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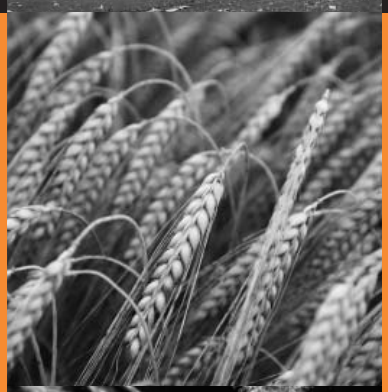

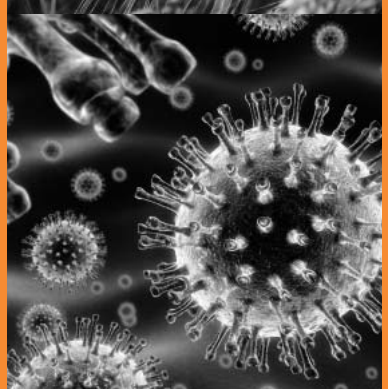

SYNTHETIC BIOLOGY

INFLUENCING DEVELOPMENT

LLOYD'S EMERGING RISKS TEAM REPORT

DISCLAIMER

DATE AND VERSION: JULY 2009, VERSION 1

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EXECUTIVE SUMMARY

1. SYNTHETIC BIOLOGY IS A NEW AND EXCITING TECHNOLOGY. Humans have engaged in selective breeding for millennia and in genetic modification since the 1970s, however the new science of Synthetic Biology promises a step change in our power to shape life. Using this new technology it is possible to engineer life from the ground up allowing the formation of organisms with genetic code not found in the natural world. The technology is still in its infancy and arguably a few years behind Nanotechnology (the subject of a previous Emerging Risks Team report). However we are already seeing some commercial examples and can expect growth over the next 10 years. This presents an opportunity for insurers; but as this report discusses also some risks to monitor and manage.

2. SCARCITY TRENDS WILL DRIVE INNOVATION. There are 850 million undernourished people in a world with a population growing at more than 6 million per month. Already over 50% of people live in urban dwellings and estimates suggest this will rise to 60% by 2050 when the population will reach 9 billion. Many believe that Synthetic Biology will be one of the transformative technologies necessary to combat climate change, energy shortages, food security issues and water deficits. By rewriting the genetic code it may be possible to make plants disease resistant, and salt, heat and drought tolerant. The cost of large scale biofuel production and some medicines could be reduced as engineered bacteria produce the raw materials. Such scarcity trends represent a powerful need for technological development and therefore it is critical that we ensure responsible innovation.

3. THERE IS NO SINGLE SET OF REGULATIONS. There is no consistent global view on the appropriate approach to regulating Synthetic Biology; public opinion on the use of this technology appears to differ regionally. Within regions it is typical that there are several agencies with potential jurisdiction over processes using the new methods. It would be useful (as in the case of nanotechnology in the US) if a single body was set up in each region to oversee and coordinate the approach and to aim for global consistency. The data for a traditional risk analysis will often be lacking in which case a precautionary approach is appropriate when the risks are potential very high. Regulations should require developers to consider low probability, high impact events as part of the risk management process. The use of Synthetic biology should be tracked carefully and labelling be introduced if it is used directly in food.

4. THERE ARE VALID CONCERNS AND ACTIONS SHOULD BE TAKEN TO ADDRESS THEM. There are fears that, as the ease of use of the technology develops, terrorists or criminals could procure segments of seemingly innocuous DNA and then recombine the pieces into bio hazardous substances. Alongside this “bioterror” there are also concerns around “bioerror”; the accidental release of synthetically engineered organisms that could lead to environmental or health problems. Ecosystem effects are hard to predict and there have already been examples of unexpected gene transfer between GM crops and their nearby natural neighbours. Although scientists have made great leaps in their understanding of genetics in recent years there is still much we do not understand; unexpected results regularly arise. It is important to map the current uncertainties and set up research programs to fill knowledge gaps around the risks.

5. DEBATE AMONGST KEY STAKEHOLDERS IS ESSENTIAL. A common complaint is that the views of all stakeholders are not taken into account. Some fear the creation of monopolies in food and energy production; others object to the concept of “patenting life”. Focus groups involving the public (including a variety of religious views), biotech industry, security advisors, developing countries, governments/regulators, insurers and research scientists should be held to ensure all views are understood. Some adverse scenarios (for example widespread and potentially irreversible ecological damage) might lead to large scale aggregations of liability though this would be decided in the courts if it were to occur. Insurers should consider the extent to which they wish to be exposed to such systemic risks; the inclusion of appropriate limits may be appropriate. For now keeping a close watch on developments is advisable.

PURPOSE

Humans have been breeding animals and plants with the most desirable characteristics for thousands of years. For example, the fattest pigs and the cows with the highest yield of milk were chosen for breeding. Fruits and vegetables are carefully selected and those that have grown fuller than others are used as the prime source of seeds for the following harvest.

However, breeding and cross breeding entered a more complex dimension in the 1970s with the discovery of genetic engineering and more recently synthetic biology. The manipulation or creation of biological components to form systems that are not found in the natural world has given us yet more power to direct evolution.

The long term impact of these fabricated systems on the environment is unknown and effective regulation is not evolving as rapidly as the number of potential applications. The production of organisms and systems that do not naturally occur and the ability to 'redesign' life spark an additional ethical and moral debate too, yet this debate does not have a well established forum. Concerned parties often have a variety of backgrounds, not all scientific, and often raise valid concerns yet can sometimes be dismissed by scientists as "anti-progress". Other issues stem from the difficulties to contain genetically engineered organisms, health effects and the potential to use genetic modification as a weapon – bio terrorism.

So why is this different to selective breeding? Some would argue that it is not; others believe these new techniques dramatically increase the risks. Synthetic Biology promises many exciting and desirable advances such as: increased crop yields, cheaper better drugs and a solution to energy shortages. Whilst genetic modification has been used by industry since the late 1970s, many of the capabilities of synthetic biology are more than a decade away from full commercialisation. However, now is the time to call for a debate on the direction, pace and extent of development, before the technology becomes embedded. Policymakers and appropriate regulation must ensure such powerful techniques are carefully monitored during development, to avoid irreversible impacts but without stifling innovation. This is not a simple goal! There are strong parallels with nanotechnology which was the subject of a previous Emerging Risks report; synthetic biology is arguably running a few years behind, but catching up fast.

This report aims to introduce the subject of Synthetic Biology and to alert the Lloyd's market and wider insurance community of the potential risks and opportunities that exist now and in the future.

EMERGING RISKS TEAM

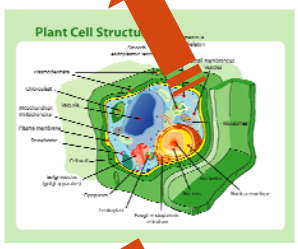
The Emerging Risks team is part of the Franchise Performance Directorate at Lloyd's. We define an emerging risk as an issue that is perceived to be potentially significant, but which may not be fully understood or allowed for in insurance terms and conditions, pricing, reserving or capital setting. Our objective is to ensure that the Lloyd's market is aware of potentially significant emerging risks so that it can decide on an appropriate response to them.

The Lloyd's Emerging Risks team maintains a database of emerging risks that is updated regularly through conversations with the Lloyd's emerging risks Special Interests Group, which consists of experts within the Lloyd's market put together with help from the Lloyd's Market Association. The team also maintains contact with the academic community, the wider business community and government. Contact with academics is often facilitated through the Lighthill Risk Network, an organisation that is run as not-for-profit funded by AonBenfield, Catlin, Guy Carpenter and Lloyd's.

More details can be found at www.lloyds.com/emergingrisks.

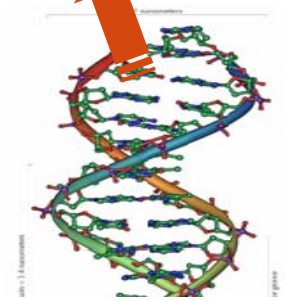
STRUCTURE OF LIFE

ORGANISM: Living things that are capable of reacting to stimuli, reproduction, growth, and homeostasis. Plants, animals, fungi and microorganisms (such as bacteria) are examples of organisms. They tend to adapt to their environment over many generations through evolution. **Evolution** relates to the change in genetic material in an organism often eventually resulting in a new species. It can be difficult to define a **species** but put simply animals of the same species can mate; whereas different species cannot.

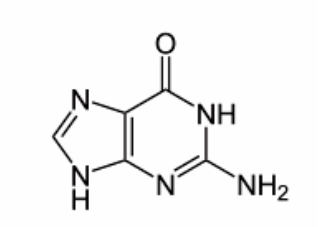


CELL: is the smallest part of an organism that is considered living. Some simple forms of life (e.g. many bacteria) have only one cell; more complex life forms are multicellular. A cell has a membrane which defines its boundary, a nucleus which contains the **chromosomes** and various other structures which carry out important functions such as energy production or protein creation. Cells can reproduce by dividing into two. The size of a typical cell is around 10 micro meters (one micro meter (μm) is one millionth of a meter).

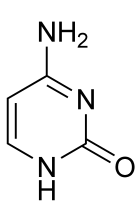
CHROMOSOME: a single strand of DNA, containing up to a billion base pairs (see below). Humans have 46 chromosomes arranged in 23 pairs; other animals have different numbers. Damage to the chromosomes is often the cause of genetic conditions. For example Downs Syndrome results from an extra copy of chromosome 21. Although we speak of "**genes**" they are not a well defined concept biologically. Originally Gregor Mendel suggested that the visible characteristics (phenotype) of offspring were inherited from their parents through a *hypothetical* biological factor called a genotype, later shortened to "gene". Genes were one thought to correspond exactly to portions of DNA (see below) – but this view is now under revision by leading biologists. A **Genome** is the complete set of genes within one organism's set of chromosomes.



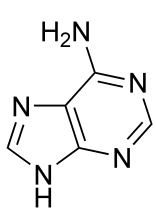
DNA: Deoxyribonucleic acid is the molecule which makes up the chromosomes. It has a double helix structure which was discovered in 1953 by Watson and Crick building on the work of Rosalind Franklin and Maurice Wilkins. It contains pairs of molecules that fit together and are called "**base pairs**". The base pairs are: adenine/thymine and guanine/cytosine. These pairs create a "binary code" that in some sense provides the instructions to create the building blocks for cells or regulate their use. DNA can be replicated by splitting the two strands and creating the opposite strand from raw materials within a cell. For all living creatures and most viruses, DNA contains many of the instructions for life; however scientists are beginning to understand the process is more complex than previously thought.



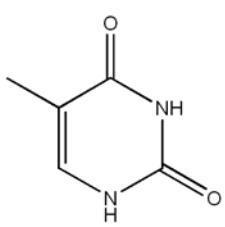
GUANINE



CYTOSINE



ADENINE



THYMINE

TRADITIONAL GENETIC ENGINEERING

DNA sequencing

DNA sequencing[1] determines the precise code of base pairs in a strand of DNA. This is an outstanding achievement in itself; a strand of DNA is only 2 nanometers thick (1nm = billionth of a meter) and 10 base pairs can fit on a section just over 3nm long. Despite the tiny scales it is possible to identify individual base pairs and accurately describe their order.

Initially, the process was laborious and used chromatography. Nevertheless, by 1975 the genome of a bacteriophage (or "phage", a virus that can infect a bacterium) had been sequenced. In 1987 automated sequencing machines were available and faster, safer dye based methods were published in the mid 1990s. At present the DNA chain has to be divided into strips up to 1000 base pairs long, which can be sequenced in one go. Despite this restriction the total human genome, comprising around 6bn base pairs, had been sequenced by 2003[2].

The speed of DNA sequencing has increased 500 fold over the past 10 years and is now doubling every 24 months. At the same time the cost of extracting each base pair has fallen from $30 twenty years ago to $0.001. If this rate of development were to continue it would be possible to have a personalised genome map for under $1000 by 2020; leading to some interesting questions for life assurers.

Recombining DNA

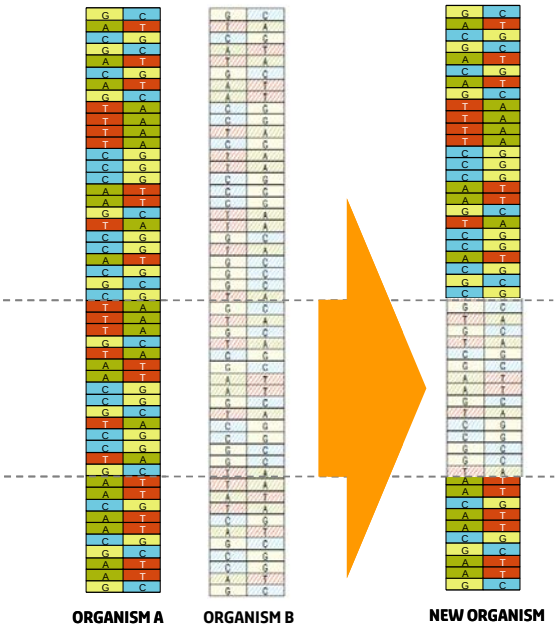
It is possible to alter naturally occurring DNA resulting in "Recombinant DNA" (rDNA) which has been created by combining DNA strands that would not normally occur together. The first technique for this process was published in 1973 by Boyer and Cohen.

Given an organism (A) this can be modified by first identifying a desired piece of DNA in another organism (B). Then the desired DNA strand is "cut" (using natural enzymes) from organism B and "pasted" (again using enzymes) into the DNA of organism A. (See illustrative figure). This process creates a single strand of new DNA; the next step is to create multiple copies of this. To create multiple copies of an rDNA strand it is typically inserted into a host bacteria cell. As the cell reproduces it replicates the new DNA at the same time.

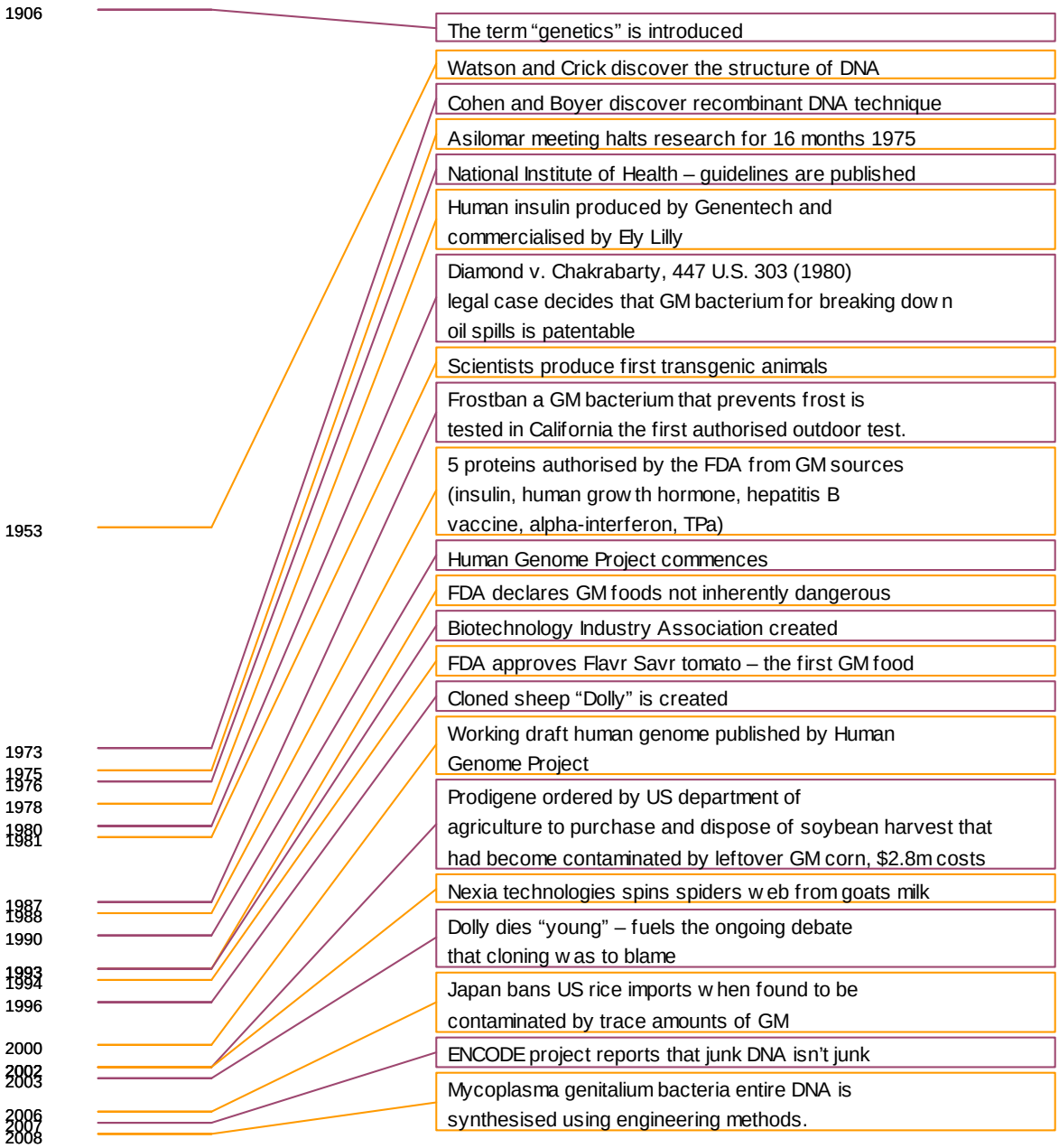
By 1974 some scientists were becoming concerned that the new techniques could introduce novel risks into the environment. A landmark conference was convened in Asilomar in 1975 which established principles on how to safely conduct experiments. The principles included: the use of appropriate containment, the education of all involved in the process about the risks, the suggested use of biological barriers (such as using host bacteria that could not survive in the natural world). Ultimately the recommendations of the Asilomar conference lead to the formation of the Recombinant DNA Advisory Committee of the National Institute of Health (NIH) (see the regulation section for more details).

Organisms produced using rDNA are called "Transgenic" and include examples from plant, animal and bacterial kingdoms.

ILLUSTRATIVE rDNA PRODUCTION PROCESS



HISTORY OF BIOTECH



WHAT IS SYNTHETIC BIOLOGY?

"*the deliberate design of novel biological systems and organisms that draws on principles elucidated by biologists, chemists, physicists and engineers…in essence it is about redesigning life..*" **Royal Society**[3]

Scientists are still arguing over whether Synthetic Biology is a new discipline or simply an extension of existing methods such as systems biology. These seemingly esoteric discussions can have major ramifications on public perception and on which set of regulations have jurisdiction to dictate procedures. The key distinction between Synthetic Biology and traditional Genetic Modification methods is the desire to build from the ground up using engineering and computer programming techniques. Traditional genetic engineering takes existing DNA and inserts DNA from another organism to create rDNA[4]. Synthetic biology techniques can build the base pair sequences from component parts and assemble them from scratch.

A simple computing analogy can be used:

- traditional genetic modification is the process of cutting code from one working program and pasting it into another
- Synthetic Biology involves writing your code from scratch, or editing specific lines of existing code.

SYNTHETIC BIOLOGY WILL ALLOW THE CREATION OF DNA STRANDS THAT ARE NOT CURRENTLY SEEN IN THE NATURAL WORLD.

Synthetic Biology will allow the creation of DNA strands that are not currently seen in the natural world.

Engineering lies at the heart of this new approach and provides a framework into which the disciplines of biology, chemistry and information technology can fit. Proponents believe that joining together these disciplines will be a powerful force for innovation. Those concerned suggest that some of these disciplines, for example engineering, do not put the consideration of ethical issues at the heart of their thinking and that this poses a risk.

Synthetic Biology is in its infancy and the first commercial applications are likely to appear as incremental to traditional genetic modification. However, the next generation of this technology is expected to be very different; inevitably coming with novel risks that must be thought through carefully.

Arguably the first two areas that are likely to see full commercialisation are: the engineering of microbes to create bi-products such as ethanol; and the creation of medicines within the pharmaceutical industry. Depending on the pace of development we might expect to see fully commercialised outputs from Synthetic biologists in full production within the next 10 years.

SOME EXAMPLES OF EXISTING GM USES

Genetic engineers have already succeeded in creating many new organisms or processes. The following examples illustrate the range of activity and benefits these methods produce. However in later sections we will see that many groups are still concerned with these techniques.

Medicine

The first commercial use of genetic engineering was to produce **human insulin** from bacteria to treat diabetes, developed by Genentech and Eli Lilly and Co. in 1982. Prior to the development of GM techniques insulin was produced using a pig or cow's pancreas; the use of this method has declined significantly.

New Materials

Nexia Biotechnologies have genetically altered a goat embryo[5] by inserting spider's genes into the genome in order to develop a goat that produces milk containing the spider silk protein. The milk contains significant quantities of protein and is spun to create a fibre similar to those used in a spider's web. The fibre created is called **BioSteel** which is stronger than steel but lighter than carbon fibre.

Understanding biological processes

Researchers at the South western Medical Centre in Dallas genetically engineered mice so that their fat stem cells would glow green. For many years the location of "progenitor" fat cells (precursors to full grown cells) was not known; by using this technique the researchers were able to find their location. This can now enable them to find their human equivalents and determine how they operate. They hope that therapies can be created to help people with obesity or diabetes.

Crop efficiencies

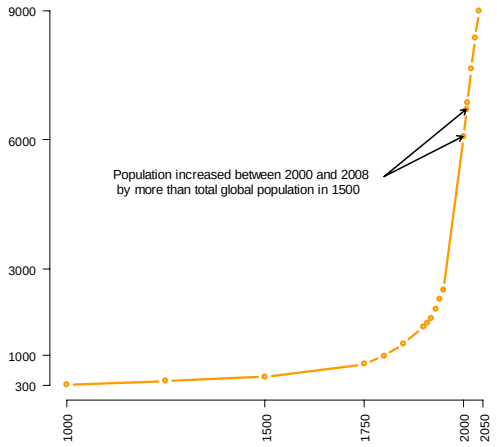
Roundup ready crops: Roundup is the brand name of an herbicide produced by US Company Monsanto. Seeds are also produced which are resistant to this weed killer. Genetically Modified "Roundup Ready" Soya was available in 1996 and Corn from 1998. These genetically modified seeds allow for higher yields.

Flavr Savr: The Flavr Savr tomato was the first GM food to gain a licence for human consumption. First sold in the US in 1994 the tomato was made resistant to rotting by adding a gene which interferes with this natural process. The FDA determined that these tomatoes were "substantially equivalent" to natural tomatoes and, as such, required no specific labelling or pre-approval before sale. This rule contrasts with the requirement for food additives which must be pre-approved. In order to make the modification easily identifiable another "marker" gene was added. Whilst this may seem a prudent step, the chosen marker actually conferred resistance to the antibiotic kanamycin. Experiments led to concerns that might lead to antibiotic resistance in certain bacteria. Also some scientists had concerns that the tomatoes were not necessarily safe following experiments that suggested that stomach lesions may be caused. Ultimately the tomatoes were withdrawn having been sold in only a few US states. This example illustrates amongst other things that public opinion is critical to the success of food products.

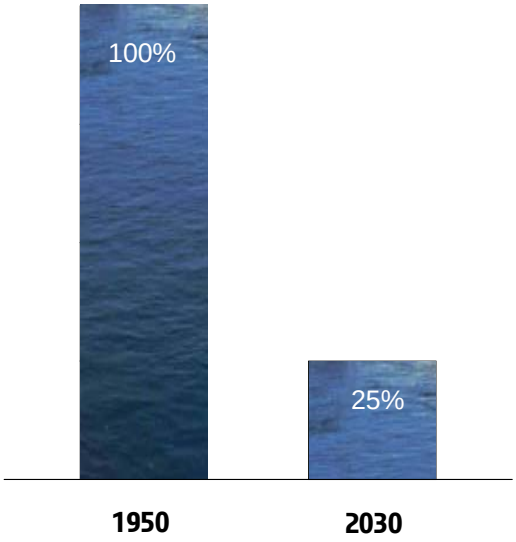
PUBLIC OPINION IS CRITICAL TO THE SUCCESS OF FOOD PRODUCTS

SCARCITY TRENDS WILL DRIVE THE USE OF NOVEL TECHNOLOGY

GLOBAL POPULATION SINCE 1000AD



PER CAPITA WATER PROJECTIONS



The attitude of the general European public to Genetically Modified food can be characterised as one of suspicion. Nevertheless there are good reasons to believe that GM food will become mainstream around the world over the next few decades.

Although poverty levels fell between 1990 and 2000 there are still 850m undernourished people, with around 160m in what is termed “ultra poverty” meaning they live on less than 30p per day. Yet net population growth exceeds 6m people per month. By 2050 global population is expected to exceed 9bn and by 2030 estimates suggest that 60% of the global population will be urban dwellers. Without careful management food shortages are likely. Many believe that GM crops are a key solution to this problem. Looking around the world in sub-Saharan Africa total food production has increased but this has been due to conversion of previously non - arable land into farmland. Conversely in Asia, yields have increased without using more land due to the use of scientific farming methods.

As wealth grows, so does the demand for meat which increases demand for grain for feed. One billion people rely on fish for their primary protein source and one third of the animal production globally comes from the oceans, seas, rivers and lakes. Yet 75% of marine stocks are over exploited often beyond legal limits. One in three people are facing water shortages with per capita water availability projected to fall to one quarter of 1950 levels by 2030.

As people come out of poverty they will wish to use more energy. Yet mitigation requirements for climate change will require us to use less fossil fuels; hence there will be a strong desire for biological sources of fuel that are more efficient than those available today.

In summary, despite significant decreases in fresh water supply, reductions in availability of food and constraints on sources of energy and carbon dioxide emissions we can expect a 50% increase in energy demand, a 50% increase in food demand and 30% increase in water demand.

Adding to these concerns: a number of disease resistant crops developed by selective breeding around 50 years ago are becoming susceptible to new strains of disease (such as stem rust). As sea levels inexorably rise, water tables are rising too and becoming more saline in some cases.

There will be a very strong urge to use new technologies to solve these problems. Many scientists believe sugar density can be increased to improve the efficiency of biofuels; crops can be made salt resistant; crops to produce fertiliser for the next year’s crop can be developed; yields can be increased; disease resistance can be improved.

CASE STUDY BIOFUELS

BACKGROUND: Fossil fuels are based on long dead plant or animal matter; biofuels conversely use live or only recently dead materials. They have the potential to avoid contributing excess carbon dioxide to the atmosphere, unless significant energy is required in their production. Given the urgent need to mitigate climate change through a reduction in the use of greenhouse gasses there is a strong desire to develop large scale biofuel production in a sustainable way. Many also see biofuels as providing energy security. It appears that one of the first commercial uses of synthetic biology will be as part of the production process of these fuels. In most cases biofuels are biodegradable so do not harm the environment in the long term, if accidentally released.

FIRST GENERATION BIOFUELS: Whilst there are several variations there are two main processes: (i) those that extract sugar or starch from crops and then, using yeast, ferment them into ethanol and (ii) those that extract vegetable oils and then either burn these directly or convert them to biodiesel. The raw materials can also typically be used for either human or animal food; therefore there is a concern that overuse of this type of biofuel may lead to an increase in the price or even availability of food.

SECOND GENERATION BIOFUELS: These use the component of crops that cannot be used for food (for example stems, some leaves and husks) or use whole plants that are not used in the human food chain. These components typically contain tough woody material (cellulose or lignin) and are difficult to break down into fuel. Processes involve the use of chemicals or enzymes to break the raw materials into sugars which can then be fermented. This technology is often still in the developmental phase. Recently a new fungus (Gliocladium roseum) has been discovered in the rainforests of Patagonia which converts cellulose to molecules very similar to those in biodiesel; underlining the importance of preserving the rainforests and their, mostly unexplored, biodiversity.

THIRD GENERATION BIOFUELS: These create fuel from algae (including sea weed). They have a benefit over second generation fuels because the raw material need not stress freshwater resources and indeed can be based in the oceans. The algae are relatively easy to grow but the oil can be difficult to extract. Some have suggested that up to 30 times as much fuel per acre can be produced compared to second generation fuels so if this technology can be commercialised it could be highly successful. At the moment the costs appear prohibitive but if, as many expect, the cost of oil rises or the processes become cheaper the technology could be become viable.

USES OF SYNTHETIC BIOLOGY: Recently [6] scientists have synthesised new enzymes that can break down cellulose into sugar. Until their groundbreaking work only 10 similar, fungal based, enzymes were known; they have added another 15 to this. Their process involved creating 6000 new gene sequences in a computer based environment and, using models, finding which of these would have desirable characteristics (such as being able to withstand heating). Those thought to be promising were then physically created (by a company DNA2.0). The designer DNA was then inserted into yeast cells which then produced the enzymes as a by-product. This example is one of many processes that being researched. It is not clear how ownership issues and the use of patents will work in this field. Companies are currently attempting to assert their rights at various stages of the process and some fear this will significantly hold up development; others are uncomfortable with the idea of “owning life”.

PUBLIC OPINION: In a recent survey of around 1000 adults by the UK Royal Academy of Engineering[7] researchers found support from the public for the use of synthetic biology to create new micro organisms for biofuels; however fewer of them liked the idea of modifying existing life forms. Ironically the latter option is more likely to be used in the short term. The survey also found that the lay public struggled to understand the concept of synthetic biology and were very wary of processes that could damage the environment.

RAPESEED

PALM OIL

SUGARCANE

CURRENT REGULATIONS

While not an exhaustive review of the various GMO regulations around the world the notes below cover institutions with a global focus, then three regional examples are given in the United States, Europe and Japan. We intend to illustrate the plethora of approaches, and that in many cases there is more than one regulatory body involved within a region. There is a concern that this can lead to a lack of focus and ownership. Some are calling for more coordination from a single body; much as the Nano Coordination Office does for nano-technology in the US.

IN MANY CASES THERE IS MORE THAN ONE REGULATORY BODY INVOLVED WITHIN A REGION.... THERE IS A CONCERN THAT THIS CAN LEAD TO A LACK OF FOCUS AND OWNERSHIP

The recently published report "New Life, Old Bottles"[8] from the Woodrow Wilson Centre in the US points out the "goldilocks dilemma" facing regulators: that processes must be neither too precautionary (and suppress innovation) nor too business friendly (and perhaps invite unexpected risk), but "just right". Whether Synthetic Biology requires specific regulation or is seen as a variant of other forms of GM organisms needs more debate. One thing seems clear – the regulatory process should require developers to consider unconventional and low probability risks as part of their scenario planning and risk mitigation process. The data required for a traditional risk appraisal may be lacking, in which case a precautionary approach seems appropriate whenever the potential risks are high.

The regulatory system in the US has allowed many products to be produced including over 200 new therapies and vaccines. The USDA and EPA have reviewed and approved thousands of field trials over the past 25 years. Containment methods have had a long and generally safe history. However, the problem with such a "track record" is that a short history is, by definition, not likely to contain an extreme adverse event (for example one with 1 in 200 probability). These are often described as "Black Swans"[1,][9]; the key question is whether the good safety record is due to good regulation; prudent experimentation; or just statistical shortcomings of a short historical record.

THE KEY QUESTION IS WHETHER THE GOOD SAFETY RECORD IS DUE TO GOOD REGULATION; PRUDENT EXPERIMENTATION; OR JUST STATISTICAL SHORTCOMINGS OF A SHORT HISTORICAL RECORD

The mad cow disease food crisis (Bovine spongiform encephalopathy) which hit the headlines in the late 1980s in the UK led to a drop in EU public confidence in the food industry. The Woodrow Wilson Centre report, mentioned above, suggests this was one of the factors causing the EU to largely reject GM food. BSE highlights that the use of processes thought to be safe (i.e. feeding herbivores the meat products which were left over from the slaughtering process) can in due course be shown to give rise to unintended and unwanted effects. Such issues can lead to a social tipping point and underscore the importance of public engagement, including education as a prerequisite, in new technologies. The example of the US and EU show how outcomes can depend on how the technology is presented. In the US regulators accepted that rDNA organisms are just a next step; an incremental change from their natural counterparts; they are "substantially equivalent". Whereas in the EU, rDNA organisms are thought of as "new"; requiring their own, more precautionary, regulations.

Although there have been no major health scares; there has been unexpected gene flow from both approved and experimental GM crops

[1] Until the discovery of Black Swans in Australia, the statement "all swans are white" had an unquestioned track record in Europe for thousands of years.

into conventional food, sometimes leading affected farmers to have to dispose of “contaminated” crops at great expense.

Global guidelines

The **World Health Organisation (WHO)**[10] works with the **Food and Agriculture Organisation of the United Nations (FAO)**[11] to propose international food standards. The WHO has stated that it will work on four major areas related to biotechnology:

> *“A. Establishing scientific safety assessment frameworks based on sound science*
>
> *B. Standardising methods for nutritional aspects in safety assessments of food derived from modern biotechnology.*
>
> *C. Linking risk assessments to risk management and communication.*
>
> *D. The broader perspective of health and development policy”*

The FAO seeks to provide “sound and unbiased advice” on the safety of GM food. In particular it aims to consider the risks and benefits of GM food using a science based methodology. It is also concerned with appropriate labelling of GM produce and determining nutritional impacts of such food.

The **Codex Alimentarius Commission (CAC)** is an intergovernmental body created to implement the Joint FAO/WHO Food Standards Programme which was established by an FAO Conference resolution in 1961 and a World Health Assembly resolution, WHA 16.42, in 1963. The commission seeks to protect the health of consumers and facilitate trade. It sets international standards on foods.

The **OECD** also has also had a strong interest in biotechnology since the 1980s considering agriculture, health, industry and science. The Directorate for Science, Technology and Industry of the OECD and provides information to policymakers on a number of issues including biotechnology.

United States

The **National Institute of Health (NIH)** in the US provides guidelines[12] on the use of recombinant DNA. These apply to researchers who receive NIH funding and it is important to realise these do not apply to privately funded activities unless they opt to be covered. The guidelines themselves state *“The purpose of the NIH Guidelines is to specify practices for constructing and handling: (i) recombinant deoxyribonucleic acid (DNA) molecules, and (ii) organisms and viruses containing recombinant DNA molecules.”* Non compliance can result in withdrawal of funding. It is the responsibility of the individual scientist or organisation to adhere to the spirit of the guidelines which openly admit they do not cover all foreseeable circumstances. The guidelines are therefore principles based. The NIH requires researching institutions to form an **Institutional Biosafety Committee** which in turn is responsible for assessing the proposed research. Their assessment will consider issues like: containment, expertise of the researchers, training, procedures and practices.

The degree of control required relates to the biosafety risk group.

> "*(1) Risk Group 1 (RG1) agents are not associated with disease in healthy adult humans.*
>
> *(2) Risk Group 2 (RG2) agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available.*
>
> *(3) Risk Group 3 (RG3) agents are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available.*
>
> *(4) Risk Group 4 (RG4) agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available.*"

POTENTIALLY APPLICABLE US FEDERAL LAWS

US Department of Agriculture	Environmental Protection Agency	Food and Drug Administration
National environmental protection act	National environmental protection act	National environmental protection act
Federal meat inspection act	Food, drug and cosmetic act	Food, drug and cosmetic act
Poultry products inspection act	Federal insecticide, fungicide etc act	
Egg products inspection act	Toxic substances control act	
Animal damage control act		
Animal welfare act		
Plant protection act		
Virus serum toxin act		
Animal health protection act		

Source: Woodrow Wilson, quoting Pew Initiative (2004),[20]

The NIH are considering revising the definition of an rDNA molecule in their guidance to be "*Synthetic nucleic acids are nucleic acids that are chemically synthesised or amplified and may solely or partially contain functional equivalents of nucleotides*"; according to a Woodrow Wilson study[8] this will address some perceived deficiencies in the previous definition.

If the product is used in food or medicine then the **U.S. Food and Drug Administration (FDA)**[13] will have jurisdiction. They have a duty to ensure that the products are safe for the public to use. There is a voluntary consultation process to assist developers to meet safety standards. Some argue that the process should be compulsory but the FDA believes that stakeholders are cooperating and this step is not necessary. Many consumer groups have urged for compulsory labelling of food, noting that there is no way to track GM produce. However, the FDA has ruled that there must be something different about the product itself, not the process used to create it.

The **Environmental Protection Agency (EPA)** considers wider environmental impacts of GM crops including the regulation of toxins and pesticides. Plants that have been modified to be herbicide resistant will fall under their jurisdiction.

The **US Department of Agriculture (USDA)**[14] determines whether it is safe to grow GM crops. Many crops that are not regulated by the EPA fall under its jurisdiction including crops that are disease resistant or drought tolerant. The USDA can prevent the import or export of plants and can require their destruction. For example the USDA seized 500,000 bushels of corn which had been contaminated with a small amount of bio-corn from the biotech company Prodigene in 2002; the company was required to purchase the wasted corn. The **Animal and Plant Health Inspection Service (APHIS)** is part of the USDA and ensures the health and care of animals and plants. Its rules cover the import and export of GM animals and plants and their release into the environment.

Synthetic Biology may make the production of bio weapons much simpler. Therefore the **US Department of Energy and Biosecurity** are also watching developments in this field.

Europe

EU Council Directive 2001/18/EC strictly controls the release and marketing of GMOs in the European Union. It requires full risk analysis of GMOs throughout their development. After consent, a GMO can be imported and cultivated anywhere in the EU but is subject to compulsory monitoring and labelling. In the UK 2001/18 is implemented by Part VI of the Environmental Protection Act under the jurisdiction of DEFRA[15].

EC Regulation 1829/2003 requires that a safety assessment be carried out prior to consent being granted for any GM food and feed. A key phrase in this legislation is "*Whilst substantial equivalence is a key step in the procedure for assessment of the safety of genetically modified foods, it is not a safety assessment in itself*" which appears to be contrary to the views of the FDA in the US. **EC Regulation 1830/2003** requires traceability and labeling for all GM produce. The legislation is practical in that it allows for minute traces of GM contained within foodstuffs to be exempt from labeling it includes the phrase "*Traceability requirements for GMOs should facilitate both the withdrawal of products where unforeseen adverse effects on human health, animal health or the environment, including ecosystems, are established …"*

In the UK all GM activities are initially carried out in containment (for example in a laboratory). The **Health and Safety Executive** closely controls this process via Statutory Instrument 2000 No. 2831. The regulations include a requirement to reduce risk to the lowest level reasonable practicable including creation and maintenance of an emergency plan. Accidents must be notified immediately.

The **European Food Safety Authority (EFSA)**[16] has a panel devoted to monitoring of GMOs including food and feed. It also provides guidance on how to carry out a risk assessment as required by 1829/2003.

The UK Biotechnology and Biological Sciences Research Council (BBSRC) held a meeting[17] in September 2008 attended by representatives from the Medical Research Council (MRC), Engineering and Physical Sciences Research Council (EPSRC), regulators and government advisory committee members. The meeting concluded:

*"…**none of the …scenarios suggested a paradigm shift that would necessitate amending the UK's regulatory framework**. However some issues may require particular attention… **The onus is on the applicant to convince regulators and their advisory bodies that the product will not cause harm** to human health or the environment in the context of the proposed use… **participants recognised the importance of transparency** in the UK regulatory framework, including public meetings, and of holistic approaches…. A **precautionary approach** may be appropriate initially in cross-disciplinary areas,… **Products produced outside the EU would need to conform to EU Directives** and domestic regulations if used in Europe.."*

PRODUCTS PRODUCED OUTSIDE THE EU WOULD NEED TO CONFORM TO EU DIRECTIVES

It is interesting to note that the UK Advisory Committee on Releases to the Environment are already considering applications to test synthetic genes outside the laboratory, as discussed in their annual report[18]; according to this report they are treading carefully.

Japan

Japans food sanitation laws require foodstuffs produced by recombinant DNA techniques to be assessed for safety. The **Ministry of Health, Labour and Welfare (MHLW)** receives applications and the **Food Safety Commission** assesses their safety. In April 2001 labelling of GM also became mandatory and is run by the MHLW and also the **Ministry of Agriculture, Forestry and Fisheries (MAFF)**. There have been examples where the Japanese authorities have banned imports because they contain unapproved genetic material[19].

WHAT COULD GO WRONG?

THE NEW TECHNOLOGY AND GROUND UP APPROACH MAY SIGNIFICANTLY INCREASE THE EASE WITH WHICH SUCH GROUPS CAN CREATE HARMFUL PATHOGENS.

Terrorism: Terrorists, are very clearly seeking to do harm. The new technology and ground up approach may significantly increase the ease with which such groups can create harmful pathogens. For many hazardous materials there is international scrutiny of their purchase and transit; however if a terrorist group can mail order the (apparently innocuous) raw materials and assemble viruses or alter bacteria themselves it significantly changes the risk landscape. A UK government paper notes that simply engineering antibacterial resistance into a bacterium significantly strengthens it as a weapon; and we have seen that this technology already exists.

Rush to market: Some stakeholders are concerned that governments are pushing innovation and there is a rush to market the outputs of these new technologies. Large companies and governments have invested significant sums into research and need to get a return on their investment.

Confusion of regulation: As illustrated in the regulation section many government bodies are involved in regulation of biotechnology. However there is no specific regulation for synthetic biology which presents many new features and processes when compared to existing GM methods. The emerging field of nanotechnology, the subject of a previous Emerging Risks report, has a National Nanotechnology Coordination Office which is a key point of contact for government, industry and academia. There is no equivalent for synthetic biology.

Self regulation aims: The Synthetic Biology industry has a preference for self regulation[20], some protagonists even suggesting that early regulation will kill innovation. Yet early GM industry examples suggest that it is very difficult for an industry to take account of the concerns of all stakeholders.

Engineering and ethics: Synthetic Biology borrows heavily from engineering and ITC using terms like: design, modelling, construction even “debugging”. The concept of ethics is not central to professional education in these fields. There is no doubt that they aspire to carrying out a “professional” job that is error free. Their methods tend to consider the robustness of components on a case by case basis. But Synthetic Biology is about biology, it is about ecosystems and has social and public safety implications. Some observers we have consulted are concerned that the mindset of those involved does not concern itself with these wider issues.

THE INCREASINGLY EASY AVAILABILITY OF DESIGNER AND MAIL ORDER DNA LEADS TO A CONCERN THAT A BIO-HACKER MIGHT GENERATE A REAL VIRUS.

Hackers and real viruses: In the computing world we have seen “hackers” produce viruses just for the kudos of having disrupted global trade. It is to be hoped that developers in the bio-industry will be more responsible when physical health is concerned and there is certainly no evidence to suggest the contrary. The point is that if it is possible then there is a risk. The increasingly easy availability of designer and mail order DNA leads to a concern that a bio-hacker might generate a real virus. In IT systems a whole industry has grown around virus checking data as it moves around the virtual world. Physical checks do not appear to be this well developed; yet are surely even more important.

Creation of monopolies: Many NGOs and governments in developing countries are concerned that GM seed in general (possibly exacerbated by Synthetic Biology) can lead to monopolies amongst major seed producers. Whilst these companies' intentions may be benign this issue can still lead to international political tensions.

Unexpected gene transfer: Although efforts are made to prevent the unwanted transfer of genes from GM crops to other species this has been shown to occur by a number of routes. Viruses can affect GM crops, they can then "cut out" a portion of altered DNA and then when transmitted to other plants can "paste" the altered DNA back into their genetic code; this is called "horizontal transfer". Pollen can drift for several kilometres on the wind or be carried long distances by insects. Wild relatives of certain crops can hybridise with their GM cousins and produce a wild version with the unwanted gene. The sorts of questions that must be asked include "Might the use of animal tissues in humans cause a dormant retrovirus to reactivate?"

Unexpected release: GM organisms may be released into the environment by mistake. The term "bio error" has been used to contrast with "bio terror" in this case. A recent example of this was seen in the UK in 2007. The Pirbright laboratory centre held 5000 strains of the Foot and Mouth Virus which escaped from a broken pipe after localised flooding causing an outbreak of the disease in Surrey. Such a release could (for example if a new virus escaped) lead to harm to employees even if the outbreak was contained.

Evolution: GM organisms may behave as we expect in the short term; but organisms evolve. In the lab if properly contained this may not be an issue, we can replace one culture with another. However, once released into the environment we do not know how GM organisms may develop. How will a GM crop react to an unexpected disease? Will they be as able to survive in the wild as their natural counterparts? This is specifically relevant for Synthetic Biology with its search for "minimal genomes"; perhaps the DNA that is not thought to be "needed" helps confer resilience? Do they have any natural counterparts?

We don't fully understand: Great credit is due to scientists working in this field. They have pushed forward our understanding of biology significantly. But we are far from understanding how genomes work. A good example is the recent ENCODE project under the National Institute of Health in the US. Prior to this study, scientists believed that much of our DNA was "junk", carried over from previous epochs in our evolution. The study showed that in fact the genome is a complex system and "genes" could not really be identified with segments of DNA. This has resulted in a complete rethink of how DNA interacts with itself and the other components of the cell. This is how science works; we have a theory for a period and then new information causes us to change our mind. The danger is that we take action based on our understanding now to find later that there were unintended and unimagined consequences. It is possible that two or more benign strands of DNA will interact so that the risk is far greater than the sum of the parts. In the lab this risk is, arguably, containable; even in a contained industrial process it is manageable; but loose in the environment the risks are far greater.

Courtesy: National Human Genome Research Institute

Ecosystem effects are hard to predict: It is hard enough to predict how a single strand of DNA will behave when a new gene is inserted. Even harder to consider how it will affect a cell or whole multicellular organism. But the difficulties in predicting how an ecosystem will behave are staggering. Weeds may, conceivably, inherit herbicide resistance from

GM crops and then become more difficult to control than before. Insect populations may be affected adversely. Bacteria, as described earlier, may inherit immunity to our usual methods of control. Synthetic organisms may infect or displace natural ones; they may find a new niche and become hard to eradicate. The future is uncertain and just because something hasn't happened yet does not mean it cannot happen.

Moral and ethical issues, the backdrop to litigation: Genetic modification is a highly emotive subject. Certain environmental and religious groups are deeply opposed to "playing God". Some perceive that the public does not gain much with the profits going to industries; yet in the event of a serious systemic event the public, and possibly the insurance industry, bears much of the risk. This asymmetry of outcome is a source of dissatisfaction for some groups. Some farmers are concerned that "patenting life" will disenfranchise them. A company (and its directors) that spends significant sums of shareholder money only to find that the public will not purchase food containing Synthetic DNA may find itself a target for legal action if people were to conclude that market testing should have been carried out in advance. Some regions have embraced GM methods, others have banned them. There appears to be a disconnect between societal opinion on GM and those developing it; this is likely to be amplified with Synthetic Biology.

SUGGESTED ACTIONS

Synthetic Biology is a nascent technology. However, it is rapidly growing and we can expect significant developments over the next 10 years. Now is the time for the insurance industry to play a role in the much needed debate on risk management of this technology. Several individuals and organisations including Denise Caruso[21],[22] from the Hybrid Vigour institute and the Woodrow Wilson International Centre for Scholars[8] are calling for a variety of actions which will help to better manage these risks. Several of the following suggestions are closely based on their recommendations, which we support:

Map uncertainty and fill knowledge gaps: a process should be instigated to map all known uncertainties in this field. Traditional Genetic Modification methods should be included in this as well as the new risks posed by Synthetic Biology. Once these "known unknowns" are articulated, programs of research should be set up to fill the knowledge gaps. More research budget should be spent on understanding risk levels. A starting point would be to produce a comprehensive review of existing literature. The practice of using high dosage as a proxy for long term exposure when testing in labs may not be appropriate.

Consider existing regulations: given the variety of regulation globally it would be useful for countries to consider a harmonisation of regulations. This would also be an appropriate time to consider whether existing regulation is appropriate for Synthetic Biology. It would be appropriate to include Nanotechnology in this review as they share many of the same issues.

Plan for unintended consequences: Risk assessments must consider the impact if all controls fail. If the consequences to the ecosystem are potentially severe then contingency plans should be put in place to limit damage. In the most extreme cases it must be questioned whether the risks are worth taking; even if the probabilities are low. For organisms that are planned to be released into the environment this is particularly critical.

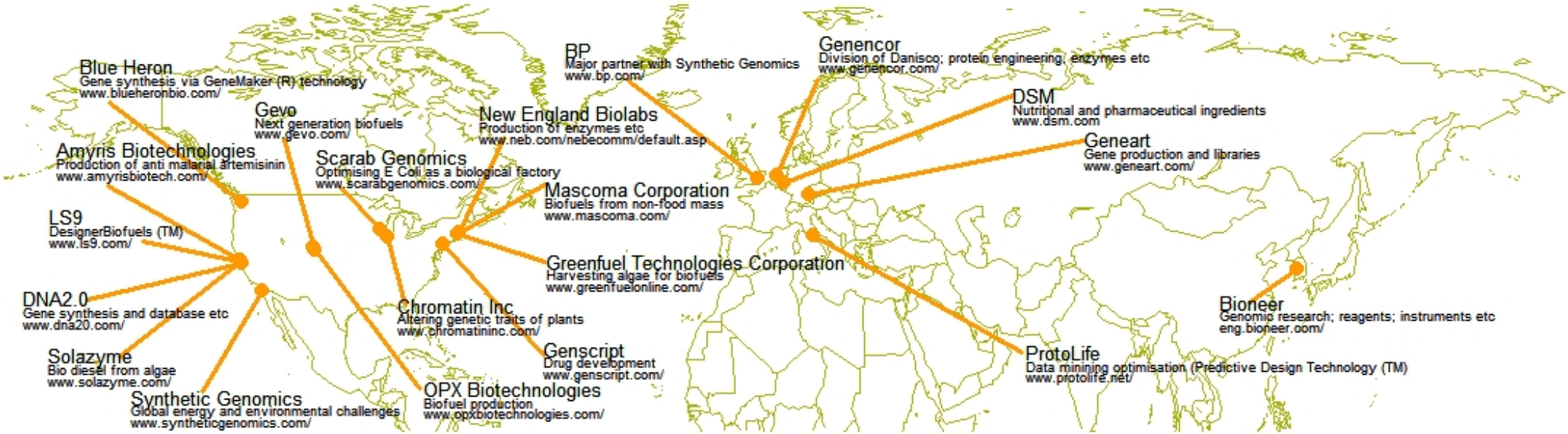
Risks should be tracked: The long term impacts of GM are hard to assess. It must be possible, in today's highly computerised and networked age, to track the use of Synthetic Biology and an international system of tracking and labelling should be agreed. Labelling will give consumers choice and may reduce litigation costs if damages arise.

Run focus groups involving all stakeholders: A common complaint is that that the views of all stakeholders are not taken into account and indeed there is little debate at all. Focus groups involving all stakeholders including: the public, biotech industry, developing countries, governments, insurers, and scientists, should be held by policymakers to ensure that all views are understood. It is important that cross disciplinary groups are encouraged to meet for example those engaged in anti-terrorism and those offering mail order DNA services.

Consider policy limits: Insurers should consider the extent to which they wish to be exposed to such systemic risks. It is likely that a "working layer" of cover can be provided; but the enormity of some adverse scenarios suggests the inclusion of various forms of sub-limit in the future. A number of product lines could conceivably be affected, including: crop, Public Third party liability insurance (general), terrorism (biological), war, pollution, product contamination, product recall, health, life, medical malpractice and blood products. For now keeping a close watch on developments is an appropriate action

COMPANIES INVOLVED IN SYNTHETIC BIOLOGY

SOME EXAMPLES



Sources: [8] and [23]

CONCLUSIONS

The technology to genetically modify organisms has been available since the 1970s. Recently a new technology “Synthetic Biology” has begun to be developed which will greatly increase our power to shape life. The time required to decode genetic information has reduced rapidly in recent years and the new “engineering” techniques allow scientists to create genetic code from the ground up; to “synthesise” life. These new methods, still nascent, may allow organisms to be created or modified with no parallel in nature and this is both a great opportunity and a risk that requires careful management.

Synthetic biology may have the power to transform society. Possible (and widely hoped for) uses include: adapting bacteria so that they produce critical drugs (including vaccines), or biofuels as a by-product of their metabolism and harvesting these on a large scale; modifying plants to become higher yielding, salt tolerant or heat resistant, understanding biological processes better and modifying viruses so they can deliver drug treatments in a very targeted way. Global projected scarcity trends such as water shortages, climate change, population growth, food/energy security and urbanisation will fuel the desire to use this new technology; as will the need to get a financial return from significant investments in research.

There is a concern that current regulations are too disjoint to manage the risks of these novel technologies. There are differences in the regulatory approach to traditional genetically modified crops and animals across the world; and the perception of society in these regions also differs. Global consistency on: monitoring, assessing risk, tracking use and labelling of products would be desirable.

Although the potential societal benefits are many, varied and significant there are valid concerns about this new technology on several levels. Not least that there doesn’t seem to be a healthy debate, across a spectrum of key stakeholders, on which of the risks are worth taking and which are not. Concerns include: whether the ease of generating new DNA from innocuous raw materials may make bioterrorism easier and cheaper to carry out and whether accidental or deliberate release into the wider environment could lead to unforeseen adverse ecological or health impacts. There are religious or ethical concerns over “playing god”, which need to be discussed and addressed. If the new technology is commercialised, a number of liability impacts could arise leading to potential litigation if things go wrong. In turn this could conceivably lead to claims against insurance policies providing cover against liability; though it is far too early to explore this possibility in detail.

Action can be taken now to support the responsible development of these technologies. These include mapping knowledge gaps and attempting to fill them; planning robustly for unexpected consequences and considering extreme scenarios as part of this process; review existing regulations and aim for a precautionary and consistent global approach. Insurers should consider whether they wish liability products to be exposed to large scale aggregating events and, if not, whether limits should imposed or other policy amendments made. Most of all, we should take part in a broad debate on the use of this new technology before it becomes embedded.

SOURCES OF INFORMATION

The following were useful sources of information used when drafting this report. Links are shown for ease of use and were valid at the time of publishing the report:

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[23] Synthetic Biology: Scope, applications and implications, royal academy of engineering. http://www.raeng.org.uk/news/publications/list/reports/Synthetic_biology.pdf

PICTURES

Rape oil picture http://commons.wikimedia.org/wiki/File:Brassica_napus_2.jpg

Palm oil picture http://en.wikipedia.org/wiki/File:Palm_oil_Ghana.jpg

Sugarcane picture http://upload.wikimedia.org/wikipedia/commons/2/29/Cut_sugarcane.jpg

Chromosome picture from http://en.wikipedia.org/wiki/File:HumanChromosomesChromomycinA3.jpg

DNA picture : http://en.wikipedia.org/wiki/Image:DNA_Overview.png

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