require states to destroy or divert to peaceful purposes already existing biological agents and toxins, not to transfer or assist other state or non-state actors to manufacture or acquire biological agents and toxins, to take necessary measures to prevent development, production, stockpiling, acquisition or retention of agents within their own territory and to file complaints if it finds that another state violates the convention.

8.1.2 The Australia Group Guidelines

The Australia Group first met in 1985 in Brussels and initially consisted of 15 countries. The first meeting addressed the use of chemical weapons by Iraq in the Iran-Iraq war, and posed the question of how to prevent Iraq from acquiring materials for the production of chemical weapons through otherwise legitimate trade. The response of the 15 countries was a proposal to harmonize national export controls. Since then, the Australia Group has grown to include 38 countries plus the European Commission and has developed common control lists of material and technologies whose export and trade should be restricted to prevent proliferation of chemical and biological weapons. Restriction and control of export is achieved through licensing of certain chemicals, biological agents, and dual-use chemical and biological manufacturing facilities and equipment.

It is important to note that the Australia Group is an informal arrangement that operates without the use of legally-binding obligations, relying heavily on the fact that all members are also members of the Biological Weapons Convention. The purpose of Australia Group is to explore the scope for increasing the effectiveness of existing controls through information exchange and the harmonization of national policies. All members of the Group require licenses for the export of biological agents, plant pathogens, animal pathogens, and dual-use biological equipment in addition to those for chemicals. Biological agents include a range of organisms and toxins that have the potential to cause harm to human health, such as bacteria, viruses, and fungi (The Australia Group 2005).

8.1.3 United Nations Security Council Resolution 1540

Resolution 1540 was adopted by the Security Council in April, 2004 to facilitate an effective response to global threats posed by nuclear, chemical and biological weapons by strengthening non-proliferation activities. The resolution decides that states must refrain from providing any form of support to non-state actors who seek to develop, acquire, manufacture, possess, transfer or use nuclear, chemical or biological weapons. States must also adopt and enforce laws that prohibit non-state actors to develop, acquire, manufacture, possess, transfer or use nuclear, chemical or biological weapons, especially for terrorist purposes, and to establish domestic controls to prevent the proliferation of such weapons. To do this, states are required to develop and maintain effective physical protection measures, border controls, laws to control export, transit and end-user control of such weapons and law enforcement mechanisms to detect, deter, prevent and combat illicit trafficking.

8.2 The US Policy Framework

The US policy framework has been strengthened considerably since September 11 and the anthrax attacks, especially for the control of activities that could increase risks of bioterrorism. Because of the political importance of the 2001 Anthrax attacks, they are
reviewed briefly at the beginning of this section. After this historical background, concrete policies and regulations are presented, including the National Strategy for Countering Biological Threats, the Export Administration Regulations, the Select Agent Regulations, and the Guidance for Providers of Synthetic Double-Stranded DNA.

8.2.1 The 2001 Anthrax Attacks

The Anthrax attacks occurred over the course of several weeks beginning on September 18, 2001, just one week after the New York terrorist attacks, and became the worst biological attack in US history (FBI 2011). At least five envelopes containing spores of Bacillus anthracis (the Ames strain) were sent to United States Senators Patrick Leahy and Thomas Daschle in the District of Columbia and to media organizations located in New York City and Boca Raton, Florida. At least 22 individuals contracted anthrax as a result of the mailings, five of which died as a result of their infections. Half of the victims contracted anthrax by inhalation while the other half contracted the disease by absorbing anthrax through the skin. Thirty-five postal facilities and commercial mailrooms were contaminated, and anthrax was detected in seven of the 26 building tested on Capitol Hill.

The first victim, Robert Stevens, was diagnosed with having contracted anthrax and died from the infection the next day. Stevens death marked the beginning of the seven year long investigation of the case, called the Amerithrax case, at the Federal Bureau of Investigation (FBI) in cooperation with the United States Postal Inspection Service. The investigation is one of the most complex in US history; expending over 600,000 investigator work hours, spanning six continents, involving over 10,000 witness interviews, 80 searches, and collection of more than 6,000 items of potential evidence and 5,700 environmental samples.

In the beginning of the investigation, the FBI did not know whether the letters were isolated acts, the work of an international or domestic terrorist organization or state-sponsored acts of terrorism. In the beginning, the investigation focused on the possibility that the attacks were the result of state-sponsored terrorism or from an international terrorist organization such as al Qaeda. They thus specifically focused their efforts on governments known to have, or have had, an offensive biological weapons program and international terrorist groups. While it has been shown that al Qaeda were seeking to establish an offensive bioweapons program in 2001 (National Commission on Terrorist Attacks 2004), the FBI was unable to find any links between al Qaeda and the Anthrax attacks in the United States.

Eventually, breakthroughs in scientific analysis and microbial forensics made it possible to identify the parent material for the letter spores. It was then determined that the parent material of the spores was created and maintained by Dr. Bruce E. Ivins at the United States Army Medical Research Institute of Infectious Diseases; evidence gradually established that Dr. Ivins alone mailed the anthrax letters. Dr. Ivins took his life in July 2008, after being presented with the evidence and before charges were filed (U.S. Department of Justice 2010). The Amerithrax case is still an open case, currently involving 17 FBI special agents and 10 U.S. postal inspectors (FBI 2011).

The 2001 anthrax attacks had significant political influence, especially if understood in a broader context together with the 9/11 terrorist attacks. In 2002, Congress passed the Public Health Security and Bioterrorism Preparedness and Response Act to improve the ability of...
the United States to prevent, prepare for and respond to bioterrorism and other public health emergencies’. In 2004, President George W. Bush founded the National Security Advisory Board for Biosecurity (NSABB), which is discussed in greater detail later in the chapter. Furthermore, the US focus on biosecurity risks of synthetic biology, which is not at all present to the same extent in Europe, indicates the significance of the Anthrax attacks on the American political and cultural context.

8.2.2 National Strategy for Countering Biological Threats

The National Strategy for Countering Biological Threats was published by the National Security Council in November 2009. The strategy argues that the unparalleled period of advances within the life sciences holds extraordinary potential for beneficial progress but can also empower those who seek to use biological agents for ill purpose. The decreasing barriers of technical expertise and monetary costs, which is one of the major features of synthetic biology, is especially mentioned as a central problem, especially if coupled to the evolving nature of the threat landscape since the 1980s with additional and severe threats coming from terrorist groups or individuals.

The strategy calls for broad government action to address these novel and severe threats. This will be done by reinforcing norms of safe and responsible conduct, by obtaining timely and accurate insight on current and emerging risks, by taking reasonable steps to reduce the potential for exploitation and by transforming the international dialogue on biological threats. The strategy does not articulate any direct responsibilities; the implementation of the strategy and specific actions to be taken by Federal entities are directed separately (National Security Council 2009).

8.2.3 Export Administration Regulations

The Export Administration Regulations (EAR) were enacted to implement the Export Administration Act of 1979, which provided legal authority to the President to control U.S. exports for reasons of national security, foreign policy, and/or short supply. The Bureau of Industry and Security under the US Department of Commerce is responsible for implementing the EAR, found in Title 15, chapter VII, subchapter C of the US Code. The Commerce Control List specifies the items that are subject to export controls. Category 1 contains “Materials, Chemicals, Microorganisms and Toxins” and this is hence where biological dual-use items are specified.

The biological agents that are controlled include a range of viruses, bacteria, zoonoa, rickettsiae, toxins, fungi that are able to cause disease in humans, animals and/or plants. Further, genetic elements that contain nucleic acid sequences associated with the pathogenicity of controlled microorganisms are also covered. Items are specified according to the reason for control, a classification which is then used to determine whether a license is required for export to a specific country. The license requirements vary significantly between different countries based on the threat level that an individual state or actors within that state are seen as posing. The most restricted destinations include embargoed countries and those designated as supporting terrorist activities, including Cuba, Iran, North Korea, Northern Sudan, and Syria (US Department of Commerce 2010).
8.2.4 Select Agent Regulations

The Select Agent Regulations (applicable to both GM and non-GM organisms) were endorsed in 2005 to implement the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, passed by Congress as a response to the September 11 and Anthrax attacks to “improve the ability of the United States to prevent, prepare for and respond to bioterrorism and other public health emergencies.” The act requires the Department of Human Health Services (HHS) to establish and regulate a list of biological agents and toxins that could pose a severe threat to public health, while the USDA is required to establish and regulate a list of biological agents and toxins that pose a severe threat to plant health and plant products or animal health and animal products.

The Department of Human Health Services

The Center for Disease Control (CDC) and Prevention of HHS implements its part of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 through regulation 42 C.F.R. §73 Select Agents and Toxins. This regulation provides CDC with the authority to control and monitor the possession, use and transfer of select agents and toxins. §73.3 provides a list of select agents and toxins that are considered to have the potential to pose a severe threat to human health and safety, while §73.4 provides a list of select agents and toxins that pose a severe threat to public, animal and plant health and safety, also known as overlap select agents and toxins since APHIS also has authority over them. Examples of select agents and toxins include Bacillus anthracis, the Ebola virus, Clostridium botulinum and Yersinia pestis. Further, all work involving genetically modified select agents and toxins, nucleic acids that can produce the infectious forms of any of the select agent viruses, or recombinant nucleic acids that encode for the functional form of the toxins in vivo or vitro are also considered for review.

§73.7 establishes that no individual or entity is allowed to possess, use, or transfer select agents or toxins without a certificate of registration issued by the HHS secretary. To obtain a certificate of registration, which is valid for three years, an individual or entity must submit the information requested in the HHS/CDC Form 1. Necessary information includes measures for safety and containment, training, and response to accidents. Based on this information the Attorney General conducts a security risk assessment which must be approved by the HHS Secretary or APHIS Administrator. Registered entities must also develop a written security plan to safeguard against unauthorized access, theft, loss, or release. The security plan must include information about procedures for physical security, inventory control, information system control, control of access, reporting of unauthorized activity and so forth. Further, a biosafety plan for containment of the select agent or toxin during laboratory work must also be written and implemented.

The US Department of Agriculture

APHIS of the USDA implements the Agricultural Bioterrorism Protection Act of 2002, a subpart of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 through regulations 7 C.F.R. §331 (plants) and 9 C.F.R. §121 (animals), both named Possession, Use, and Transfer of Select Agents and Toxins that control the possession, use, and transfer of select agents and toxins that have the potential to pose a severe threat to plant health and plant products or animal health and animal products. The two regulations are essentially the same as CDC’s regulation 42 C.F.R. §73, except that other select agents and
toxins are considered. Other than this, the information and forms required for obtaining a certificate of registration are identical, as well as the review process and other procedures.

8.2.5 Screening Guidance for Providers of Synthetic Double-Stranded DNA

On October 13, 2010, HHS published Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA in the Federal Register (Federal Register, Vol. 75, No. 197 2010). Following the guidance is voluntary, but it nonetheless provides insights into how the government could and might aim to limit risks to security in an age of synthetic biology. The guidance establishes two responsibilities for providers of synthetic, double-stranded DNA, first they should know to whom they are distributing a product and second they should know whether the product they are synthesizing and distributing contains a “sequence of concern”.

To achieve this, providers are suggested to conduct a customer and sequence screening. The purpose of the customer screening is to establish the legitimacy of customers ordering synthetic double-stranded DNA sequences by verifying the identity and affiliation of customers and identifying any “red flags” of which there is suspicion that the order could be used for inappropriate ends. Providers are also recommended to check the customer against several lists of proscribed entities, such as the Department of Treasury Office of Foreign Asset Control list of Specifically Designated Nationals and Blocked Persons and the Department of Commerce Denied Persons List for domestic orders, and are required to follow the laws and regulations of US trade sanctions and export controls for international orders.

The purpose of the sequence screening is to identify whether “sequences of concern” are ordered. Sequences of concerns are defined as those that code for the select agents and toxins identified by CDC and APHIS in the Select Agent Regulations. If the complete sequence or unique parts of the sequences are identified, providers must make sure that customers have a certificate of registration from CDC or APHIS for using select agents or toxins. For international orders, providers should also screen for items on the Commerce Control List to ensure that they are in compliance with the Export Administration Regulations (EAR).

If either the customer or sequence screening cause concern, a follow-up screening must take place to verify the legitimacy of the customer and end-use of order. What a follow-up screening is to be composed of is less specific than for the two initial screening, but as far as possible, the identity, affiliation, and legitimacy of the customer must be obtained as well as the intended use of the ordered DNA. If the follow-up screening does not solve the concerns raised, the provider should contact the US Government, or more specifically either the FBI, the Select Agent Programs of CDC and APHIS or the Department of Commerce, for assistance and further action.

8.3 The EU Policy Framework

EU has not been as proactive as the US in designing policies to limit the spread of biological agents. The export regulation for dual-use items, as specified in Regulation 428/2009, is the main European legal instrument addressing biological threats to security.
8.3.1 EU Strategy against Proliferation of Weapons of Mass Destruction

The EU Strategy against Proliferation of Weapons of Mass Destruction was adopted in 2003 as the European response to growing concerns over the threat of weapons of mass destruction. Terrorists are believed to pose the highest levels of threat, while a small number of states acting outside of the international legal framework are seen as a little less troubling. The threat of proliferation of biological weapons is seen as increasing due to rapid developments in the life sciences. Biological weapons are also seen as more difficult to detect and contain, and thus to have particular attractions for terrorists. To address these threats, the strategy suggests strengthening the international cooperation and coordination of policies concerning weapons of mass destruction. The coordination and improvement of multilateral treaties and export control regimes is seen as especially important in this regard, with the UN Security Council as an important actor (European Council 2003).

8.3.2 Regulation No 428/2009

Regulation No 428/2009 was implemented by the Council of the European Union in 2009 to set up a regime for the control of exports, transfer, brokering and transit of dual-use items and technology, consolidating previous amendments to Council Regulation (EC) 1334/2000 and implementing the United Nations Security Council Resolution 1540/2004. Regulations, as opposed to directives, become immediately enforceable as law in all member states simultaneously and constitute one of the most powerful forms of law in the European Union.

The dual-use items over which Regulation 428/2009 has authority over are listed in Annex I, all of which require authorization from the responsible authority in individual member states prior to export. Covered organisms include human, animal and plant pathogens such as viruses, rickettsiae, bacteria, toxins and fungi. Genetic elements and genetically modified organisms that contain nucleic acid sequences that are either associated with pathogenicity of covered organisms or encode toxins are also covered.

8.4 Analysis of the Policy Framework for Security

As was mentioned in the beginning of the chapter, regulations for biosecurity are analyzed with respect to their overall scope, the risks that they address, general applicability to synthetic biology, and their methods for dealing with uncertainty. The analysis will differ slightly to that for biosafety because of differences in the regulatory systems, especially with regards to risk assessment and specificity to genetically modified organisms, which are both much less pronounced in biosecurity regulations. As was shown in the review, biosecurity regulations typically operate by limiting the spread of organisms, genetic elements and toxins that have already been defined as hazardous. Further, there are no legally binding biosecurity regulations that address genetically modified organisms per se.

The analysis begins with an overview of which of the three identified biosecurity risks that are addressed by current regulations (see Table 8.1), continues with some general remarks over international, American and European regulatory frameworks, and finishes with the evaluation of the applicability of regulations to synthetic biology and their respective approaches to uncertainty.
Table 8.1 Analysis of regulatory coverage of security risks of synthetic biology.

<table>
<thead>
<tr>
<th>Risk</th>
<th>International Regulation</th>
<th>US Regulation</th>
<th>EU Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spread to state actors</td>
<td>Biological Weapons</td>
<td>Export Administration Regulations</td>
<td>Regulation 428/2009</td>
</tr>
<tr>
<td></td>
<td>Convention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spread to non-state actors</td>
<td>UN Security Council Resolution 1540, Biological Weapons Convention</td>
<td>Select Agent Regulations, Export Administration Regulations</td>
<td>Regulation 428/2009</td>
</tr>
<tr>
<td>More effective biological agents</td>
<td>-</td>
<td>(Select Agent Regulations, Export Administration Regulations)</td>
<td>(Regulation 428/2009)</td>
</tr>
</tbody>
</table>

Table 8.1 shows that international, US and EU regulations have been designed to limit the dissemination of biological agents and weapons to state and non-state actors, while there is little attention to the possibility for creating novel genetic constructs and more effective biological weapons. There has been increasing attention paid to risks of dissemination of biological agents to non-state actors since September 11 and the Anthrax attacks, especially in the US, as will be discussed more later in the analysis.

Furthermore, the international framework for biosecurity is much more homogenous and powerful than the international framework for biosafety, the problems of which were discussed in the previous chapter. There is, for example, more UN activity in limiting the spread of biological agents and even voluntary groups such as the Australia Group set-up to provide an arena for regulatory harmonization between countries. As a result, the definitions of covered organisms, toxins and genetic elements are identical in the EU and US, a situation that appears highly unlikely for biosafety today.

This finding traces us back to the discussion in Chapter 4 about physical and non-physical risks. As was show in Chapter 6, biosecurity risks show the greatest potential for causing physical harm of all three categories of risks of synthetic biology. In general, it is easier to reach broad consensus over the treatment of physical risks than for non-physical risks that are more intertwined with moral values. An international framework for biosecurity is thus easier to achieve than an international framework for biosafety that contains stronger elements of non-physical hazards. The willingness of the academic-industrial complex to address security risks of synthetic biology and relative unwillingness to seriously discuss ethics and safety concerns also illustrates this point. Security risks are thus likely to be the most uncontroversial area of synthetic biology regulation.

8.4.1 Applicability to Synthetic Biology

Table 8.2 shows that most biosecurity regulations are, just like those for biosafety, mainly addressing changes in the genetic material of organisms obtained through rDNA technologies. It is unclear whether chemically synthesized nucleic acids coding for select agents and toxins are covered under the current regulations, especially in US regulations. Clarifying that synthetically derived nucleic acids are also covered is a first necessary step in adopting regulations.
Table 8.2 Analysis of the major threat that biosecurity regulations are attempting to address and their incorporation of genetic engineering.

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Level</th>
<th>Year</th>
<th>Major threat response</th>
<th>Genetic engineering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Weapons Convention</td>
<td>UN</td>
<td>1975</td>
<td>State use of bioweapons in conventional war</td>
<td>No</td>
</tr>
<tr>
<td>UN Security Council Resolution 1540</td>
<td>UN</td>
<td>2004</td>
<td>Non-state use of bioweapons</td>
<td>No</td>
</tr>
<tr>
<td>Export Administration Regulations</td>
<td>US</td>
<td>1979</td>
<td>State and non-state use of bioweapons</td>
<td>Yes. Covers DNA that can produce infectious forms of any of the select agent viruses, rDNA that encodes for the functional forms of controlled toxins, and genetically modified select agents and toxins.</td>
</tr>
<tr>
<td>Select Agent Regulations</td>
<td>US</td>
<td>2005</td>
<td>Non-state use of bioweapons</td>
<td>Yes. Covers DNA that can produce infectious forms of any of the select agent viruses, rDNA that encodes for the functional forms of controlled toxins, and genetically modified select agents and toxins.</td>
</tr>
</tbody>
</table>

Table 8.1 and Table 8.2 indicate that regulations are mainly concerned with limiting dissemination of biological agents to malicious actors and are only partly addressing increased capacity to engineer more effective biological agents. As of today, regulations manage increased capacity to engineer biological agents by controlling DNA sequences that are known to code for pathogenicity in already controlled organisms or toxins. Thus, DNA sequences that code for novel organisms, toxins or pathogenicities remain uncovered. The main method for assessing and governing risk in biosecurity is based on comparison with natural counterparts, just as in biosafety. This type of approach will be increasingly ineffective in dealing with genetic elements and organisms produced by synthetic biology, and regulatory frameworks in biosecurity will most likely need to adapt as synthetic biology develops.

8.4.2 Approaches to Uncertainty

The positions of the EU and US in dealing with uncertainty over risks to biosafety are inversed for biosecurity, with the US adopting a more precautionary approach than the EU. The US policy response after September 11 and the Anthrax attacks has been profound with the development of a number of statutes, regulations and policies aimed at proactive reduction of threats to the US population from terrorism in general and bioterrorism in particular. The Select Agent Regulations and HHS voluntary screening guidelines for providers of synthetic DNA are both part of this response, as is the activity of the NSABB and FBI in synthetic biology. The EU employs a more reactive policy system relying mainly on the use of export controls that are the same for all covered technologies. As of date, the
EU has not developed any regulations or directives specifically addressing threats from bioterrorism.

The voluntary screening guidelines for providers of synthetic DNA published by HHS have not been included in the more formal analysis since they are not legally-binding, but they are nonetheless interesting for several reasons. First of all, they illustrate the severity with which the US government views and addresses biosecurity risks. Second, they represent the first synthetic biology specific rules issued by a government, and as such provide an indication of the direction that governments could take in addressing synthetic biology.

Control of genetic material is obtained by limiting suspicious orders of nucleic acids that have been found to code for biological function and pathogenicity in existing organisms. Sequence screening is done by comparison with GenBank, as opposed to the lists of controlled biological agents that govern the Export Administration Regulations and Select Agent Regulations. Comparison with GenBank is potentially more effective since it is regularly updated and reflects present knowledge about pathogenicity and toxicity. Customer screening is done by support from the Export Administration Regulations and Select Agent Regulations lists of “denied” customers, lists that are also updated regularly. Finally, there is a clear element of self-regulation since industrial actors are responsible for carrying out the screening and alerting the government if problems occur. The rules thus seem to embody much of the current US debate about synthetic biology regulations; focusing on self-regulation and flexible technological systems based on comparison with natural counterparts for assessing risk.

Finally, it is interesting to compare the US regulatory framework for biological security risks with that for safety risks. Authority to implement the Select Agents Regulations rests both with the HHS and USDA, who have published separate regulations to implement the requirements. Because of the common statutory basis for their actions they are, however, able to cooperate and share many of the key documents. This creates a regulatory framework that is coordinated across agencies and more efficient for agencies as well as those that are obliged to follow the regulations.

This approach stands in stark contrast to the Coordinated Framework that lacks a common statutory basis and is characterized by lack of coordination between federal agencies and associated problems. As was mentioned in the previous chapter, enacting a new statute for managing the safety of biotechnology products similar to the statute designed to manage security risks would lead to a smoother, less expensive and more effective regulatory system.

8.5 Conclusion

The analysis of international, US and EU regulatory frameworks for biosecurity has led to three principal conclusions. First of all, regulations are mainly attempting to limit dissemination of biological agents to malicious agents, with little or no attention to the possibility of creating new or more powerful biological agents. Further, the determination of whether an organism, toxin or genetic element is covered rests on its similarity with the lists of controlled agents, hence leaving novel pathogens, toxins or genetic elements unregulated and leading to potential problems if synthetic biology develops increased capacity to engineer completely new organisms or genes.
Second, international policies for biosecurity were found to be more homogenous and powerful than corresponding policies for biosafety, a situation which is in part explained by the physical nature of risks to security and the relative ease of reaching consensus over physical risks compared to those of non-physical risks. Third, the US was found to adopt a more precautionary approach to assessing and addressing threats from bioterrorism than the EU, in part because of the September 11 and the Anthrax attacks.
CHAPTER 9 The Policy Framework for Ethics

While previous chapters have shown that moral principles and values are important and integrated in the decision-making process both within biosafety and biosecurity, Chapter 6 showed that there are a number of ethical concerns that are uniquely ethical, and not simply elements of safety and security. For synthetic biology, these concerns include uneasiness over its capacity to interfere with life, reduce life and inflict on nature as well as concerns over the distribution of risks and benefits and effects on trade and global justice.

This chapter aims to describe the regulations that impact the degree to which concerns are realized, and is focused on intellectual property rights as these are one of the few, if not only, legal instruments that directly impact ethical concerns. The chapter thus provides an overview of the international TRIPS agreement, the US Patent Act and the EU Patent Convention, as well as a discussion about patenting practices for genetic material and information. Intellectual property rights frameworks will be evaluated to determine which ethical concerns that they address and their applicability to synthetic biology.

9.1 The International Policy Framework

The international framework impacting ethical concerns of synthetic biology consists of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement.

9.1.1 The TRIPS Agreement

The TRIPS Agreement is an international agreement under the WTO. It has been in force since 1995 and is the most comprehensive multilateral agreement on intellectual property. The TRIPS Agreement requires all WTO members to adapt their laws to the minimum standards of intellectual property rights protection defined in the agreement, and to develop methods for the enforcement of intellectual property rights. Before TRIPS, many countries provided patent protection only to processes, but not products, and had patent durations that were significantly shorter, some as short as five to seven years after filing of the patent application. Furthermore, international conventions prior to TRIPS did not specify minimum standards for patents (WTO 2011).

All major elements of the TRIPS Agreement corresponds to intellectual property rights systems in the US and EU. Patents shall be available for any inventions in all fields of technology, provided that they are new, involve an inventive step and have industrial application, circumstances under which they can be protected for a minimum term of 20 years from the filing date of the application. Protection of plants and animals other than microorganisms, essential biological processes and inventions whose commercialization would threaten ordre public or morality are excludable.

9.2 The US Policy Framework

Like on the international level, the intellectual property rights system is the main US framework that impacts ethical concerns of synthetic biology.
The US Patent Act (35 U.S.C. §1–376) was enacted in 1790 to fulfill Congress' power granted by the Constitution "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries" (U.S. Const. art. I, § 8(8) 1787). Patentable subject matter is defined in §101 as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" (35 U.S.C. §101 1790). Aside from fulfilling the criteria of patentable subject matter, an invention must fulfill four criteria for patentability: it must be novel, nonobvious, have utility, and be described in sufficient detail to enable one skilled in the field to use it for the stated purpose.

The US Patent and Trademark Office (USPTO) is responsible for interpreting the statute when examining applications and granting patents, while the judiciary has the final power to determine the intent of Congress and meaning of the Patent Act under controversy. Patenting of biological material and genetic information is an area in which such controversy has been unusually profound (Rai and Boyle 2007), as is explored in more detail below.

Patenting of Genetic Information

The practice of granting patents to biological material was initiated in the United States in 1980, with the landmark case Diamond v Chakrabarty. The General Electric engineer Chakrabarty requested a patent for a genetically engineered microorganism but was initially turned down by the patent examiner, who claimed that living things constituted unpatenable subject matter under the law. Chakrabarty appealed to Board of Patent Appeals and Interferences, lost again and appealed to the United States Court of Customs and Patent Appeals, who overturned the case, arguing that the living status of microorganism is without legal significance to patent law. Diamond, Commissioner of Patents and Trademarks, appealed to the Supreme Court, that, with a vote of 4-5, upheld the ruling of the United States Court of Customs and Patent Appeals and allowed granting of the patent.

The Supreme Court argued that addition of specific genes to an existing microorganism transformed the organism enough and was inventive enough for patent rights to be issued. An alive, human-made microorganism was found to be patentable subject matter under §101 since it was found to constitute a "manufacture" or "composition of matter" within that statute. In coming to its conclusion the Court found that Congress intended "anything under the sun that is made by man" to constitute patentable subject matter.

This position has subsequently been adopted by the USPTO and the granting of patents for genetically modified microorganisms, plants and certain eukaryotes is today routine procedure. The granting of patent rights to genetic information and material is tightly coupled to this development, and has also become standard, albeit controversial. The USPTO published guidelines about the patentability of genetic material in 2001 to clarify its position. Essentially, genetic material can be patented if it has been isolated and purified from the naturally existing gene and if the application discloses a specific, substantial, and credible utility for the isolated and purified gene (USPTO 2001). As a result, a wide range of human and non-human genes have been patented in the US.
9.2.3 Early Patents and Ownership Models in Synthetic Biology

In 2007, Craig Venter applied for, and was subsequently granted, patent rights covering 381 essential genes of *Mycoplasma genitalium* and a synthetic organism carrying those genes (US patent 2007/0122826A1). The central claim of the patent covers the 381 “essential” genes required for maintaining life and self-replication. Further, the patent claims any synthetically constructed organism that lacks more than 55 of the 101 nonessential genes disclosed. ETC has critiqued and challenged the patent on the grounds that its claims are too broad and represent an unmoral ownership of life (Nature Biotechnology 2007).

Other similarly broad patents include a minimized *Escherichia coli* genome (US patent 6,989,265) and one on molecular computing elements, gates and flip-flops (US patent 6774222). Patent 6,989,265 contains claims that could cover any synthetic cell derived from the minimal *E.coli* genome. Since *E.coli* is the most used and best understood bacteria in biology, the patent could become very useful as a chassi for future applications of synthetic biology (Nature Biotechnology 2007). Patent 6774222 covers novel molecular constructs that act as various logic elements, and is also useful to in a range of synthetic biology applications.

In combination, these and other early patents to innovations in synthetic biology indicate that the concerns expressed by ETC, Friends of the Earth and other organizations and individuals that the patent system could be used to limit access and distribution of benefits of synthetic biology to the narrow groups of people or institutions that hold the patent rights. There are, however, other movements in synthetic biology that drive the development of open-source platforms, such as the BioBrick standard for biological parts and Biofab. More about ownership models will be discussed in the concluding part of this chapter and thesis.

9.3 The EU Policy Framework

The EU policy framework applicable to synthetic biology is also limited to the intellectual property right system.

9.3.1 The European Patent Convention

The European Patent Convention of 1973 is an intergovernmental treaty that establishes a common legal framework for patents in 36 European member states. To be eligible for a patent, an invention must be susceptible of industrial application, new and involve an inventive step (European Patent Convention. Part II, Chapter II, Article 52 1973). Article 53 explicitly excludes patents on plants and animals, excluding microorganisms; however plants that are characterized by a particular (inserted) gene as opposed to its whole genome constitute patentable subject matter.

9.3.2 Directive 98/44/EC on Legal Protection of Biotechnological Inventions

Directive 98/44/EC was enacted in 1998 after a 10-year debate (Rutz 2009), and came into force in all member states in July 2000, in part as a response to the fast developments in biotechnology in the United States and the perceived need for Europe to catch-up, a process to whose success patents were seen as central (Emmott 2001). Indeed, the Directive starts by acknowledging the increasing importance of biotechnology in various industries and the
need for adequate legal protection of inventions from high-risk biotechnological investments.

Article 3(1) determines that inventions containing biological material or processes by which biological material is produced, processed or used are patentable if they fulfill the requirements for patentability in the European Patent Convention (new, inventive and susceptible of industrial application). Article 4(1) excludes plants, animals and essential biological processes from patentability; inventions concerning plants are only patentable if their technical feasibility is not confined to a particular plant or animal variety. Further, Article 5(2) establishes that an element isolated from the human body, including gene sequences, are patentable even if the structure of the element is identical to that of the natural element.

Notwithstanding the utilitarian framing of the Directive, there are articles that attempt to counterbalance some of the moral and socio-economic effects of biological patents. For example, inventions whose commercial exploitation would be contrary to ordre public or morality from patentability are excluded from patentability, with specific examples including human cloning, germ line modification and commercial use of human embryos. Another article establishes rules for compulsory licensing as a way to limit blocking patents, while pre-amble lays down that, if an invention is based on biological material of plant or animal origin, the patent application should include information regarding the geographical origin of such material. Even though such information is without prejudice to the rights granted by the patent, this is an encouragement to mentioning the origin of biological material in line with the Convention on Biological Diversity.

9.4 Analysis of the Policy Framework for Ethics

As was mentioned in the beginning of the chapter, intellectual property regimes are evaluated to determine which ethical concerns that they address and their applicability to synthetic biology. The analysis is different from those for biosafety and biosecurity because of the more limited nature of ethical frameworks.

The policy framework for ethics is the least developed of the three studied frameworks, consisting only of policies for intellectual property rights. As a result, intrinsic ethical concerns to synthetic biology are left largely unaddressed, as is shown in Table 9.1.

<table>
<thead>
<tr>
<th>Risk</th>
<th>International Regulation</th>
<th>US Regulation</th>
<th>EU Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interfering with life</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reducing life</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inflicting on nature</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trade and global justice</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 9.1 Analysis of regulatory coverage of ethical concerns of synthetic biology.
As is shown in Table 9.1, intellectual property rights mainly address ethical concerns over the distribution of risks and benefits of innovations in synthetic biology. While they do typically contain provisions that enable denial of patent protection for innovations whose commercial exploitation would be contrary to ordre public or morality, these provisions are generally quite weak and difficult to implement effectively (European Group on Ethics in Science and New Technologies 2009), ultimately limiting their impact on intrinsic ethical concerns over interference with life and nature.

This observation leads us straight to a central conclusion: frameworks for dealing with ethical concerns of synthetic biology and biological engineering are generally much less developed than those dealing with security and safety concerns. As was discussed above, intrinsic concerns over technological developments in synthetic biology are especially neglected. This is a crucial finding that will be discussed in deeper detail and in comparison with safety and security regulations in the concluding chapter.

Furthermore, the TRIPS Agreement is the most robust of the studied international frameworks, and significantly more robust than the Convention on Biological Diversity and the Cartagena Protocol that apply to biosafety. This could be explained by the fact that the TRIPS Agreement is administered by the WTO, whereas biosafety and biosecurity frameworks are administered by the UN. Additionally, and probably more importantly, the EU and US have similar perspectives on the purpose and proper scope of intellectual property rights and aligned interests in driving the establishment of a strong international regime in this area because of their relatively developed industrial economies. Again, this goes to show how important the agreement on underlying goals, principles and interests between leading nations is to establishing an effective international regime.

Finally, a number of early patents in synthetic biology have already been granted, and a substantial amount of them contain broad claims that could hinder further development and innovations as well as their diffusion in society and the equivalent distribution of benefits. However, since the patent system is also a mechanism for making information publicly available and promoting innovation, the balance between its beneficial and detrimental effects needs to be carefully monitored. Furthermore, the emergence of open source platforms, such as the BioBrick standard for biological parts, is an interesting parallel development that also needs to be analyzed. More about ownership issues of synthetic biology will be discussed in the concluding chapter.

9.5 Conclusion

The analysis of international, US and EU regulatory frameworks that deal with ethical concerns has led to three principal conclusions. First of all, frameworks that address ethical concerns generally only apply to distributional issues and do not tackle intrinsic concerns or those related to trade and global justice. This makes them much more limited than those addressing safety and security concerns of synthetic biology. Second, the TRIPS Agreement is the most robust of the studied international frameworks, a situation that is likely caused by the alignment in perspectives and interests between the EU and US in developing a strong international regime for intellectual property rights. Finally, ownership issues in synthetic biology are quite unclear at this point, with parallel developments of broad, tight patent protection and open-source movements.
PART IV:
Conclusions and Recommendations
CHAPTER 10 Conclusions & Recommendations

This chapter provides an overview of the major conclusions reached in previous chapters and recommendations for addressing identified weaknesses in and challenges to regulatory frameworks. Far from all conclusions from previous chapters are reiterated; focus is instead placed on major conclusions that lead to recommendations, of which of total of seven are made.

The chapter starts by mentioning the most central features of synthetic biology, the academic-industrial complex and providing a summary of the fifteen identified risks and corresponding applicable regulations. After this initial descriptive review, main features of risks associated with synthetic biology and their perceptions are outlined, focusing on risk perception and methods to reduce current scientific uncertainty in assessing risks. Second, conclusions and recommendations about regulatory frameworks for safety, security and ethics are presented. This part is divided into six sections, each corresponding to one of the following major areas of conclusion and/or concerns: differences between the EU and US, the treatment of ethical concerns, methodologies for conducting risk assessments, the US Coordinated Framework, the applicability of regulatory frameworks developed for rDNA technologies to synthetic biology and challenges to intellectual property rights. Finally, some final remarks are made to round off the study.

10.1 Synthetic Biology and its Academic-Industrial Complex

As was shown in the review of synthetic biology science and industry in Chapters 2 and 3, synthetic biology is expanding as scientific discipline and industry, with major product launches within the next few years. Synthetic biology can be divided into two dominant approaches represented by the “standardize” and “define and alter” branches. The “standardization” branch is driven by the vision of turning biology into a true engineering discipline through standardization, modularization and decoupling, while the “define and alter” branch is driven by a desire to define the minimal genetic and metabolic requirements for life and to alter life at the biochemical level. These two branches unite in industry applications of synthetic biology, which are currently focused on engineering organisms for conversion of feedstocks or carbon dioxide into biofuels.

In sum, synthetic biology is currently being established as scientific discipline and emerging as industrial sector. This development has been analyzed for its impact on society and implications for risk by a number of societal actors, opinions which form the basis for the second part of the study.

10.2 Summary of Risks and Applicable Regulations

A total of fifteen risks and concerns of synthetic biology were identified in Chapter 6, and corresponding regulatory frameworks were described and analyzed in Chapters 7, 8 and 9. Table 10.1 on the next page provides an overview of the identified risks and regulations designed to assess and manage those risks, illustrating the “patchwork” style of the current regulatory framework.

The complexity and large number of regulations that in one way or another impact both the development of synthetic biology and the assessment and management of its risks is quite remarkable, and this study does not even include all applicable regulations; such a review
could go on almost forever. The great complexity of regulatory frameworks and multiple layers of government intervention highlight the need for coordination of policies and regulations both within governments and between nations, a point that is elaborated further below. I do not wish to go into risks and regulations in more detail here, Table 10.1 is merely meant to serve as a reminder of the identified risks and applicable regulations, which are discussed and evaluated in the remainder of this chapter.

Table 10.1 Summary of identified risks and concerns of synthetic biology and current regulations.
10.3 Risks and their Perception

The evaluation of risks and their perceptions in Chapters 5 and 6 resulted in three key conclusions. First of all, the analysis of risks identified the following three characteristics of synthetic biology risks:

1. Low scientific certainty and consensus in assessing the degree of risks;
2. Multidimensional character with mixing of physical and non-physical risks;
3. Characteristics that tend to increase the perception of risk.

Together, these three characteristics could make synthetic biology an exceptionally difficult area to regulate. First of all, low scientific certainty and consensus in assessing the degree of risk has been shown to be a difficult issue for regulatory frameworks, as was also shown in the case study of GM crops. Second, a risk space that is characterized by a mixing of physical and non-physical risks challenges traditional, technocratic approaches to risk assessment and regulation, as was also shown in the GM crops study. Finally, the embodiment of several attributes that increase the degree to which a technology is perceived as risky increases both the likelihood for public debate and demands for governmental regulation. A number of more specific recommendations for how to improve treatment of these characteristics of synthetic biology risks are provided in the regulatory analysis later in the chapter.

Second, the two branches of synthetic biology defined in Chapter 2, were argued to give rise to quite different types of risks, as is illustrated in Table 10.3. The focus on dissemination and modularity of the “standardization” branch creates new types of risks to security and safety, whereas the focus on defining and creating life found in the “define and alter” branch, produces new types of mainly ethical concerns.

Table 10.2 Impact of the two branches of synthetic biology on risk categories, including main features of the technological developments that lead to the potential of increased risks.

<table>
<thead>
<tr>
<th>Branch</th>
<th>Safety &amp; Environment</th>
<th>Security</th>
<th>Ethics</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Standardization”</td>
<td>Secondary impact</td>
<td>Primary impact</td>
<td>Primary impact</td>
</tr>
<tr>
<td>synthetic biology</td>
<td>Standardization and modularization leads to</td>
<td>Standardization and</td>
<td>Defining and creating</td>
</tr>
<tr>
<td></td>
<td>increased capacity to engineer synthetic</td>
<td>modularization leads to</td>
<td>life leads to intrinsic</td>
</tr>
<tr>
<td></td>
<td>organisms for uncontrolled use</td>
<td>dissemination and deskilling</td>
<td>ethical concerns</td>
</tr>
<tr>
<td>“Define and alter”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>synthetic biology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the analyzed reports make this distinction between the two branches of synthetic biology and the risks that they produce; most of them typically provide a quite rudimentary description of synthetic biology. The resulting reports are generally confused about what it is they are actually analyzing and what the effects are on risks. Typically, they show a general tendency to frame risks of synthetic biology in terms of those generated by the “define and alter” approach (i.e. with initial focus on ethical concerns), while ultimately discussing actual developments, applications and regulations that relate more to the “standardization”
branch. This is probably not the most useful approach to producing a structured analysis of synthetic biology and its societal impact. Hence, the first recommendation of this study is as follows:

**Recommendation 1:** Organizations and governments engaging in synthetic biology should develop their knowledge about what synthetic biology actually is and wherein the novelty lies, especially with regards to risks and benefits. They should be careful to distinguish between the different types of synthetic biology and their respective impacts on risks. This is especially important for governments that are tasked with designing and implementing regulations for synthetic biology.

### 10.3.1 Risk Framing and Perception

Third, the framing of risks of synthetic biology was found to be considerably broader than that for rDNA technology. The controversy over European regulations of risks of GM crops effectively introduced ethical and socio-economic elements of risk framing, while the September 11 and Anthrax terrorist attacks introduced security elements, especially the fear of bioterrorism. These transitions are reflected in current regulatory systems; biosafety regulations in the EU incorporate ethical and socio-economic values while the US has adopted a number of regulations to specifically limit the dissemination of biological agents or genetic elements correlated with pathogenicity or toxicity to non-state actors.

Nonetheless, biosafety remains the traditional and dominant framing of risks of biological engineering. This is also reflected by the considerably more encompassing and complex regulatory system applicable to biosafety as compared with biosecurity and ethics. Further, biosafety regulations tend to be specific to genetic engineering, whereas biosecurity and ethical regulations are general to biology or even technology in general. Risk perception of synthetic biology, as distinct from framing, can be analyzed by using the framework developed in Chapter 6, which is presented again in Table 10.3.

**Table 10.3 Attributes of synthetic biology that are likely to influence risk perception.**

<table>
<thead>
<tr>
<th>Emotive attribute</th>
<th>Relevance to synthetic biology</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involuntary</td>
<td>Inability to detect and distinguish synthetic from natural organisms and hence to avoid risk</td>
<td>Very important</td>
</tr>
<tr>
<td>Uncontrollable</td>
<td>Ability of living organisms to propagate, mutate and evolve</td>
<td>Very important</td>
</tr>
<tr>
<td>Immoral</td>
<td>Defining minimal requirements of life, creating new life and often for specific purposes</td>
<td>Very important</td>
</tr>
<tr>
<td>Unfamiliar</td>
<td>Creation of new life and new building blocks for life (XDNA)</td>
<td>Very important</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Uncertainty in assessing the safety, security and ethical risks of synthetic biology</td>
<td>Important</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>Relation to September 11 and anthrax attacks</td>
<td>Somewhat important</td>
</tr>
<tr>
<td>Unfair</td>
<td>Strong IP rights to discoveries in synthetic biology</td>
<td>Somewhat important</td>
</tr>
<tr>
<td>Untrustworthy</td>
<td>Strong ties between scientists and industry could undermine public trust in scientists</td>
<td>Somewhat important</td>
</tr>
</tbody>
</table>
It is important to be sensitive to the attributes in Table 10.3 when designing organisms, applications and regulations. Understanding the emotive foundations that influence people’s stand-point towards synthetic biology allows regulators and policy makers to design and implement regulations that are more effective at addressing the concerns that people express. Furthermore, awareness from the scientific community about perceptions of synthetic biology and differences between organisms and application areas enables scientists to develop a socially aligned scientific base and industrial applications of synthetic biology, hopefully leading to more socially acceptable products and further developments in the field.

10.3.2 Scientific Uncertainty

Finally, it is likely that scientific uncertainty in the assessment of risks of synthetic biology will be profound. Table 10.4 provides an overview of the main uncertainties in assessing the risks that synthetic biology research and applications pose to security, safety and ethics.

Table 10.4 Main uncertainties involved in assessing the risks that synthetic biology poses to security, safety and ethics.

<table>
<thead>
<tr>
<th>Area</th>
<th>Main uncertainties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>• Assessing the interactions between synthetic and natural organisms</td>
</tr>
<tr>
<td></td>
<td>• Assessing the broader environmental effects of releasing synthetic organisms</td>
</tr>
<tr>
<td></td>
<td>• Assessing the human health effects of consuming organisms with novel properties, especially for novel building blocks (such as new amino acids and XDNA)</td>
</tr>
<tr>
<td></td>
<td>• Assessing the potential (if any) interactions between XDNA and DNA</td>
</tr>
<tr>
<td>Security</td>
<td>• Assessing the capacity (both resources and knowledge) of malevolent actors (state and non-state) to engage in the construction and redesign of biological agents</td>
</tr>
<tr>
<td></td>
<td>• Deriving biological function and potential pathogenicity from short strands of DNA</td>
</tr>
<tr>
<td>Ethics</td>
<td>• Distribution of benefits and risks of synthetic biology</td>
</tr>
<tr>
<td></td>
<td>• Effects of synthetic biology on trade patterns and marginalized communities</td>
</tr>
<tr>
<td></td>
<td>• Understanding which ethical concerns that are most central to the public</td>
</tr>
</tbody>
</table>

Scientific uncertainty is a serious impediment to the efficiency of regulatory systems. Lack of empirical data and scientific consensus limits the sources of knowledge that regulatory agencies can draw on to assess risks and leaves them caught in a situation where they are exposed to and have to choose from different knowledge claims from stakeholders without having an agreed upon body of scientific knowledge to rely upon, ultimately producing a more unstable regulatory system. Development of an effective and stable regulatory system for synthetic biology requires a better understanding than what is currently available about its risks and their potential for realization. This finding leads to the second recommendation.

**Recommendation 2:** Perform systematic and preferably government funded research to address the uncertainties in assessing risks and concerns of synthetic biology. Currently, approximately between 2 and 4 percent of all government spending in synthetic biology is spent on research on legal, ethical and social implications, while none appear to be spent on risk research (The Woodrow Wilson Center for International Scholars 2010). The minuscule attention given to risk research is surprising and quite alarming, especially for governments that need to make regulatory decisions for synthetic biology.
10.4 The Regulatory Frameworks for Safety, Security and Ethics

A number of conclusions have been drawn about the regulatory frameworks governing risks of synthetic biology, the most important of which relate to differences between the EU and US, the treatment of ethical concerns, methodologies for conducting risk assessments, the US Coordinated Framework, the applicability of regulatory frameworks developed for rDNA technologies to synthetic biology and challenges to intellectual property rights. Each finding is discussed in separate sections below.

10.4.1 Differences between the EU and US

Differences between the EU and the US in the framing and regulation of risks are most apparent within biosafety; this is also the arena within which recent conflicts over GM crops took place. In many ways, the debates over risks present in the conflict between the EU and US over biosafety regulations and risk assessments of GM crops was less about actual estimations of risk and more about ethical, socio-economic, and political pressures.

However, as we have seen, risk assessments are perceived as scientifically based activities to be kept void of value judgments as much as possible, and the fight over values had thus to be played out within the realm of risk assessment rather than an open discussion about different framings of risk, understanding of the relationship between the state and the market, the role of agriculture and industry, and the relationship between society and nature. This inability to discuss the foundations upon which risk assessment and regulation are based explains much of the lock-in and failure to reach a mutual understanding between the EU and US. This point, and its implications, is elaborated in more detail in the next section on risk assessment.

The failure in reaching a consensus over safety regulations for biotechnology products between the EU and US manifests itself in the ambiguity of the international framework, most notably in the Cartagena Protocol on Biosafety. Persistent conflict between the US and EU appears even more problematic in light of the developments in synthetic biology that promise more widespread adoption of biologically based products and processes. Hence, it would be beneficial to reach a solution of the WTO trade dispute and develop a consensus between the EU and US in the field of biosafety regulation, preferably sooner than later.

Finally, it is interesting to note that the EU and US both use precautionary approaches to dealing with uncertainty in areas that carry political significance and are perceived as having the potential to cause great harm. The EU focuses on biosafety risks and employs a precautionary approach in governing such risks, while the US employs a similarly strict precautionary approach in managing bioterrorism. This indicates that the choice of whether to employ a precautionary or reactive approach to dealing with uncertainty has less to do with political culture in general and more to do with the severity with which specific risks are viewed, pointing once again to the significance that the societal framing of risks has to their assessment and regulation.

10.4.2 Inadequate Treatment of Ethical Concerns

As was discussed in the previous chapter, almost all ethical concerns are left unaddressed by regulatory frameworks. Regulations within biosafety and biosecurity are much more developed, comprehensive and specific. Furthermore, ethical provisions incorporated into
regulations governing safety, security and intellectual property rights are generally weak and peripheral to the regulation. My conclusion is hence that modern societies and their regulatory machineries are consistently failing to address ethical concerns in a sufficiently systematic and comprehensive manner.

I think that the inability to deal with ethical concerns is caused by a general incompatibility between moral principles and technocratic regulatory systems. The framework on post-industrial risks and risks assessment presented in Chapter 4 demonstrates that risks and their assessment have traditionally been framed in scientific and technical terms, a framing that is effective at addressing risks to safety and the environment, somewhat less effective at tackling risks to security, and more or less useless at addressing risks to moral principles, whose value-based character make them difficult to both define in scientific terms and reach consensus on. Technocratic regulatory systems thus fail to address ethical concerns arising from technological developments, even though there are a number of other legal systems in which moral principles are integrated, such as criminal codes.

The fact that ethical impacts of technologies are more incompatible than safety and security concerns does, however, not imply that they are less important or influential. The analysis of GM crops clearly showed that moral principles can be crucial to establishing the framing of a technology, the societal perception of it, and overall public willingness to accept it. Rather than first neglecting and then being surprised by, and unprepared for, public responses to new technologies and calls for regulation, governments should develop tools that assess and manage ethical concerns of the public. This is especially important for technologies that provoke reactions based on moral principles, such as synthetic biology. Hence, the third recommendation is as follows:

**Recommendation 3: Identify all significant stakeholders to the development of synthetic biology, including the general public, and perform a detailed analysis of their interests and ethical concerns.** Identification and analysis of interests and ethical concerns of relevant stakeholders will provide governments with valuable information about their constituents and possible routes for regulatory actions. Assessment of stakeholders and their concerns provides an important complement to the current narrow focus on assessment of risks.

10.4.3 Methods for Risk Assessment and Incorporation of Value Judgments

As was mentioned in the earlier section comparing the EU and US, risk assessment methodologies for biotechnology products appear overwhelmingly based on the compartmentalized approach and the notion that science alone provides the best foundation for risk assessment. If ethical and socio-economic values are allowed to enter the management of risk, which is quite rare, it is after the establishment of risk, not as integral elements during it. It is actually somewhat surprising that the this approach is still seen as the best approach to risk assessment despite the failures and problems that modern societies have experienced while applying it in the decision-making processes for a vast number of technologies, including GM crops.

The demarcation between science and values is to both artificial and undemocratic, granting vast power to the scientific establishment on the expense of other social groups. The
integrated model developed in *Understanding Risk: Informing Decisions in a Democratic Society* appears more suited for managing risks and concerns of synthetic biology and their mixing of physical and non-physical harm. This argument leads to the fourth recommendation.

**Recommendation 4: Develop and implement methodologies for risk assessment that incorporate ethical and socio-economic value judgments as integral elements in the process.** Risks to social, ethical, or ecological values are equally important factors to consider as risks to safety and human health. Frameworks that systematically incorporate ethical principles and concerns into the central processes that determine the outcome of regulatory decision-making need to be developed in order for society to make appropriate decisions and resolve conflicts about technologies whose application impact ethical and moral principles.

10.4.4 Inadequacy of the US Coordinated Framework

The patchiness of the regulatory approach outlined in the Coordinated Framework has led to an US regulation of biotechnological products that is poorly coordinated and inefficient. For example, review of genetically modified animals that are not used directly as food is more or less unregulated, while genetically modified crops with plant-incorporated protectants are reviewed by all three agencies. Furthermore, the stringency of the risk assessment and approval process is more dependent on the specific product category, and hence upon the responsible agency, than on the actual riskiness of the product. Finally, the degree to which current statutes, such as the TSCA, can be stretched to include and effectively handle synthetic biology remains unclear.

Even the rationale of the US government in not enacting a separate statute for biotechnology has effectively been undermined by the specific regulations promulgated by responsible agencies. I therefore see few reasons for why it would not be beneficial to replace the Coordinated Framework with a single statute for biotechnological products. Such a statute could still divide responsibility between the three current agencies but could make sure that all product types are covered and that information, risk assessment methodologies and risk levels for approval are similar. This would increase clarity, cooperation and effectiveness of the overall regulatory system and lead to a similar approval process for all products types.

**Recommendation 5: The US government should enact a separate statute for the regulation of biotechnological products to replace the Coordinated Framework.** Enactment of a single statute for biotechnological products would increase agency cooperation, information sharing and coordination and thus overall regulatory efficiency. Responsibility for specific product categories could still be divided between the EPA, USDA and FDA and their respective regulatory expertise. Inspiration for the statute could be gathered from the implementation of the Select Agent Regulations that, as a single statute, divides responsibility between two agencies.

10.4.5 Applicability of rDNA Regulations to Synthetic Biology

The review of the applicability of current biosafety and biosecurity regulations to synthetic biology in Chapters 7 and 8 showed that even the most basic definitions of covered genetic
material and organisms typically do not apply to synthetic biology, especially in US regulations. Methodologies for establishing risk appear even less applicable, as they tend to rely on comparison with natural counterparts and characteristics of the donor and recipient organisms. The move towards increasingly complex and unnatural biological systems in synthetic biology efficiently renders such approaches obsolete, and leads to the sixth recommendation of this study.

**Recommendation 6: Develop risk assessment methodologies that rely on assessing the biological function of genetic elements and organisms for determining risk rather than on comparison with natural counterparts.** Elements of such methodologies could include standards and methods for testing biological function and interaction effects. The estimation of risks of synthetic organisms needs to be more holistic and systematic and in a sense follow the scientific transition towards systems biology underpinning developments in synthetic biology. Such methodologies would be applicable to the assessment of risks of synthetic organisms and genetic elements to both security and safety.

For example, xenobiology, in its alterations of the basic biochemical properties of biology, such as codon assignments, amino acids and sugar backbones of nucleic acids, is perceived as being able to address many of the biosafety risks of synthetic organisms because xenobiological organisms would supposedly be unable to interact with natural organisms. This argument needs to be tested empirically and regulatory agencies must ultimately be able to assess biosafety risks of such organisms, something that they appear incapable of doing at the moment.

### 10.4.6 Intellectual Property Rights and Ownership

A number of concerns are associated with the relationship between synthetic biology and intellectual property rights. First of all, the distribution of risks and benefits of synthetic biology is impacted by the strength and duration of patent protection. Second, it has been argued that certain types of biological and genetic information rightfully belongs to all of humankind and should not be patentable. The evaluation of ethical concerns has, however, been discussed in at great lengths earlier in this chapter and this section will focus on more technical aspects of intellectual property rights and synthetic biology.

The parallel development of broad, tight patent protection and open-source movements in synthetic biology is indicative of the struggles that the field has had in defining ownership. In this regard, the question of what level in the biological hierarchy of the “standardization” branch (parts, devices or biological systems) that constitutes the most appropriate level at which to place patent protection is especially important. The “standardization” branch relies on the assembly of a vast number of parts and devices into biological systems, and one must be careful to develop ownership methods that both stimulate innovation and assure dissemination and use of developed genetic constructs and products. This issue has been left mainly unexplored by governments and patent agencies thus far but will become increasingly important to tackle as BioFab, BioBricks and other platforms for modularized and standardized assembly of biological systems become increasingly available. The seventh and final recommendation of this study is thus as follows:
Recommendation 7: The US government, European Union and/or patent agencies should evaluate the concerns expressed over patenting practices within the “standardization” branch of synthetic biology, and pay special attention to the effects of placing patent protection on various levels of the biological hierarchy (parts, devices and systems). Such an evaluation could include both a principal assessment of the novelty, creativity and utility that is required for patentability of genetic information, and a practical assessment of the tradeoffs between effects on innovation and dissemination of knowledge provided by patent protection on various levels of the biological hierarchy. The ultimate goal of the evaluation would be to design patent practices in synthetic biology that are more sustainable and likely to achieve their overall goals than current practices.

10.5 Final Remarks

The goal of this thesis has been to describe synthetic biology and its academic-industrial base, to evaluate its risks and the regulations that govern those risks. In so doing, it has provided the answers to the four research questions:

- What is synthetic biology?
- What is synthetic biology as an academic-industrial complex?
- What are the perceptions of risks of synthetic biology?
- How do current regulations govern the management of risks of synthetic biology?

The results of the analysis show that regulatory frameworks in security, safety, and ethics suffer from significant deficits. They are not well grounded on technical understanding of synthetic biology, lack methodologies for risk assessment of organisms without close natural counterparts, frame risk assessment as a technocratic process without substantial input from stakeholders, and emphasize physical risks to safety and security over non-physical threats to ethics and values. Finally, the study suggests that the US government and European Union modify existing regulations governing risks associated with synthetic biology and processes for developing such regulations to mitigate some of the identified deficits.
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