Biological machines?

Anticipating developments in synthetic biology

COGEM Report CGM/080925-01

Commission on Genetic Modification (COGEM)
The Netherlands Commission on Genetic Modification advises the Government on the potential risks of genetically modified organisms (GMOs) and informs the Government about ethical and societal issues linked to genetic modification (Environmental Management Act, Article 2.3).

Summary

Synthetic biology is a new research field that seeks to modify existing organisms to perform useful functions and to design and synthesise artificial genes and complete biological systems.[1] By unravelling the functioning of living cells step by step and using this knowledge to construct artificial cell components, researchers hope eventually to be able to create a completely artificial cell. This could be considered to be a living machine. Synthetic biology can therefore be described as a further stage in the development of genetic modification. It is no surprise that the emergence of synthetic biology has reignited the cycle of public debate that flared up during the initial stages of genetic modification.

COGEM published an initial report on this matter in 2006. Over the last two years media attention and the number of scientific papers on the topic have risen rapidly. Scientists and others have been speculating in the media about future developments, sometimes conjuring up visions of the most fantastic applications; others warn of the possible consequences of this new and groundbreaking technology. The media has played host to an exchange of 'dream' and 'doom' scenarios.

In response to this media interest and to parliamentary questions, the Minister of Housing, Spatial Planning and the Environment (VROM) asked COGEM for further advice (Appendix 1). This included questions about whether the current risk analysis method and the assessment framework for GMOs will be suitable assessing future developments in synthetic biology. The minister also enquired about how government can best facilitate the public debate on synthetic biology.

Risk analysis and safety
Synthetic biology is a 'converging technology', formed by the amalgamation of various technologies such as genetic modification, genomics, IT and (bio)nanotechnology. The question of whether synthetic biology and its future applications could endanger human and environmental safety can be divided into three parts: 1) is there a legislative framework for action, 2) can technical safety measures be taken to manage risks, and 3) can the risks be assessed?

It is assumed that legislation governing genetic modification is fully applicable to synthetic biology. In both cases genetic material is altered in a way that cannot take place in nature. Moreover, the same recombinant DNA techniques are used in synthetic biology and genetic modification. We note, therefore, that for the time being there is no need for new safety legislation.

[1] Synthetic biology can best be defined in the words of a European Commission expert group (NEST): *Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems, which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way.*

The safety of laboratory work with biological organisms (such as GMOs and wild type pathogens) is guaranteed by taking a range of measures relating to the laboratory equipment and working practices. These safety measures are designed to prevent organisms escaping from the laboratory or harming laboratory staff. The regulations apply to all organisms, regardless of whether they are wild type pathogens, GMOs or synthetic organisms. If the risks cannot be properly assessed, the precautionary principle dictates that activities involving GMOs are assigned to the highest containment level.

The current risk analysis method assesses the potential risks of working with GMOs by investigating the characteristics of the GMO, the nature of any negative effects and the chances that they will occur. If the characteristics of a synthetic organism cannot be adequately assessed, the precautionary principle dictates that the work is assigned to the highest safety level. As this involves considerable costs it may form an impediment – possibly an unnecessary one – to the development of synthetic biology and its applications.

A distinction must be made between the developments and potential applications in the short and long term. It is perfectly possible to estimate trends over a period of five to ten years (short term) based on current developments in the field and so it is possible to make an adequate decision about the possible risks associated with this work. Within this time frame it looks as if work will be restricted to apathogenic and biologically contained organisms. It is not expected that during the next ten years any hereditary material will be introduced into an organism without knowing its function or without a predetermined plan. Such knowledge would in any case be needed in order to produce a functional organism. In addition, all work with synthetic organisms will be in laboratories, where potential risks can be controlled, and not in the wider environment. The potential risks of working with synthetic organisms can therefore be adequately assessed and managed over the short term under the current risk policy and using the current risk analysis method.

Forecasting potential developments over the long term is more difficult. The suitability of the current risk analysis in the long term is consequently also hard to predict; at this stage we may simply not know enough about genes, gene products and the possible interactions between them. However, as our knowledge increases in parallel with the technological possibilities and trends, it will become easier to assess the risks of future activities. This is in line with the ‘step-by-step’ approach that has always been applied to GMOs.

Synthetic biology as a technological hype

Synthetic biology is developing in the same way as other promising technologies. One description of this process is the *Technology Hype Cycle*, which consists of five distinct stages. The initial stages are characterised by considerable media attention. Researchers have high expectations about the new field, but get no further than expectations and promises. The whole thing closely resembles a hype. After a time, this media and public

attention wanes because of the sluggish rate of technological development and the apparent lack of concrete applications. Later, when concrete applications do come onto the market, interest grows again. However, the level of media attention will never again reach the heights of the first peak (hype). We should also bear in mind that the future development of the technology is partly shaped by the expectations put forward by scientists in the 'hype stage'.

If the technological innovation is highly controversial, the first 'hype stage' will involve considerable discussion. This debate will be largely chaotic and generally noncommittal because of the lack of concrete applications. In the later stages, when concrete applications are available, the public debate is actually hampered because developments have already crystallised. Any options for influencing developments will have been considerably weakened or already foreclosed. Technological developments and applications take shape in the last period of the hype phase and the subsequent period of lowest media interest.

Synthetic biology is still in the very first stage of the process described above. Besides the claims by scientists of the potential advantages, the first warnings about the possible disadvantages and risks of this technology can also be heard.

Old and new questions about synthetic biology: a repeat performance?

The questions and concerns that synthetic biology appears to provoke are largely the same as those that were raised during the early stages of genetic modification. One difference is that the questions posed by synthetic biology about the boundary between life and non-life and between man and machine are more explicit than those raised by genetic modification.

The arguments put forward can be reduced to a few core themes, as described earlier in the COGEM report 'The Gentech Debate Analysed' (*Het gentech debat ontleed*):[1] 'safety, health and wellbeing', 'social relations, freedom of choice and public trust' and 'nature and the integrity of life'. A difference with the debate of thirty years ago is not so much the nature of the arguments, but rather the part played by modern communication technologies. Civil society organisations can now react much more quickly to developments in the field than during the debate on genetic modification. Modern communication techniques keep them up to date on new scientific developments. Moreover, the same means of communication allow groups to organise more quickly and easily and acquire a network.

What can government do?

At the present initial stage of the debate the task of government is to keep itself informed of current developments. The government has done this by requesting advice from COGEM, the Royal Netherlands Academy of Arts and Sciences (KNAW), the Advisory Council on Health Research (RGO) and the Health Council of the Netherlands

(*Gezondheidsraad*).[2] In this stage of the debate the role of government is to provide information, for example on the safety and economic aspects, and also to stimulate an effective exchange of information between the parties involved and impress on them their own roles and responsibilities. But this by no means implies that government has no further part to play during this initial stage in the development of the technology. The government can give shape to the further development of synthetic biology by adopting stimulus measures, such as research programmes and subsidies. It can also see to it that synthetic biology is included in the teaching curriculum in order to create a shared knowledge base.

It is when media and public interest wane that the first concrete applications take shape. This is the period when policy should be formulated and it is important that government determines its position in the debate, including a decision on whether or not to take an active part in it. Over the next few years the government has the opportunity to prepare its *policy agenda*, based on research into the ethical issues raised by this technology. COGEM and the Rathenau Institute will review the activities which could be undertaken by the government in this period of 'quiet before the storm'.
In the coming years the challenge facing the government is to facilitate the debate in a period of dwindling interest in the topic.

In order to pinpoint where action can support and encourage debate, the government will have to closely monitor developments. Over the next few years it will have to keep abreast of technological developments before they become manifest in market activity. The government can use a number of instruments for such an 'early warning' system.

Government is kept informed of the emergence of concrete applications and trends via the progress reports and project reports from publicly funded research programmes. Media content on synthetic biology can be monitored, as well as patent and licence applications. Tools like the 'Biotechnology Trend Analysis' can also be of use.

However, we should realise that the government and the public debate can only have a limited effect because developments in synthetic biology are global in scale and take place largely outside the Netherlands. Decisions about the acceptability of applications and about legislation on biotechnology – and thus also on synthetic biology – are an EU matter. Public debate and policy formulation must therefore take place in a European arena. Moreover, it is to be expected that the first market introductions will occur outside Europe and that Europe will first be confronted with them in the form of imports.

Not only government but also stakeholders have a responsibility and a part to play
Besides government, stakeholders, such as scientists, also have a responsibility for and a

[2] The Minister of Education, Culture and Science asked the Royal Netherlands Academy of Arts and Sciences (KNAW), the Health Council of the Netherlands (Gezondheidsraad) and the Advisory Council on Health Research (RGO) to advise on synthetic biology. In joint discussions they agreed to avoid duplication of effort. Whereas in its report COGEM focuses on risk analysis and the relevant legislation and the ethical and societal aspect, KNAW, RGO and the Health Council concentrated on technological developments and the opportunities these present to the Netherlands.

part to play in the debate. The scientific community in particular should take the lead in informing the wider public, especially about applications that could be developed. They should not wait until partial applications are already available and society is faced with a *fait accompli*.

Contents

SUMMARY **3**

1. INTRODUCTION **11**

2. SYNTHETIC BIOLOGY: WHAT IS IT? **13**

2.1 DEFINITION OF SYNTHETIC BIOLOGY 13
2.2 DEVELOPMENTS WITHIN SYNTHETIC BIOLOGY 13
2.2.1 Metabolic pathway engineering – the chemical factory of the future *14*
2.2.2 Minimal genome organism – minimalist life *14*
2.2.3 Changing the 'chemistry of life' *15*
2.3 DEVELOPMENTS ARE MOVING FAST 16

3. WILL THE RISK ANALYSIS FOR GMOS SUFFICE FOR SYNTHETIC ORGANISMS? **17**

3.1 LEGISLATION ON GMOS CAN ALSO BE APPLIED TO SYNTHETIC ORGANISMS 17
3.2 GMO RISK MANAGEMENT CAN ALSO BE USED FOR SYNTHETIC ORGANISMS 17
3.3 RISK ANALYSIS METHOD SATISFACTORY IN MOST CASES 18
3.3.1 Short-term expectations *19*
3.3.2 Long-term expectations *21*
3.4 SUMMARY 24

4. ANTICIPATING THE PUBLIC DISCUSSION ON SYNTHETIC BIOLOGY **25**

4.1 PROMISES AND EXPECTATIONS OF SYNTHETIC BIOLOGY 25
4.2 TECHNOLOGY DEVELOPMENT 26
4.2.1 The dynamics of promises and expectations *26*
4.2.2 Synthetic biology as a technological hype *28*
4.2.3 Collingridge dilemma: too early until it's too late *31*
4.3 THE COURSE OF AN ETHICAL AND SOCIETAL DEBATE 31
4.3.1 Simple, complex, uncertain and ambiguous issues *31*
4.3.2 A framework for ethical and societal debates *33*
4.3.3 Each actor in the debate has their own task *34*
4.4 THE ROLE OF GOVERNMENT IN THE PUBLIC DEBATE 35
4.4.1 Debate as a means of guiding developments *36*
4.4.2 Debate as policy support *36*
4.4.3 Debate as a survey of opinions and arguments *39*
4.5 SYNTHETIC BIOLOGY: OLD WINE IN NEW BOTTLES? 40
4.5.1 Core themes in the public debate on synthetic biology *40*
4.5.2 Safety, health and wellbeing *41*
4.5.3 Social relations, freedom of choice and public trust *42*
4.5.4 Nature and the integrity of life *42*
4.6 THE GENETIC MODIFICATION DEBATE: A LEARNING PROCESS 43

5. THE POSITION AND ROLE OF GOVERNMENT **48**

6. CONCLUSIONS **50**

REFERENCES **53**

1. Introduction

More than two years ago COGEM published its first report on synthetic biology,[2] a technology that, broadly speaking, is about adapting existing organisms or building biological systems. At that time COGEM observed that synthetic biology was evolving from genetic modification and that expectations for the new technology were high. These expectation have not lessened over the last two years. The Rathenau Institute also examined this topic in 2006 and various questions on synthetic biology were raised in the Dutch House of Representatives (*Tweede Kamer*).[3,4] In response to these parliamentary questions, the environment minister asked COGEM a number of questions on various aspects of synthetic biology (Appendix 1): [5]

1. *What developments can we expect for which the current risk analysis method for GMOs could prove inadequate?*
2. *Over what period are these developments expected to occur?*
3. *Are there any developments in synthetic biology that are likely to fall entirely outside the scope of the current assessment framework?*
4. *What need do you see for structural monitoring of this policy field and what possibilities are available for doing this?*
5. *What are the ethical and societal implications of synthetic biology and how can government best facilitate the public debate on synthetic biology?*

Furthermore, the Minister of Education, Culture and Science has requested advice from the Royal Netherlands Academy of Arts and Sciences (KNAW), the Advisory Council on Health Research (RGO) and the Health Council of the Netherlands (*Gezondheidsraad*).[6] In response to these requests a joint committee drew up a position paper which includes a state-of-the-art on science on the field of synthetic biology. The report also examines in detail the research in this area being carried out in the Netherlands. Moreover, it looks at the opportunities synthetic biology offers the Netherlands and the requirements for exploiting these opportunities.[7]

Although most research in the field of synthetic biology is being carried out in the United States, the position paper reveals that Dutch scientists are also active in the field, one of their research areas being the modification of microorganisms to enable them to perform new functions. They are also active in bionanotechnology, in which biomolecules, not complete organisms, are modified to perform new functions or provide a model for new components to be chemically synthesised. As developments in the field of synthetic biology in the Netherlands have been reviewed in the position paper, COGEM has not conducted a separate study of this itself.

In this report, COGEM addresses the questions concerning the legislation, the risk analysis, monitoring of the research field and the ethical and social aspects of synthetic biology. First, we briefly explain some relevant aspects of synthetic biology in Chapter 2.

2. Synthetic biology: what is it?

2.1 Definition of synthetic biology

The question of what exactly is meant by synthetic biology has no clear-cut answer. Various definitions can be found in reports on the subject and research by the American National Science Advisory Board for Biosecurity (NSABB) showed that there is no consensus among scientists on what exactly synthetic biology is.[8] Furthermore, the difference between genetic modification and synthetic biology is often not clear. In 2002 a virus (polio virus) was synthetically restructured for the first time.[9] At the time this was considered to be genetic modification, whereas it is now referred to as an example of synthetic biology.
A European Commission expert group has drawn up the following definition: *Synthetic biology is the engineering of biology: the synthesis of complex, biologically based (or inspired) systems, which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures – from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of 'biological systems' in a rational and systematic way.*[10] This definition is also used in the position paper by KNAW, RGO and the Health Council.

In its 2006 report, COGEM described synthetic biology as a technology that not only modifies existing organisms to enable them to perform useful functions, but also seeks to design and synthesize artificial genes and complete biological systems.[11] By unravelling the functioning of living cells step by step and using this knowledge to construct artificial cell components, researchers eventually hope to be able to create a completely artificial cell. Synthetic biology can therefore be seen as a further development of genetic modification and (nano)biotechnology, in which biological material is reconstructed or constructed with a view to its eventually use, for example to produce useful substances such as raw materials for medicines or the development of biosensors. Designing and building such organisms requires close collaboration between molecular biologists, physicists, chemists, IT specialists and technologists. The field thus presents itself as a truly multifunctional technological discipline.

2.2 Developments within synthetic biology

Developments in this research field can be divided broadly into *in vivo* (living organisms) and *in vitro* (test tube) approaches. The position paper referred to in the previous section also adheres to this distinction.[7] The *in vivo* method works with cellular systems, primarily on engineering microorganisms to obtain large-scale production systems. By contrast, the *in vitro* methods make use of non-cellular biological systems, such as systems based on polymers of biological building blocks (for example nucleic acids or amino acids), or built from molecules that resemble these building blocks.[7] Elements of (bio)nanotechnology also fall under this approach. Various research groups in the Netherlands are active in the field of nanotechnology and bionanotechnology.[12]

Besides this division into *in vivo* and *in vitro* methods, the field can also be divided into bottom-up and top-down approaches. This division is used mainly in the international literature and will also be used in this report. Bottom-up approaches attempt to build functions from scratch and introduce them into existing organisms. An example is the construction of various genetic networks by linking together 'genetic building blocks', or *BioBricks*. These are fragments of hereditary material that can carry out a certain function, such as turning genes on or off. The aim is to use these standardised biological units to construct organisms that function predictably. It can be compared with the construction of new dishwashers, cars, computers or aircraft using standard parts.

The top-down approach aims to modify existing organisms for specific ends. The idea is to develop a minimal organism by removing all genes not essential for the organism's survival. *Metabolic pathway engineering*, in which researchers adjust the metabolic pathways of an organism, is also grouped under this approach (although this technology can also be found in the bottom-up category). This and several other developments are described briefly below.

2.2.1 Metabolic pathway engineering – the chemical factory of the future

Metabolic engineering was originally exemplified by the optimisation of genetic and regulator processes in cells to increase the production of a desired substance. Synthetic biology takes this a step further. Besides optimising metabolic pathways, elements are replaced or added to enable an organism to produce a completely new compound. In the short term, metabolic pathway engineering is served better by a top-down approach than a bottom-up approach. To build pathways from the bottom up it is essential to have detailed information on their working and structure, but at the moment the available information is too limited.

The best known example of metabolic pathway engineering within synthetic biology is the production of a precursor of artemisinine by a genetically modified bacterium and yeast.[13,14] Artemisinine is used as a raw material for the production of a medicine for malaria. Traditionally this material is refined from the annual wormwood plant (*Artemisia annua*), but this a time-consuming and expensive task. To make a bacterium or yeast produce the artemisinine precursor, genes from various organisms have to be inserted into it. After the precursor has been formed, it is converted to artemisinine in several chemical steps.[13,14] This allows artemisinine to be obtained in a relatively cheap and environmentally friendly way.[13]

An American research group led by the well known synthetic biologist Jay Keasling is working on *metabolic engineering*. He claims this will enable us to build the chemical factories of the future. The production of the anti-malaria medicine mentioned above was his work. Other developments include the production by synthetic organisms of biobutanol for use as a biofuel.[15]

2.2.2 Minimal genome organism – minimalist life

A minimal genome organism is an organism that possesses only the most essential hereditary material. Non-essential genes are removed in the laboratory. The organism's

hereditary material is reduced to such a minimal level that it requires a highly specific incubation medium to function and be able to reproduce. Such an organism is therefore highly biologically contained.

Constructing organisms with a minimal genome serves two purposes. First, it makes it possible to study fundamental processes in an organism. What are the functions of individual genes and what interactions are there between the gene products? What are the minimum requirements for life? Second, besides this more fundamental research, more applied research is being carried out with the aim of obtaining an ideal production organism. The idea behind this is to develop an organism with the least possible amount of 'ballast'. This will be a basic organism to which a whole range of genes can be added. It will, for example, allow desired products to be produced in large quantities.

A minimal genome organism can be created using either a top-down or a bottom-up method. A well-known example of the top-down approach is the reduction of the number of genes in *Mycoplasma genitalium.* In the bottom-up approach organisms are built up from individual building blocks. It cannot be predicted when, and if, this bottom-up approach will actually lead to the construction of complete (replicating) organisms.

2.2.3 Changing the 'chemistry of life'

A development that will probably only lead to applications in the distant future is adapting the genetic code to obtain artificial systems or even artificial organisms. Expanding the genetic alphabet could increase the ability of an organism to store, pass on and express information.[16] Some scientists want to use this technique to develop, among other things, new personalised medicines.[10] Others, such as Steven Benner, are attempting to answer the question of how life on earth began and how it is evolving.[17] A few years ago Benner succeeded in expanding the number of nucleotide bases in DNA from four (in its natural form) to six.[17] He suggests that even twelve nucleotides should be possible.[18] Using such new models, Benner is trying to discover how life functions with an unnatural genetic system.[17] Benner's alternative genetic system of six nucleotides is also used in various diagnostic tests to detect, among other things, respiratory virus infections in patients.[19] However, developments in this field are not likely to lead to applications in living organisms soon.

The natural alphabet

A DNA molecule is composed of two strings of building blocks that together make up the well-known DNA double helix. These building blocks contain molecules called bases. There are four types of bases: adenine, thymine, guanine and cytosine, abbreviated to A, T, G and C. The sequence of these bases forms the natural alphabet, or the genetic code. The bases on the two strings are bound together by hydrogen bridges, with A bonding only to T and C bonding only to G.

One way of creating an alternative genetic alphabet is to increase the number of bases. Some 'unnatural bases' have been developed by changing the order and combination of bonding locations of the hydrogen bridges on the bases. In addition, bases have been produced that form stable base pairs via hydrophobic interactions instead of hydrogen bridges.

2.3 Developments are moving fast

The speed at which developments in synthetic biology are taking place depends, among other things, on the speed at which hereditary material can be constructed. Synthesising large amounts of DNA is becoming easier and faster as techniques improve. Until recently the longest DNA fragment to be constructed consisted of 32,000 base pairs,[20] but early in 2008 Craig Venter, America's best known genomics researcher, succeeded in completely reconstructing the genome of the bacterium *M. genitalium*.[20] Although this bacterium, with 582,970 base pairs, has the smallest genome of all organisms, reconstructing it was an important step forward in the synthesis of long DNA molecules.

Some researchers have high expectations about the speed at which the technology will develop. One of the founding fathers of synthetic biology is Drew Endy. In an interview with BBC News he said: "*I would be surprised if by 2012 it were not technically possible to routinely design and construct the genomes of any bacteria or single celled eukaryote, which also means that it will be possible to construct some mammalian chromosomes*".[21] Some other scientists think that such comments only help to turn synthetic biology into a hype, with unrealistic plans and timescales. After all, before such developments can actually occur, much research still needs to be done, for example into the structure and working of genetic circuits and metabolic pathways, and into the part played by environmental factors in cell regulation processes.

3. Will the risk analysis for GMOs suffice for synthetic organisms?

While many have high expectations about the applications of synthetic biology, some scientists have reservations. Technological advances may lead to undesirable effects for people and the environment and some risks may be hard to assess or may simply not be identified at all. At the same time, others are of the opinion that the risks are not so big because the organisms are built according to a predetermined plan.

To make a judgement on whether developments in synthetic biology will affect human and environmental safety three things have to be considered:

- Legislation: is there a legal framework for action?
- Risk management: can technical safety measures be taken to manage risks?
- Risk analysis: can the risks be assessed?

We look into these aspects in more detail below. Then we make a judgement on the suitability of the current risk analysis method for synthetic organisms.

3.1 Legislation on GMOs can also be applied to synthetic organisms

European directives have been adopted to protect humans and the environment against the effects that could result from working with GMOs. These directives have been transposed into Dutch law in the Environmental Management Act, the Genetically Modified Organisms Decree (Environmentally Hazardous Substances Act) and the Ministerial Regulation on GMOs.[22] This legislation covers organisms that have been genetically modified in a way that is not possible through reproduction or natural recombination.[23] Moreover, the definition of genetic modification in EU Directive 2001/18 also includes the use of specific techniques (such as recombinant nucleic acid techniques).[23] This definition is fully applicable to synthetic organisms. Moreover, the techniques used to create synthetic organisms are the same as those used for GMOs. Synthetic organisms therefore fall within the legislative framework for GMOs. COGEM concludes from this that new legislation governing synthetic biology is not necessary.

3.2 GMO risk management can also be used for synthetic organisms

The safety of humans and the environment during laboratory work with both GMOs and wild type microorganisms is guaranteed by taking several measures geared to preventing the organisms from being released from the laboratory to the outside environment or infecting laboratory workers. One of the consequences of this is that laboratories must meet a range of regulations on laboratory design and equipment. These regulations cover, for example, the finishings to be used for work surfaces, floors and walls, a possible safety cabinet or ventilation system in the room, and the presence of an air lock for entry and exit.[22]

A number of regulations governing working practices also apply. These may be of a general nature (eating and drinking in the work area is forbidden), but may also be about working practices (including wearing gloves and protective clothing), cleaning up after work (such as disinfecting work surfaces) and treating waste and contaminated material (for example keeping biological waste in leakproof containers).[22] The facilities and equipment in the work area determine the degree of physical containment. Laboratories are divided into four levels of containment, the lowest level being I and the highest IV. The higher levels are also subject to more working practice regulations than the lower levels. A containment level IV laboratory meets all the regulations governing the laboratory suite and working practices, permitting high risk activities to be carried out in these areas. There is also a comparable system of containment levels for experiments with animals and plants.

Such regulations are applied to prevent and/or manage the potential risks associated with working with biological organisms. The appropriate containment level depends in part on the biological characteristics of the organism involved and the nature of the activities and is determined by a systematic risk analysis. Should it not prove possible to assess the risks (to a sufficient degree) because of scientific uncertainties – for example the risks of biological functions or systems that do not occur in nature – these activities involving GMOs are assigned to a higher containment level than might be strictly necessary under the precautionary principle. The precautionary principle states that new technologies may not be used without taking precautionary measures if they are likely to involve risks to human or environmental health, even if those risks have not (yet) been established without doubt by scientific research.
The above applies not only to GMOs, but also to synthetic organisms, which can also be contained by the previously mentioned safety measures. If the risks associated with the activities can be assessed (this is discussed in the next section) the appropriate containment level can be determined. If the risks cannot be assessed, the relevant activities with synthetic organisms are assigned to a high containment level under the precautionary principle. This means that in principle the potential risks to humans and the environment arising from every possible situation can be managed. However, a high level of containment implies additional costs and in some cases can be difficult to achieve because the laboratory does not have the necessary measures in place. Placing activities in a (too) high containment category can therefore slow down scientific and commercial progress.

3.3 Risk analysis method satisfactory in most cases

To assess the risks of activities involving GMOs, the current risk analysis method focuses on:

- the properties of the GMO and of the vector and donor sequences of the parental wild type;
- the exposure of humans and the environment;
- the nature of any negative effects caused by the GMO or the parental wild type;
- the probability that these effects will occur.

To come to a conclusion about these risks, consideration is given to, among other things, the biological containment and pathogenicity of the donor and recipient organism, the vector used and the presence of a characterised or uncharacterised insert. In addition, the activities involving the GMO are taken into consideration. Once all these things have been assessed, a statement can be made about the risks of the activities in question. It should be noted that the greater the difference between the parental organism and the modified organism, the more difficult it is to compare the characteristics of both organisms. The predictive value of the risk analysis thus declines.

The question that then arises is whether the current risk analysis for GMOs can also be used for the manufacture of synthetic organisms and activities involving them, now and in the future, given that the risk analysis focuses mainly on the characteristics of the organism. What in fact are the characteristics of an organism that has been created via the bottom-up approach, for example, or of an organism to which various new metabolic pathways have been added? It is important to know whether the current risk analysis method can adequately assess the risks of future developments in synthetic biology and whether we can expect any difficulties. Although it is possible to assign activities to a high containment category as a precaution when the risks are difficult to assess due to scientific uncertainties, this may present an unnecessary impediment to scientific and commercial progress.

COGEM sees developments in the field of synthetic biology as a further development of genetic modification. Technological possibilities and developments advance in parallel withan increased understanding of genes and the possible interactions between gene products. When more knowledge becomes available, the assessment of risks may become easier. This means that as the technology develops the possibilities for assessing risks will usually improve. Accordingly, any risks associated with future activities will usually become more predictable over time. In this respect, COGEM refers to the step-by-step approach used for GMOs. This means that the first experiments are carried out on a small scale in the laboratory until sufficient data have been obtained. Once these data are available, the activities can be carried out on a slightly larger scale. The experiment is thus increased in scale at every step and at each subsequent step more data become available.

To verify whether the current risk analysis will suffice for developments within synthetic biology a distinction is made between developments in the short term and those that can be expected in the long term. It is possible to make a good assessment of the trends over the next five to ten years based on experiments now being carried out in the laboratory. Forecasting potential developments in the long term is more difficult. In view of this a few examples are examined to explore possible future developments over the long term.

3.3.1 Short-term expectations

In this section we examine the aspects mentioned earlier that are important for carrying out the current risk analysis.

Researchers work with apathogenic and biologically contained organisms

Given the recent developments in the field and the experiments now being carried out in laboratories, COGEM expects that in the short term researchers will generally only work with known apathogenic or low-pathogenic organisms. For example, much of the work being done in synthetic biology is on *Escherichia coli* K12. This bacterium is apathogenic[22] and has been commonly used in research for more than 40 years. Further, the apathogenic *Saccharomyces cerevisiae* (baker's yeast) is used to produce artemisinine and has been used in laboratory research for decades.

Also, for some time to come, only biologically contained organisms will be used. These will have characteristics that restrict their survival or dispersal in the environment. *E. coli* K12 and *S. cerevisiae* belong to this group. 'Minimal genome organisms' are biologically contained given that they only possess the most essential genes and can replicate only in special culture media and under specific conditions.[3]

Gene functions will be known in almost all cases

It seems unlikely that within the next ten years hereditary material will be introduced into an organism without knowledge of its function or a predetermined plan. Knowledge about the genome and the characteristics of an organism is indispensable for obtaining a functional organism. A good example of this is metabolic pathway engineering. Without knowledge about the genes to be introduced, which may also come from various sources, there is little chance of creating a functioning pathway.

It is not only possible to build pathways with existing genes; another increasingly popular technique for building pathways is linking together several 'biobricks'. The functions of biobricks are fully known because they are well defined pieces of hereditary material. Knowledge of the introduced hereditary material is also essential for the synthesis of a minimal genome organism via the bottom-up approach. These genes will be inserted according to a predetermined plan, which is only possible if the functions of those genes are known.

An exception to the above is the theoretical example of a researcher who randomly inserts a large number of genes from various sources into an organism all at the same time. This method bears close resemblance to a so-called 'shotgun' experiment: the manufacture of a genetically modified organism in which sequences are used that consist entirely or partly of non-characterised genetic information.[22] *Shotgun* experiments are now frequently used to make gene banks. Although in most cases the resulting organism will be less fit than the parental organism, there is a theoretical possibility that it could be harmful. This why more safety measures have to be taken when carrying out shotgun experiments compared with activities involving the introduction of fully characterised hereditary material. A difference between a shotgun experiment and the example given above is that in the latter a conscious effort is made to create an organism with the desired function. Given the lack of knowledge about the introduced genetic information any risks will be hard to assess. This means that under the precautionary principle

[3] No sequences incoding for undesirable and harmful gene products (such as toxins) or resistance to antibiotics may be introduced into biologically contained organisms. Neither may any introduced hereditary material undermine the containment.

experiments in which many genes are inserted into synthetic organisms in a random manner should be carried out in a high level containment laboratory.

Work involving synthetic organisms is carried out in laboratories

COGEM is of the opinion that within a period of five to ten years work on synthetic organisms will remain restricted to laboratories and production facilities where potential risks can be controlled. Synthetic biology is still in its infancy and it will take many years to develop a product or commercial application. Consequently, it will be a long time before a 'synthetic organism' is introduced into the environment or before commercial applications become available. It should be noted, though, that in future some applications of 'genetic modification' may be labelled as synthetic organisms. These may include GMOs into which several genes have been introduced, for example to modify metabolic pathways. COGEM points out that such applications are not new and that the potential risks of these organisms can be properly assessed.

Subconclusion: Analysis of the above-mentioned three aspects makes it possible to adequately assess and manage the potential risks of working with synthetic organisms over the short term using the current risk analysis method under the current risk policy.

3.3.2 Long-term expectations

What are the long-term expectations? We examine whether the current risk analysis will suffice by looking at a number of examples.

Example 1: Metabolic pathway engineering

The textbook example of metabolic pathway engineering is the production of a precursor of artemisinine by genetically modified *E. coli* bacteria and *S. cerevisiae* yeast cells, as mentioned above.[13,14] The production of artemisinic acid in *S. cerevisiae* requires increasing or reducing the expression of certain genes in the yeast cell.[13] In addition, several genes from *E. coli* and the plant *Artemisia annua* (the natural producer of artemisinine) are introduced into the yeast.[13] The introduced pathway consists of twelve genes in total.

In this example the number of introduced genes is relatively limited and so the potential risks can be adequately assessed within the current risk analysis framework. The organism involved is biologically contained and known genes are introduced. Moreover, the function of the introduced gene is such that it is highly unlikely that the biological containment will be circumvented.

It is possible that in future pathways consisting of hundreds or even thousands of genes will be built into organisms. Moreover, these genes could come from various different sources. Can the risks associated with these organisms also be assessed, or are the many modifications and mutual interactions so complex in nature that it would be impossible to assess the risks? A risk that might arise is the unintentional production of a toxic metabolite due to interference between an introduced pathway and an existing pathway. However, it is expected that in future more possibilities will become available for

detecting and predicting changes in metabolites and unintentional effects of interactions between them.

At the moment the available knowledge is insufficient to allow a large pathway to be built and introduced into an organism and we expect that this is a long-term proposition. We do not therefore consider it necessary at this very early stage to make a judgement on the suitability of the current risk analysis. When these developments are closer to becoming reality, advances in our understanding will make it easier to assess the potential risks. However, this is subject to the condition that the further development of synthetic biology also includes consideration of any relevant ecological aspects.

Example 2: Minimal genome organism

In 2006 the number of genes in the bacterium *M. genitalium* was reduced to the minimum.[24] Of the 482 protein coding genes, 100 proved not to be essential for its survival in a culture medium.[24] Besides this top-down approach, researchers are conducting preparatory work for building a minimal genome organism according to the bottom-up approach.[20] Once a minimal genome organism has been created, hereditary material can be added to give it the desired function.

The production of minimal genome organisms under the top-down approach will only involve the use of host whose complete genome sequence is known. Clearly, modifying the genome of an organism for a specific purpose, involving either an increase or decrease in the size of the genome, requires knowledge of which elements or genes it contains. This will not change in future. Crafting a minimal genome organism via the bottom-up approach will always follow a predetermined plan; the chance of obtaining a functioning organism through the random assemblage of genes or DNA fragments is very small. It appears that in all cases knowledge of the host and the genes or biobricks to be introduced will be available in the long term. This means that, as far as we can tell at the moment, it will be possible to carry out a risk analysis.

Example 3: Alternative alphabet

Recently a set of two new nucleotides has been developed that can be recognised by a natural polymerase.[25] However, the hereditary material in this case was not present in a living cell, but in a test tube. In the future these two nucleotides could possibly be incorporated into genetic material as extensions to or replacements for existing nucleotides. More than 30 unnatural amino acids have already been added to proteins in various organisms.[26]

At the moment progress with developing an alternative alphabet is at such an early stage that it is limited to applications in non-living systems, such as the diagnostic tests described in chapter 2. COGEM does not expect that developments in this field will proceed so fast that the risk analysis will become unsuitable within the foreseeable future. In 2004 Benner made the following prediction: "*I suspect that, in five years or so, the artificial genetic systems that we have developed will be supporting an artificial life form that can reproduce, evolve, learn and respond to environmental change*".[27] Now,

four years later, developing an artificial alphabet seems closer to science fiction than possible fact.

In the distant future it may be possible to alter an existing organism in such a way that it can make use of new nucleotides and/or amino acids. To do this, though, polymerases and/or ribosomes also have to be modified. If organisms with an alternative alphabet cannot produce the modified building blocks themselves, these will have to be taken up from the surrounding environment. As the altered building blocks do not exist in nature, the organism is totally dependent on specific culture conditions in a laboratory for replication and/or protein synthesis. These systems are therefore biologically contained and the risks can be assessed.

A step further is engineering a replicating organism that is capable of producing unnatural nucleotides and passing them on to future generations. It is unclear whether these developments will ever happen. In any case, they can only be expected to occur in the long term. For this reason COGEM makes no comment on the suitability of the risk analysis, other than that it will probably be more difficult to perform. Over the years, however, our understanding of such developments will increase and we will be able to define the risks better. That will probably be a more appropriate time to state which characteristics of an organism will have to be known in order to perform an adequate risk analysis.

Example 4: Introduction into the environment

The above examples relate to developments that take place in a laboratory (‘contained use’). It is possible that in future a synthetic organism will be used for activities outside the laboratory, which is known as ‘introduction into the environment’. Researchers are currently freely speculating about the use of synthetic organisms to trace and break down contamination or to render land mines harmless.

To perform a risk analysis on an organism used outside the laboratory, information is needed on not only the host organism (including a full molecular characterisation) and the inserted genes, but also on the environment in which the organism will be introduced and any possible interactions between the organism and the ecosystem. Furthermore, it is important to know whether the presence of the organism will be restricted to the place of introduction or if it can or will disperse over wider areas. This also applies to synthetic organisms that are introduced into the environment.

We note that current laboratory work almost exclusively involves the use of biologically contained organisms. These organisms will therefore be the first to be introduced into the environment. Extensive experience has been gained with these organisms and the current risk analysis will suffice for these cases.

At the moment we cannot foresee what developments will take place in future, to what ends these will be used and what the characteristics of the relevant organisms will be. COGEM therefore considers that it is presently not possible to make any judgements about the suitability of the risk analysis in the long term

Subconclusion: We cannot now foresee how synthetic biology will have developed in ten years time. This makes it impossible at the moment to make a judgement on the suitability of the current risk analysis at that time. Besides, any developments that may require changes to the risk analysis method will be identified in advance from the nature of the introduced characteristics.

3.4 Summary

Although some researchers believe that developments in synthetic biology will proceed very rapidly, the majority of the applications will only become available in the long term (after five to ten years). Within this time period we expect that work will be restricted to biologically contained or apathogenic and low-pathogenic organisms. Moreover, these experiments will be carried out in laboratories. COGEM is of the opinion that risks can be assessed and that the current risk analysis method will suffice for these cases.
Given that it not possible to foresee how far the science will have progressed in ten years time, it is now too soon to make any judgements about the suitability of the risk analysis in the long term. We note here that initial new developments and applications will make use of microorganisms. Developments with plants, and certainly with animals, lie further in the future.

4. Anticipating the public discussion on synthetic biology

This section of the report focuses on the minister's question about which ethical and societal issues are raised by synthetic biology and how the government can best facilitate public discussion on this subject.[5]

To answer these questions the development of the science of synthetic biology must first be placed within a wider framework. To this end we explore the general process of technology development from the perspectives of technological development, ethical discussion and policy formulation. We then look at the objectives that can be set for a public discussion and the possible role of government in such a debate. The specific questions relevant to synthetic biology are then highlighted. Lastly, we examine the part government can play in facilitating the public discussion on this topic.

4.1 Promises and expectations of synthetic biology

Articles on synthetic biology have appeared regularly in the press and popular science magazines since the end of 2003. These articles are mainly about the potential applications and associated risks of this technology. Although there are no concrete applications yet, the growth of interest in this topic has been explosive. 'Life Forms to Order', 'Making Life', 'DNA Lego', 'Extreme Genetic Engineering' and 'Rewriting the Rules of Life' are just a few of the provocative headings that have appeared in the media.[3,28,29,30,31] Such articles introduce these developments to the general public and prompt people to form an opinion on the possible applications of this innovative technology.

Developments in synthetic biology

2002	Reconstruction of the Spanish Flu virus with synthetic DNA
2005	Establishment of the Biobricks Foundation (MIT)
2005	Students present photo taking bacteria
2007	Craig Venter synthesised the first complete genome of a bacterium species

The media not only reports on the latest developments and breakthroughs in the field of synthetic biology, but also paints a picture of the goals and possible futures these developments might lead to: why are we doing this?[32] The expectations articulated by researchers in the initial stages of a revolutionary new technology set the public thinking along certain lines. What can we expect from this technology and why should we support the direction it is taking? The potential of synthetic biology is described in the TESSY project (see text box):

TESSY (*Towards a European Strategy for Synthetic Biology)* is a European Union initiative to pull together the scattered research activities in synthetic biology.[32] Promises and expectations seem to play an important role in the early stages in the development of a technology or innovation.

Promises of synthetic biology (TESSY, Europe)
Synthetic Biology has the potential to create new applications out of all life science fields, including improved health-care leading to individualized, highly efficient medicine with low side effects; the deployment of Synthetic Biology methodology in environmental technologies and the design of non-food plants. Synthetic Biology is also a promising avenue for providing a more efficient supply of bio-energy and improve nutrition in quality and quantity.

4.2 Technology development

Such promises and expectations become more specific as a technology develops. We look first at the dynamics of promises and expectations within technology development. Major breakthroughs or disappointing results can influence the expectations people have or make it necessary to revise the promises made. We then examine synthetic biology and the ethical and societal debate from two different angles. Each of these perspectives has a different 'reach' and thus positions the ethical and societal discussion differently within the wider whole. The perspectives that are examined are the course of a technological development and the course of an ethical discussion. The contours of the ethical and societal discussion defined by these perspectives are then used to investigate the options available for facilitating the public debate.

4.2.1 The dynamics of promises and expectations

Scientific research is not done for its own sake but with the underlying idea that eventually it will lead to applications that will benefit humankind. A strong belief in technical and scientific progress makes this dynamic almost unquestionable. Researchers make promises about the outcome or eventual applications of their research and explain why this outcome is so important and therefore deserves to be supported. The promise of the outcomes (benefits) of the research should justify the costs of the research and thus generate support in the form of public acceptance, financing or other resources.

Promises create a protected space and generate resources

A general belief in technological progress makes it possible for promises of new technologies to be made that spur researchers, companies and governments into action.[33] Promises create certain expectations and hard work is needed to fulfil them. To generate resources in the form of financing, public support or an expansion of the network, it is important that policy makers, whether they are supported by opinion leaders, the general public and the business community or not, recognise the needs and purposes of a certain research project. Examples of past technological advances can be put forward when seeking support for a specific technological development. For example, the Human Genome Project (HUGO), which set out to map the human genome, was put on a par

with the project to put a man on the moon and was thus afforded the same (symbolic) significance and urgency.

Synthetic biology is sometimes referred to as the 'third technological revolution': an overall concept which, when combined with a strong belief in technological progress, can become a common goal worth pursuing. This common goal creates a protected space within which researchers can work to deliver on the expectations. It is also possible to make use of an existing protected space. Once a protected space for research on a specific topic has been created, new promises in this field are accepted more easily, as long as they are in the right format to fall within that protected space. In a certain sense, this applies to synthetic biology as well. Although there is no clear-cut definition of research that does or does not fall within the field of synthetic biology, when research grants, subsidy schemes and joint research projects are being set up there suddenly appear to be many researcher which associates itself with the field and lay claim to this protected space.

Promises structure research

Technology is not something that happens outside the social order. Technology is directed and formed by perceptions, intentions, interactions and interests. Expectations and promises can coordinate activities and help to set agendas.[34] The initial results of a new technology, and the considerable promises and expectations based on them, give rise to agendas and incentive programmes at local, national or even global level that cast the promises in a more tangible form. Actions are coordinated by the initial outlines of a new technology and its functions, while the emerging configuration is fleshed out, giving the new technology clearer outlines and more substance.

Expectations and promises are thus incorporated into a script or scenario in which roles are allocated to the project itself and the actors involved. If these roles are accepted (when the scenario appears to be probable, desirable and feasible), those involved adopt a shared vision of the future to work towards. The stronger the initial research findings and expectations for the future shared by other researchers in the field and by investors (resources), the greater the depth of the support will be to fulfil these expectations. The support base can be further broadened by linking different disciplines, as in synthetic biology, in which biologists, engineers and physicists work together. The programme is defined in more detail by setting up joint research agendas and coordinating activities. An example of this is the EU TESSY project. The goal of this initiative is to design a European strategy based on a roadmap that provides the essential steps that have to be taken with regard to regulation, financing, integration into the public sector and scientific milestones. In addition, attempts are being made to create wider awareness and understanding of synthetic biology, its potentials and results.

Transforming promises into requirements

The actors, the interests and the rules of the scenario are made increasingly explicit in the promises, and the actors act accordingly. This coordination is actively taken up by the actors, but cannot later be traced back to a single actor.[33] Promises therefore seem to acquire a self-fulfilling nature. But in fact, their form and substance inspire action and provide the impulse to actively turn them into reality. There is therefore no question of a

self-fulfilling prophecy; rather, hard work is needed to meet the promise. Researchers are given the freedom to do their research, but the flipside of this freedom is obligation: the promises made have to be fulfilled. The promises become increasingly detailed and concrete, in the form of conditions, product specifications and requirements. In other words, during the process promises are slowly transformed into requirements.

The credibility, likelihood and desirability of promises

The promises and expectations of a new technology can justify research and generate resources. Besides that, promises play an important role in structuring the research; as promises and expectations are made more concrete, a scenario emerges that guides activities. The degree to which research is justified, the mobilisation of resources and the appearance of a protected space depend on the quality of the scenario and thus the efficacy of the promises that make up the scenario. Both the credibility as well as the likelihood and desirability of the scenario play a role. The fact is, promises also raise questions like 'Promises for what purpose and for whom?', 'Are these the promises society wants and why should we realise these promises in this way, while other routes are also open?' and 'What disadvantages are there to these promises?' These types of questions can invoke reactions, criticism or resistance.

Credibility is closely linked to the likelihood of a promise. A promise that is unlikely to materialise will not be credible either. However, a promise that is credible may be unlikely because it is linked to an unfeasible timescale. Moreover, credibility can also diminish when promises are not met. If earlier promises of a technology have not been fulfilled, there is a good chance that new, comparable promises will be perceived to be unlikely.

Nowadays the desirability of a technology or innovation is often considered at an early stage of its development, as evidenced by this report on synthetic biology. Attempts are made to prepare for any possible ethical and societal aspects that may be associated with a new technology or application. In addition, the government tries to prepare the public for new applications by providing information that will make it easier to put the technology to practical use. In doing so, it anticipates the social context within which technology development takes place.

4.2.2 Synthetic biology as a technological hype

This section looks at the various stages the development of a technology goes through and the changes in the visibility of these developments. This perspective therefore also determines to some extent when a public debate can or must be held. At the moment there are no concrete applications of synthetic biology and the first real synthetic organisms have yet to be made – but there is no shortage of scenarios and prognoses. Synthetic biology is now primarily an innovative technology and the expectations of what can be achieved are high. Within the protected group there is much speculation about the use of synthetic organisms, for example for counteracting climate change and producing bioethanol and other industrial products. It is also suggested that synthetic biology can be used to improve health services. These considerable promises and expectations are an intrinsic part of technology development. At the same time, scenarios are put forward about the misuse of the technology and the creation of organisms that are

in essence machines. The expectation is that these extreme scenarios will abate as developments progress and it appears that both the dream scenarios and doom scenarios are unrealistic in the short term, or at any time at all.

This is a recognisable pattern when new technologies are introduced. When a technology is introduced, all future possibilities are still open and speculation about possible applications is rife. A hype is created, which subsides when it becomes clear that applications will appear only after a few years or further into the future, or when it appears that developments are going to be more difficult than originally thought. This pattern is also referred to as the Technology Hype Cycle.

The Technology Hype Cycle

The Technology Hype Cycle is a graphic representation of the visibility of new technologies that have been introduced, go through a period of development and growth and are subsequently put to practical use.[35] In 1995 Gartner proposed the Technology Hype Cycle to characterise the phases a new technology goes through. The hype cycle consists of five phases: Technology Trigger, Peak of Inflated Expectations, Trough of Disillusionment, Slope of Enlightenment and Plateau of Productivity.

The first phase in the Technology Hype Cycle is the breakthrough that leads to the initial media interest; it is called the Technology Trigger and may be a breakthrough, product introduction or other event that causes significant press interest. In the next phase a snowball effect arises in which enormous media interest in the subject is generated. This is called the Peak of Inflated Expectations and speculation about possible applications reaches a fever pitch. Many expectations are unrealistic and there are no concrete signs that these applications will ever come about. No firm promises are made yet, but many expectations are ventilated.

Because the expectations are not met in the short term and the news value of the topic fades, enthusiasm for the new technology drops into the Trough of Disillusionment. The press gives hardly any attention to the topic and the technology.

Although the press abandons the topic, development of the technology continues steadily. In the Slope of Enlightenment phase the technology continues to be developed and the first more realistic applications come within reach. Promises become more concrete and the outlines of the scenario can be sharpened and filled in through national and international research programmes and roadmaps. The first successes, along with the considerable expectations and promises, provide a stimulus for other researchers, companies or even disciplines to contribute to these developments.

Eventually the technology reaches the Plateau of Productivity. Applications of the technology provide clear benefits and are widely accepted. The evolution of the technology becomes increasingly stable and second and third generation applications are produced. This division into different phases is not intended as a rigid description and should not be taken literally. Initial (small-scale) application may even be presented at the start of the development of the technology and a second Peak of Inflated Expectations may also occur in the last phase. The public debate is also a part of the Technology Hype Cycle. The initial media interest encourages people to think about the topic. Nowadays this occurs much sooner than in the past because of modern communication technologies.

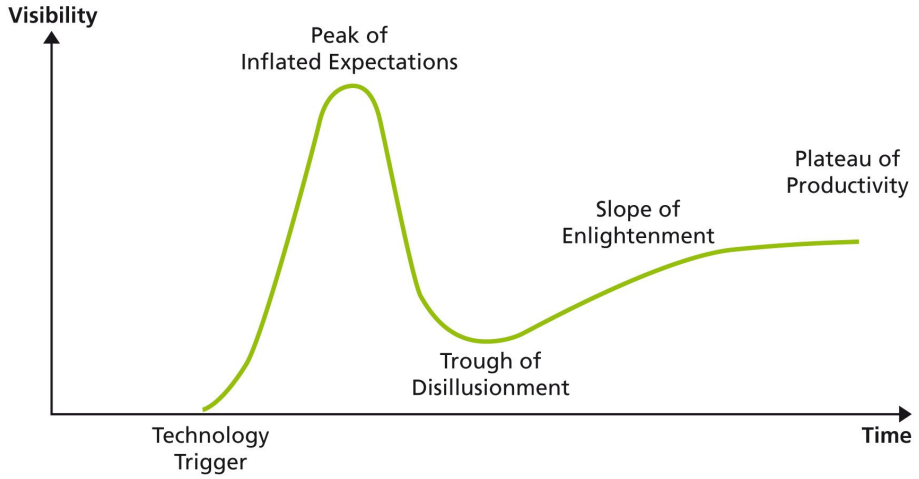

Figure 1: Gartner's Technology Hype Cycle

Whereas in the past civil society organisations launched a debate about the desirability of the first applications only when they where publicly launched, this process now begins when announcements are made about the possible applications of a new technology. This certainly applies to synthetic biology as well. The debate on synthetic biology seems to be slowly getting off the ground now that the media is beginning to pay more attention to it, despite the fact that there are no concrete applications yet (see Figure 2). The public debate is currently on the steep rise to the Peak of Inflated Expectations. These expectations also have a negative side given the (partly) unknown risks and the ethical and societal aspects associated with this technology. There is a frenzy of speculation about possible applications but also about the threats they imply.

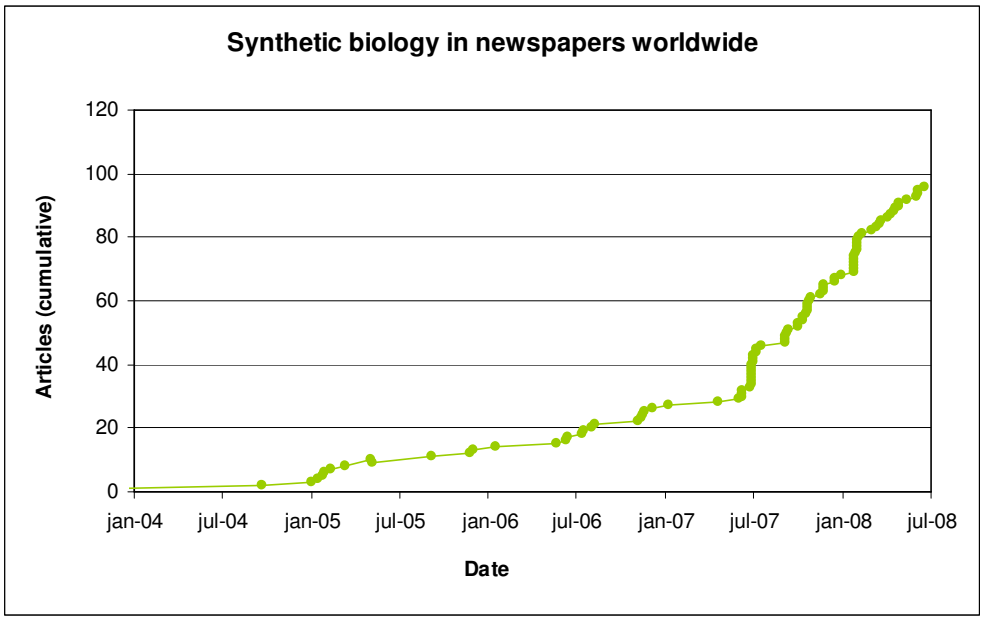

Figure 2: Indication of media interest in synthetic biology in newspapers

4.2.3 Collingridge dilemma: too early until it's too late

In the early stages of the development of a technology such as synthetic biology many options remain open in the technological, economic and social spheres. There are also many uncertainties about the possibilities and impossibilities of a technology; often too many to allow a decision to be made on the desirability and direction in which a technology should be developed and put to practical use. This is particularly the case during the Technology Trigger and Peak of Inflated Expectations phases.

In the more advanced stages in the development of a technology (the Slope of Enlightenment and Plateau of Productivity) the path dependence of earlier design decisions has become so great that little scope for choice is left. This illustrates how technological choices can sometimes create a strong path dependence. Path dependence explains how decisions made in the past can influence the choices we (can) make in the present. It also shows how political choices, economic options and technological developments influence each other. In the initial phases all these choices are made mainly on the basis of expectations and promises about future applications. This dilemma is also referred to as the Collingridge dilemma, or intervention dilemma. A dilemma can be defined as a choice from several alternatives that are equally attractive or unattractive or whose possible consequences are equally unclear.

The debate surrounding genetic modification has demonstrated that a lasting period of alternating progress and deadlock can arise. To an important degree such situations are fed by uncertainties about the possible consequences of biotechnological research. This raises the question of how and when the debate surrounding synthetic biology can be influenced. In fact, can these developments be influenced at all? And if we hold a debate about a technology at an early stage in its development, will there then be more potential development routes open than if the debate were held at a later stage? The question that needs to be answered first is how public debates in general progress and what they can deliver.

4.3 The course of an ethical and societal debate

The course of an ethical and societal debate, just like the development of a technology, has various phases in which promises and expectations play a key role. In the literature on the ethical and societal questions that arise when a new technology or innovation is introduced often a distinction is first made between the various types of issues involved.

4.3.1 Simple, complex, uncertain and ambiguous issues

In 'Making Life' the Rathenau Institute identified three different issues: simple, complex, and uncertain and ambiguous issues.[3] These issues can also be linked to various phases in the Technology Hype Cycle. Ethical questions are ambiguous and are prominent during the initial phase in the development of a technology (Peak of Inflated Expectations). Ambiguous issues demand the most wide-ranging form of social participation. These sorts of issues are dominated by differences in outlook and beliefs about what is permissible and possible. Achieving a consensus on such questions is often a difficult and lengthy process and is sometimes not even possible at all. The same goes

for the uncertainties surrounding issues that lie in the future (what impacts on humans and the environment can be expected from developments in synthetic biology, for example). Addressing these types of issues involves striking a balance between overprotection and underprotection of the environment and public health. These questions are relevant when the first applications of a technology comes within reach, following the Trough of Disillusionment. The same applies to complex issues. Complex issues, such as how the development of a technology can contribute to sustainable development, require input from different actors. When discussing such issues it is desirable to bring technical and social-scientific expertise into the discussion. Simple issues include problems that can be quantified, such as the toxicity of a chemical compound. These problems can be solved by involving experts.

A similar distinction is made in the COGEM research report 'Governance of Biotechnology' (*Governance van biotechnologie*) in which a distinction is made between structured and unstructured issues.[36] Structured problems are characterised by a consensus on the goals and the way in which they can be achieved. In these situations there is generally sufficient confidence in government authorities and scientific knowledge. Science supports policy formulation, decision making and the enforcement of those policies and decisions. Situations in which attitudes and thinking are disparate are more complex. These involve unstructured issues on which there is no agreement on goals or possible solutions. Such situations are characterised by considerable scientific uncertainty, not only about the research facts but also about the precise role the various scientific disciplines should play. In these situations scientists also have a monitoring role. Besides furnishing scientific facts, they can rule out certain aspects and make suggestions for further research or for improving the problem definition.
The development of synthetic biology can be said to involve uncertain or unstructured issues. There is considerable scientific uncertainty about the results and applications that this technology can produce. In addition, the considerable expectations prompt a wider public debate about the desirability of these outcomes. In view of this, one of the recommendations in the 'Governance of Biotechnology' report is not to restrict the issues to risks alone but also to encourage open discussion of the underlying motives and goals of the proposed applications. Making the underlying motives and goals more explicit can reveal social dilemmas more clearly and help to make them negotiable. This wider appraisal is a learning process which requires input from various sides as well as the willingness to jointly explore options for a socially robust long-term objective. Scientific knowledge is certainly not a luxury and is even essential for this process, states the report. In the governance of biotechnology, technoscientific knowledge and expertise in risk assessment should be integrated with insights into the social possibilities and impossibilities of the proposed applications. The core idea of governance is to give a voice to parties outside the vested interests and governing elites and permit a wider range of inputs and expertise to be taken into consideration. Governance seeks to strike a balance between allowing innovation and change and preventing society from being presented with *faits accomplis*.

The idea of societal engagement in setting the direction of scientific research in developing applications is not new. These aspects are still relevant when a technology with possibly controversial applications is introduced. The question is not whether, but primarily how this engagement can be structured and in which phases of the technology development. It is stated that ethical and societal debates on scientific research generally go through several phases.

4.3.2 A framework for ethical and societal debates

In 1990 the Dutch House of Representatives (*Tweede Kamer*) asked education and science minister Jo Ritzen to provide a framework for discussions on the ethical aspects of research. After setting the broad outlines of this framework[37] a detailed version of the course of an ethical discussion was presented in 1991. It divides the progress of an ethical discussion into four phases that can be recognised in a public debate.[38] The parliamentary paper identifies four phases: 'Identification', 'Articulation', 'Value Assignation' and 'Analysis'. The paper also identifies which actors bear specific responsibilities for certain points. The order of the stages in the following description of the course of an ethical discussion is not necessarily chronological; the different stages may overlap and there may be feedback loops between stages.

Identification

Groups in society indicate that certain values and norms are being tested by scientific and technological developments. These are ethical questions arising from basic normative beliefs and propositions about the type of society and way of life that is desirable or admissible. People consider scientific and technological developments from the perspective of these moral convictions. The opinions and feelings that stem from this determine to a large extent how specific developments are 'received' and the degree to which those developments are considered acceptable.

An example of the identification of such issues in the debate on synthetic biology is the open letter from a number of civil society organisations to the Second Synthetic Biology Conference in Berkeley, USA in 2006.[39] In the letter they express their concern about developments in synthetic biology and attempt to bring them to the notice of bodies which they believe are able to take up such issues. The (potential) problem has been identified. The contents of this letter are discussed in section 4.5.

Articulation

In the second phase of the public debate larger and federative organisations become involved. They define and clarify the contentions and suggest how the issues can be broken down into topics for discussion. The problem becomes articulated. Reports by the Rathenau Institute, for example, or COGEM reports, can provide input to this articulation.

Authoritative value assignment

In the social and political debate agreement is reached between the parties involved on which forum is given the authority to make a binding statement on the delineation of the ethical problem area. The results of ethical science research are fed into this process. The

loosest form is when the responsibility and authority for such statements rests with the parties involved, or even left to individual decisions. More structured forms are temporary committees, followed by standing committees with the competence to make decisions on specific cases within defined legal boundaries. The most formal form of authoritative value assignment is the use of binding rules and legislation by government. The parliamentary paper emphasises that the government also has a responsibility for identifying and articulating ethical issues.

Developments in synthetic biology are currently in the phase of identification and articulation. We have yet to test the desirability or necessity of establishing an authoritative body (for example an ethics commission) that can make binding decisions on the delineation of the ethical problem areas.

Analysis and underpinning of values

This last phase consists of philosophical and ethical studies to critically examine the underlying basis and substance of values. To adequately conduct a discussion on ethical aspects it is desirable for both researchers and non-researchers to clarify and deepen the concepts used. This can be facilitated by intensifying the level of philosophical/ethical research.

4.3.3 Each actor in the debate has their own task

The process described above of identification, articulation, forming a judgement, value assignment by an authoritative body and finally regulation involves many different parties. The parliamentary paper by Minister Ritzen stressed that the nature of the ethical and societal aspects of research in the first instance requires a cautious attitude by the government. A discussion must first be set in motion that in time should lead to a certain societal consensus on defining the boundaries of research and its implications. In most cases, only then will the time be ripe for political decision making.[37] Nevertheless, government can take part in the identification and articulation of ethical issues. Although the natural role of government lies in the field of legislation, it also encompasses promoting the uptake of issues by other parties with expertise in specific areas. Government can call on them to fulfil their responsibilities and duties to articulate these topics. Parties that can take part include the following:[38]

- Researchers, who should be aware of the social context in which they work and the moral questions their research can throw up. Scientists should take a broad view and explore how specific research questions relate to other variables, other systems and other themes, such as ethical and societal issues.[36]

- Institutions that carry out research or provide financing; ethical questions relating to research are often put to organisations rather than individual researchers. Such organisations provide a point of contact between research and society. They have expertise in the type of research being carried out and are also engaged in disseminating research results to the wider community (publicity, media) and in the applications of the research.

- Organisations that can serve as discussion platforms to facilitate a process of deliberation in which the research community, experts and social groups can take part. This integrated participation by various stakeholders has proved difficult to put into practice. Although it is possible to create a platform for discussion, often only one of these groups is represented.

- The media: in a democratic society it is important that citizens have an idea of the type of research that is being done. Public information and news coverage in the media play a crucial role here. Nowadays reports of possible new developments in a research field appear at a very early stage. An advantage of this is that people are not presented with a *fait accompli* when an application comes onto the market. A possible disadvantage is that there are still many uncertainties in this phase. There is much speculation about possible outcomes and applications that will provoke considerable public unrest, whereas later these turn out to be unfeasible or without risk.

- Citizens and consumers, who reflect on reports in the media about possible applications of a new technology. What form this reflection takes depends on the fundamental attitudes of individuals and groups. These fundamental attitudes are shaped by a whole range of socially or culturally determined values, which are sometimes even formalised in legislation. These values form the framework within which opinions on a certain topic can be formed. The perception of citizens and consumers depends largely on the information given to them by the media.

4.4 The role of government in the public debate

When the development of a technology involves questions about its desirability and possible applications, government will seek to address any possible problems as early as possible and steer developments accordingly. The Rathenau Institute has also stated that it is judicious to involve all relevant parties in discussing important policy issues about potentially significant and controversial technologies.[3] However, they also concluded that it is not easy to channel public involvement in a meaningful and effective way. Structuring a public debate may be at odds with the regulatory task of the government, which means that the debate on synthetic biology requires more of a facilitating hand than an organisational input from government.

It is important that when government takes on such a role it has a clear reason for facilitating the public debate and a clear idea of what it aims to achieve by doing so. There can be various reasons for government to participate in the development of a new technology (for example by organising or facilitating a debate), such as:

- To protect the rights of the public (for example, by passing legislation to protect public safety);
- To check whether any aspects or risks have been overlooked;
- To prevent discussions stalling.

In addition, government can participate in a public debate:

- When it is itself an active stakeholder,
- When a technology can induce a fundamental shift in the direction society is going (which involves the question of whether it is the task of government to alert stakeholders, such as universities and research institutes, to their responsibilities to society).

A debate can also have several different objectives, which partly depends on the stage of development the technology is in. The goal of a debate may be to steer the direction in which the technology is developing, or it may be used as an input to shaping or supporting policy, or to gauge opinions and the level of public support for a development.

An important consideration here is that the Dutch government has limited scope for policy making. Most of the legislation on biotechnology, and thus synthetic biology, is drawn up by the EU. In addition, trade agreements, such as the WTO treaties, restrict the scope for discretionary policy making even more. In this respect, a totally sovereign Dutch state that can legislate for the wishes and ethical and social choices of its people does not exist. A public debate should therefore be held across the whole of the EU.

4.4.1 Debate as a means of guiding developments

On the one hand the course taken by technological developments is partly determined by what is technically possible and what is not; on the other hand it is influenced by the opinions of individuals and the views expressed by civil society organisations on the desirability of the course of those developments. This vision is reflected in the legislation adopted by government and the resulting funding streams. Discussion or debate as a means of guiding the direction taken by developments mainly takes place at conferences and through the action of coordinating bodies such as TESSY, which try to steer the development of a technology in a certain direction. Such debates mainly attract stakeholders, such as researchers, financial institutions and companies or other users of technology. Users of a technology or application will in turn try to satisfy the wishes of the consumer or create a certain demand/need for their product.

4.4.2 Debate as policy support

Under certain conditions, ethical and societal discussions can contribute to policy formulation. In response to scientific developments it may be decided that policy needs to be amended to enable a development to take place. The basis for policy making, regulation and enforcement may be provided not only by scientific knowledge but also by inputs from a public debate. The policy-making process can be divided into several stages, depending on the phase the technology development and also the public debate are in.

Policy cycle

As a technology develops a decision has to be made on the question of whether or not it

is desirable, or even necessary, to formulate a policy for this technology. The development of policy can generally be broken down into four phases (Winsemius, 1989):

- ❖ Recognition: limited political interest, indicative monitoring (extensive), for example surveys to determine and articulate the nature of the problem.
- ❖ Policy formulation: rising political interest, policy formulation and exploratory (intensive) monitoring to establish the seriousness of the problem.
- ❖ Solution: declining public interest, routine monitoring (relatively intensive) to assess the effects of measures.
- ❖ Management: further drop in political interest, evaluation of measures, regulatory/background monitoring (extensive).

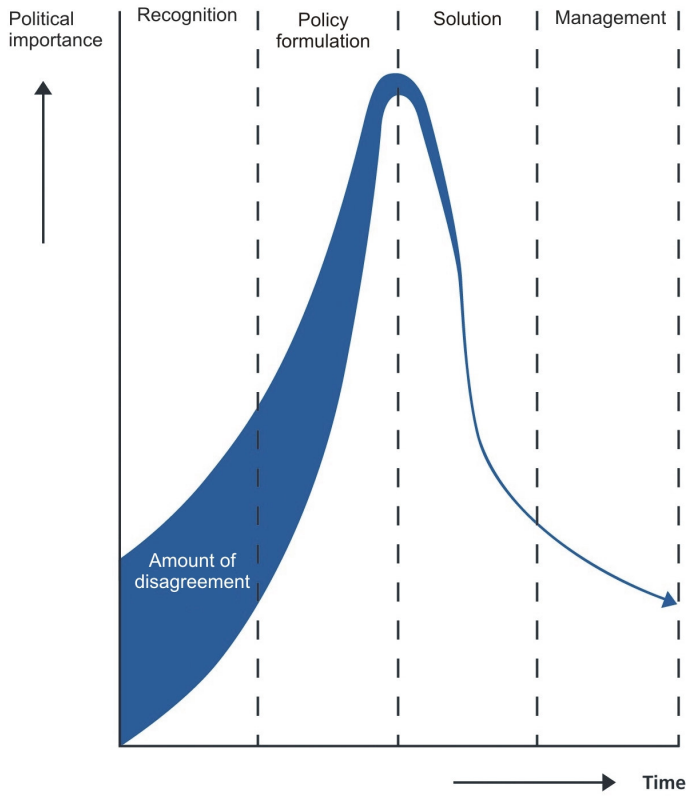

Figure 3: Winsemius's course of policy cycle

Synthetic biology has been an emerging and innovative field of research for some years. The initial results and expectations of the future of this technology imply that the consequences could be momentous and therefore evoke a strong public reaction. Developments in this field raise questions about the current risk analysis and at the same time fuel the public debate on what life is. We are currently in a phase of increasing political interest.

In Winsemius's policy cycle the topic of synthetic biology can be placed at the beginning of the second phase, policy formulation. Government recognises that developments in synthetic biology have implications for society or raise issues of public safety and risk. It is trying to itemise the possible consequences of the developments and when they might be expected to occur. In addition, the government is scrutinising the current risk analysis method and trying to anticipate possible ethical and societal issues.

Need and purpose of interactive governance

Organising a public debate is a form of interactive governance. Since the beginning of the 1990s experiments have been carried out in which citizens were involved at an early stage in plan preparation or policy making. These include digital debates, need and purpose discussions, public debates and futures studies. Interactive governance is often used in the phase of agenda-setting and futures studies, as in The Netherlands 2030, Food and Genes (*Eten en Genen*) and Future of Food.[40] However, an interactive approach is not always useful. A number of situations have been mentioned in the literature for which a network management or interactive approach is a desirable option:

- Others have specific knowledge or expertise that provides added value to the subject area (knowledge).
- The government does not have an effective chains of command over the field, or the parties involved can prevent policy from being formulated (presence of a 'hindrance/counterforce').
- The parties involved are needed for financing (money).
- For reasons of principle, responsibilities relating to the issue are shifted to companies, citizens or civil society organisations (responsibility/accountability).
- Tackling the issue effectively requires an integrated approach in which interaction between government and society is necessary or desirable (need for cooperation).

Other situations are outlined, however, for which an interactive approach may not be desirable, for example when:

- The margins and scope for policy are very restricted, both in practical and in legal terms;
- The political outcome is already fixed;
- There is no willingness to let the outcome be an explicit consideration in the political decision-making process;
- The topic has already been reduced to a principle yes/no decision (such as ethical questions) to which an interactive approach would add little, and at best would amount to an opinion poll;
- There is insufficient time or resources to organise an adequate process;
- The cost-benefit balance for time, money and expected added value is negative.

The final point to mention is that it is not useful to take an interactive approach in every phase in the development of a technology. The first discussion or hype should have more or less run its course. Government should not be called upon too early to adopt a position

on whether and how a development can be regulated. There should be clarity on the decisions that need to be made, what needs to be considered, which expert opinions should be taken on board and where the decision making could lead. This means that the discussion must have crystallised to the extent that there is broad public recognition of the need for regulations and that the standards to be applied are clear. Moreover, the nature of the issues under discussion must be suitable subjects for regulation, which must be workable and enforceable.

If discussions are still at an early stage, a debate serves little use as a means of supporting policy. In such cases a debate should first and foremost seek to gauge opinions and collect the arguments. In 2005 the Rathenau Institute held a workshop to clarify and discuss arguments on how to deal with new and controversial technologies.[41] The role of debate in the process of forming political judgements and decision making was also discussed. The workshop concluded that a debate at an early stage is worthwhile but should not be geared towards developing policy or legislation. A debate at an early stage can mainly provide insight into the desirability or otherwise of possible applications of the technology.

4.4.3 Debate as a survey of opinions and arguments

Besides being instruments of governance and policy formulation, debates are often used to survey opinions and arguments. Debates on potentially controversial topics, such as synthetic biology, are not intended to create a consensus or direct the course of developments. The main goal of these debates is to identify potential problem areas to allow early action to be taken in response to anticipated future problems. In a debate potential problems can be examined from different angles and possible avenues for acceptable solutions, and under what conditions, can be explored to reduce the chances that the application of a technology could lead to socially undesirable situations.

This first phase of a public debate is characterised by chaos and uncertainty. The first reports about the results of a new research field appear in the media and speculation rages about future applications. Both highly optimistic and negative scenarios on when the technology will come of age are put forward. They prompt stakeholders, researchers, discussion fora, interest groups and citizens to think about the desirability of possible future applications of the technology. The fact that many of these scenarios later prove to have been far-fetched is not a problem. This information is useful as an input to thought experiments to define acceptable boundaries.

Synthetic biology is still in its infancy as far as applications go, but developments can be rapid and media attention is growing explosively. This gets the public debate going, feeding high expectations but also concerns. There is much speculation about the desirability or not of possible applications of this technology. Synthetic biology also appears to throw up several fundamental ethical and societal questions that play an important part in discussions about these applications.

The first initiative for surveying opinions and arguments has already been set up. Early in 2007 the scientific community, supported by the European Commission,

introduced an online e-conference to identify the risks and the ethical and societal aspects of synthetic biology.[42] However, the discussion on this forum did not really get going and most reactions were from scientists. It seems that a real public hype is still in its very early stages.

4.5 Synthetic biology: old wine in new bottles?

From the scientific literature and the many articles in the media it appears that developments in synthetic biology, just like genetic modification, raise a number of fundamental ethical and societal issues. Civil society organisations have therefore indicated that they would like to be involved in the process from an early stage.

In 2006, 35 organisations sent an open letter to the Second Synthetic Biology Conference in Berkeley expressing their concern about developments in this area.[43] They called on scientists to involve society in setting up and organising a social dialogue about all aspects and applications of synthetic biology at global, national and local level. In addition they argued that self-regulation is not effective for researchers and is undemocratic: it is not for researchers to decide what research, and especially which applications, should or should not be allowed. Finally, they emphasised that when formulating policy, consideration should be given not only to possible misuse but also to broader social, economic, cultural, health and environmental impacts of developments in synthetic biology. The open letter was signed by organisations like Greenpeace, Friends of the Earth, the Canadian Farmers Union, ETC Group and the International Centre for Technology Assessment.

In addition, a critical report by the ETC Group on the social significance of developments in synthetic biology was published in 2007.[43] This raises a number of the same issues as in the open letter. It also stresses that synthetic biology entails new and possibly catastrophic risks for society. These social implications should be kept under close scrutiny, coordinated by an international body. Finally, the report urges that DNA should not be privatised by issuing patents on sequences.

4.5.1 Core themes in the public debate on synthetic biology

Developments in the field of biotechnology have almost always led to public discussion. Synthetic biology is no exception. Like genetic modification, synthetic biology concerns life itself. It appears to be taking genetic modification a stage further: from reading and modifying genetic code to writing and designing it. Many of the issues are not entirely new. The introduction of the research field of synthetic biology has rekindled questions that were topical mainly during the initial stages of genetic modification. The first images that come to mind are of scientists recklessly creating new organisms or life forms, companies only interested in profit or a government unable to guarantee the safety of a technology, leading to misuse and calamities.

But synthetic biology also throws up a few new questions. One of these is the observation by Eckard Wimmer, one of the researchers involved in the reconstruction of the polio virus, that this has made it impossible to completely eradicate the polio virus or other viruses.[44] The blueprint of the virus, the genetic code, is known and the virus can be reconstructed, even if the original natural virus no longer exists.

Another new question is about the 'digitisation' of biology. It is becoming increasingly easy to gain access to (synthesised) biological components and customised DNA sequences can be ordered via internet at the press of a button. To build biological systems it is no longer necessary to have a range of natural organisms and a large laboratory suite. Not only has access to the biological design process been simplified, but also part of this design process can circumvent the normal regulatory systems. In the US this situation is sometimes referred to as 'biohacking'

Most questions that lie at the root of the concerns and doom scenarios can be distilled down to a few topics or core themes that COGEM has identified in its report *Het gentech debat ontleed; een analyse van terugkerende kernthema's en argumenten* (Dissecting the gentech debate: an analysis of recurring core themes and arguments).[1] This report defines six core themes that keep recurring in different combinations and forms in the debates on biotechnology.[45] These core themes are: safety, sustainability, health and wellbeing, social relations, freedom of choice and public trust, and nature and the integrity of life. Most of these core themes can also be broken down into questions that are now re-emerging in response to developments in synthetic biology.

4.5.2 Safety, health and wellbeing

The core themes of safety and health and wellbeing are closely linked. New technologies such as genetic modification and synthetic biology can present an opportunity as well as a threat. On the one hand, there are high expectations regarding the use of technology for the production of medicines, increasing diagnostic possibilities, increasing the range of medical research and treatment methods and even new applications to help tackle climate change or food shortages. On the other hand, questions are raised about the safety implications and the consequences of the possible misuse of the technology. These are fed in part by the feeling that scientists and companies are working on 'dangerous' new organisms without any controls or consideration of the social consequences. The core theme of safety includes issues like food safety and environmental risks as well as public safety and bioterrorism. A few examples of questions:

- Is the technology safe for humans and the environment?
- Can it improve our health?
- What are the possible consequences arising from misuse of the technology?

4.5.3 Social relations, freedom of choice and public trust

Social relations is a broad core theme in which authority and governance in the field of technology development and the balance of power are at stake. Developing applications of gene technology requires many years of research and investment. Large companies and research institutes can afford to do this, but smaller, locally-based operations are less able to command such resources. This raises issues such as a fair distribution of costs and benefits, the position of individuals in relation to multinationals and authority over the types of applications to be developed. For example, the development of a metabolic pathway for the production of artemisinine using microorganisms may negatively impact African producers of artemisinine from *Artemisia*.

Autonomy and justice are relevant values in this theme. The key values in the freedom of choice and public trust core theme are consumer sovereignty and public trust.

- Who has access to the technology?
- What is government doing to guarantee that the technology is safe?
- Does the technology offer benefits for the public or primarily financial gain to the producers?
- Will the technology widen the gap between rich and poor?

The last core theme, nature and the integrity of life, raises several other questions that were far less prominent in the debate on genetic modification than they are now in relation to synthetic biology.

4.5.4 Nature and the integrity of life

The main question in this core theme is what a technology means for the physical environment, for life or nature. Protecting life, nature or biodiversity against potential threats is considered by many to be a worthy goal.

Nature and the integrity of life relate to the way in which people experience their humanity and their relation with the non-human environment, with animals and nature. This vision also determines how people view human intervention in this context. There are many differing views and beliefs about the values that play a role in this core theme. A decisive aspect is whether people have a static or a more dynamic idea of nature and the integrity of life and the degree to which they think that human intervention in nature is permissible.

The question of what life really is is more explicit in synthetic biology than in genetic modification. Genetic modification was primarily about ‘tinkering with life’ whereas the goal of synthetic biology is ‘designing and creating life’. Synthetic biology therefore creates the impression that life can be reduced to DNA alone, which can threaten the notion that life is something special and that living beings differ from organised material in that they are ‘beings’ (exist as entities). In line with this, many people think that a reductionist approach to life (particularly human life) cannot explain all dimensions of the human experience. The complex metaphysical side of life cannot be explained by the presence or absence of a specific set of genes. Reducing life to a set

of genes, DNA or even an alternative alphabet is of fundamental significance for numerous critical social discussions:

- Where does life begin?
- What is the essential nature of human beings (or other life forms)?

The name 'synthetic biology' is in fact an oxymoron: synthetic (unnatural, artificial) as opposed to biology (nature, natural). Synthetic biology throws the discussion about attributing innate value to an organism into sharper relief because this technology appears to blur the distinction between natural and artificial. In *Leven Maken* (Making Life) De Vriend noted that especially the question of what the application of technological design principles to biological systems means for our concept of life will come increasingly to the fore.

- Is everything that is built from natural or synthetic DNA a 'living creature'?
- Even if that creature does not exist in nature?
- What is the difference between a fully artificial cell used for production purposes and a machine?
- What references and criteria do we use to define life?

4.6 The genetic modification debate: a learning process

In the previous chapter we identified several questions arising from core themes in the discussion about synthetic biology. A number of these questions were also raised in the early stages of the development of genetic modification. The debate on synthetic biology therefore draws heavily on the debate on genetic modification. However, this brings with it a danger of 'tunnel vision' in which the arguments are used to generate to similar outcomes. For some people the discussion about genetic modification is a textbook example of an intractable debate without a workable outcome.

COGEM is of the opinion that the debate on genetic modification should be seen primarily as a learning process. The gene technology debate took place in a different social context. COGEM prefers not to talk of mistakes in the gene technology debate from which we can learn. What we can learn from is the experience. It is most important that we have the opportunity to learn from these types of process, and especially that we are willing to learn from them.[46] In his presentation on the role of science in innovation policy at the COGEM anniversary meeting in 2005, de Wilde observed that whatever choice is made there is always a price to pay in technology development. Sometimes a society would do well, as a precaution or because of ethical and societal objections, to reject a research topic at an early stage of development. Possible irrevocable damage may be avoided by simply abandoning the research. Whether this damage would actually have occurred, however, will never be known because the learning process, including learning from mistakes, is terminated. A prudent innovation policy tries to find a balance. It respects the desire for facts, but this must include both types of facts: facts about the perceived risks and about the opportunities. Those who ignore the former fail to appreciate that scientific knowledge can only grow on a bed of social acceptance. But

those who realise that the second type of fact is at least as important for the legitimacy and funding of scientific research will always try to create sufficient scope for the long-term process of variation and selection. This learning space, however, has no boundaries. Limitations do not have to be an obstacle to learning – they frequently make researchers more inventive – but it is essential that society lets science learn through experimentation. The size of the learning space depends heavily on the degree to which society wishes to learn about a specific subject and has confidence in our ability to control any risks that arise.

The identification of possible risks or undesirable effects of a technology can result in precautionary measures being taken or the course of the technology development being redirected. These steps can be evaluated later in the process. When more has been learned, the risks may appear to be less serious than had been thought and the relevant measures relaxed. If, in fact, the risks turn out to be real, the precautionary principle will have worked. In this case there is a learning process in which interaction takes place between government, science and society. However, this is not always possible. It should be noted here that halting the development of a technology also has a disadvantageous side. Economic or other opportunities cannot be exploited and solutions to social problems, such as disease, do not materialise.

If some stakeholders cling to their own perceptions and interpretations of the opportunities and risks of biotechnology, this can be a serious stumbling block for a fruitful dialogue. A certain amount of reflection and introspection is desirable, particularly with respect to the normative issues associated with modern biotechnology.

This lack of reflection is encouraged by a fixation on topical issues at the expense of the longer term. After all, you cannot learn by focusing on what is currently unknown and taking this as a legitimate reason for terminating a line of research. A learning process can be set in motion by formulating more universally shared goals for the future and anticipating possibilities for managing potential risks.[36]

The gene technology debate in brief

In the early years of DNA research in laboratories it was the scientists themselves who first became concerned about possible health risks. This concern was largely alleviated when rules were drawn up for safe working practices with these organisms. However, an intense debate was sparked off again when the first field trials were held in the early 1980s. In the mid 1990s Greenpeace and others initiated another wave of criticism, this time directed at the safety of genetically modified food. In Europe and elsewhere media interest grew and the vast majority of European consumers rejected GM foods. This eventually led to a moratorium on GM foods in the EU, which was only lifted in 2003.

In the early stages of genetic modification most of the reactions were from individual scientists; it was only when the first applications emerged that civil society organisations joined in the debate. The debate became heated, driven by concerns about the safety of these techniques for human health and the environment, and also by more ethical questions and the possibilities of misuse of the technology. Attempts to keep the debate on the right track proved to be largely ineffective. The public felt they were informed too late in the day, when the GM crops were already in the fields and the products were already on the supermarket shelves. Public trust was undermined.

Belated attempts by government, scientists and the corporate sector to demonstrate that the safety of the technology and its products was guaranteed led to nothing. When the government tried to organise a public discussion, such as the *Eten en Genen* (Food and Genes) debate, social groups said they did not agree with the way the issues were presented and the approach taken and pulled out. However, as applications in the field of human health appeared objections began to subside somewhat. These applications are still the least controversial. Nevertheless, the same questions keep on cropping up as discussion about GM food and industrial applications regularly flares up.

When social groups say they have been informed too little and too late, some scientists claim that this lack of basic knowledge is the result of a deliberate choice: people simply do not want to know. The different parties also regularly accuse each other of taking a biased view (either being too scientific or focusing only on ethical and societal considerations).

The book Biotechnologie en de dialog der doven; dertig jaar genetische modificatie in Nederland (Biotechnology and the dialogue of the deaf, thirty years genetic modification in the Netherlands) concludes that the dialogue on genetic modification did not really get going, or only with great difficulty. Moreover, the debate on genetic modification is frequently used in the literature as an example of how a public discussion should not be conducted.

able 1: PHASES IN TECHNOLOGY DEVELOPMENT, PUBLIC DEBATE AND POLICY MAKING					
Technology (Technology Hype Cycle - Gartner)	**Technology Trigger**	**Peak of Inflated Expectations**	**Trough of Disillusionment**	**Slope of Enlightenment**	**Plateau of Productivity**
Ethical discussion (Parliamentary paper 21 319 – Ritzen)	**Identification**	**Articulation**	**Authoritative Value Assignment**		**Analysis and Underpinning of Values**
Policy formulation (Policy cycle – Winsemius)	**Recognition**		**Policy Formulation**	**Solution**	**Management**

Description	First reports appear in the scientific literature, popular science magazines and the media. The actual developments and future technological possibilities cannot be foreseen.	By now more is known about the course of various developments and the technical possibilities. Media interest grows explosively. The topic is also discussed in newspapers and on TV and radio. Stakeholders are asked to give their (expert) opinions. In addition, the public and interest groups articulate their expectations of possible applications or express their concerns.	Media attention declines; neither the dream scenarios nor the doom scenarios turn out to be realistic. Although no applications are on the market yet, they are taking on concrete shape beyond the gaze of the media.	The first applications of the technology come onto the market and receive media coverage. Media interest grows again.	As a well-oiled machine the technology delivers new applications which are introduced and implemented in society.
Scientists / Companies	Inform government and the media about the current state of developments. Reflect on the possible implications in terms of risks and ethical and societal aspects.	Inform government and the media about the current state of developments. Take responsibility for issues of public safety and the desirability of applications and communicate these.	The scientific and business communities draw closer as more concrete applications come into view. These parties should inform government and the media.	Inform government and the media about the current developments. Evaluate suppliers of applications: do these applications meet previously agreed statements, promises and expectations about the potentials?	Inform and evaluate
NGOs	Keep abreast of reports in the media and make further enquiries. Where possible put the topic on the agenda.	Articulate possibilities and impossibilities and points for discussion. Possible interaction with the media to highlight these points.	Interest in the topic declines, but does not disappear. Interest groups continue to air their opinions.	Interest in the topic grows again. Issues raised for debate are focused more on concrete applications.	Interest in the topic continues. Specific viewpoints are still expressed, but meet with less response in the media and among stakeholders.
Media	Inform the public via attention-grabbing articles				
Citizens	The public sees the first reports in the media. The possible applications put forward seem to be a long way off, but appeal to	A wide range of possible applications and both dream and doom scenarios are presented to the public. They can use them to brainstorm about the desirability of	Interest among the wider public declines and few or no new questions are added. The lack of concrete applications creates the	The first applications are made available to the public and interest grows again. The public and/or interest groups articulate their views	The technology has been embraced by society, applications are put on the market with no complaints from the public. A number of groups and individuals continue

	the imagination.	applications of the technology. Thought experiments can be used to articulate ethical and societal issues raised by the technology. Citizens can form interest groups to convey their views more forcefully.	impression that things will not happen very quickly.	on these applications.	to oppose the technology as a matter of principle with arguments put forward during the identification and articulation phases.
Government	Gather information with a view to identifying and affirming whether a new development is emerging. In this phase questions of safety and risks may arise. Government must take action and obtain information and advice in order to answer these questions.	Can provide information about developments and how government is guaranteeing the safety of its citizens. Based on the information obtained, government articulates opportunities and problems that may be thrown up by the new technology, for example, in the areas of risk management and legal, economic, ethical and societal issues. The government must decide whether or not to encourage the developments by providing subsidies or research programmes.	Realisation that this is the stage in which the first applications begin to take shape. It is important for government to remain up to date on developments in the scientific world. Which scenarios are realistic and when will they be relevant? The ethical questions that are of practical relevance to the technology have been clearly defined. Which parties could have a judgement to make on these (e.g. a review committee) and how could this be structured? Is it necessary to formulate new policy or amend existing policy?	The safety issue has been defined. Implementation of the policies made. Key activities in this phase are evaluation and learning. Government must keep the situation under scrutiny to check that the problems it has defined and that any policies formulated in response meet with public approval. The appearance of new (unexpected) developments may make it necessary to amend some aspects of the risk analysis.	Monitor the situation and make policy amendments should unexpected situations arise. Remain informed about public expectations and concerns.

5. The position and role of government

Developments in synthetic biology are currently in the initial stage of the Technology Hype Cycle, in the Technology Trigger and Peak of Inflated Expectations phases. The public debate is getting started and various groups are expressing either concern about the possible applications of the technology or their expectations for the future. At the moment the public debate is in the 'chaos' phase. There is widespread speculation about possible applications of synthetic biology, but no possibility of making any firm statements about the feasibility of these applications.

At this time there is little point in the government facilitating a debate. In the first phase the debate should be allowed to run its course and the actors involved should be given the chance to articulate potential points for discussion. In this 'chaos' phase government should first and foremost keep itself informed of the current situation. The government has acknowledged this and has brought in various bodies (KNAW, COGEM) to inform and advise on the latest situation regarding the risk analysis and the ethical and societal discussion. The government's responsibility towards society can take the form of making information available to enable people to articulate their opinions.

This by no means implies that government takes no further part during this initial stage of development. It can also influence the development of synthetic biology in other ways, for example by managing expectations, stimulating developments (research, subsidies) and promoting knowledge through education so that citizens can take part in the discussion. Moreover, government must be aware of its role in the governance of technology. The government can respond to expectations and help to shape the course of developments in synthetic biology by providing subsidies and financing research in specific programmes.

When developments move into the next phase (the Trough of Disillusionment) and the dust settles in the wake of the Peak of Inflated Expectations, the first phase of the discussions comes to fruition and more concrete statements can be made about the possibilities and impossibilities of synthetic biology. This is the point when government can take on a different (more visible) role in the debate. But it is hard to identify exactly when this will be. During this phase the interest in synthetic biology is on the rise. It is not possible to predict when the level of interest will peak and this will depend in part on scientific breakthroughs or indeed the lack of them. Monitoring of media interest can be a way of identifying when the transition to the next phase (Trough of Disillusionment) is likely to occur. When this phase begins media attention will decline. However, developments will start to take shape beyond the gaze of the media, and it will become clear whether the anticipated public safety issues and social impacts will actually materialise.

The progress reports on publicly financed research projects provide the government with information on the development of tangible products of the emerging technology. A possible impediment to this process is compartmentalisation within government. Reports will tend to be written for their direct financiers, such as the Netherlands Organisation for Scientific research (NWO) and the government ministries responsible for education, culture and science, economic affairs, etc. However, these will often be the government departments that are not directly involved in the public debate. The government should be aware of this and ensure that

information on the results of research and development flows freely between the various government departments and agencies.

Over the next few years the government has the opportunity to develop its policy agenda based on research into the ethical issues raised by this technology. COGEM and the Rathenau Institute will review the activities which could be undertaken by the government in this period of 'quiet before the storm'.

During the Peak of Inflated Expectations phase the actors involved have time to think about the limits to the acceptability of possible applications. This can serve as a framework for examining concrete applications that arise during the Trough of Disillusionment and Slope of Enlightenment phases. Whereas the public were previously faced with wild promises and expectations, they can now be introduced to more concrete applications. However, because media interest is waning, government will have to act to keep developments in the public eye to prevent applications of the technology being introduced outside public scrutiny and society being confronted later with a fait accompli (Slope of Enlightenment or even Plateau of Productivity). In this phase, government can ensure continued attention for the topic by putting it on the public agenda, informing the public and encouraging interested parties (scientists and companies, for example) to keep society informed of progress. Because this is the phase in which the first concrete applications emerge, it may be possible to discuss the desirability and safety of individual applications in specific cases. Table 1 (page 56) summarises the various phases of technology development, public debate and policy making, and the role of the various stakeholders, especially that of the government.

To guarantee the safety of developments and applications within synthetic biology it is important to identify potential risks at an early stage. COGEM will therefore monitor developments, as announced in its evaluation report of 2007.47 We will do this with the instruments normally at our disposal, including the Trendanalyse Biotechnologie (Biotechnology Trend Analysis), a triennial report by COGEM, the Committee for Animal Biotechnology (CBD) and the Health Council.

6. Conclusions

Synthetic biology is currently attracting much interest, probably because some researchers are making exciting claims about the potential applications of synthetic organisms, for which the sky appears to be the limit. Whether these high expectations will ever be met remains questionable. But the fact remains that various organisations have been spurred on to examine this mater in more depth. The House of Representatives has also considered the subject and the environment minister has asked COGEM several questions. The minister has asked COGEM to report, among other topics, on the suitability of the current GMO risk analysis for applications of synthetic biology (particularly synthetic organisms), the monitoring of developments within the research field and the ethical and societal implications of synthetic biology. She has also asked COGEM how government can best facilitate public discussion about this technology. The answers are given point by point below.

Question 1: What developments can we expect in future for which the current risk analysis method for GMOs could prove inadequate or unsuitable?
Although some researchers foresee countless applications of synthetic biology, most Dutch scientists have more modest expectations, especially in the short term. COGEM points out that for the next ten years activities will be confined mostly to laboratory work with biologically contained organisms. Within this period we therefore expect no developments that fall outside the framework of the existing risk analysis.

Question 2: When are these developments expected to occur?
As stated under Question 1, developments that fall outside the scope of the current risk analysis will only take place in the long term. We cannot now predict when this will be.

Question 3: Are there any developments in synthetic biology which by definition are likely to fall entirely outside the scope of the current assessment framework?
Work with synthetic organisms falls under the definition of GMOs and therefore under the GMO legislation. Whether the risk analysis will suffice in all cases far into the future is difficult to say. It is too soon to be able to comment on the development of applications that will indeed be introduced in future. A development that may fall outside the current risk analysis method is a reproducing organism that does not occur in nature, for example one with an alternative genetic alphabet. However, in future our knowledge about the various organisms, genes and their function will improve greatly. This will make it easier to assess potential risks. When the current risk analysis method is no longer adequate for a particular situation, new assessment criteria can be drawn up that will permit the risks to be appraised. However, as far as COGEM can assess the situation at the moment, within the next ten years we can expect no developments that we know will fall outside the scope of the risk analysis used for GMOs.

Question 4: What need and opportunities do you see for systematic monitoring of this policy field in future?
Given that we cannot now predict all future scientific developments, COGEM concludes that it is important to recognise potential risks at an early stage. We will therefore monitor developments, as announced in our evaluation report of 2007.[47] We will do this using our usual

tools, including the Biotechnology Trend Analysis. Government can also play a part in keeping track of developments in synthetic biology to inform the public debate. This and other ethical and societal implications of synthetic biology are dealt with under Question 5.

Question 5: What are the ethical and societal implications of synthetic biology and how can government best facilitate the public debate on synthetic biology?
Current developments in synthetic biology raise questions of safety, sustainability, health and wellbeing, social relations, freedom of choice and public confidence, and nature and the integrity of life. Some of these questions were already raised at the time when genetic modification was debated. Synthetic biology poses much more explicit questions about the boundaries between life and non-life and between man and machine: to what extent can a totally synthetic organism be considered to be 'life' and not a machine? Other new elements in the ethical and societal debate are the reconstruction of extinct organisms and the digitisation of biology. It is often not possible to formulate a position on substantive aspects of new developments in science and technology because the dimensions and implications of the ethical problems they raise have not yet been clearly defined.[32,38]

As mentioned before, developments in synthetic biology are currently in the initial stage of the Technology Hype Cycle, the Technology Trigger and Peak of Inflated Expectations phase. There is widespread speculation about possible applications without knowing whether these are actually feasible. In this 'chaos' phase, facilitation of a debate by government has little point. The government should first and foremost keep abreast of the latest developments. It has acknowledged this and has brought in COGEM, among others, to inform and advise on the situation regarding the risk analysis and the ethical and societal discussion. At the same time, government can make information available about the safety and economic aspects. It can also inform the public about new technologies through the education system. Moreover, by providing subsidies and research funding for specific programmes government can respond to expectations and help shape the direction of developments in synthetic biology.

When developments have moved into subsequent phases we can make more specific observations on the possibilities and impossibilities of synthetic biology. Only at that stage can government take on a different role in the debate. At the moment, though, it is not clear when these phases will be reached.

Over the next few years the government will have the opportunity to prepare its policy agenda, drawing on research into the ethical issues raised by this technology. COGEM and the Rathenau Institute will explore the activities that could be undertaken by the government in this period of 'quiet before the storm'.

References

[1] COGEM (2007). Het gentech debat ontleed. Een analyse van terugkerende kernthema's en argumenten. CGM/071004-01

2 COGEM (2006) Synthetische biologie, een onderzoeksveld met voortschrijdende gevolgen. CGM/060228-03

3 Vriend H, van Est R en Walhout B (2007). Leven maken: Maatschappelijke reflectie op de opkomst van synthetische biologie. Rathenau Instituut, werkdocument 98

4 Gill'ard, Waalkens en Besselink (2007). Vragen aan de ministers van Onderwijs, Cultuur en Wetenschap , van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer, van Landbouw, Natuur en Voedselkwaliteit, van Economische Zaken en van Justitie en de staatssecretaris van Volksgezondheid, Welzijn en Sport over synthetische biologie. Kenmerk 2070800670

5 Cramer J (2008). Verzoek om advies synthetische biologie. Kenmerk SAS/2007124333

6 Hoeven van der MJA (2006). Adviesaanvraag synthetische biologie. Kenmerk OWB/WG/2006/29331

7 Gezondheidsraad, RGO en KNAW (2008). Synthetische biologie: kansen creëren. Den Haag: Gezondheidsraad; publicatienr. 2008/19

8 Relman D (2008). Assessing Biosecurity concerns related to synthetic biology; update by the NSABB working Group on synthetic genomes. Presentatie op 27 februari bij NSABB

9 Cello J, Aniko V et al. (2002). Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural templatse. Scienc 297: 1016-1018

10 NEST (2005). Synthetic biology: applying engineering to biology. Report of a NEST high level expert Group

11 COGEM (2006). Synthetische biologie; Een onderzoeksveld met voortschrijdende gevolgen. CGM/060228-03

12 Dekker, Cees. Homepage. Internet: http://www.ceesdekker.net/publications.htm (2 september 2008)

13 Ro DK, Paradise EM *et al*. (2006). Production of the antimalarial drug precursor artemisinic acid in engineered yeast. Nature 440: 940-943

14 Martin VJJ, Pitera DJ *et al.* (2003). Engineering a mevalonate pathway in Escherichia coli for production of terpenoids. Nature biotechnology 21(7): 796-802

15 Keasling JD en Chou H (2008). Metabolic engineering delivers next-generation biofuels. Nature biotechnology 26: 298-299

16 Leconte AM, Hwang GT, Matsuda S *et al.* (2008). Discovery, characterization and optimization of an unnatural base pair for expansion of the genetic alphabet. J Am Chem Soc 130: 2336-2343

17 ETC Group (2007). Extreme genetic engineering. An introduction to synthetic biology

18 Benner SA, Hutter D en Sismour AM (2003). Synthetic biology with artificially expanded genetic information systems. From personalized medicine to extraterrestrial life. Nucleic Acids Res Suppl 3: 125-1256

19 EraGen Biosciences. Internet: www.eragen.com (10 juni 2008)

20 Gibson DG, Benders GW, Andrews-Pfannkoch C *et al*. (2008). Complete chemical synthesis, assembly and cloning of a *Mycoplasma genitalium* genome. Science 319: 1215-1220

21 Briggs, H. Synthetic life 'advance' reported. BBC news 24 jan 2008

22 Integrale versie van de Regeling genetisch gemodificeerde organismen en het Besluit genetisch gemodificeerde organismen. Mei 2004

23 Richtlijn 2001/18/EG van het Europees Parlement en de Raad inzake de doelbewuste introductie van genetisch gemodificeerde organismen in het milieu en tot intrekking van Richtlijn 90/220/EEG van de Raad (2001)

24 Glass JI, Assad-Garcia N, Alperovich N *et al.* (2006). Essential genes of a minimal bacterium. PNAS 103(2): 425-430

25 Leconte AM, Hwang GT, Matsuda S *et al.* (2008). Discovery, characterization and optimization of an unnatural base pair for expansion of the genetic alphabet. J Am Chem Soc 130: 2336-2343.

26 Xie J en Schultz PG (2006). A chemical toolkit for proteins – an expanded genetic code. Nat Rev Mol Cell Biol 7: 775-782

27 Ball P (2004). Starting from scratch. Nature 431: 624-626

28 Hulspas van M. (2007). Levensvormen op bestelling. De Pers, wetenschap, 20 augustus 2007

29 Hesselmans M. (2008). Lego van DNA. NRC Handelsblad. Wetenschap. 6 januari 2007

30 ETC Group (2007) Extreme Genetic Engineering: An introduction to synthetic biology, Action group on Erosion, Technology and Concentration, january 2007

31 The New Scientist (2008) Rewriting the rules of life

32 Internet: www.tessy-europe.eu (mei 2008) synthetic biology in Europe. Information leaflet

33 Van Lente, H., 'Een culturele ruimte voor technische beloftes', Filosofie en Praktijk, 1994 (15/2), 57-74

34 Van Lente H, Rip A. (1998) Expectations in technological developments; an example of prospective structures to be filled in by an agency. In C. Disco en B. van der Meulen. Getting new technologies together. Studies in making sociotechnical order, new York p. 203-229
35 Internet: www.gartner.com/pages/story.php.id.8795.s.8.jsp#top
36 COGEM (2006) Governance van biotechnologie; de veranderende rol van wetenschappelijke adviescolleges. CGM 2006-01
37 Kamerstuk 1990 Ritzen: schets kader discussies over ethische aspecten van wetenschappelijk onderzoek. Vergaderjaar 1989-1990, 21 319, nr. 9
38 Kamerstuk 1991 Ritzen: Kader voor discussies over ethische aspecten van wetenschappelijk onderzoek. Vergaderjaar 1990-1991, 21 319, nr. 12
39 ETC Group (2006) Global coalition sounds the alarm on synthetic biology (news release 19th may 2006)
40 Enthoven G (2005) representatief en participatief; een tussenbalans na 10 jaar interactief besturen. Bestuurskunde, maart 2005, nr. 2
41 Rathenau Instituut (2005) Debat ter Discussie; wie mag meepraten over medische technologie?
42 Internet: www.synbiosafe.eu
43 ETC Group (2007) Extreme Genetic Engineering: An introduction to synthetic biology, Action group on Erosion, Technology and Concentration, january 2007
44 Wimmer, Eckard. The test-tube synthesis of a chemical called poliovirus: The simple synthesis of a virus has far-reaching societal implications. EMBO Reports Vol. 7, 2006, p. 53-59
45 COGEM (2007) Het gentech debat ontleed; een analyse van terugkerende kernthema's en argumenten. CGM/ 071004-01
46 De Wilde, R. (2005). *De rol van wetenschap in innovatiebeleid*. Lezing jubileumsymposium COGEM. 22 juni, Amsterdam.
47 COGEM (2007). COGEM Evaluatierapport 2007. CGM/071127-04