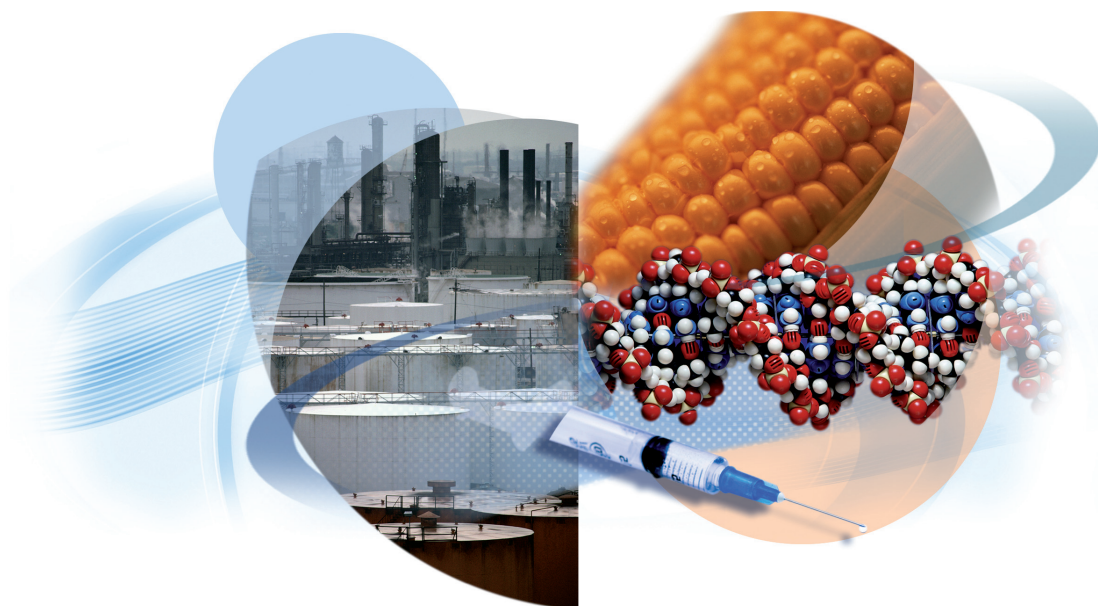


# Consequences, Opportunities and Challenges of Modern Biotechnology for Europe

Eleni Zika, Ilias Papatryfon, Oliver Wolf, Manuel Gómez-Barbero,  
Alexander J. Stein, Anne-Katrin Bock

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## ■ Preface

Biotechnology is often considered to be one of the key technologies that will help enable the long-term sustainable development of the European Union (EU), particularly in terms of economic growth, environmental protection and public health. However, despite the high levels of research funding, both public and private, and the high expectations, especially regarding biotechnology-enabled medical advances, there has been a lack of reliable information on the contribution that biotechnology is really making and on its economic, social and environmental consequences.

The “Bio4EU study”, which had its origins in a request from the European Parliament, intends to contribute to closing that knowledge gap.

The study was developed by the European Commission’s Joint Research Centre (JRC), working in harmony with a group of other services of the Commission concerned with biotechnology, and coordinated by the Commission’s Secretariat-General. The work was led by a team at the JRC’s Institute for Prospective Technological Studies (JRC/IPTS). Much of the data was gathered by the European Techno-Economic Policy Support Network (ETEPS), a consortium of highly regarded European policy studies institutes linked to the JRC/IPTS, which also provided valuable input to the analysis.

Throughout the study, the JRC has involved stakeholder groups, keeping them abreast of progress and inviting them to provide input and comments. We are grateful for their participation. Also, a public website (<http://bio4eu.jrc.es/>) has provided a wider platform for publishing up-to-date information on the study and for receiving feedback.

I would also like to thank the Bio4EU Advisory Committee of distinguished scientists, chaired by Professor Patrick Cunningham, for their support. They have followed the study from its beginning and have been instrumental in guiding it to a successful conclusion.

The present document, the Bio4EU synthesis report, sets out the main findings of the study. It presents the first comprehensive picture of the applications of modern biotechnology and their contribution to the EU’s chief policy goals. We hope that it will become a valuable basis for a better understanding of biotechnology and its impacts and challenges. It has already been used by the Commission to help draw up its mid-term review of the EU Strategy on Life Sciences and Biotechnology.

For those wishing to delve into this interesting subject in more detail, the full report and all its supporting documents can be found on our Bio4EU website (<http://bio4eu.jrc.es/>).

Roland Schenkel



## ■ Executive Summary

This report sets out the main findings of the Bio4EU study. It is based on a series of more detailed background documents that are available on the Bio4EU website (<http://bio4eu.jrc.es/>). The study provides the first comprehensive evaluation of the contributions that modern biotechnology is making in the context of major European Union (EU) policies.

### The policy context

The study was set in the context of the EU's **Lisbon Strategy** and **Sustainable Development Strategy**. At its March 2000 Lisbon summit the European Council endorsed the objective of making the EU “the most competitive and dynamic knowledge-based economy in the world, capable of sustainable economic growth with more and better jobs and greater social cohesion”. In 2005 the Lisbon Strategy was refocused on economic growth and more and better jobs<sup>1</sup>. In 2001, one year after the Lisbon summit, the Sustainable Development Strategy was adopted by the Gothenburg European Council, complementing the Lisbon Agenda<sup>2</sup>. It was revised in 2005, identifying key challenges such as climate change, clean energy, public health and sustainable consumption and production<sup>3</sup>.

Biotechnology in general, and **modern biotechnology**<sup>4</sup> in particular, is considered **one of the key enabling technologies of the 21st century** to support the Lisbon Strategy and sustainable development. However, there are few data on the actual availability and uptake of modern biotechnology products and processes. As a result, there is a lack of reliable information on the contribution that modern biotechnology is making to the Union's objectives.

### The genesis of the Bio4EU study

Against this background, in response to a request from the European Parliament, the European Commission decided to carry out **a study assessing applications of modern biotechnology**. The study was designed to provide input for the reflection on the role of life sciences and biotechnology in the renewed Lisbon Strategy and to help increase public awareness and understanding of them<sup>5</sup>.

- 1 European Commission (2000) DOC/00/7: The Lisbon European Council – An agenda of economic and social renewal for Europe. Contribution of the European Commission to the special European Council in Lisbon, 23-24 March 2000; European Commission COM (2005) 24: Communication to the Spring European Council – Working together for growth and jobs – a new start for the Lisbon Strategy.
- 2 European Commission COM (2001) 264 final: Communication from the Commission – a sustainable Europe for a better world: a European Union Strategy for Sustainable Development (Commission's proposal to the Gothenburg European Council).
- 3 European Commission COM (2005) 658 final: Communication from the Commission to the Council and the European Parliament on the review of the Sustainable Development Strategy – A platform for action.
- 4 Modern biotechnology can be defined as use of cellular, molecular and genetic processes in production of goods and services. Its beginnings date back to the early 1970s when recombinant DNA technology was first developed. Unlike traditional biotechnology – which includes fermentation and plant and animal hybridisation – modern biotechnology involves a different set of technologies, including industrial use of recombinant DNA, cell fusion and tissue engineering amongst others.
- 5 European Commission COM (2005) 286 final: Report from the Commission to the European Parliament, the Council, the Committee of the Regions and the European Economic and Social Committee Life sciences and biotechnology – a strategy for Europe. Third progress report and future orientations.

The study was conducted between autumn 2005 and spring 2007<sup>6</sup> under the leadership of the European Commission's Joint Research Centre. It focused on current applications of modern biotechnology in its three main fields: medicine and health care; primary production and agro-food; and industrial production processes, energy and the environment.

## Modern biotechnology in medicine and health care

Human medicine and health care is the most prominent field of application of modern biotechnology, as the high share of biotechnology publications and patent applications targeted at this sector confirms. Modern biotechnology has widespread applications in human medicine and health care which make a significant contribution to the EU economy. Modern biotechnology directly contributes to around 0.04% of the EU's gross value added (GVA)<sup>7</sup> (based on 2002 data). The main product groups are:

- biopharmaceuticals, with a share of 9% of turnover from all pharmaceuticals in the EU in 2005. Examples include recombinant insulin or monoclonal antibodies for cancer treatment;
- recombinant vaccines, with a share of 17% of turnover from all vaccines in the EU in 2005. Most recombinant vaccines are targeted at hepatitis B;
- modern biotechnology-based *in vitro* diagnostics (IVD), mainly immunoassays and nucleic-acid-based tests, with a share of about 30% of turnover from all IVD in the EU in 2005. Examples include detection of HIV by nucleic-acid-based tests and cardiac diagnostic assays for detecting biomarkers associated with heart attacks.

Beyond that, modern biotechnology provides **powerful tools for research and development** work on biopharmaceuticals, but also on small molecule drugs, vaccines and diagnostics. These and indirect effects stemming from use of modern biotechnology products and the potentially improved state of health of EU citizens would add to the contribution to GVA.

The USA takes the largest market shares (in terms of value) for biopharmaceuticals, vaccines and modern biotechnology-based *in vitro* diagnostics. However, the similar numbers of modern biotechnology products available on the EU and US markets indicate that EU citizens are also able to reap **the benefits which modern biotechnology can yield**, for example:

- unique therapeutic and diagnostic solutions (e.g. enzyme replacement therapy and genetic testing);
- unlimited supplies of potentially safer products (e.g. insulin and hepatitis B vaccine);
- superior therapeutic and diagnostic approaches (e.g. monoclonal antibodies and cardiac diagnostic assays).

Mounting **health care costs** are a challenge for many European health care systems. Applications of modern biotechnology could contribute to reducing health care costs by virtue of their superior cost-effectiveness over alternative products. Often, however, appropriate cost-effectiveness studies are missing or no alternative treatments are available. Apart from a few examples, such as nucleic-acid-based HIV testing which appears to be cost-effective, a conclusive overall assessment is therefore difficult.

6 The ETEPS network carried out a large part of the data gathering and provided input to the analysis, whereas DG JRC/IPTS was responsible for design and coordination of the study and overall data analysis.

7 Modern biotechnology can be either a core technology or just a supporting technology in production processes or products. In every application of modern biotechnology, 100% of the product value added or turnover was considered a contribution by modern biotechnology.



Modern biotechnology products tend to be relatively high-value products. For example, biopharmaceuticals and recombinant vaccines are dynamic market components displaying higher average growth rates than conventional products. The EU shows less development activity on biopharmaceuticals: only 15% of the biopharmaceuticals currently available were developed by EU companies compared with 54% by US companies. Moreover, US companies have about twice as many drug candidates in clinical trials as EU companies, whereas the share of biopharmaceuticals out of all drugs in clinical trials has been similar in both regions in recent years.

## Modern biotechnology in primary production and agro-food

Modern biotechnology affects large parts of **primary production and the agro-food sector**. It is mainly applied in the input sectors and contributes to 13% to 23% of their turnover and 0.01% to 0.02% of the EU's GVA (based on 2002 data). This includes:

- breeding and propagation of crops, livestock and fish, e.g. use of genetic markers, genetic modification and embryo transfer;
- feed additive production, e.g. the amino acid lysine and the enzyme phytase;
- veterinary and food diagnostics, e.g. detection of BSE<sup>8</sup>, salmonella, genetically modified crops and food;
- veterinary vaccines, e.g. for pseudorabies eradication;
- enzymes for food production, e.g. in fruit juice production.

However, uptake of modern biotechnology depends on the application and subsector. The EU holds **large shares of the global markets** for which biotechnology-derived products are relevant (e.g. breeding and propagation material, veterinary products and feed additives), with the notable exception of GM crops. Use of biotechnology-derived products further downstream by the EU agro-food sector contributes to about 32% to 38% of its turnover and to 1.3% to 1.55% of the EU's GVA (based on 2002 data).

**Modern biotechnology-based veterinary and diagnostic applications** help to monitor and control some of the major animal diseases (e.g. pseudorabies or foot and mouth disease), zoonoses and food safety concerns (e.g. salmonella and BSE) and maintain consumer confidence (e.g. GMO traceability).

The applications of modern biotechnology in primary production and agro-food mostly affect production efficiency, leading to **lower use of resources and emissions** per unit output (e.g. improved crop varieties or phytase and the amino acid lysine in feed additives).

## Modern biotechnology in industrial production, energy and the environment

**Industrial biotechnology** (including modern biotechnology in industrial production processes, energy and the environment) in EU manufacturing industry is currently limited to specific processes and individual steps in the production process, including:

- textile finishing (e.g. enzyme-based de-sizing of cotton fabric);
- pulp and paper manufacturing (e.g. enzyme-supported pulp bleaching);
- detergents (e.g. enzymes in laundry and automatic dishwasher detergents);

8 BSE: bovine spongiform encephalopathy.

- certain chemical products, e.g. enzymes, biotechnology-based polymers, antibiotics, amino acids, drug compounds (individual steps in the production process or fully biotechnological production);
- bioethanol production.

In bioremediation, approaches based on traditional biotechnology still predominate.

Industrial biotechnology contributes to around 0.08% of the EU's GVA (based on 2002 data, without the chemical sector, due to lack of data, and without food processing, which is included in the agro-food sector). However, **wherever industrial biotechnology is applied it has positive economic and environmental implications:**

- industrial biotechnology increases labour productivity by 10% to 20% compared with conventional processes;
- industrial biotechnology reduces energy and water consumption and emissions, including the greenhouse gas CO<sub>2</sub>.

The EU is the leading producer of enzymes (75%), the prerequisite for many industrial biotechnology processes. However, in many industrial applications of biotechnology the USA (e.g. bioethanol and biotechnology-based polymers) and Asian countries, in particular China (chemicals), are outperforming the EU or strongly increasing their market shares.

## The economic, social and environmental impact of modern biotechnology

Overall, **modern biotechnology products and processes are an integral part of the EU economy**, particularly in manufacturing, including pharmaceuticals, agro-food and health care. While some products are invisible to the general public (e.g. use of genetic markers in livestock breeding), others are used on a daily basis (detergents with enzymes and recombinant insulin) or have become a topic of public discussion (e.g. genetically modified crops).

Production and use of products derived from modern biotechnology products **supports the generation of around 1.43% to 1.69% of the EU's GVA** (based on 2002 data). Pharmaceutical R&D and further induced economic benefits would add to this estimate. This is in the same order of magnitude as entire sectors of the economy, such as agriculture (1.79%) or chemicals (1.95%).

Modern biotechnology **bolsters the competitiveness of EU companies**, in particular on more traditional markets, renewing their competitive base, e.g. in breeding crops and livestock or in enzyme production. However, on new expanding markets the EU is often not at the forefront of development, e.g. in the cases of biopharmaceuticals, bioethanol, biotechnology-based polymers and GM crops. Patent applications and bibliometric data confirm this trend. In particular, the USA seems to embark on new developments much quicker and with strong policy support. China and other Asian countries are also strongly increasing their involvement.

Modern biotechnology **contributes to employment**, mainly in the form of "better jobs", reflecting the higher level of training often necessary to develop and deal with biotechnology products and processes. However, by supporting competitiveness, it also helps to safeguard jobs. The effect in terms of "more jobs" is unclear because of lack of data and replacement effects.

Turning to sustainable development in the EU, including both the environmental and the public health aspects, modern biotechnology contributes via a variety of applications. Industrial biotechnology, along with applications in primary production and agro-food targeting **production efficiency, reduces use**

**of resources and emissions.** The energy savings offered by these applications and the potential to replace fossil fuels by renewable sources (bioethanol) address challenges such as global warming and security of energy supply and provide an opportunity to break the link between economic growth and pressure on the environment.

Modern biotechnology in human and animal medicine and in veterinary and food diagnostics provides effective, better or unique treatments and diagnostics and facilitates control of zoonoses such as BSE or salmonella. In this way, modern biotechnology **contributes to reducing the burden which disease places on EU citizens** and potentially supports the health of an ageing population. However, the **effect on health care costs is less clear** because of the lack of conclusive cost-effectiveness studies on several applications of modern biotechnology and the dependence of cost-effectiveness calculations on the specific product and specific indication analysed.

Although modern biotechnology provides a wide range of beneficial applications, some of them also raise **new challenges and concerns that demand attention.** Examples include human embryonic stems cells, use of genetic data for non-medical purposes, animal welfare in R&D and farming, potential environmental risks of new applications or the implications of large-scale use of agricultural food and feed products for non-food industrial purposes. Considering the rapid conversion of advances in research into products and processes, **monitoring of developments in modern biotechnology** seems necessary to identify policy-relevant emerging issues and carefully assess the risks and benefits early on in the process.



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# 1

## Consequences, Opportunities and Challenges of Modern Biotechnology for Europe

### 1. Introduction



# ■ 1 Introduction

Given the potential of modern biotechnology applications in many different sectors, such as biopharmaceuticals, plant breeding, and biotechnological production of chemicals, modern biotechnology is seen as one of the key enabling technologies of the 21st century. At the same time it has contributed to major advances in basic science and is the subject of EU and national research funding programmes. Modern biotechnology potentially offers new opportunities to address many needs and is thus regarded as a major contributor to achieving EU policy goals on economic growth and job creation, public health, environmental protection and sustainable development.<sup>9</sup>

On the other hand, modern biotechnology has raised high expectations, in particular regarding novel therapeutic approaches (e.g. gene therapy), which have not materialised as quickly as anticipated. Furthermore, certain modern biotechnology applications raise new issues and spark controversial discussions involving the broader public (e.g. genetically modified crops, human embryonic stem cells, or use of personal genetic data). However, data on the actual uptake of modern biotechnology by the various sectors and its socio-economic and environmental consequences in the EU is still scarce.

Against this background, and in response to a request from the European Parliament, the European Commission, in its third progress report on the strategy on life sciences and biotechnology, announced that it would carry out this Bio4EU study for two main purposes: *“First of all, an*

*evaluation of the consequences, opportunities and challenges of modern biotechnology for Europe, in terms of economic, social and environmental aspects, is important both for policy-makers and industry. The study would therefore constitute the primary input to [the reflection on the role of the Life Sciences and Biotechnology in the renewed Lisbon Agenda]. Secondly, this kind of independent study should help to increase public awareness and understanding of life sciences and biotechnology.”*<sup>10</sup>

The Commission assigned the “Biotechnology for Europe” (Bio4EU) study to its Joint Research Centre, where the study was carried out by the Institute for Prospective Technological Studies (JRC-IPTS). It focused on current applications of modern biotechnology, i.e. analysing the successful developments of modern biotechnology in the EU until the present day. The study was designed in a way that allows identifying and quantifying as far as possible the economic, social and environmental implications of modern biotechnology applications in different sectors, and the contributions they make to major EU policy goals. A representative set of 29 in-depth case studies provided the basis for the analysis. Data were collected between April and December 2006 by the European Techno-Economic Policy Support Network<sup>11</sup> and JRC-IPTS. Details regarding the methodology are described in Annex 2. Throughout the study, the JRC involved European-level stakeholder organisations to inform about the study and to provide an opportunity for input<sup>12</sup> and

9 European Commission COM (2002) 27: Communication from the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions Life Sciences and Biotechnology – a strategy for Europe.  
10 European Commission COM (2005) 286 final: Report from the Commission to the European Parliament, the Council, the Committee of the Regions and the European Economic and Social Committee Life sciences and biotechnology – a strategy for Europe. Third progress report and future orientations.  
11 European Techno-Economic Policy Support Network (ETEPS; <http://www.etepe.net/>). Participating institutes are listed with the Preface. References to ETEPS reports refer either to the main report or to the application sector specific case study reports in which 28 case studies are presented in detail.  
12 The submissions by stakeholder organisations are available on the Bio4EU website <http://bio4eu.jrc.es/stakeholders.html>.

comments. The Bio4EU Advisory Committee of distinguished scientists, chaired by Professor Patrick Cunningham, provided guidance on the approach, methodology, scope and results of the study<sup>13</sup>.

This report summarises the data gathered and the analysis carried out in the course of the study. The detailed background documents are available on the Bio4EU study website (<http://bio4eu.jrc.es/>).

Chapter 2 will assess the direct and indirect uptake of modern biotechnology and the resulting socio-economic implications for the three main application sectors, i.e. medicine and health care, primary production and agro-food, and industrial production processes, energy and environment. While the analysis of the social and environmental implications is more of a qualitative nature, the economic significance was quantified using a common methodology.

Modern biotechnology may play different roles where adopted, i.e. it may be the core technology employed (e.g. biopharmaceuticals, genetically modified seeds), it may have a key function (e.g. the use of enzymes in individual stages in the textile finishing process), or it may have more of a supportive character in production processes or products (e.g. the use of molecular markers assisting in the breeding of plants/animals). Moreover, the nature of the different applications will affect the way in which adoption may be measured and presented. Thus, in medicine and health care, it is straightforward to reason in terms of shares of products, whereas in agriculture, it is more appropriate to talk about shares of total output. Furthermore, data are available to varying degrees for the different application sectors, data coverage being best for health applications.

The *direct* contribution of modern biotechnology adoption to the EU economy is measured in terms of gross value added (GVA, or turnover if GVA data were not available) attributable to output for which modern biotechnology was used in the production process. The relative contribution of modern biotechnology to the reported GVA/turnover differs depending on its use: it is highest where biotechnology is a core technology, and the GVA generated may be allocated 100% to modern biotechnology; it is lowest where it is a supportive technology, and its main role is in improving the efficiency of production processes and hence overall competitiveness. However, the relative contribution to GVA is usually not quantifiable, so in all cases 100% of the product value added or turnover was considered a contribution of modern biotechnology. The same approach was used to measure the *indirect* contribution to the economy of modern biotechnology adoption, attributable to output for which modern biotechnology-derived inputs were used in the production process: e.g. the use of biotechnology-derived seeds by the farmer, or the use of enzymes in food processing.

In Chapter 3 the prerequisites for the development of modern biotechnology applications in the EU compared to other regions are analysed, based on scientific publication and patent application data and on data on the biotechnology sector.

Chapter 4 discusses the implications of modern biotechnology in terms of contributions to major EU policy objectives such as the Lisbon Agenda and the Sustainable Development Strategy.

Additional information on modern biotechnologies and methodology can be found in the Annex.

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13 A list of members of the Advisory Committee can be found with the Preface.

# 2

Consequences, Opportunities  
and Challenges of Modern  
Biotechnology for Europe

## 2. Modern biotechnology applications and their economic, social and environmental implications



## ■ 2 Modern biotechnology applications and their economic, social and environmental implications

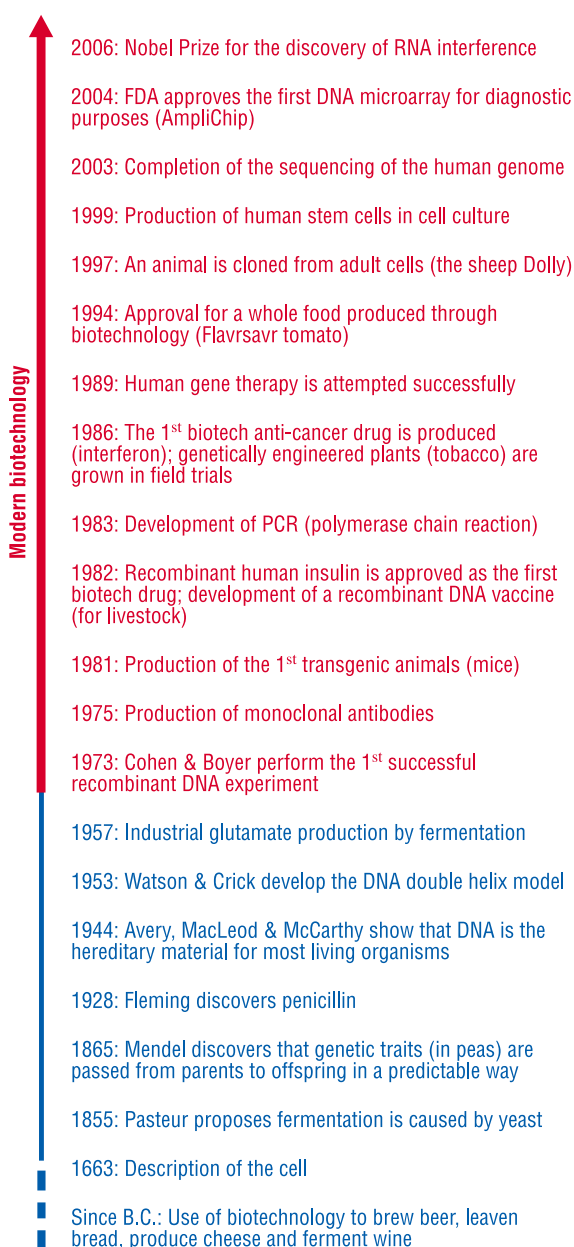
*Biotechnology is “the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services”<sup>14</sup>.*

Biotechnology had its beginnings in the use of microorganisms for making bread or brewing beer millennia ago. Since then the knowledge about biological processes has increased considerably, resulting in many more applications (Figure 2-1). With the development of recombinant DNA technology in the 1970s, which enables the targeted modification of genetic material in organisms, the possibilities for biotechnology applications have enlarged further. This breakthrough marked the beginning of so-called modern biotechnology, albeit encompassing a broader range of technologies used not only in research and development, but also in production. These include technologies for the analysis and modification of DNA and proteins, technologies for the transformation of organic compounds using enzymes, and technologies using cells for repairing biological tissue. Modern biotechnology has contributed significantly to enhancing our knowledge of biological systems, thanks partly to the development of tools for the large-scale analysis of DNA. These tools, also known as micro-arrays or chips, were invaluable for producing the human genome map in 2003, and are now emerging for the analysis of proteins as well.

The biotechnologies considered in this study as modern biotechnology, further refining the above definition of biotechnology, are described briefly in Annex 1. Traditional biotechnology processes, e.g. used in end-of-pipe treatment of contaminated soil or sewage (bioremediation),

are not included. However, combinations of well established fermentation processes with modern biotechnology, e.g. cheese-making using the recombinant enzyme chymosin, are considered.

■ **Figure 2-1 Biotechnology milestones**



14 OECD (2006). OECD Biotechnology Statistics 2006, Paris.



## 2.1 Modern biotechnology in medicine and health care

Modern biotechnology is applied in medicine and health care in **therapeutics**, mainly for the discovery, development and production of novel drugs (biopharmaceuticals, but also small molecule drugs), in **preventives** for the development of recombinant vaccines, and in **diagnostics**, for protein- and nucleic acids based tests (i.e. mainly immunoassays and genetic tests).

Modern biotechnology has a direct impact on the pharmaceutical sector (NACE DG 24.4)<sup>15</sup>, which in 2002 created EUR 58 billion of added value<sup>16</sup>, or about 4% of the total value added of the manufacturing sector (NACE D). In 2003, the pharmaceutical industry comprised 4111 companies in total, with 75% of these located in six EU countries (Germany, France, Spain, Italy, UK, and Poland). The 2006 EU Industrial R&D Investment Scoreboard demonstrates a similar geographic concentration: the majority of the total 64 pharmaceutical companies included in the top 1000 EU companies, ranked by R&D investment, were located in Germany (11), the UK (22) and France (9). According to Eurostat, these countries are also the largest producers of pharmaceuticals in terms of value-added. The production value of the EU pharmaceutical industry has grown steadily since 1993, at a higher growth rate than the average of the chemicals sector,<sup>17</sup> and its trade surplus in 2004 was more than EUR 32 billion, having increased almost five times since 1990<sup>18</sup> (USA, Switzerland and Japan being the top three trading partners).

### 2.1.1 Biopharmaceuticals

Biomedical research has increased our understanding of molecular mechanisms of the human body, revealing many proteins and peptides produced by the human body in small quantities but with important functions, which makes them interesting for therapeutic applications. Examples are growth factors such as erythropoietin, stimulating red blood cell production, the human growth hormone, or immune system stimulating interferons. Modern biotechnology, in particular recombinant DNA technology, made it possible to produce these substances in larger quantities using microorganisms or cell cultures as “cell factories”, facilitating their therapeutic use. These products are subsumed under the term “biopharmaceuticals”. The first biopharmaceutical to reach the market was recombinant human insulin in 1982. Since then about 142 biopharmaceutical products have been launched worldwide (not including vaccines, see Chapter 2.1.2). The main product classes of marketed biopharmaceutical products are recombinant hormones such as human insulin, monoclonal antibodies used to treat e.g. cancer but also used for diagnostic purposes, and recombinant interferons and interleukins.

#### Economic significance of biopharmaceuticals

Over the last ten years (1996-2005) in the EU, an average of six new biopharmaceutical products have been launched per year,<sup>19</sup> accounting for about 9% of pharmaceuticals launched in this period (Figure 2-2). Overall, in 2005, about 85 biopharmaceutical products were available in the EU, more than twice as many as in 1996.

15 It includes the manufacture of basic pharmaceutical products and pharmaceutical preparations, such as medicaments, vaccines, homeopathic preparations, dental fillings, bandages and dressings.

16 Eurostat.

17 Eurostat, European Business: Facts and Figures 1995-2004, 2005 Edition.

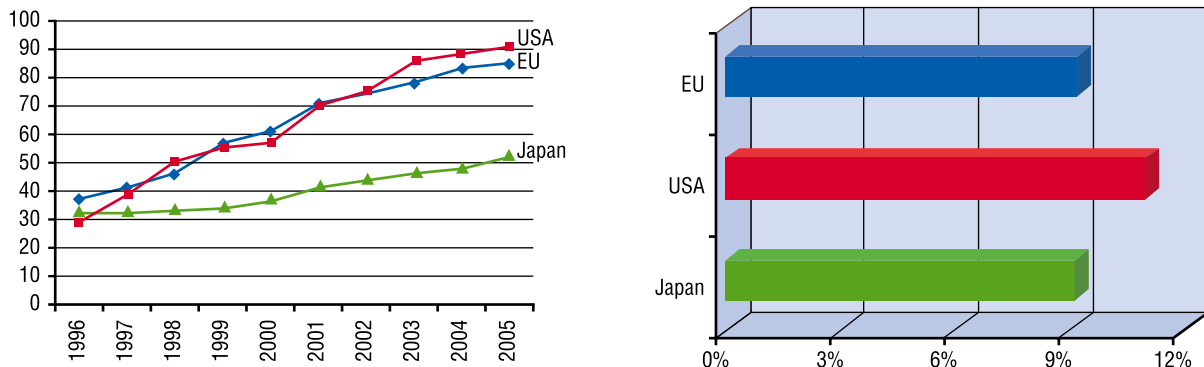
18 EFPIA (2006), The pharmaceutical industry in figures and Eurostat.

19 Data on pharmaceutical and biopharmaceutical products were retrieved by ETEPS from the PJB database pharmaprojects (<http://www.pjbpubs.com/pharmaprojects/index.htm>). The EU is covered as a group with the exception of Estonia, Latvia, Lithuania, Malta, Slovenia and Cyprus; for these countries no data are available in the pharmaprojects database.





■ Figure 2-2 Accumulated numbers of biopharmaceuticals launched (left panel) and the share by numbers of biopharmaceuticals out of all pharmaceuticals launched between 1996 and 2005 (right panel), by region

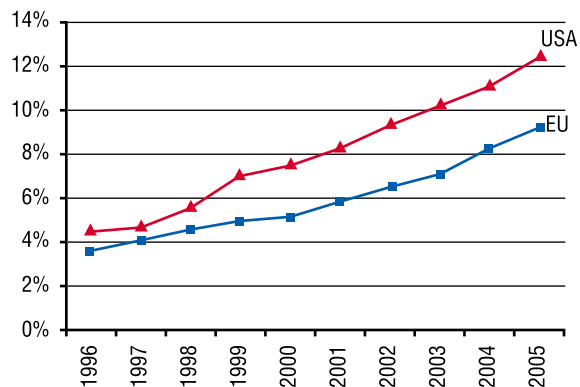


Source: ETEPS<sup>20</sup>, IPTS calculations.

The combined pharmaceutical market in 2005 of the USA, the EU and Japan was about EUR 372 billion (about 80% of the worldwide market), the EU having a share of 33%. Biopharmaceuticals in the USA, EU and Japan represented a market of EUR 38.5 billion in 2005,<sup>21</sup> about 10% of the corresponding pharmaceutical market. The EU has a market share of 30%, similar to the market share for pharmaceuticals.

The biopharmaceutical market in the EU seems to be more dynamic than the pharmaceutical market, with average annual growth rates (23%) twice as high as for pharmaceuticals (11%). Accordingly, overall, the shares of biopharmaceuticals in the turnover of pharmaceuticals are increasing, indicating the growing importance of biopharmaceuticals from an economic perspective (Figure 2-3). The average turnover per marketed biopharmaceutical in the EU has tripled over the last 10 years and, in 2005, reached a value of EUR 133 million per year.

■ Figure 2-3 Share of turnover of biopharmaceuticals out of all pharmaceuticals, by region



Source: ETEPS<sup>22</sup>.

#### International comparison

The share of biopharmaceuticals in the pharmaceutical markets in the USA and Japan is similar to the EU, at 11% and 9%,

20 ETEPS (2006). Bio4EU Task 2 Main report.

21 (Bio)pharmaceutical revenues were analysed on the basis of the manufacturer ex-factory prices by ETEPS in the database IMS MIDAS, owned by IMS Health. All biopharmaceuticals (not including recombinant vaccines) approved by FDA or EMEA as listed by Walsh (Nature Biotechnology (2006), 24, (7), p. 769) were used by their generic name(s) as the basis for biopharmaceuticals. Of this list 16 products (among them six monoclonal antibodies, one insulin analogue, two growth hormones and three morphogenic proteins) could not be found in the database.

22 ETEPS (2006). Bio4EU Task 2 Main report.



Table 2.1 Top ten biopharmaceuticals ranked according to sales in 2005

Top 10 products	Country	Sales (M €, 2005)	Change over 2004 (%)	Market share 2005 (%)
<b>Global biotech market</b>		<b>41 175</b>	<b>17.1</b>	<b>100.0</b>
Erypo/Procrit (Johnson & Johnson)	USA	2897	-8.8	7.0
Enbrel (Amgen/Wyeth)	USA	2887	40.7	7.0
Aranesp (Amgen)	USA	2800	38.0	7.0
Remicade (Johnson & Johnson/Schering-Plough)	USA	2331	17.3	5.7
Epogen (Amgen)	USA	2240	-0.8	5.4
Mabthera/Rituxan (Roche)	Switzerland	2112	23.6	5.1
Neulasta (Amgen)	USA	1925	31.7	4.7
Avonex (Biogen Idec)	USA	1188	9.6	2.9
Lantus (Sanofi-Aventis)	France	1174	47.5	2.9
Herceptin (Roche)	Switzerland	1106	48.2	2.7
<b>Total (top ten)</b>		<b>20 661</b>	<b>19.4</b>	<b>50.2</b>

Source: IMS Health, MIDAS, MAT Dec 2005, taken from EuroBio 2006 Press Kit.<sup>24</sup>

respectively (Figure 2-2). Japan represents a much smaller biopharmaceutical market, with two biopharmaceutical products launched per year, whereas in the USA a similar number of biopharmaceuticals to the EU reached the market in the period 1996-2005. However, the USA clearly dominates the combined pharmaceutical and biopharmaceutical markets of the USA, EU, Japan, with market shares of 54% and 65% respectively. Japan, in contrast, plays a lesser role, with market shares of 10% and 5% respectively. The higher market shares of the USA coincide with a slightly higher average growth than in the EU (14% compared to 11% for pharmaceuticals and 28% compared to 23% for biopharmaceuticals), as well as a higher average turnover per biopharmaceutical (in 2005: EUR 275 million in the USA compared to EUR 133 million in the EU). This could indicate higher sales in the

USA or a higher price level, or a combination of both. It might also reflect the different health care policies in the USA and the EU Member States, the first relying more on competition and a less regulated market approach, whereas within the EU a broader mix of policies can be found, ranging from free pricing of pharmaceuticals to fixed prices.<sup>23</sup>

The EU seems to have a comparatively weak position in the development and marketing of biopharmaceuticals. Only 15% of all available products were developed by EU companies, whereas Swiss companies alone developed 10% and US companies 54%. This trend is also evident when we look at the top ten biopharmaceuticals according to sales, which make up more than half of the overall market. These products (see Table 2.1) are largely produced by US companies (7

23 US (2004). "Pharmaceutical price controls in OECD countries: implications for U.S. consumers, pricing, research and development, and innovation." International Trade Administration, US Department of Commerce, Washington, DC; <http://www.ita.doc.gov/drugpricingstudy>.

Mrazek, M.F. (2002). *Croatian Medical Journal* 43: 453-461.

24 <http://www.eurobio2006.com/DocBD/press/pdf/18.pdf> (conversion: 1 U.S. Dollar = 0.7765 Euro).



out of 10), two are produced by a Swiss company and only one is produced by an EU company. It should be noted that half of these products are produced by biotechnology companies, and the other half by pharmaceutical companies. The most successful product class is erythropoietin, with three products in the top ten list (Erypro/Procrit, Aranesp, Epogen; 19% market share). Furthermore, monoclonal antibodies (Mabthera/Rituxan, Remicade, Herceptin; 14% market share), hormones (insulin product Lantus; 3%) and interferon (Avonex; 3%) seem to be successful product classes. The second best-selling product (Enbrel) is a growth factor inhibitor used for the treatment of inflammatory diseases such as rheumatoid arthritis.

### Biosimilars

The emergence of biogenic drugs or biosimilars will be an important factor in the future economic performance of biopharmaceuticals, especially as the patents of several biopharmaceuticals expire.<sup>25</sup> The introduction of biosimilars in the market is expected to increase competition, which could not only help reduce health care costs, but also lead to improved products.<sup>26</sup> At the same time, biosimilars (just like generics) are linked to the emergence of new national players in the global pharmaceutical market, such as India,<sup>27</sup> China or South Korea. However, several issues complicate the development and regulatory approval of biosimilars. The manufacturing of a recombinant protein drug is very complex and may involve many steps, which could influence its biological properties. In this context, some experts argue that two biopharmaceuticals based on the

same protein can never be completely identical and therapeutically equivalent. Hence, the question of whether it is possible to demonstrate bioequivalence is under debate, and the European Medicines Agency (EMA) has issued the recommendation that a full preclinical and clinical data package is required for approval where such equivalence cannot be demonstrated.<sup>28,29</sup> In spite of these uncertainties, the first biogenic drug, Omnitrope (a recombinant growth hormone) was recently approved in the EU, following a positive evaluation by EMA, and it is also approved in Australia and – even in the absence of a specific regulatory pathway for approval of biogenerics – in the USA.

### Social implications of biopharmaceuticals

Biopharmaceuticals are the most visible result of modern biotechnology applications in medicine, both in terms of available products and economic significance. The ability to use natural proteins has opened up new possibilities for disease treatment, and potentially safer, more reliable product sources. Major therapeutic fields for which biopharmaceuticals have been developed are cancer, metabolic disorders and musculoskeletal and immunologic disorders.

The performance of biopharmaceuticals regarding disease treatment and effects on health care systems were analysed on the basis of four case studies:

- Recombinant human insulin for the treatment of diabetes
- Interferon-beta for the treatment of multiple sclerosis

25 Schellekens, H. (2005). *Nephrology Dialysis Transplantation* 20, suppl. 4: 31-36.

26 Schellekens, H. (2004). *Trends in Biotechnology* 22: 406-410.

27 Jayaraman, K.S. (2003). *Nature Biotechnology* 21: 1115-1116.

28 Committee for Proprietary Medicinal Products (2003). Guideline on Comparability of Medicinal Products Containing Biotechnology derived Proteins as Active Substance. Quality Issues. Evaluation of Medicines for Human Use, The European Agency for the Evaluation of Medicinal Products, London.

29 EMA (2005). Guideline on Similar Biological Medicinal Products, European Medicines Agency, London; <http://www.ema.eu.int/pdfs/human/biosimilar/043704en.pdf>.



- CD20 antibodies against non-Hodgkin's lymphoma
- Enzyme replacement therapy for Gaucher's disease

The case studies present different biopharmaceutical product classes and target different diseases, partly being the only currently available treatment, as in the case of Gaucher's disease, or replacing animal insulin, as in the case of recombinant human insulin. The assessment focused on improved treatment, thus helping patients to live healthier and more productive lives, increasing social welfare and individual well-being, and on the cost-effectiveness of treatments with a view to efficiency of health care systems.

#### Recombinant human insulin

Recombinant human insulin was the first biopharmaceutical product to reach the market, launched in 1982. Since then, it has largely replaced animal insulin; today only 30% of the worldwide available insulin is isolated from the porcine or bovine pancreas of slaughtered animals.<sup>30</sup> At least 15 recombinant human insulin products are currently on the market, representing about 15% of the biopharmaceutical market by value. In developed countries animal-based insulin is hardly available any more.

Insulin is primarily targeted at Type 1 diabetes patients, mainly children and adolescents (about 5-10% of all diabetes patients) who have lost their ability to produce insulin and need regular injections of insulin. About 30% of Type 2 diabetes patients require additional insulin to regulate their blood glucose levels. The underlying cause of Type 2 diabetes is an acquired loss

of sensitivity to the hormone insulin, which affects adults usually over the age of 40 and is linked to diet and body weight. In 2003, there were about 194 million diabetes patients worldwide; this figure is expected to increase to more than 330 million by 2025 due to an increase of obesity worldwide.<sup>31</sup> Complications from diabetes, such as stroke, renal failure, blindness, coronary artery and peripheral vascular disease, often reduce quality of life and life expectancy and entail considerable health care costs.

Although recombinant human insulin does not appear to have significant therapeutic differences compared to animal insulin, clinical adoption of recombinant insulin is high: about 95% of Type 1 diabetes patients in the EU use recombinant insulin. Recombinant human insulin seems to be more expensive than animal insulin in most countries where both are available, e.g. in European countries (including non-EU countries) the average price of recombinant human insulin was twice as high as for animal insulin.<sup>32</sup> One explanation for the widespread adoption could be the potentially improved safety of recombinant insulin regarding the risk of immune reaction and contamination of animal insulin. It is also important to realise that, according to a study carried out in the USA, the actual cost of insulin, including delivery, amounts to only 7.6% of diabetes-related health care expenditures.<sup>33</sup>

Recombinant human insulin is the starting point for the development of human insulin analogues, which reached the market several years ago. The analogues are developed by using genetic engineering to produce fast acting and slow acting human insulin. They are designed to improve the control of insulin requirements over

30 IDF (2003). *Diabetes Atlas*, 2nd ed. International Diabetes Federation, Brussels.  
31 IDF (2003). *Diabetes Atlas*, 2nd ed. International Diabetes Federation, Brussels.  
32 IDF (2003). *Diabetes Atlas*, 2nd ed. International Diabetes Federation, Brussels.  
33 American Diabetes Association (2003) *Diabetes Care* 26: 917-932.



the day, with obvious advantages for the patients. However, the generally higher prices may reduce their cost-effectiveness, especially in the case of diabetes type 2 patients.<sup>34</sup>

Recombinant human insulin and insulin analogues are effective in the treatment of diabetes; however, for these products there is currently limited experimental evidence showing additional efficacy compared with conventional animal insulin. Hence, the contribution of biotechnology-derived insulin products to reducing the burden of diabetes *per se* compared to animal insulin may need to be considered marginal. However, insulin analogues may improve the quality of life of diabetes patients, which could be seen as the major contribution of recombinant insulin. Judging such qualitative improvements would require more specific cost-utility analyses and more fundamental ethical decisions.

#### Interferon-beta for multiple sclerosis

Until 1993, when interferon-beta reached the market, multiple sclerosis (MS) was treated with corticoids to accelerate recovery from relapses. Corticoids do not cure MS, and neither do any of the treatments currently available. Also, interferon-beta belongs to the group of disease modifying drugs: it does not cure MS, but it may slow down the development of some disabling effects and decrease the number of relapses. As such, it has developed into the first line treatment for MS. Currently, four interferon-beta products are available, representing about 8% of the biopharmaceutical market by value.

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system. Its onset occurs primarily in young adults and it affects women more often than men. The exact cause of the disease is unknown, but a genetic predisposition is suspected. The disorder can manifest in a remitting or progressive development, and it is characterised by lesions that occur throughout the brain and spinal cord, which have severe consequences such as loss of memory or loss of balance and muscle coordination; other symptoms include slurred speech, tremors, and stiffness or bladder problems. Estimates of the prevalence of MS in the EU differ between about 257 000 in Western Europe<sup>35</sup> to over 563 000 cases in the EU.<sup>36</sup> Given the number of people who suffer from MS and the fact that it primarily affects young adults, the individual consequences of this disease are severe and the economic and social costs are substantial.<sup>37,38</sup> This is also reflected in the high share of “indirect” costs – i.e. of costs that occur outside the health care system, like productivity losses, costs for informal health care or estimates of intangible costs – that usually make up more than half of total costs.<sup>39</sup>

Regarding cost-effectiveness, no conclusive studies have been identified. The use of interferon-beta for the treatment of MS is not without controversy. In 2002, the UK’s National Institute for Health and Clinical Excellence (NICE) issued a guidance not recommending interferon-beta

34 IQWiG (2006). “Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2.” Institute for Quality and Efficiency in Health Care, Cologne. Warren, E., E. Weatherley-Jones, J. Chilcott and C. Beverley (2004). *Health Technology Assessment* 8(45).  
35 WHO (2006). “Point prevalence for selected causes: by sex, age and WHO subregion: 2002.” Health statistics and health information systems. World Health Organization, Geneva.  
36 MSIF (2006). “European Map of MS database.” Multiple Sclerosis International Federation, London. (The figure reported for the EU does not include data on Cyprus, Lithuania and Malta.)  
37 Phillips, C.J. (2004). *CNS Drugs* 18: 561-574.  
38 APF (2006). *Le Livre Blanc de la sclérose en plaques*. Etats Généraux de la SEP, Association des Paralysés de France, Paris.  
39 Kobelt, G. and M. Pugliatti (2005). *European Journal of Neurology* 12: S63-S67.



or the current alternative treatment glatiramer acetate (available since 2000 in some EU Member States) for the treatment of MS based on clinical performance and cost-effectiveness considerations.<sup>40</sup> More recent evaluations show modest benefits of interferon-beta for the progression of MS in the short to medium term.<sup>41</sup> Data on long-term effects are not yet available.

### CD20 antibodies against non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a type of cancer in which malignant cells form in the lymph system. Because the lymph tissue is found throughout the body, NHL can begin in almost any part of the body and spread to the liver and many other organs and tissues. NHL is more common in men and older age groups. Over the last three decades the incidence of NHL in western industrialised countries has been consistently on the rise, and it now ranks amongst the most frequent malignant diseases.<sup>42,43</sup> In 2001 there were over 30 000 deaths within the EU due to NHL.<sup>44</sup>

Lymphomas were classically treated with radiotherapy and systemic chemotherapy (like "CHOP", a specific combination of anti-cancer drugs). Over recent years these treatments have been supplemented by autologous (i.e. derived from the recipient) and allogeneic (derived from a donor other than the recipient) stem cell transplantation and by immunotherapy with monoclonal antibodies.<sup>45</sup> In immunotherapy,

the immune system is put on a higher level of alertness with respect to cancer cells; in the treatment of NHL, genetically engineered CD20 antibodies have proven to be effective. The success of these antibodies relies on the fact that approximately 90% of the malignant B-cells in NHL express a CD20 antigen at their surface. This antigen is recognised by the corresponding CD20 antibody, which triggers the immune system to mount a targeted attack on the malignant cells – while sparing most normal tissue. The need to engineer these antibodies is because patients do not generally produce effective antibodies against the relevant antigens.<sup>46</sup> The first CD20 antibodies received authorisation in the EU in 1998. Currently two products are authorised in the EU, marketed by a Swiss and an EU company. Worldwide, three CD20 antibody products are available; none has been developed by EU companies.

To date, studies on the effectiveness and cost-effectiveness of CD20 antibodies are scarce. A systematic review that was carried out in the UK identified only one randomised controlled trial, which however confirmed the effectiveness of one CD20 antibody product (rituximab) in the treatment of aggressive NHL (in combination with CHOP) in certain patient groups. In the same review a cost-effectiveness analysis showed that the addition of rituximab to the CHOP treatment regime might extend the patients' lives by about one "quality-adjusted life year" (QALY; the weighted equivalent of one healthy life year) at a cost of about EUR 15 000, which qualifies as a cost-effective intervention. These results also confirm the data provided by industry.<sup>47</sup> Given

40 NICE (2002). Technology Appraisal Guidance No. 32, National Institute for Clinical Excellence, London.  
41 Prosser, L.A., K.M. Kuntz, A. Bar-Or and M.C. Weinstein (2004). *Value in Health* 7: 554-568. Phillips, C.J. (2004). *CNS Drugs* 18: 561-574. Amato, M.P. (2004). *Expert Opinion on Pharmacotherapy* 5: 2115-2126. Hoch, J.S. (2004). *Expert Review of Pharmacoeconomics & Outcomes Research* 4: 537-547. McCormack, P.L. and L.J. Scott (2004). *CNS Drugs* 18: 521-546.  
42 Trümper, L., P. Möller and A. Neubauer (2004). "Maligne Lymphome." In: Hiddemann, W., H. Huber and C. Bartram (eds.) (2004). *Die Onkologie* (Teil 2). Springer Verlag, Berlin, pp. 1709-1774.  
43 Morgan, G., M. Vornanen, J. Puitinen, A. et al. (1997). *Annals of Oncology* 8: S49-S54.  
44 IARC (2006). "CANCER*Mondial*," update of July 2006. Descriptive Epidemiology Production Group, International Agency for Research on Cancer, Lyon. (Does not include Cyprus; data for Belgium from 1997.)  
45 Trümper, Möller and Neubauer (2004), cf. footnote 42.  
46 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.  
47 Knight, C., D. Hind, N. Brewer and V. Abbott (2004). *Health Technology Assessment* 8(37).



this scarcity of information, NICE for instance has recommended the (general) use of rituximab only in some cases of NHL.<sup>48,49</sup> Another recent literature review of economic studies of currently available NHL treatment options also found (preliminary) evidence for the cost-effectiveness of rituximab in the treatment of various forms of NHL. However, this study also concluded that more and better economic evaluations are needed for a more comprehensive assessment of the various effective treatments for NHL – not only CD20 antibodies.<sup>50</sup>

#### Enzyme replacement therapy for Gaucher's disease

Gaucher's disease is an inherited metabolic disorder caused by one or more genetic defects that result in functional deficiency of an enzyme called glucocerebrosidase (or glucosylceramidase). This deficiency causes a lipid (glucocerebroside) to accumulate in the spleen, liver, lungs, bone marrow and sometimes in the brain, causing functional abnormalities. The resulting course of the disease can be quite variable, ranging from no outward symptoms to severe disability and death. Gaucher's disease belongs to the rare diseases with a prevalence of fewer than 5 individuals in 10 000. For instance, the prevalence of all types of Gaucher's disease combined is one in 57 000 in Australia and only one in 86 000 in the Netherlands.<sup>51</sup>

Given these prevalence rates, for an EU population of 458 973 024 in 2004,<sup>52</sup> there could be around 5 000 to 18 000 individuals who suffer from Gaucher's disease in the EU.

The treatment of choice for Gaucher's disease, a rare inherited lipid-storage disorder, is an enzyme replacement therapy. Other options, such as bone marrow transplantation or removal of part of the spleen, are less used due to higher risks and the need for matching bone marrow donors.<sup>53,54</sup> The enzyme, glucocerebrosidase, can be sourced from human placentas; however, the amount of enzyme needed to treat one patient required about 22 000 placentas per year. Since 1997 (1994 in the USA) a recombinant enzyme has been commercially available (Cerezyme), and has proved as effective in treating Gaucher's disease as the natural enzyme, but was more readily available and free of potential contamination.<sup>55</sup> A more recent alternative, a small molecule drug approved in 2002 in the EU, makes use of an enzyme inhibitor, reducing the creation of the lipid.<sup>56</sup> It is currently being marketed for patients who do not respond well to the enzyme drug.<sup>57</sup>

Enzyme replacement therapy in Gaucher's disease has proven to be effective from a clinical point of view, with only a few mild adverse reactions, and it also improves the quality of life from the patients' perspective.<sup>58,59,60</sup> Estimates of

48 NICE (2003). *Technology Appraisal* No. 65, National Institute for Clinical Excellence, London.

49 NICE (2002). *Technology Appraisal* No. 37, National Institute for Clinical Excellence, London.

50 van Agthoven, M., C.A. Uyl-de Groot, P. Sonneveld and A. Hagenbeek (2004). *Expert Opinion on Pharmacotherapy* 5: 2529-2548.

51 GOLD (2006). "Gaucher disease," Disease Information Search. Global Organisation for Lysosomal Diseases, Buckinghamshire.

52 Eurostat (2006). "Population by sex and age on 1 January of each year." Theme: Population and Social Conditions. European Commission, Eurostat, Luxembourg.

53 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.

54 NINDS (2006). "Gaucher's Disease." Disorder Index. National Institute of Neurological Disorders and Stroke, Bethesda, MD.

55 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.

56 Actelion (2006). "All milestones," company information. Actelion Pharmaceuticals, Allschwil.

57 Actelion (2006). "Zavesca: balance by substrate reduction," homepage. Actelion Pharmaceuticals, Allschwil.

58 Whittington, R. and K.L. Goa (1992). *Drugs* 44: 72-93.

59 Whittington, R. and K.L. Goa (1995). *Pharmacoeconomics* 7: 63-90.

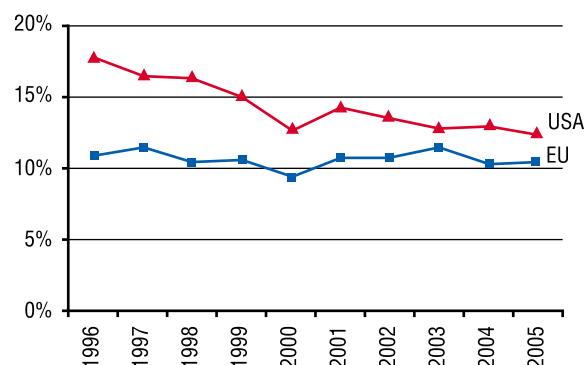
60 Damiano1, A.M., G.M. Pastores and J.E. Ware Jr. (1998). *Quality of Life Research* 7: 373-386.

the costs of procuring the quantities of the drug for one patient per year range from about EUR 100 000 to several times that amount.<sup>61,62,63</sup> Gaining one “quality-adjusted life year” (QALY<sup>64</sup>) with the enzyme replacement therapy may cost EUR 150 000 to EUR 2 million, beyond any usually applied cost-effectiveness thresholds.<sup>65,66</sup> This highlights the specific ethical questions linked to “orphan drugs”,<sup>67</sup> namely whether scarce public money in the health care sector should be spent according to equity (all individuals are entitled to the same minimum quality of health care) or efficiency considerations (limited resources should be used to treat a large number of people who suffer from a disease that can be treated at a relatively low cost).<sup>68</sup>

### Biopharmaceuticals in clinical trials

Clinical trials provide an indication of what is in the pipeline of pharmaceutical products and the significance of biopharmaceuticals for the coming years. Cancer seems to be the dominant therapeutic field at which biopharmaceuticals in the pipeline are targeted.<sup>69</sup> The absolute numbers of pharmaceuticals and biopharmaceuticals in clinical trials by EU companies increased between 1996 and 2005 by about 40%. In 2005, EU companies had 109 biopharmaceutical products in clinical trials. The share of biopharmaceuticals in clinical trials is stable at about 11% (Figure 2-4).

Figure 2-4 Share of biopharmaceuticals out of all pharmaceuticals in clinical trials, by region



Source: ETEPS<sup>70</sup>.

US companies had about twice as many biopharmaceuticals in clinical trials than EU companies (190 candidates in 2005). Absolute numbers increased between 1996 and 2005 by 28%, which is much less than the number of pharmaceuticals, which increased by about 80%. This results in an overall decrease of the share of biopharmaceuticals in clinical trials from 18% to about 12%, reaching the EU level in 2005. These shares indicate that a pronounced change in the significance of biopharmaceuticals within the pharmaceutical sector is not probable in the near future.

61 Whittington, R. and K.L. Goa (1995). *Pharmacoeconomics* 7: 63-90.

62 Clarke, J.T.R. et al. (2001). *Canadian Medical Association Journal* 165: 595-596.

63 Connock, M. et al (2006). *Health Technology Assessment* 10(24).

64 A QALY represents the weighted equivalent of one healthy life year.

65 Whittington, R. and K.L. Goa (1995). *Pharmacoeconomics* 7: 63-90.

66 Connock, M. et al. (2006). *Health Technology Assessment* 10(24).

67 Orphan drugs are medicinal products for diagnosing, preventing or treating a life-threatening, seriously debilitating or serious and chronic condition affecting fewer than five in 10 000 persons (in the EU). Because these conditions occur so infrequently that the cost of developing an appropriate drug and bringing it to the market would not be recovered by the expected sales of the product, the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products." *OJ L* 018: 1-5.

68 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.

69 Walsh, G. (2006). *Nature Biotechnology* 24(7): 769-776.

70 ETEPS (2006). Bio4EU Task 2 Main report.





## Intellectual Property

Modern biotechnology advances have led to the development of new drugs and enabling tools for the diagnosis of diseases. Additionally, completion of the human genome project has made it easier to associate specific genes (or gene combinations) to a disease, and thus to identify novel putative drug targets. Because of their potentially significant economic (and public health) implications, modern biotechnology applications are increasingly being patented.

Patenting is considered to have a stimulating effect on innovation, by allowing the inventor “freedom to operate”, which may in turn drive investment.<sup>71</sup> However, there is also a suggestion that patenting may limit patients’ access to novel treatments (e.g. as a result of high licensing fees which would influence the cost of the treatment) and inhibit research, especially as a result of the proliferation of DNA patents.<sup>72</sup> The most pertinent issues relate to the breadth of claims and the potential development of a patent thicket (a situation where different owners have overlapping patent rights, requiring multiple licences). Such broad claims could inhibit research, although a recent study indicates that presently there is not enough evidence to support this notion.<sup>73</sup> However, the future development of patent thickets cannot be ignored. For diagnostics too (see Chapter 2.1.4) this may be a critical issue. For example, multiple patents might affect the development of microarray tests, where a specific combination of genes is used to diagnose (or predict) disease. In such a case, and if each gene to be used on the array has already been patented, then multiple licenses would be required prior to the development of the test to ensure no infringement takes place. This would probably affect the cost of the test, and perhaps its accessibility to services and patients.

### 2.1.2 Vaccines

Vaccines are an important prophylactic medical approach in which modern biotechnology plays an increasing role. The “traditional” vaccine consists of live attenuated bacteria or viruses, of dead or inactivated bacteria, or of specific surface proteins of pathogens, e.g. harvested from the plasma of infected patients. Modern biotechnology makes it possible to specifically produce on a large scale only those proteins of pathogens which trigger the immune reaction. These recombinant vaccines have the advantage that they are produced in a non-pathogen host, ensuring that no pathogen will be present in the vaccine product, and making it clinically safe in that respect. The supply can easily be controlled and the approach allows the production of a defined, consistent product. Currently, there is growing interest in DNA vaccines which provoke an immune response utilising “naked” DNA instead of proteins (several are in phase I clinical trials for AIDS, malaria and influenza).

#### Economic significance of recombinant vaccines

Vaccines play a minor role in the pharmaceutical market, representing about 1% (EUR 563 million) of the worldwide market. The number of available vaccines has increased considerably: in the USA and the EU, over the last ten years the number has doubled. Overall the EU is the main producer of vaccines (52%) (Figure 2-5). Recombinant vaccines represent about 20% of all available vaccines, most products targeting hepatitis B. EU companies developed 26% of all recombinant vaccines, US companies about 17%.

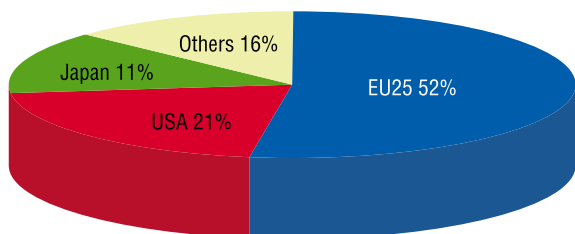
71 Nunnally, A.C. et al. (2005). *Community Genetics* 8: 209-216.

72 Jensen, K. and Murray, F. (2005). *Science* 310: 239-240.

73 National Research Council (2005). *Reaping the benefits of genomic and proteomic research: intellectual property rights, innovation, and public health*. The National Academies Press, Washington DC.



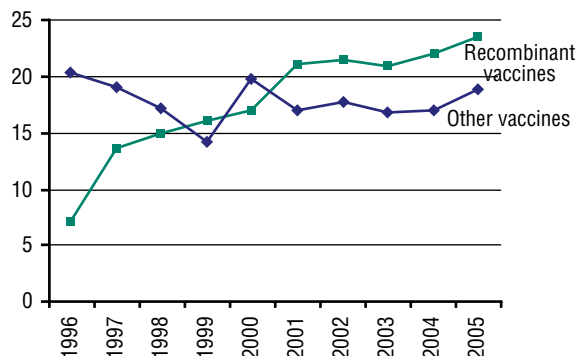
Figure 2-5 Share of global vaccine production in 2005, by location of company headquarters



Source: ETEPS<sup>74</sup>, IPTS calculations.

In the EU, the number of recombinant vaccines on the market has been stable since 2001, while the number of conventional vaccines has continued to increase, leading to a drop in the share of recombinant vaccines from 25% to about 14%. Still, in absolute terms, the market value for recombinant vaccines in the EU has nearly quadrupled over the last ten years, with revenues growing from EUR 65 million in 1996 to EUR 259 million in 2005. This corresponds to 46 % of the total vaccines market, compared to 54% for the USA. It seems that recombinant vaccines are more successful in economic terms, generating on average higher turnover (EUR 23.5 million compared to EUR 17 million for conventional vaccines; 2005) and showing a more positive growth path (Figure 2-6). This could indicate that recombinant vaccines sell at higher quantities and/or prices than conventional vaccines.

Figure 2-6 Average turnover per vaccine in the EU (€ million)



Source: ETEPS<sup>75</sup>, IPTS calculations.

### Social implications of recombinant vaccines

Most recombinant vaccines are targeted at Hepatitis B. Walsh<sup>76</sup> lists 15 recombinant hepatitis B vaccine products (also combination products including other vaccines) available in the EU and the USA. Two other recombinant vaccines are currently on the market, targeting cholera (including the recombinant cholera toxin B subunit of the pathogen *Vibrio cholerae*), and human papilloma virus (HPV). The latter reached the market only recently, with expectations of helping to reduce the cervical cancer rate in women, the main cause of which is an infection with HPV. Since it was impossible to propagate the virus in culture, recombinant DNA technology provided a critical tool for developing a vaccine<sup>77</sup>.

74 ETEPS (2006). Bio4EU Task 2 Main report.

75 ETEPS (2006). Bio4EU Task 2 Main report.

76 Walsh, G. (2006). *Nature Biotechnology* 24(7): 769-776.

77 Crum, C. et al. (2006). *Nature Reviews Drug Discovery* 5(8): 629-630.



Hepatitis B is a widespread virus. According to WHO, about 6% of the world population are infected. For the EU it can be assumed that about 100 000 new infections occurred in 2004, although the rate decreased since 1996 from 6.55 per 100 000 inhabitants to 3.49.<sup>78,79</sup> Hepatitis B can cause acute and chronic infections; the latter might develop into liver cirrhosis and liver cancer, leading to about 1 million deaths each year.

According to Ulmer et al.<sup>80</sup> the main driver for recombinant vaccine development in the case of hepatitis B was the need to develop a safer, better characterised vaccine. An additional benefit was the unrestricted availability of the vaccine compared to the conventional alternative, a vaccine derived from the plasma of infected individuals. Since the available literature gives no indication of adverse reactions to the plasma-derived vaccine, it can be assumed that the experience with AIDS/HIV contamination of blood products in the 1980s pushed the development and use of a potentially less risky vaccine. The recombinant vaccine was launched in 1986 and in industrialised countries replaced conventional vaccines within a few years.

Studies indicate that vaccination is 95% effective in preventing chronic infections in uninfected individuals,<sup>81</sup> not distinguishing between the conventional or the recombinant vaccine. There seems to be consensus regarding the effectiveness of available hepatitis B vaccines, with different vaccination strategies being analysed and from a cost-effectiveness perspective. No studies were identified comparing the different vaccines in terms of cost-effectiveness impacts. It can be assumed that the confidence in the recombinant vaccine and its ready availability

might have contributed positively to the decline in hepatitis B incidence rates in the EU over the last 15 years.

#### Recombinant vaccines in clinical trials

A look at the share of recombinant vaccines in clinical trials of vaccines reveals the growing importance of recombinant biotechnology in vaccines development over the last ten years. In 2005 the share of recombinant vaccines out of all vaccines in clinical trials reached 75%, up from about 40%-50% in 1996,<sup>82</sup> and indicating an increasing number of recombinant vaccines on the market in the future. Examples for recombinant vaccines in development are a recombinant anthrax vaccine and a vaccine against several serogroups of *Neisseria meningitides*, the cause of meningitis.<sup>83</sup>

#### 2.1.3 Modern biotechnology in drug development and production

Drug development is a lengthy process (it takes up to 10-12 years before a drug reaches the market) consisting of the following main steps:

- i) drug discovery and preclinical development (includes target identification and validation, lead screening and optimisation, preclinical studies),
- ii) clinical trials (phases I, II, and III).<sup>84</sup>

With respect to drug discovery, biotechnology provides a combination of enabling techniques utilised in identifying putative targets and drug candidates. Recent advances in “omics” technologies (genomics, proteomics etc.), in

78 In 2004 approx. 3.49 new hepatitis B infections per 100 000 individuals were reported for the EU. This amounts to some 16 000 new cases. Considering that 50% of hepatitis B infections go unreported and that two thirds are asymptomatic, a 6-times higher figure can be assumed to be more realistic, i.e. about 100 000 infections per year.  
79 WHO (2006). “European Health for All Database (HFA-DB),” June 2006. World Health Organization Regional Office for Europe, Copenhagen.  
80 Ulmer, J.B. et al. (2006). *Nature Biotechnology* 24(11): 1377-1383.  
81 WHO (2006). “Hepatitis B.” Fact sheet No. 204. World Health Organization, Geneva.  
82 ETEPS (2006). Bio4EU Task 2 Main report.  
83 Ulmer, J.B. et al. (2006). *Nature Biotechnology* 24(11): 1377-1383.  
84 DiMasi, J.A., et al. (2003). *Journal of Health Economics* 22: 151-185.



combination with bioinformatics, have improved our understanding of the molecular genetic contribution to diseases, leading to identification and selection of multiple potential drug targets at the same time (high-throughput/microarray approach). Modern biotechnology has also impacted on target validation, e.g. through the development of genetically modified (transgenic or knockout) animals (mostly mice) as disease models or antibody-based assays. Finally, biotechnology is contributing to drug safety by way of improved delivery methods (e.g. for gene therapy and vaccines).

At the clinical trial level, where the safety and efficacy of a drug candidate is tested, the use of pharmacogenetic approaches, i.e. identification of the underlying genetic differences in patients' drug response in order to modulate therapy, is increasing (see Chapter 2.1.5). In the design of clinical trials, such information may help determine the appropriate drug dosage for a specific subset of patients, minimising adverse drug reactions.<sup>85</sup> This approach can also be applied in validating predictive biomarkers, for example in cancer treatment.<sup>86</sup> As a result, the use of pharmacogenetic data is considered to have a potentially positive impact, at least on the cost of clinical trials, both by helping select the most appropriate patient populations and by minimising toxicity effects.<sup>87</sup> In this context, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have recently published guidelines for the submission of pharmacogenetic data.<sup>88</sup>

In spite of the rapid development in science and the use of modern biotechnology techniques,

the attrition rate remains high (only about one drug candidate out of every ten subjected to clinical trials is actually licensed),<sup>89</sup> and the costs associated with drug development have increased (average cost to develop a new biopharmaceutical has recently been estimated at about EUR 920 million, slightly higher than the development costs of conventional drugs),<sup>90</sup> indicating a potentially widening gap between scientific advancement and bedside application. However, certain experts argue that the high attrition rates may stem from the complexity of the targeted diseases and the somewhat fragmented scientific knowledge related to them, whereas the high costs may be at least partly attributed to the long development times and design of large clinical trials to meet regulatory requirements (particularly regarding safety). At the same time, some analysts have suggested that the application of new technologies may further increase costs (at least in the short run), as these might lead to the identification of numerous potential drug targets which are not presently well understood.<sup>91</sup>

Thus, it is unclear whether modern biotechnology has significantly improved the R&D process, but it is suggested that its potential could be harvested through better co-ordinated interdisciplinary and translational research to foster the development of therapeutic products.<sup>92</sup> The EU is taking steps to this end, e.g. by setting up the Innovative Medicines Initiative, a platform that brings together stakeholders from industry, academia, SMEs, regulatory authorities, health care providers, and patient organisations.<sup>93</sup>

85 Hopkins, M.H. et al. (2006). *Nature Biotechnology* 24: 403-410.

86 Sargent, D., Conley, B., Allegra, C. and Collette, L. (2005). *J. Clin. Oncol.* 23: 2020-2027.

87 Lesko, L.J. and J. Woodcock (2002). *The Pharmacogenomics Journal* 2: 20-24.

88 EMA (2006). Draft guideline on briefing meetings. EMEA/81167/2006. FDA (2005). Guidance for industry: pharmacogenomic data submissions. U.S. Food and Drug Administration, Rockville, M.D. EMA (2006). Guiding principles processing Joint FDA-EMA Voluntary Genomic Data Submissions (VGDSs) within the framework of the confidentiality agreement. European Medicines Agency, London.

89 "Climbing the helical staircase. A survey of biotechnology." *The Economist* (London), 29 March 2003, pp. 3-18.

90 Tufts Center for the Study of Drug Development Impact report 2006 Nov/Dec. 8(6).

91 DiMasi, J.A., et al. (2003). *Journal of Health Economics* 22: 151-185.

92 Pisano, G.P. (2006). *Harvard Business Review* 84(10): 114-125.

93 The Innovative Medicines Initiative (IMI) Strategic Research Agenda (2005), [http://ec.europa.eu/research/fp6/pdf/innovative\\_medicines\\_sra\\_final\\_draft\\_en.pdf](http://ec.europa.eu/research/fp6/pdf/innovative_medicines_sra_final_draft_en.pdf)



Modern biotechnology currently plays only a limited role in the production process of small molecule drugs. Expert interviews<sup>94</sup> indicate that the share of biotechnological related to chemical production processes is between 10% and 15%. The share is expected to increase in the future.

#### The use of animal models in research

Animals are employed in scientific research and drug development for purposes ranging from gene function studies to drug target validation and toxicity testing. Recent estimates indicate that worldwide 75-100 million vertebrates are used each year in research for various purposes ranging from drug or cancer research to toxicity tests.<sup>95</sup> Most commonly, animals are used as research models for the study of a specific biological or molecular process that is associated with a disease or a genetic condition in humans.<sup>96</sup> This use has increased, particularly since researchers uncovered the similarity of important molecular pathways between human and non-human species (e.g. mice and rats) by sequencing and comparing their genomes.

There are many instances of the contribution of animal models to medical advances, e.g. the development of the polio vaccine or therapies for genetic conditions such as cystic fibrosis.<sup>97</sup> Nevertheless, it has been suggested that experimental animals may be compromised immunologically, which might in turn lead to unreliable conclusions.<sup>98</sup> The suitability of animal models as such has been questioned, because it is

argued that the differences that do exist between humans and animals compromise their validity. In either case it is recognised, though, that careful research design is paramount.

Apart from these concerns about the suitability of animal models, concerns also relate to the welfare of the animals themselves: some reports indicate that experimental animals may experience distress ranging from minor discomfort to moderate and severe effects.<sup>99</sup> Specific animal models are most typically developed through genetic modification (e.g. gene insertion or deletion, introduction of targeted mutations), which might, have a potential negative impact on the animals, either because of the procedures employed (e.g. microinjection of transgenes) or the modification itself.<sup>100</sup> With the production of genetically modified animals for research on the increase, these welfare concerns gain in importance.<sup>101</sup>

In this context, the 3-R-principle<sup>102</sup> (replacement, reduction and refinement) has been proposed to guide research using animals in a way that minimises their use and potential discomfort: replacement refers to the substitution of animals by non-animal alternatives, reduction to minimising the number of animals used, and refinement aims at minimising animal discomfort. The 3-R-principle has been acknowledged by the existing legislation on animal protection (Directive 86/609/EEC<sup>103</sup>) but is also a key component of the recently adopted Community Action Plan on the Protection and Welfare of Animals, which

94 Interviews were carried out by ETEPS. In total 28 companies were approached. These included enzyme, fine chemicals and pharmaceutical companies. Companies whose main field of activities are enzymatic applications or chemistry in general were also included.

95 Baumans, V. (2005). *Rev. sci. tech. Off. Int. Epiz.* 24: 503-514.

96 "The use of non-human animals in research: a guide for scientists." The Royal Society, UK, February 2004, <http://www.royalsociety.org/displaypagedoc.asp?id=11514>.

97 "The use of non-human animals in research: a guide for scientists." The Royal Society, UK, February 2004, <http://www.royalsociety.org/displaypagedoc.asp?id=11514>.

98 Poole, T. (1997). *Lab Anim.* 31: 116-124.

99 Baumans, V. (2005). *Rev. sci. tech. Off. Int. Epiz.* 24: 503-514.

100 EuroGroup for Animal Welfare submission to the Biotechnology for Europe Study (<http://bio4eu.jrc.es/submissions.html>) and Baumans, V. (2005). *Rev. sci. tech. Off. Int. Epiz.* 24: 503-514.

101 Baumans, V. (2005). *Rev. sci. tech. Off. Int. Epiz.* 24: 503-514.

102 Russell, W.M.S. and S.L. Burch (1959). *The principles of humane experimental technique.* Methuen, London.

103 Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes. OJ L 358, 18.12.1986.



outlines specific measures for the promotion of animal welfare in the EU until 2010.<sup>104</sup> Modern biotechnology applications can contribute to these objectives. For instance, the increasing use of *in vitro* methods for toxicity testing or as screening tools helps reduce animal use. At the same time, knowledge gained through genomics improves experimental design, which could in turn reduce the number of animals needed per experiment.

#### 2.1.4 *In vitro* diagnostics

*In vitro* diagnostics<sup>105</sup> (IVDs) are tools (e.g. reagents, chips etc.) for testing specimens taken from the body and intended for use in a broad spectrum of health care applications, including evaluation of an individual's likelihood of developing specific diseases or conditions, their early detection and/or diagnosis, identification or quantification of treatment, monitoring of treatment effectiveness etc.

Modern biotechnology diagnostics are a subgroup of *in vitro* diagnostic tests which are either protein-based or DNA-based. The first category refers to tests that can be used to identify changes in the levels of proteins during disease (e.g. hepatitis, prostate cancer specific enzymes). In addition, protein-based assays have been developed to identify foreign proteins during an infection (e.g. HIV tests). In general, this involves detecting a protein by a specific antibody (e.g. immunoassays). DNA-based tests (also often referred to as molecular diagnostics) identify alterations in the DNA sequence correlating with a disease or a heightened risk of developing a disease.

Diagnostics based on modern biotechnology are mainly found in the area of immunochemistry

testing and molecular testing. Immunochemistry tests are utilised to detect immune reactions by measuring the body's antigen/antibody reaction to foreign agents. The main components of such tests are recombinant antibodies, and they can be used to test for a broad range of conditions including cancer, allergies, and infectious diseases. Molecular testing involves the investigation of disease association with a specific genotype. The most established application of this group of diagnostics is genetic testing for various monogenic disorders (e.g. muscular dystrophy) or other diseases such as cancer (e.g. BRCA1 and two tests used for the identification of predisposition to breast cancer), and infectious diseases (e.g. HIV testing). Genetic testing might be used to support diagnosis, and to identify individuals with increased risk of developing a certain disease (predictive). Genetic testing may also be utilised in reproductive decision-making and is usually pertinent when parents are at high risk or have previously experienced a serious genetic disorder in the family. This application includes carrier testing, prenatal testing and preimplantation genetic diagnosis (done in conjunction with *in vitro* fertilisation). It is estimated that DNA testing is currently available for over 1000 genetic disorders. The number of genetic tests performed for diagnostic, confirmatory or predictive purposes was recently estimated to be likely above 700 000 per year with an economic dimension of around EUR 500 million.<sup>106</sup>

#### Economic significance of modern biotechnology diagnostics

The lack of relevant statistical data and databases means that only a superficial analysis of the economic significance of modern

104 European Commission COM (2006) 13: Communication from the Commission to the European Parliament and the Council on a Community Action Plan on the Protection and Welfare of Animals 2006-2010.

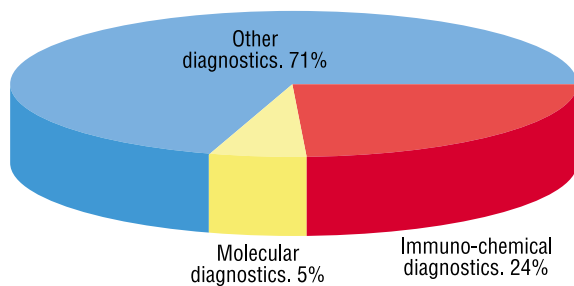
105 The US FDA defines *in vitro* diagnostics as: reagents, instruments and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and examination of specimens taken from the human body.

106 Ibarreta, D., A.K. Bock, C. Klein and E. Rodríguez-Cerezo (2003). Towards quality assurance and harmonisation of genetic testing services in the EU. European Commission, DG JRC/IPTS, EUR 20977.



biotechnology in diagnostics can be made for the sector and for the EU. The global IVD market was estimated at more than EUR 22 billion in 2004,<sup>107</sup> which equals about 6% of the combined pharmaceutical markets of the USA, EU and Japan. Immunochemistry and molecular testing represented about 30% of the market, or EUR 6.6 billion (EUR 5.4 billion for immunochemical tests, EUR 1.2 billion for molecular diagnostic tests) (Figure 2-7).

■ *Figure 2-7 Share of modern biotechnology diagnostics out of the global IVD diagnostics market in 2004*



Source: ETEPS<sup>108</sup>, IPTS calculations.

Five EU countries (UK, France, Italy, Germany, and Spain) account for about 26% of the modern biotechnology related diagnostics market in 2004 (EUR 1.7 billion), a similar share as for the overall IVD market. The US market share for IVD diagnostics represents about 42%, while the share of modern biotechnology diagnostics is even higher at 51% (EUR 3.4 billion). Considering that the population in the five EU countries and the USA are roughly similar, the USA seems to spend about twice as much on modern biotechnology diagnostics than the EU countries. This is also reflected in the higher share that these types of diagnostics have in the regional IVD market (37%; Table 2.2).

No information is available on the positioning of EU companies regarding modern biotechnology diagnostics. An indication can be derived from the list of the top 15 companies according to IVD sales,<sup>111</sup> which, based on the sales figures, might represent more than 80% of the IVD market. Only two EU companies are listed in the top 15 IVD companies (Bayer Diagnostics, Germany; bioMerieux, France), with sales of about EUR 2 billion or 9% of the world market. The share attributable to modern biotechnology diagnostics is not known. The majority of the top 15 companies are based in the USA.

■ *Table 2.2 Estimate of biotechnology-based diagnostics<sup>109</sup> and IVDs revenues in 2004*

	Biotechnology-based diagnostics (billion €)	Share of total	IVDs (billion €)	Share of total	Share of biotech in IVDs
Europe*	1.7	26%	5.8	26%	29%
USA	3.4	51%	9.3	42%	37%
Others	1.5	23%	7.0	32%	21%
<b>Total</b>	<b>6.6</b>	<b>100%</b>	<b>22.1</b>	<b>100%</b>	<b>30%</b>

Source: ETEPS<sup>110</sup>, IPTS calculations, \*Includes: UK, France, Spain, Italy, and Germany.

107 ETEPS (2006). Bio4EU Task 2 Main report.  
 108 ETEPS (2006). Bio4EU Task 2 Main report.  
 109 Immunochemistry and molecular diagnostics.  
 110 ETEPS (2006). Bio4EU Task 2 Main report.  
 111 ETEPS (2006). Bio4EU Task 2 Main report.



Social implications of modern biotechnology diagnostics

Diagnostics are gaining importance for health care, constituting an invaluable set of tools for diagnosis, but in recent years this has been even more true for prognosis and prevention. As they are often a central part of first-line clinical decisions, diagnostics have become a crucial component of health care, with growing social implications in terms of their impact on health outcomes and health care delivery and costs.<sup>112</sup>

In an era of increasing health care expenditure, the use of sophisticated diagnostics based on biotechnology is costly and may therefore pose a further economic strain on health care systems in spite of their potential positive role in improving public health through earlier diagnosis and prevention. In this context, assessing their impact on both quality of life and health care delivery and costs is essential. This is being done by way of three case studies, covering a broad spectrum of important communicable and non-communicable conditions. These include HIV/AIDS testing, cardiac diagnostic assays and genetic testing (phenylketonuria).

#### Modern biotechnology-based HIV/AIDS testing

The main types of HIV tests used currently for diagnosis, evaluation, monitoring and treatment of disease are based on modern biotechnology. These tests fall largely into two categories: i) protein-based (immunoassays) and ii) nucleic acid-based tests (NATs). The first category detects the presence of HIV (antibody or antigen) in a patient's blood sample and is typically used for diagnosing an infection or screening blood donations. Some immunoassays have been designed to give rapid results in a non-laboratory setting.

Nucleic acid tests detect DNA (or RNA) sequences, which are highly specific to the virus. These tests can detect HIV genetic material in very small amounts and with a quick turnaround, which makes them a vital tool for the early detection of an infection and for identifying mutated strains (genotyping). This application is crucial for monitoring drug resistance and disease management (e.g. applying appropriate therapy, monitoring transmissions etc.) and is widely applied. Their ability to identify emerging mutations before the phenotypic onset of drug resistance is another crucial advantage in terms of making a timely change in therapeutic strategy.

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). HIV belongs to the group of retroviruses typically characterised by the long interval between infection and symptom development. Infected individuals suffer gradual but severe deterioration of their immune system. The first case of HIV/AIDS was reported more than 20 years ago; by the end of 2005 an estimated 38.6 million people were infected worldwide.<sup>113</sup> Antiretroviral therapy became available a decade ago and increased patient survival considerably, converting HIV/AIDS into a chronic disease. However, the high mutability of the virus and the resulting drug resistance remains a challenge for therapy. Currently, sub-Saharan countries are most affected. According to UNAIDS, about 1.2 million people in the USA were living with HIV at the end of 2005, and approximately 40 000 new infections occur each year. In 52 countries of the WHO's European region, it has been estimated that 2.2 million people were living with the virus<sup>114</sup> in 2005. The majority of these are in Eastern Europe and central Asia, where the overall rates of newly diagnosed HIV infections

112 The Lewin Group (2005). The value of diagnostics, innovation, adoption and diffusion into health care. AdvaMed, Washington, DC.

113 UNAIDS (2006). Report on the global AIDS epidemic. UNAIDS, Geneva.

114 WHO Europe (2005). "HIV/AIDS in Europe: Overview." Fact sheet EURO/14/05.





have increased significantly since 1998. In the same report, it is predicted that by 2010 100 000-580 000 people will need antiretroviral therapy, indicating the growing importance of HIV/AIDS for health care.

A recent study indicates that in Europe drug-resistant virus variants are frequently present in patients who have been recently infected or patients suffering from a chronic infection.<sup>115</sup> The early identification of such variants is critical for monitoring the progression of the disease but more importantly for adjusting the therapy accordingly.<sup>116</sup> Thus, resistance testing is now recommended for treatment-naïve patients, persons newly infected within two years and patients who are not responding to therapy or during pregnancy<sup>117</sup>. However, as these tests are relatively expensive, their widespread application is a matter for debate.

Several studies<sup>118</sup> have investigated the cost-effectiveness of routinely using genotyping for drug resistance in different scenarios (e.g. treatment failure or treatment-naïve patients, prevalence etc.). In the studies reviewed, genotyping was shown to be cost-effective although at different ratios and depending on the prevalence of the disease. Although most of the studies investigate the situation in the USA (there testing is already reimbursed in all but two states) one European study reports a similar result i.e. that routine testing after each treatment failure increases both life expectancy and health care costs per patient.<sup>119</sup> The cost-effectiveness of immunoassays is not clear.

The uptake of HIV genotyping in routine clinical practice is predicted to be driven by the high costs of new drugs. As monitoring drug resistance is essential for the effective management of HIV-infected patients, these biotech tests may have a significant impact on the epidemic by minimising its spread.

#### Modern biotechnology in cardiac diagnostic assays

The term cardiovascular disease (CVD) collectively refers to a class of diseases affecting the heart or the blood vessels. Individuals suffering from cardiovascular disease, particularly arteriosclerosis, are at high risk of an Acute Myocardial Infarction (AMI, heart attack),<sup>120</sup> which is currently the leading cause of death in the adult population in the USA (one out of every five deaths<sup>121</sup>). The rapid diagnosis of an AMI episode (and its distinction from other non-critical conditions with similar symptoms) is crucial for the effective management of the disease.<sup>122</sup>

Cardiovascular disease (CVD) was estimated to have contributed to a third of global deaths in 1999 (WHO) and it is predicted to become the leading cause of death in developing countries by 2010.<sup>123</sup> In the EU, cardiovascular disease causes more than 1.9 million deaths per year and is the main cause of years of life lost due to premature deaths.<sup>124</sup> The overall cost of CVD in the EU was recently estimated at EUR 169 billion annually.<sup>125</sup>

115 Wensing, A.M.J. et al. (2005). *The Journal of Infectious Diseases* 192: 958-966.

116 Blum, R.A., N. Wylie, T. England and C. French (2005). *Pharmacogenomics* 2: 169-179.

117 Guidelines have been published by the US Department of Health and Human Services Panel on Clinical Practices for treatment of HIV infection, the EuroGuidelines Group, and the British HIV Association.

118 Weinstein, M.C. et al. (2001). *Annals of Internal Medicine* 134: 440-450. Sanders, G.D. et al. (2005). *The New England Journal of Medicine* 352: 570-585. Paltiel, A.D. et al. (2006). *Annals of Internal Medicine* 145: 797-806.

119 Corzillius, M. et al. (2004). *Antiviral Therapy* 9: 27-36.

120 A heart attack is caused when the supply of blood and oxygen to the heart is blocked. This is typically a result of a clot in the coronary artery.

121 American Heart Association (<http://www.americanheart.org/presenter.jhtml?identifier=4591>).

122 American Heart Association, "Heart and Stroke Facts", <http://www.americanheart.org/downloadable/heart/1056719919740HSFacts2003text.pdf>.

123 [http://www.who.int/cardiovascular\\_diseases/priorities/en/](http://www.who.int/cardiovascular_diseases/priorities/en/).

124 Petersen, S. et al. (2005). "European cardiovascular disease statistics." British Heart Foundation, London.

125 Leal, J. et al. (2006). *European Heart Journal* 27: 1610-1619.



Tests for the diagnosis of AMI are based primarily on detecting a defined set of biomarkers associated with this condition. These assays are based on the use of monoclonal antibodies to detect AMI-associated proteins. Their use in the clinic has made it possible to rapidly identify patients suffering an AMI episode, and to distinguish them from patients who display similar symptoms but are not actually in danger of an AMI. Additionally, these assays can be applied in monitoring disease progression in response to specific therapies.

The economic benefit for health care systems resulting from the clinical application of cardiac diagnostics is not entirely clear, although it is estimated that a positive impact may be made by saving, for example, the costs of treating patients who are not in danger (it is estimated that only 15% admitted to hospitals for chest pains are actually experiencing a heart attack).<sup>126</sup> Certain studies support this estimation. For instance, one investigation explored the cost-effectiveness of various diagnostic strategies for patients suffering chest pain (one of the main symptoms of AMI but also of other non-life-threatening conditions). The study showed that immediate cardiac immunoassay testing alone had incremental cost-effectiveness as compared to immunoassay testing combined with overnight hospital admission for further observation.<sup>127</sup> Some hospitals have reported savings from using cardiac immunoassays (mainly as a result of minimising the number of days a patient might spent in hospital just for observation), in spite of the high cost of the test.<sup>128,129</sup>

## Genetic testing

Modern biotechnology techniques have led to a wealth of genetic information, especially in correlation to specific diseases. This has in turn facilitated the rapid development of tests that can diagnose or identify the risk of disease by analysing an individual's genetic makeup. Genetic testing mainly refers to DNA testing<sup>130</sup>. It is estimated that DNA testing is currently available for over 1000 genetic disorders, and the methods rely mainly on detecting specific mutations through PCR and DNA sequencing.<sup>131</sup>

The most common diseases for which genetic testing is performed are those with a higher frequency in a population. These include cystic fibrosis, Duchenne muscular dystrophy, haemophilia A and B, familial breast cancer, fragile-X syndrome, myotonic dystrophy, haemochromatosis, and hereditary non-polyposis coli. The association of specific mutations with these diseases is well established; this may be one reason for the increased use of the respective tests. In certain cases, genetic testing has replaced other diagnostic methods. For instance, the genetic test for myotonic dystrophy is widely used in clinical practice as it is less invasive and more accurate than the previously applied electromyography, which failed to distinguish between this condition and other less severe types of myotonia.<sup>132</sup>

In addition to disease testing, other quite common, but perhaps less visible, non-medical applications of genetic testing include paternity testing and forensics. Other applications, which are only indirectly related to human health, include testing for animal diseases and food

126 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.

127 Goodacre, S. and N. Calvert (2003). *Emergency Medicine Journal* 20: 429-433.

128 Gwynedd Hospital Bangor, Wales.

129 Polanczyk, C.A. et al. (1999). *Annals of Internal Medicine* 131: 909-918.

130 Genetic testing is defined in this report as DNA-based testing used to identify variations in the DNA sequence that correlate with a disease or higher risk to develop a disease.

131 McPherson, E. (2006). *Clinical Medicine and Research* 2: 123-129.

132 McPherson, E. (2006). *Clinical Medicine and Research* 2: 123-129.



testing (discussed in more detail in Chapter 2.2.2.3)

However, one broader clinical implementation of genetic testing is largely missing. For instance, testing for phenylketonuria, a genetically inherited metabolic disease, uses primarily biochemical methods, rather than DNA testing per se, partly because the biochemical tests are very efficient and not as costly, but also because the association of specific mutations with the disease phenotype is not yet entirely clear.<sup>133</sup>

The frequent lack of a clear association between a particular genetic composition and a pathology stems primarily from the complex nature of the human genome but also from the fact that several genetic-based diseases may be influenced by the environment, which makes it difficult to design highly specific and sensitive DNA tests (this is less likely to affect monogenic disorders where one specific gene is linked to a certain condition). However, the limited application of genetic testing in the clinic may be a result of several other factors, including the lack of proven utility in clinical, social and ethical terms, and associated costs (both direct and indirect, e.g. for genetic counselling).<sup>134</sup> For instance, BRCA1 and 2 testing and counselling for breast cancer was estimated to cost more than EUR 1500 per test in 2001.<sup>135</sup>

The cost-effectiveness of genetic testing depends on many factors,<sup>136</sup> and it is an essential tool for decision-makers and stakeholders when considering genetic testing (e.g. government, insurers etc.). However, only few economic analyses of genetic testing exist, and those that are available have covered a limited number of diseases. The overall scarcity of cost-effectiveness studies for genetic testing makes it difficult to

evaluate their potential impact on the efficiency of health care systems. This is further complicated by the unclear reimbursement situation and the limited information on patients' views on these diagnostic technologies (e.g. are they willing to pay for these tests even if their benefit is not clear). More research would be needed on these aspects, which will affect the wider clinical use of genetic testing in the future.

One important implication of genetic testing relates to the development of systematic collections of human biological samples and associated data, known as biobanks. These have become an important research tool, particularly in the context of genetic association studies.<sup>137</sup> While the importance of biobanks in improving the understanding of disease is accepted, ethical concerns may be raised with regard to the use and protection of the collected data and/or samples. At the EU level, the regulatory framework for protecting personal data is provided by Directive 95/46/EC.<sup>138</sup>

### **2.1.5 Emerging biotechnology applications in medicine and health care**

#### Cell-based therapies

Cell-based therapies are a new therapeutic approach which is in development. Tissue engineering (TE), aimed at regenerating diseased tissues and organs through the use of cells and the aid of supporting structures and/or biomolecules, is currently the most advanced cell-based therapy. About 40 products are available on the market, mainly autologous skin replacements, cartilage and bone products, generating sales of about EUR 60 million/year. The field is considered to

133 ETEPS (2006). Bio4EU Task 2 Case studies report – Human Health Applications.

134 Higashi, M.K. and D.L. Veenstra (2003). *The American Journal of Managed Care* 9: 493-500.

135 Lawrence, W.F. et al. (2001). *Cancer Epidemiol. Biomarkers Prev.* 10: 475-481.

136 Phillips, K.A. et al. (2004). *The American Journal of Managed Care* 10: 425-431.

137 Smith, G.D. et al. (2005). *The Lancet* 366: 1484-1498.

138 Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. OJ L281/31 23.11.1995.

be in an early development phase; R&D activities are targeting diabetes (targeting insulin producing cells) and cardiovascular diseases (engineering e.g. heart valves and blood vessels), but also full organ replacement as a long-term objective. Besides a number of technical challenges (e.g. suitable biomaterial for scaffolds, understanding and controlling cell differentiation, off-the-shelf products, prevention of immunogenic rejection, scaling up manufacturing processes, quality control tools), the lack of a harmonised EU regulatory framework and the fact that current TE products do not provide unique life-saving treatments and face substantial competition with (less expensive) conventional products presents challenges for the development of TE. A proposal for a new regulation covering TE is currently being discussed by the EU institutions<sup>139</sup>.

Other cell-based therapies such as those for the treatment of Parkinson with foetal cells are still in early clinical development. The emerging character of cell-based therapies is also reflected in the increasing, albeit low, numbers of clinical trials carried out by US and EU companies. EU companies show increasing activity since 1999, with about 15 clinical trials in 2006. US companies account for about twice as many clinical trials (30 in 2006), with no significant growth since 2002. However, many cell-based therapies are probably tested on an individual patient's basis with autologous cells, and have not yet reached the stage of a defined product to be developed. Thus the number of clinical trials might underestimate the applications in the clinic.

## Stem cells

Stem cells are non-specialized cells that have the capacity for self-renewal and the ability to differentiate under certain physiologic or experimental conditions, into various types of specialized cells<sup>140</sup>. This unique ability to generate any type of cell has brought stem cells to the forefront of medical research particularly with respect to treatment of diseases (e.g. cancer, cardiovascular and neurodegenerative disorders) but also including tissue engineering<sup>141,142</sup>. At the same time, the use of stem cells in drug discovery is recognized as important and is gaining ground<sup>143,144</sup>.

There are two main categories of stem cells: embryonic stem cells (ESCs), which are derived from the inner cell mass of embryos at the blastocyst stage, and somatic (adult) stem cells, which are derived from various fetal and post-natal organs<sup>145</sup>. The main difference between the two types is that ESCs are pluripotent, i.e. have the capacity to differentiate into any one of the more than 200 cell types found in the body, whereas adult stem cells can differentiate only into the cell types found in the tissue in which they reside. However, adult stem cells are difficult to access and isolate in some cases, and, unlike ESCs, they do not replicate indefinitely in culture.

One application of stem cells in the clinic, namely bone marrow transplantation, has been a reality for over 40 years. This process is mainly used with the aim of replenishing haematopoietic stem cells in leukaemia patients. Currently, clinical trials are being carried out testing the use

139 <http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/>.

140 <http://stemcells.nih.gov/info/basics/basics1.asp>.

141 Vats, A. et al. (2005) *J. R. Soc. Med* 98: 346-350.

142 NIH (2001). "Stem cells: Scientific progress and future research directions". U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD.

143 Tutter, A.V., G.A. Baltus, and S. Kadam (2006). *Curr. Opin. Drug Discov. Devel.* 2: 169-175.

144 McNeish, J. (2004). *Nat. Rev. Drug Discov.* 3: 70-80.

145 O'Connor, T.P. and R.G. Crystal (2006). *Nat. Rev. Genetics* 7: 261-276.



of adult stem cells in the treatment of inherited diseases such as lysosomal storage disorders and immunodeficiencies<sup>146</sup>. Another application is in delivering gene therapy for the treatment of cancers (e.g. ovarian, lymphoma) but also for monogenic disorders (e.g. Gaucher's disease, Fanconi anaemia)<sup>147</sup>. Research involving ESCs for the treatment of diabetes, Alzheimer's, and Parkinson's disease, is still in the preclinical stage. Stem-cell-based therapies for spinal cord related disease or injuries have also attracted scientific attention. In spite of this, technical challenges (e.g. immunorejection, potential uncontrolled cell proliferation which may lead to cancer) and the limited understanding of the stem-cell differentiation process still hinder the wider clinical application of stem cells.

Research on human embryonic stem cells is controversial in many countries, due to the fact that extracting stem cells kills the embryo.<sup>148</sup> Some ethicists argue that embryonic stem cell research is an instrumentalisation of human beings and should thus be completely prohibited, regardless of the potential benefits for treating disease<sup>149</sup>. Many research efforts aim at finding solutions to facilitate the generation of ESCs without damaging or killing the embryo. Several concerns have also been raised regarding privacy of the donors of cells and embryos and the use of ESCs to create human embryos (for non-research purposes) or human/nonhuman chimeras<sup>150</sup>. Although stem cell therapies are still far from approval, a proliferation of related patents is already a reality, raising concerns about its potential impact on research. A recent survey shows that nearly 18 000 stem cell patents have been filed since 1994, with the majority coming from the USA<sup>151</sup>. Similar figures were retrieved

only considering patent applications at EPO. The results indicate that stem cell patents have share of about 6% of all biotechnology patents in the period 1995-2004, equivalent to about 5000 patents<sup>152</sup>.

### Gene therapy

The concept of gene therapy is to introduce a gene into a cell, resulting in a product which achieves a specific therapeutic goal. For instance, a defective gene may be replaced by a functional one – this approach has been applied in the treatment of one type of severe combined immunodeficiency (SCID). Worldwide, about 26 children suffering from SCID have been treated with gene therapy with some success. Gene therapy is also being tested in clinical trials for the treatment of cancer, replacing the defective tumour suppressor gene p53, one of the most common defects linked to cancer. Other gene therapy products in clinical trials target cardiovascular diseases, monogenic hereditary disorders such as cystic fibrosis and respiratory diseases such as asthma<sup>153</sup>.

Gene therapy, while considered a promising approach, has had several setbacks. In addition to difficulties in achieving the required efficacy of treatment, safety turned out to be an issue. In 1999, a patient in the USA died after having participated in a gene therapy clinical trial, and in France children developed leukaemia after having been treated with gene therapy against SCID. These difficulties may be reflected in the development of new gene therapy approaches. Since 2000 in the USA and 2001 in the EU, the number of clinical trials has not increased and is stable at about 50 and 30, respectively<sup>154</sup>. For

146 Fischbach, G. D. and R.L. Fischbach (2004). *J. Clin. Invest.* 114: 1364-1370.

147 Thomson, J.A. et al. (1998). *Science* 282: 1145-1147.

148 Nuffield Council (2000) "Stem cell therapy: the ethical issues." Discussion Paper. Nuffield Council on Bioethics, London.

149 Eurobarometer 64.3. [http://www.ec.europa.eu/research/press/2006/pdf/pr1906\\_eb\\_64\\_3\\_final\\_report-may2006\\_en.pdf](http://www.ec.europa.eu/research/press/2006/pdf/pr1906_eb_64_3_final_report-may2006_en.pdf).

150 Greely, H.T. (2006). *PLoS Medicine* 3: 571-575.

151 UK Stem Cell Initiative (2005). Report and Recommendations. UK Department of Health, London, <http://www.advisorybodies.doh.gov.uk/uksci/uksci-reportnov05.pdf>.

152 ETEPS (2006). Bio4EU Task 2 Main report.

153 O'Connor, T.P. and R.G. Crystal (2006). *Nat. Rev. Genetics* 7: 261-276. Branca, M.A. (2005). *Nature Biotechnology* 23(5): 519-521. Seymour, L.W. (2006). *Trends in Biotechnology* 24(8): 347-349.

154 ETEPS (2006). Bio4EU Task 2 Main report.



comparison, for pharmaceuticals, the number of clinical trials was in the range of 1500 and 1000 for the USA and EU in 2005. Gene therapy patent applications increased from zero in the period 1995–1997 to about 14% of all biotechnology patents worldwide in the period 2002–2004<sup>155</sup>. Only one product has currently been marketed, in China, since 2003 (p53-based Gendicine against head and neck squamous cell carcinoma).

#### Antisense and RNA interference (RNAi)-based therapies

The underlying causes of several diseases are pathogenic proteins that are produced by the human body's cells. The selective inhibition of gene expression and thus protein production is potentially a powerful tool in therapy. Two recently emerging approaches use nucleic acid to achieve this goal: antisense technology and RNA interference.

Antisense technology uses synthesised short, single stranded sequences of nucleic acids (oligonucleotides) which bind sequence-specifically to mRNA (i.e. the molecule from which a protein is generated) and initiate degradation of the target mRNA inhibiting expression and protein production. Antisense approaches are targeted at cancer and viral diseases. So far only one antisense product has been made commercially available, for the treatment of cytomegalovirus retinitis in HIV/AIDS patients<sup>156</sup>.

RNA interference (RNAi) approaches make use of a cellular mechanism for silencing gene expression. Specific mRNAs can be targeted to be enzymatically cleaved leading to a highly specific decrease in production of the respective protein. The discovery of RNAi gene silencing by two USA-based researchers in 1998 was awarded the 2006 Nobel Prize in Medicine<sup>157</sup>. Since

1998, research activities have taken off, leading to the first therapeutic products in pre-clinical and clinical development by US companies in 2003 and by EU companies two years later. In 2006, about 49 products were in development by US companies, while EU companies were developing 9 products. Worldwide, in 2005, only 5 products were in clinical trials, all developed by US companies.

#### Therapeutic vaccines

Vaccines are typically prophylactic, i.e. they are administered to healthy individuals to prevent infectious diseases. However, currently there is growing interest in developing and using vaccines for the treatment of various diseases as well, including infectious diseases. These therapeutic vaccines use disease-specific proteins as antigens to boost or induce a specific immune response in the patient with the aim of treating an already existing condition. Although the majority of the work is geared to developing vaccines against tumours, several infectious and autoimmune diseases such as AIDS, hepatitis B, tuberculosis, and substance dependence are also targeted. At the same time, current studies focus on the development of therapeutic vaccines against neurodegenerative diseases (e.g. Alzheimer's), and prion diseases such as Bovine Spongiform Encephalopathy (BSE) and Creutzfeldt-Jakob disease<sup>158</sup>. Therapeutic vaccines often include cell-based approaches, using the patient's own cells, e.g. cancer cells, to stimulate an immune response.

Currently, three therapeutic cancer vaccines are on the market in some countries. Additionally, four vaccines against infectious diseases are marketed as both prophylactic and therapeutic vaccines. In 2005, EU companies had about 30 products in clinical trials, with the numbers

155 ETEPS (2006). Bio4EU Task 2 Main report.

156 <http://ott.od.nih.gov/pdfs/VitraveneCS.pdf>.

157 [http://nobelprize.org/nobel\\_prizes/medicine/laureates/2006/](http://nobelprize.org/nobel_prizes/medicine/laureates/2006/).

158 Sela, M. and R.M. Hilleman (2004). *PNAS* 101: 14559.



steadily rising since 1995; US companies' products were increasing slightly faster with about 45 products in clinical trials in 2005.

### Pharmacogenetics

Pharmacogenetics is the study of the influence of genetic variation on inter-individual differences in drug response with the aim of tailoring therapy to individual genetic make-up. Although it is not a new discipline<sup>159</sup>, it has recently been invigorated by advances in genomics which allow the study of not just single genes but entire molecular pathways. These biotechnology tools have significantly improved not only the identification of the underlying causes of disease and adverse drug reactions, but also the search for new drug targets (the term pharmacogenomics has been coined to describe this approach)<sup>160</sup>.

Pharmacogenetics may play an important role in reducing the cost of disease management (e.g. the high cost of treating adverse drug reactions) by making treatments as safe and effective as possible for every individual or for specific populations (e.g. BiDiI – the first “race-specific” therapy approved by FDA in 2005)<sup>161,162</sup>. Additionally, it might help improve drug discovery and development (e.g. design of better/more focused clinical trials by identifying at-risk patients<sup>163</sup>, identification of drug targets etc.), which would in turn potentially reduce the costs of drug development as well.

Nevertheless, only a few products have reached the market and clinical practice. Examples include: i) the DNA chip AmpliChip which is testing for variants of two key enzymes

in drug metabolism (reached the market in 2003)<sup>164</sup>, ii) the HER-2 test which is used prior to prescribing Herceptin® to breast cancer patients (only 20-30% of women with breast cancer overexpress HER-2 and the drug affects only cancers overexpressing this molecule)<sup>165</sup>, and iii) a test for variants of the enzyme thiopurine methyltransferase before prescribing 6-mercaptopurine for the treatment of acute lymphocytic leukaemia in children. A different example, not directly related to drug response though, is Bayer's Trugene® HIV genotyping test which may be used to monitor drug resistance (as a result of the virus' mutability) in HIV-infected patients, and modify therapy accordingly<sup>166</sup>.

Several diagnostic products with a pharmacogenetic component are currently being developed. In a recent study<sup>167</sup>, 21 tests were identified as being under development by companies for applications such as drug metabolism, anti-viral drug resistance, and cancer (14 in the US, 7 in the EU). Most companies see pharmacogenetics as an integral part of the drug development process, rather than just as an approach to diagnostic test development for personalised medicine. Nevertheless, co-development of a drug with its respective diagnostic is increasingly receiving attention and it is seen as an important opportunity for identifying drug responders or individuals at potential risk for adverse events. The FDA published a concept paper on this topic in 2005 with the aim of initiating discussions between industry and government and ultimately developing draft guidance<sup>168</sup>.

159 Motulsky, A.G. (1957). *J. Am. Med. Assoc.* 165: 835-837.

160 Goldstein, D.B., S.K. Tate and S.M. Sisodiya (2003). *Nat. Rev. Genetics* 4: 937-947.

161 Henig, R.M. (2004). “The genome in black and white (and gray)” *New York Times* (New York) 47, 10 October.

162 Daar, A. S. and P.A. Singer (2005). *Nat. Rev. Genetics* 6: 241-246.

163 MORST (2005). Futurewatch: Biotechnologies to 2025. Ministry of Research, Science and Technology, Wellington.

164 Nuffield Council (2003) “Pharmacogenetics: ethical issues.” Discussion Paper. Nuffield Council on Bioethics, London.

165 Herper, M. (2005). Genentech's wall of data. *Forbes.com* (New York), April 26.

166 <http://www.fda.gov/cber/seltr/K000038L.htm>.

167 Zika, E., D. Gurwitz and D. Ibarreta (2006). Pharmacogenetics and pharmacogenomics: state-of-the-art and potential socio-economic impact in the EU. European Commission DG JRC/IPTS, EUR 22214.

168 <http://www.fda.gov/cder/genomics/pharmacococeptfn.pdf>.

## Nanomedicine

The term nanomedicine may be defined as the use of nanoscale or nanostructured materials in medicine, which, according to their structure, have unique medical effects (e.g. the ability to cross biological barriers or the passive targeting of tissues)<sup>169</sup>. The potential of nanomedicine for delivering more specific and effective therapies with minimal side-effects is well recognised, as is its contribution to the development of more elaborate and sensitive diagnostics. Nevertheless, several challenges must be overcome before nanomedicine is widely applied in the clinic.

Nanomedicine applications include drug (and gene) delivery, *in vitro* diagnostics, *in vivo* imaging and biomaterials (e.g. implants). Currently, the field is dominated by nano drug delivery systems (NDDS), which account for more than 75% of the market<sup>170</sup>. The aim of NDDS is to improve the bioavailability and the pharmacokinetics of therapeutics, thus improving efficacy and specificity while minimising side effects. Another important goal is to improve delivery (e.g. render it more specific to the site of disease).

Nanomedicine is a rapidly growing research field with significant potential to deliver improved diagnostics and innovative therapeutics. In recent years, the number of research publications on nanomedicine has greatly increased (more than 1200 in 2004)<sup>171</sup>, with 76% of these focusing on drug delivery. The EU leads in scientific output (36% of worldwide publications are European, compared with 32% from the USA). Commercial interest in nanomedicine applications has also increased in the last 5 years, a clear indication of this trend being the rise in the number of patent filings. However, in patenting (25%), the EU lags behind the USA, which holds 54% of

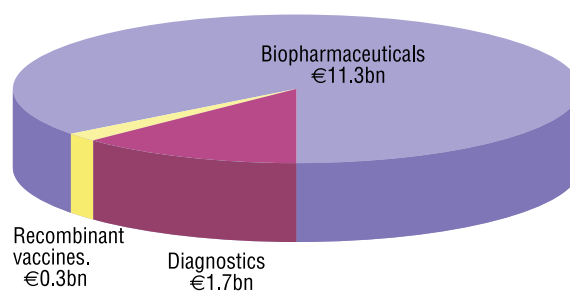
patents in nanomedicine, indicating the difficulty of translating the EU's strength in research into products. 38 nanomedicine products were found to be on the market, generating estimated sales of EUR 5.4 billion in 2004<sup>172</sup>.

### 2.1.6 Summary

#### Economic significance

Modern biotechnology in medicine and health care considering market values is strongest in biopharmaceuticals, followed by *in vitro* diagnostics and vaccines (Figure 2-8).

■ Figure 2-8 Share of biopharmaceuticals, recombinant vaccines and modern biotechnology diagnostics in the EU in 2005, by turnover (€ billion)



Biopharmaceuticals, vaccines and part of the diagnostics sector are covered by the pharmaceutical sector in NACE<sup>173</sup>. In 2002, the EU pharmaceutical sector (NACE DG 24.4<sup>174</sup>) contributed about 4% to the gross value added (GVA) of the manufacturing sector (NACE D), and 0.7% to overall EU GVA.

169 Wagner, V., A. Dullaart, A.K. Bock and A. Zweck (2006). *Nature Biotechnology* 24: 1211-1217.

170 Wagner, V., A. Dullaart, A.K. Bock and A. Zweck (2006). *Nature Biotechnology* 24: 1211-1217.

171 Wagner, V., A. Dullaart, A.K. Bock and A. Zweck (2006). *Nature Biotechnology* 24: 1211-1217.

172 Wagner, V., A. Dullaart, A.K. Bock and A. Zweck (2006). *Nature Biotechnology* 24: 1211-1217.

173 NACE is the Nomenclature of economic activities (French: Nomenclature générale des activités économiques) applied by Eurostat.

174 NACE DG 24.4 includes Manufacture of pharmaceuticals, medicinal chemicals and botanical products.





The share of GVA in the turnover of the pharmaceutical sector is about 34%. Given the EU market value of biopharmaceuticals and recombinant vaccines (EUR 7.3 billion in 2002), and assuming a similar GVA share for these products as for pharmaceuticals (although biotechnology as a new technology might improve process efficiency), modern biotechnology accounted for 5.3% of the value-added of the pharmaceutical sector in 2002, and for 0.25% of that of the manufacturing sector. This puts it on a par with agro-chemicals (NACE DG 24.2) or man-made fibres (NACE DG 24.7) (see Table 2.3). Biotechnology-based diagnostics, assuming the same turnover/GVA ratio as for pharmaceuticals, play a minor role compared to biopharmaceuticals.

This calculation only considered the direct economic contribution of biopharmaceuticals, recombinant vaccines and diagnostics. Indirect contributions stemming from the use of these products and potentially resulting in cost savings

and improved health status have not been included. A recent study investigating the link between health and the economy in the European Union finds that better health contributes to economic growth in four ways: higher productivity, higher labour supply, higher skills, and more savings available for more capital formation (e.g. in anticipation of a longer life expectancy after retirement)<sup>175</sup>. The indirect contribution of modern biotechnology to economic growth by enabling a healthier population could not be discerned from the available literature.

EU companies seem to be less competitive in product development, probably also because the biotechnology sector is less developed and less mature. In terms of products in clinical trials, US companies in 2005 had 75% more products in the pipeline than EU companies, which is also indicative of a stronger position on the market in future. In vaccines, the EU has a strong position; however, clinical trials, i.e. future products, are dominated by US companies. In modern biotechnology-based diagnostics, the situation is

**Table 2.3 Contribution of biotechnology-based applications to the economy of the EU**

EU-25 (2002)	Turnover (€ billion)	GVA (€ billion)	Share of chemicals GVA (%)	Share of manufacturing GVA (%)	Share of EU-25 GVA (%)
EU-25 (all economic activity)		8783			100
Manufacturing (NACE D)	5799	1529		100	17.4
Chemicals (NACE DG 24)	601	171	100	11	2
Agro-chemicals (NACE DG 24.2)	12	2.5	0.03	0.2	0.03
<b>Pharmaceuticals (NACE DG 24.4)</b>	<b>171</b>	<b>58</b>	<b>34</b>	<b>4</b>	<b>0.7</b>
Man-made fibres (NACE DG 24.7)	12	3	0.03	0.2	0.03
<b>Biotechnology-based products</b>					
Biopharmaceuticals*	7	2.4	1.4	0.2	0.03
Diagnostics**	1.7	0.6	0.06	0.04	0.01
Recombinant vaccines	0.3	0.1	0.4	0.007	0.001
<b>Total biotech</b>	<b>9</b>	<b>3.1</b>	<b>1.86</b>	<b>0.25</b>	<b>0.04</b>

\*EU-19; \*\* Includes: UK, France, Spain, Italy, and Germany, 2004; figures in italics are estimates.

175 Suhrcke, M. et al. (2005). The contribution of health to the economy in the European Union. European Commission, DG Health and Consumer Protection.



not clear. The small proportion of EU companies in the top 15 diagnostics companies could also indicate a relatively weak position in the relevant subsectors.

#### Contribution to employment

Modern biotechnology's contribution to employment is mainly seen in the creation of higher qualified jobs. The quantitative impact is difficult to measure, mainly due to limited data availability and the difficulties of including indirect employment effects. However, employment effects are likely to correspond to the overall diffusion of modern biotechnology applications. As with the diffusion of biotechnology applications, it can be assumed that some of the newly generated jobs take the place of existing ones.

#### Social implications

A general conclusion regarding health biotechnology's contribution to public health in terms of better disease prevention and treatment, cost-effective interventions, and better quality of life for patients is difficult to draw, as this strongly depends on the individual product and the condition treated. The case studies analysed in this study seem to indicate that biopharmaceuticals and recombinant vaccines are effective approaches to disease treatment and prevention. Modern biotechnology has enabled a safe and in principle unlimited supply of well defined products, in contrast to isolation from animal or human sources (insulin, glucocerebrosidase, hepatitis B vaccine). It has also opened up the prospect of further advances in treatment for the benefit of patients (insulin analogues). However, all these advantages come at a price, and biopharmaceuticals, partly due to their complex manufacturing and handling, are comparatively costly in general. The cost-effectiveness of the

biopharmaceuticals studied often could not be determined due to a lack of appropriate studies. In some cases there are no conventional alternatives for comparison, which, for example in the case of orphan drugs such as glucocerebrosidase, raises difficult questions concerning the affordability for health care systems of very expensive treatment for a limited group of patients. However, it seems that for example the recombinant hepatitis B vaccine is cost-effective, partly due to its preventive character.

Diagnostics based on modern biotechnology appear to be gaining importance in all aspects of clinical practice, including disease diagnosis, monitoring and prevention. However, their actual implementation in the clinic varies widely, ranging from routine (e.g. HIV testing for monitoring drug resistance) to limited use (e.g. genetic testing for phenylketonuria). Moreover, although these diagnostic tools may offer clinical benefits they potentially represent an economic strain on health care systems mainly because of their direct and indirect costs. Further cost-effectiveness studies would help elucidate their actual overall benefit. Some experts, in fact, highlight the use of these tools to complement, rather than to replace, clinical medicine<sup>176</sup>.

Cost-effectiveness analyses are still generally rather scarce, and may present diverging results depending on the methodologies applied. Thus, some of the results should be regarded as preliminary and may be difficult to extrapolate in reaching a general conclusion on the social implications of modern biotechnology applications as a whole in medicine and health care.

#### Environmental implications

The use and/or manufacturing of biotechnology-based products for the treatment

176 McPherson, E. (2006). *Clinical Medicine and Research* 2: 123-129.

(or diagnosis) of humans or animals may have a potential impact on the environment. However, direct evidence for this is scarce; it is often thought that the production of medicinal products using biotechnological approaches might have less negative effects on the environment than previous methods.

The potential environmental impact of biotechnology-based products has been recognised by regulatory authorities. In the EU, Directive 2001/83/EC<sup>177</sup> relating to medicinal products for human use first introduced a requirement for the assessment of the environmental impact of such products on a case-by-case basis, prior to marketing authorisation. In this context, the European Medicines Agency (EMA) has recently published guidelines on the environmental risk assessment of medicinal products for human use<sup>178</sup> which is focusing on the potential risks arising from the use of the products rather than their manufacturing. Another EMA guideline also addresses the environmental risk assessment of products containing or consisting of genetically modified organisms<sup>179</sup>, based on the requirement under pharmaceutical legislation (Regulation EC/726/2004<sup>180</sup>) that human medicinal products respect the environmental safety requirements laid down in Directive 2001/18/EC<sup>181</sup> on the deliberate release into the environment of genetically modified organisms. At the same time, ERApharm, an FP6-funded programme aiming at improving the scientific basis and methods for evaluating potential risks that pharmaceuticals pose to the environment, is expected to finalise its results and provide relevant recommendations in 2007<sup>182</sup>.

In addition to biopharmaceuticals, biotechnology is applied in the production



process of pharmaceutical compounds. The ratio of biotechnological to chemical processes is estimated to range between 10% and 15%<sup>183</sup> and their application in the manufacturing of health-related products such as antibiotics might have a positive impact on the environment by improving resource and energy use, emissions of other pollutants to water, air and soil, and generation of waste. One example of this is the production of cephalosporin (see Chapter 2.3.1.6).



## 2.2 Modern biotechnology in primary production and agro-food

Primary production and agro-food encompasses the primary sectors producing raw materials, i.e. agriculture, forestry, horticulture, animal husbandry, and fisheries, as well as the food processing and retailing sector beyond the “farm gate”, supplying the consumer with food products. The food chain (Figure 2-9) that connects primary production and consumers (in the “farm to fork” approach) includes complex linkages. Changes in one part of the chain (e.g. improvements in pig meat quality due to breeding efforts) impact on the other parts, e.g. providing advantages for farmers, retailers, and consumers.

Modern biotechnology is mainly applied in the sectors providing inputs to primary production, such as breeding and propagation of plants and animals, the production of feed additives, veterinary pharmaceuticals and diagnostics. Furthermore, via the use of the

177 Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community Code relating to medicinal products for human use. OJ L 358, 18.12.1986.

178 <http://www.emea.eu.int/pdfs/human/swp/444700en.pdf>.

179 <http://www.emea.eu.int/pdfs/human/bwp/13514804en.pdf>.

180 Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p.1.

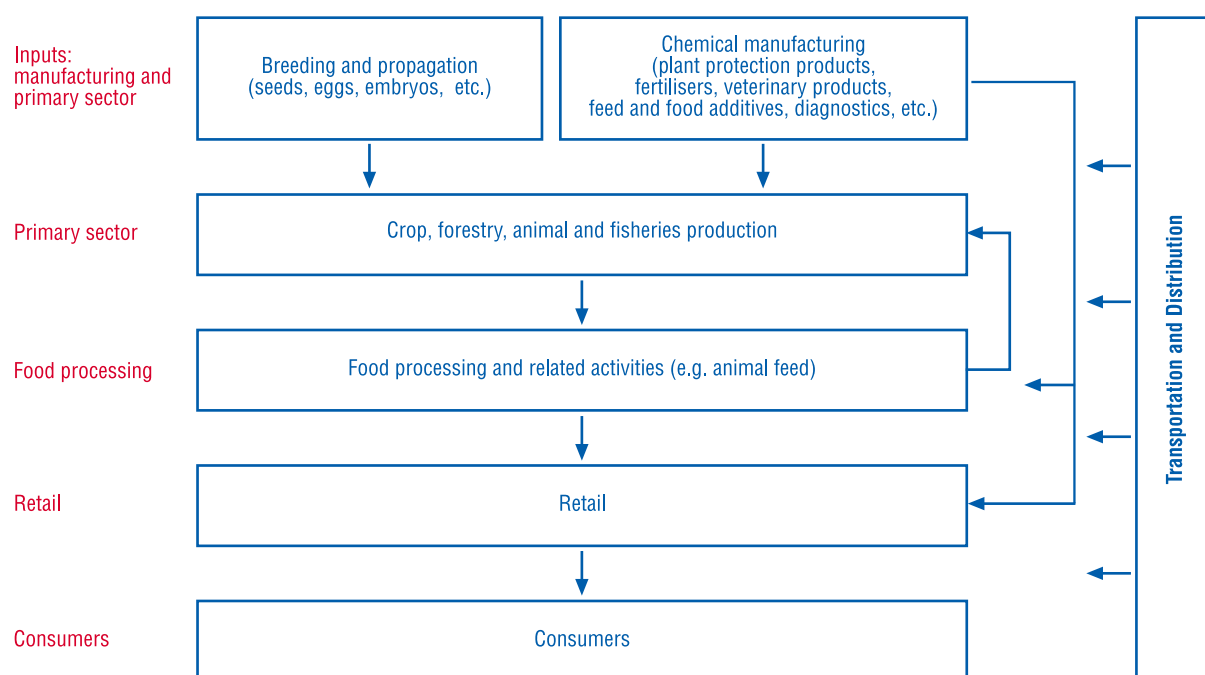
181 Directive 2001/18/EC of the European Parliament and the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ L 106, 17.04.2001, p.1.

182 <http://www.erapharm.org/>.

183 ETEPS (2006). Bio4EU Task 2 Main report.



Figure 2-9 Diagram of the food chain<sup>184</sup>



above modern biotechnology-derived products downstream, modern biotechnology has an indirect impact on the actual production of crops, livestock and fish. Further down the food chain, modern biotechnology is used in the production of enzymes, which are used as inputs for food processing (see Chapter 2.3.1.3 biocatalysis in food production), and in the traceability of food ingredients (e.g. of GM food and feed, of end products such as meat) and assurance of food safety (testing for pathogens such as salmonella).

Very often the use of modern biotechnology is not visible in the product, i.e. modern biotechnology tends to be involved in product development and production processes, where it may be used as a core, key or supportive technology. Apart from genetic modification of plants and animals, the applications of modern biotechnology in primary production and agro-food receive little public attention.

The following analysis will mainly focus on the sectors to which modern biotechnology is most relevant, namely the input sectors, in

which it is directly applied, and the primary production and food processing sectors, which are the main users of modern biotechnology-derived products. The food chain further down to retailers and consumers will only be discussed where appropriate, e.g. considering modern biotechnology applications in food-related diagnostics. For the sake of simplicity, the term agro-food sector will be used throughout, including the input sectors, primary production and food processing.

The primary sector in the EU produced a turnover of EUR 363 billion in 2003, equivalent to gross value added (GVA) of EUR 181 billion (50%). Compared to overall EU economic activity, this represents 2.06% of EU GVA. In rural areas, the economic significance of the primary sector can be significantly higher. The primary sector represents about 5% of EU employment.

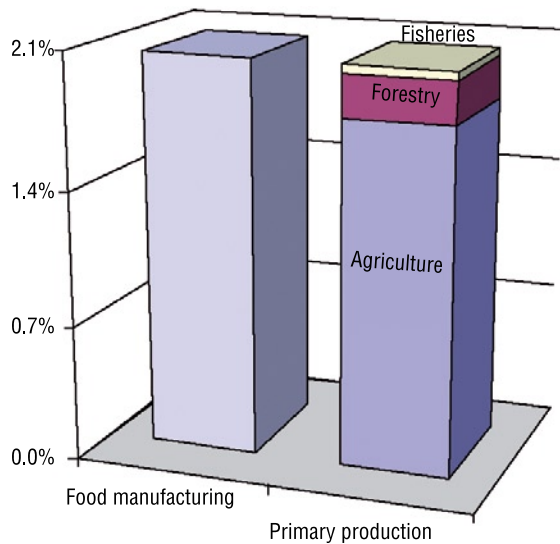
The sub-sectors of primary production have different shares in GVA (Figure 2-10). Agriculture and hunting (NACE sector A01) is the largest activity with 87% (1.79% of GVA), followed by

184 Adapted from: Tait, J., J. Chataway and D. Wield (2001). PITA project: Policy influences on technology for agriculture: chemicals, biotechnology and seeds. Final report. Scottish Universities Policy Research and Advice Network (SUPRA), Edinburgh.



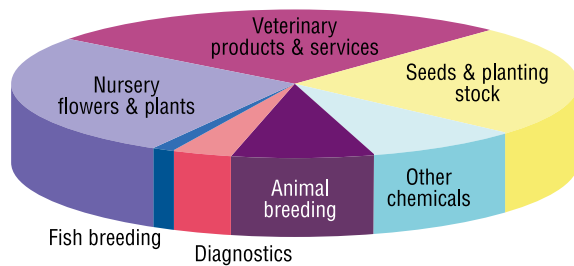
forestry with 11%. Crop production accounts for about half of primary production value; livestock production represents about 40%. Fishing and aquaculture (NACE B) are comparatively small activities with 0.027% and 0.016% of EU GVA, respectively. In terms of employment, agriculture and forestry together represent 97% of the primary production workforce, or 9.8 million employees<sup>185</sup>. Regionally, fisheries may be highly important, but it accounts for only 0.13% of EU employment. The food-processing sector (NACE DA 15), including feed production, represents 2.06% of the EU GVA, and 2.2% of EU employment. Primary production and food processing are the main users of modern biotechnology products (e.g. seeds, diagnostics, enzymes) in the agro-food sector and represent overall 4.1% of EU GVA.

■ *Figure 2-10 Contribution of the agro-food sub-sectors to EU GVA*



Modern biotechnology-derived products are provided by the sectors that supply inputs to primary production and food and feed processing, in the form of seeds, veterinary pharmaceuticals and diagnostics, feed ingredients, and enzymes for food processing<sup>186</sup> (see also Chapter 2.3.1.1). These sectors account for about 2% of the agro-food sector or 0.1% of the EU economy, with plant-related activities accounting for more than half of the total (Figure 2-11). Overall, the agro-food sector as defined here represents about 4.22% of EU GVA. As a comparison, food-related wholesale retail and catering together represent about 3.4% of EU GVA.

■ *Figure 2-11 Input sectors applying modern biotechnology, share in overall turnover*



The current state of EU agriculture in the global context has been reviewed elsewhere<sup>187</sup>. The economic importance of EU agricultural production has been declining, while the trends in terms of agricultural output vary by sub-sector. Similarly, the number of people working in

185 2002 data for the primary sector (NACE branch A) from: 'Rural Development in the European Union – Statistical and Economic Information – Report 2006, DG Agriculture and Rural Development.

186 The input sectors using modern biotechnology include the following: seeds and planting stock; nursery flowers and plants; animal breeding; fish breeding; manufacture of fine chemicals; veterinary products and services; diagnostics in the agro-food sector.

187 Scenar 2020 – Scenario study on agriculture and the rural world. European Commission, DG Agriculture and Rural Development, [http://ec.europa.eu/agriculture/publi/reports/scenar2020/indextech\\_en.htm](http://ec.europa.eu/agriculture/publi/reports/scenar2020/indextech_en.htm).



agriculture is declining, both in absolute terms and as a proportion of the total workforce. However, productivity has generally been increasing, mainly as a result of technical advances. EU shares in the global agricultural market vary by sub-sector and are influenced by a large number of factors including environmental variability, globalisation and EU Common Agricultural Policy measures. Current trends, such as further trade liberalisation and increased worldwide agricultural production (especially in developing countries where both improved productivity and area expansion are driving factors) place additional strains on the competitiveness of EU agriculture. While the economic importance of the primary sector has been decreasing in the EU, the added value generated by it is increasingly captured elsewhere in the supply chain, e.g. in the manufacturing sector involved in raw material processing. As competitiveness is correlated to comparatively lower production costs and improved productivity, technical innovations are likely to continue to be influential in the future. Moreover, the environmental pressure from agriculture has been decreasing, mainly as a result of technical innovations in production and better use of inputs, in turn driven by environmental regulations and cost savings.

Based on the available data, the direct and indirect adoption and socio-economic implications of modern biotechnology were assessed and are presented below. If data were not available, expert opinion was sought to provide estimates of adoption. The same procedure for calculating adoption was used for all modern biotechnology applications, although modern biotechnology may have different roles in the production process. The relative contribution of modern biotechnology to the measures used (GVA and turnover) may differ depending on its use: it will be highest where biotechnology is a core technology, where the value generated may be allocated 100% to modern biotechnology;

and lowest where it is a supportive technology, where its main role is in improving the efficiency of production processes and therefore overall competitiveness.

The indirect adoption and socio-economic contributions of modern biotechnology are also assessed. While analysis of the social and environmental implications is more qualitative, a common method of quantifying economic significance was used throughout. The relative importance of inputs to the overall production activity of users may vary, but is not quantifiable, therefore the same procedure was used in all cases: the indirect contribution was measured in terms of the GVA generated (or turnover if GVA data were not available) by production processes that used modern biotechnology-derived inputs, e.g. the farm-gate turnover from the share of crop output derived from seeds produced through the use of molecular markers, or the turnover generated by the sale of processed foods that use modern biotechnology-based enzymes.

### **2.2.1 Modern biotechnology in the breeding and propagation of crops, livestock and fish**

Crops and livestock used today in agriculture are the result of a long selection process. Since the early days, breeding methods have become more sophisticated and the latest innovations have come from modern biotechnology. The objective of selective breeding is to optimise plants or animals for specific purposes or conditions, and to stabilise the new characteristics throughout the subsequent generations. Selective breeding is based on differences in the genetic material of the organisms<sup>188</sup>.

The use of molecular markers and genetic modification are the most important modern biotechnology techniques applied to support breeding efforts. Molecular markers (certain DNA regions linked directly or indirectly to specific

188 Selective breeding of plants and animals is more complex than presented; for example, plant breeding makes use of a variety of techniques, such as planned hybridisation, mutation breeding, and somaclonal variation.



traits) are used in several ways: Marker Assisted Selection (MAS) and related techniques make use of them to identify and help incorporate desirable traits into selection schemes<sup>189</sup>. Molecular markers are also used indirectly to improve the breeding process, e.g. in the verification of pedigrees (through the use of microsatellites for lineage traceability in fish, for example). Overall, the use of molecular markers may simplify breeding procedures, improves the accuracy of selection and increases the rate of genetic progress (reducing the development time) by identifying organisms carrying desirable genetic variants for a given trait at an earlier age.

Genetic modification (GM), also known as genetic engineering or recombinant DNA technology, is one of the newest methods to introduce novel traits to plants and animals. Currently, the technique is more advanced for crops. GM animals are not yet used commercially for food production; recent commercial applications can be found in the production of pet fish and the production of pharmaceuticals in goats' milk. The adoption of GM crops worldwide has been faster than that of other innovations in plant varieties, such as the introduction of hybrid maize decades ago. In the first year of introduction (1996) about 1.7 to 2.6 million hectares of GM crops were grown, almost exclusively in the USA. Eleven years later (2006) the area under GM crops had expanded to 102 million hectares in 22 countries, of which 11 are high-income economies and 11 developing countries. During this period (1996-2006), two agronomic traits introduced by genetic engineering into a few major crops have dominated the market. These traits are herbicide tolerance and insect resistance (referred to as Bt crops since the gene conferring resistance comes from the soil bacterium *Bacillus thuringiensis*). Today, GM varieties have a significant world share

of the four major agricultural crops for which they are commercially available (17% of maize global area, 18% of canola, 64% of soybean and 38% of cotton)<sup>190</sup>.

Propagation techniques are used to increase the number of individuals with favourable genetic characteristics at a faster pace and in a cost-effective manner, and as such support breeding efforts. In the case of plants, cells and tissues are used for propagation in vitro, also referred to as micropropagation. This technique allows quick, space-saving multiplication of a plant with desirable characteristics, providing sufficient uniform and high quality material. It also facilitates the production of disease-free plants. It has been adopted where it promised to be cost-effective compared with conventional plant propagation methods based on plant seeds or cuttings; it is mainly used to provide young and mother plants but also for the large scale production of some cut flowers and pot plants.

In livestock breeding, modern biotechnology-based propagation refers to assisted reproduction techniques, which are mainly used in embryo transfer (ET). ET covers a number of techniques such as transfer from donor to recipient, sexing (through microsurgery on the embryo), freezing, and splitting (split embryos develop into genetically identical siblings). Related techniques that may be concomitantly applied are hormone stimulation of ovulation, semen sexing and in-vitro fertilisation. ET can be understood as a further development of artificial insemination, which has been used for about 60 years and still is the main method of livestock propagation in some species (e.g. cattle).

Currently, the main applications of modern biotechnology for fish are ploidy induction and sex reversal, and, to a lesser but increasing

189 MAS includes the use of genotyping in the identification and selection for Single Nucleotide Polymorphisms (SNPs) of single-gene determined traits and the use of genotyping coupled with mapping and other techniques in identification and selection for complex, multi-gene-determined traits through Quantitative Loci (QTL) manipulation; the latter includes most of the economically relevant traits, such as birth weight, weaning weight, growth, reproduction, milk production and carcass quality, for animal breeding.

190 James, C. (2006). Global Status of Commercialized Biotech/GM Crops in 2006. ISAAA Brief No. 35 (Ithaca, N.Y.).



extent, the use of molecular (genetic) markers to optimise breeding strategies. Ploidy induction results in an increase in sets of chromosomes from two to three by giving embryos a heat-, cold- or pressure shock shortly after fertilization. While polyploidy is lethal in mammals and birds, it has led to the development of many improved plant varieties, and triploid fish are viable and usually sterile. Triploidy can be advantageous for several reasons, including increased growth, increased carcass yield, increased survival and increased flesh quality. Sex manipulation is used to create monosex populations by hormonal treatment and appropriate breeding techniques. The resulting increased productivity is based on faster growth, reduced aggression and delayed maturation. Molecular markers in fisheries management (harvest fisheries) is still at a rather experimental/pilot phase.

The application of modern biotechnology in breeding/propagation is relevant mostly at the top of the breeding pyramid<sup>191</sup>, the aim being to facilitate and accelerate genetic improvements in the plant or animal population. For example, modern biotechnology can be used to select for or introduce desirable traits into already “elite” lines of crop plants, i.e. cultivars that are already well developed for commercialisation. Additionally, modern biotechnology may also be used throughout the breeding schemes further down the pyramid, for example in parentage identification and lineage traceability. However, impacts at the top of the breeding pyramid are felt at the bottom of the breeding and production scheme and since genetic improvements are in general cumulative over generations, the impacts are long term<sup>192</sup>. The direct impacts of modern biotechnology in this area are felt by breeding companies/departments

and other specialised biotechnology companies supporting the breeding/propagation of plants/animals, while the indirect impacts are felt by producers/farmers. The indirect impacts may also be felt further down the chain, especially through the processing stage, and perhaps also all the way through to retail and consumption. However, because of the complex structure of the agro-food sector, our assessment will mainly focus on the input and first user stage, i.e. the farm gate; qualitative descriptions of indirect impacts further down the chain will be made in cases where such information is available.

#### 2.2.1.1 Breeding and propagation of plants

Crop production accounts for about half of the value of primary production activities. Crops and plants also account for a significant share (61%, see Figure 2-11) of the input sectors of the agro-food sector. The modern biotechnology techniques currently used in plant breeding and propagation mainly relate to molecular markers, genetic modification, and micropropagation<sup>193</sup>. These technologies are used and applied either by breeding/seed companies, or by specialised laboratories involved in the supply of horticultural products and/or young plants.

#### *Economic significance of molecular markers and genetic modification in crop breeding*

##### The use of molecular markers in breeding

Molecular markers are applied in research in almost all plant-related sectors, namely crops (including vegetables), fruits, and forestry. However, they appear to be used commercially

191 A breeding pyramid consists of three main components: at the top of the pyramid (apex) are the highest-merit breeders (males and females in animals); below these are the multipliers, used to disseminate the desirable genetic makeup; at the bottom of the pyramid (and therefore largest in number) are the production plants/animals. For example, one great-grandparent boar may be responsible for the genetics of 10 800 parent females or 570 000 slaughter pigs (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.).

192 Breeding schemes are more complex than this; while, in general, genetic improvements are cumulative over generations, this may not always be the case for all individual traits.

193 There is a large variety of techniques used in plant breeding, such as hybridisation, mutation breeding, somaclonal variation, which fall outside the scope of the study unless they are used in combination with one of the three techniques discussed.





mainly in the crop sector, most commonly in maize and vegetable<sup>194</sup> breeding. Although data on the uptake for other crops is not available, a recent publication<sup>195</sup> suggests that maize breeding is more amenable to the application of MAS as compared to wheat, barley and rice, for biological as well as agronomic reasons. Maize is one of the most important crops in the EU, grown on about 6 million ha with a yield of about 55 million tonnes/year (4% of all crop production by value). Selective breeding targets agronomic traits such as cold and drought tolerance and pest resistance, but also quality traits such as protein content<sup>196</sup>.

The EU seed sector comprises more than 400 seed companies, of which approximately 10% generate 40% of the turnover, indicating that a large part of seed production is provided by a small number of medium-sized and large companies. The European Seed Association (ESA) estimated the turnover from seed sales of EU seed companies at EUR 6.1 billion for 2003<sup>197</sup> while employment is estimated at more than 30 000 employees. The share of maize in total EU seed production is estimated at EUR 405 million (6.6%), based on the maize area cultivated and seed cost information<sup>198</sup>.

The adoption of molecular markers in maize breeding seems to depend on company size. Experts indicated that medium-sized and large companies apply molecular markers 100% to maize breeding, whereas smaller companies show a lower adoption rate (as low as 33%)<sup>199</sup>. Also ESA states that molecular markers are commonly used as a tool in the seed industry<sup>200</sup>.

Given the adoption of molecular markers in maize breeding and the turnover of commercial maize seed, it is estimated that EUR 133 405 million or 2.2%-6.6% of total seed turnover at EU level is related to the use molecular marker-related technologies (for 2003), equivalent to 0.01%-0.03% of the turnover of the agro-food sector. As market shares of medium-sized to large companies are likely to be higher, the upper value might be more accurate. Indirectly, the adoption of molecular marker technologies may also contribute to the turnover generated by using the seeds for crop production. While exact data for the share of maize produced in the EU from molecular marker-derived seeds is not available, applying the breeders' adoption rate to crop production and assuming that the alternative main seed providers (mainly the USA) have also adopted the technology at similar or higher rates, results in a turnover value of EUR 2.4-7.4 billion. This accounts for 0.2%-0.6% of agro-food sector turnover. While this estimate may not be allocated completely to the use of molecular markers, it provides an indication of the indirect economic significance of the adoption of this technology.

The adoption of molecular marker-based technologies in the breeding of other crops is not known. For illustrative purposes, assuming an overall adoption rate of 33%, similar to the low adoption rate for maize, would result in EUR 2 billion seed turnover, representing 0.17% of the agro-food sector turnover. Assuming that about a third of all seeds planted are derived from the application of molecular markers in breeding, the

194 See for example <http://www.keygene.com>.

195 Koebner, R (2004). "MAS in cereals: green for maize, amber for rice, still red for wheat and barley." Paper for the workshop on: Marker assisted selection: a fast track to increase genetic gain in plant and animal breeding? 17-18 October, Turin, <http://www.fao.org/Biotech/docs/Koebner.pdf>.

196 Interviews with experts from industry and academia (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

197 Eurostat data for intermediate consumption of seeds and planting stock (first generation and certified seed) and the value of multiplied seed result in a slightly higher turnover of EUR 8.3 billion for the seed sector, but this includes propagating material other than seeds. Therefore, the ESA data will be used in the following calculations.

198 The estimate is based on the maize area cultivated (6 195 000 ha) and the cost of maize seed (EUR 65.39 per ha), resulting in EUR 405 million maize seed turnover.

199 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

200 <http://bio4eu.jrc.es/submissions.html> ESA submission excerpt: "All seed companies make use of modern technologies (including biotechnological methods and applications) in their work. e.g., DNA-markers assisted breeding and selection is a common tool in today's modern seed industry to speed up variety development and target breeding efforts".



indirect relevance of this modern biotechnology increases to EUR 55.5 billion, or 4.7% of the agro-food sector turnover.

According to ESA statistics, the EU seed sector employs about 30 000 staff. No data is available for employment in molecular marker-supported breeding, although, theoretically, direct employment (not just R&D related) would most likely correspond to the general diffusion rate.

#### Genetic modification of crops

The number of GM crops authorized for cultivation in the EU is small compared to other world regions. In practice, the only GM crop currently available to EU farmers for cultivation is a GM maize resistant to insects, commonly known as Bt maize<sup>201</sup>. Within the EU, Spain is the only country growing significant quantities

of Bt maize. Spain cultivated 53 667 hectares of Bt maize varieties in 2006. France cultivated the second largest area with about 5000 hectares in 2006. Germany, Portugal, the Czech Republic and Slovakia also grew Bt maize in 2006 but reported comparatively small areas of about one thousand hectares or less<sup>202</sup>. Table 2.4 shows GM maize adoption rates in the EU and worldwide in 2005, for which figures are more definitive.

In Spain, GM seed turnover increased from EUR 4.1 million in 2002 to EUR 11.9 million in 2004<sup>208</sup>, illustrating the annual increase of GM maize area. These figures can be taken to represent total EU GM seed turnover since the GM area in other EU Member States was negligible for the three-year period analysed (2002-2004).

On this basis, GM maize seed accounts for about 2.9% of EU maize seed turnover, reflecting

Table 2.4 GM maize adoption rates in the EU and worldwide in 2005

Adoption rates (share of GM maize area out of total grain maize area)	Source of data
Spain	53 225 ha/421 724 ha 12.62% Spanish Ministry of Agriculture <sup>203</sup>
France	500 ha/1 654 000 ha 0.03%
Germany	300-500 ha/443 000 ha 0.07%
Czech Republic	150 ha/98 000 ha 0.15%
Portugal	750 ha/110 000 ha 0.68%
EU	54 925ha/6 059 000 ha 0.90%
USA	15 649 920 ha/30 096 000 ha 52% USDA 2005 <sup>206</sup> , USDA 2006 <sup>207</sup>
South Africa	289 000ha/1 700 000 ha 17% Clive James <sup>205</sup>
World-wide	21 200 000 ha/147 000 000 ha 14% Clive James <sup>205</sup>

Note: In the USA GM maize can be either Bt maize, Herbicide Tolerant (HT) maize or HT/Bt maize while in the EU only Bt maize is grown.

201 In the EU two Bt maize events are authorised for cultivation. These are Syngenta's transgenic event Bt-176, authorised in 1997, and Monsanto's transgenic event MON-810, authorised in 2003.  
 202 James, C. (2006). Global Status of Commercialized Biotech/GM Crops in 2006. ISAAA Brief No. 35 (Ithaca, N.Y.).  
 203 Spanish Ministry of Agriculture (2006), Superficie en hectáreas de variedades de maíz GM, [http://mapa.es/agricultura/pags/semillas/estadisticas/serie\\_maizgm98\\_06.pdf](http://mapa.es/agricultura/pags/semillas/estadisticas/serie_maizgm98_06.pdf).  
 204 EUROSTAT (2006) Agriculture and fisheries statistics <http://epp.eurostat.ec.europa.eu/>.  
 205 James, C. (2005). Global Status of Commercialized Biotech/GM Crops in 2005. ISAAA Brief No. 34 (Ithaca, N.Y.).  
 206 USDA (2005). Acreage in 2005, <http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bba>.  
 207 USDA (2006). Adoption of genetically engineered crops in the U.S. in 2005: corn varieties. <http://www.ers.usda.gov/Data/BiotechCrops/ExtentofAdoptionTable1.htm>.  
 208 GM maize seed prices per hectare and the annual GM maize area are obtained from the GM crops case study for the BIO4EU project.



the generally low adoption rate of GM maize in the EU (0.9% of the total grain maize area in 2005, see Table 2.4). GM seed accounts for about 0.2% (EUR 11.9 million) of overall EU seed turnover. GM maize accounted for EUR 85 million<sup>209</sup> or 1.2% of EU maize crop production.

A recent study<sup>210</sup> analysed the agronomic and economic performance of Bt maize cultivated in Spain, compared to conventional maize. In 2002-2004, farmers using Bt maize obtained an average increase in their gross margin of EUR 85 per hectare and growing season compared with farmers growing conventional maize. This represents an increase of 12% over the average gross margin obtained by maize farmers in Spain. These benefits, however, vary widely in the three regions studied, ranging from EUR 125 per hectare to just EUR 7 per hectare. GM seed prices paid by farmers are higher than for conventional maize seeds. On average this price difference in seeds accounts for EUR 30 per hectare. The economic welfare resulting from the adoption of Bt maize in Spain is basically shared by farmers and seed companies. Bt maize belongs to the so-called first generation of GM crops which aim to provide higher production efficiency at farm level. Therefore, direct benefit for consumers could only come from a reduction of the market price. No differences in the price received by Spanish farmers for Bt maize or conventional maize crop were found in the study. In Spain, the Bt maize grain produced is used entirely for animal feed production. These findings match with Spanish feed industry claims that the introduction of Bt maize in Spain has not reduced the cost of their raw material. The largest share of welfare created by the introduction of Bt maize (74.4 % on average) went to Bt maize farmers and the rest

went to the seed companies (25.6% on average), taken to include seed developers, seed producers and seed distributors.

The same study looked at factors which might have affected the adoption of Bt maize in Spain. One of the most relevant factors is farm size because it is frequently a surrogate for other factors such as farmers' wealth. In contrast to other technologies such as machinery which require extensive capital investments and many hectares over which the farmer can spread the costs of acquisition, the adoption of Bt maize in Spain has been farm size-neutral because the technology is linked to the seeds, which are completely divisible and can be used in any amounts.

Some experts consider the potential economic impacts of GM crops not yet approved for commercial cultivation by EU farmers, but cultivated elsewhere in the world, to be an opportunity cost for the EU, in terms of forgone benefits. There is a small but growing number of *ex ante* studies addressing this potential economic impact<sup>211</sup>. Positive on-farm and aggregate economic benefits are predicted by these studies, derived from increased yields and reduced production costs for farmers. However, these analyses should also consider the novel regulatory framework on labelling and traceability of GMOs and derived products that became operative in 2004<sup>212</sup>. It introduces issues such as possible market segmentation, price differentials, and novel costs for identity preservation and labelling/traceability. Analyses of the economic impacts of introducing GM crops in agriculture in the EU should also now consider the novel concept of coexistence between GM and non-GM agriculture developed by the

209 Average GM maize yields in Spain were 11 430 kg per hectare during the three-year period 2002-2004. These yields, multiplied by the €0.128 per kilogram received by farmers in 2004, result in revenue of €85 million.

210 Gómez-Barbero, M., J. Berbel and E. Rodríguez-Cerezo (2007). Adoption and socioeconomic impacts of the first genetically modified crop introduced in EU agriculture: Bt maize in Spain. European Commission, Seville. (Publication in preparation.)

211 Gómez-Barbero, M. and E. Rodríguez-Cerezo (2006). Economic impact of dominant GM crops worldwide: a review. European Commission. DG JRC/IPTS, EUR 22547.

212 Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC; OJ L268, 18.10.2003, p.24.



EU<sup>213</sup>. Member States have begun drafting rules requiring farmers cultivating GM crops to take measures (if necessary) to ensure coexistence and consequently to bear the resulting costs. A similar framework does not exist in other areas of the world where GM crops are cultivated; this raises new questions regarding the GM crop adoption process by EU farmers and its economic balance.

As with molecular marker-supported breeding, no employment data are available for developing and marketing GM seed. As GM seeds are mainly produced in the USA and Chile, the employment impact in the EU might be low. At farm level, it seems that the adoption of Bt maize in comparison to conventional maize had no effect on the number of farm labourers<sup>214</sup>.

#### *Environmental implications of molecular markers and genetic modification in crop breeding*

The environmental effects of modern biotechnology applications in plant breeding are relevant almost entirely at the crop production stage and further down the chain for any uses that may be affected by new or improved crop traits. Breeding itself is on a much smaller scale than the grow-out phases.

Molecular markers support selective breeding. Genetic selection has been considered an important driver of productivity improvements, but is not the sole factor. Nevertheless, a substantial proportion of the improvements in resource productivity is ascribed to genetic selection. Therefore, qualitatively, the impacts to be expected are similar to those of conventional selection. The environmental implications of the use of molecular marker-based technologies will depend on the trait that is targeted, and quantitatively, depend on the difference obtained in the targeted trait and the level of adoption of

the technology. While targeted traits in maize breeding differ, it can be assumed that the adoption of molecular markers in breeding is mainly neutral or beneficial to the eco-efficiency of the primary sector because of the general aim to increase productivity and/or efficiency. While a negative effect cannot be ruled out, such as in situations where the selection for an important trait indirectly affects agricultural resource efficiency, it is highly unlikely, as resource efficiency also has substantial economic implications.

For GM crops, studies have been carried out to analyse (potential) environmental impacts. Any innovation that results in changes in the way a crop is managed may have an impact on the environment. There is scientific consensus that the impact of the introduction of GM varieties has to be analysed case by case depending on the nature of the genetic modification and the changes in field management prompted by the new characteristics of the variety (e.g. herbicide tolerance, insect resistance)<sup>215</sup>. In particular, Bt crops can potentially reduce the environmental pressure of intensive agriculture (through less spraying of insecticides) but could also have an impact on non-target insect species (since the GM plant produces its own insecticide) that must be evaluated. Data on changes in the use of pesticides due to Bt maize cultivation in Spain (from empirical evidence gathered in the survey described in the economic section) show that 42% of conventional maize growers surveyed do not use insecticides at all for controlling corn borers, and this figure increases to 70% for Bt maize growers. 21% of conventional maize farmers give two or more treatments per year, and this figure is reduced to 2% for Bt maize growers. On average, conventional maize growers applied 0.86 treatments/year compared with 0.32 treatments/year for Bt maize growers. This

213 Commission Recommendation of 23 July 2003 on guidelines for the development of national strategies and best practices to ensure the coexistence of genetically modified crops with conventional and organic farming.

214 Gómez-Barbero, M., J. Berbel and E. Rodríguez-Cerezo (2007). Adoption and socioeconomic impacts of the first genetically modified crop introduced in EU agriculture: Bt maize in Spain. European Commission, DG JRC/IPTS. (Publication in preparation.)

215 FAO (2004). The State of Food and Agriculture, 2003-04. Food and Agriculture Organization, Rome.



reduction is modest in absolute terms because insecticide control of corn borers is very difficult. The lack of effectiveness and additional cost is the reason why many maize farmers do not spray insecticides specifically for controlling corn borers, but accept the yield losses. Regarding the environmental impacts on non-target organisms and development of resistant pest populations, no detrimental effect of farm scale Bt maize cultivation in Spain has been observed on non-target arthropod activity or abundance, according to research commissioned by the Spanish Ministry for the Environment and performed by public institutions. Data collected for 5 years on commercial Bt maize plantings (1998-2003) did not show an increase in resistance for corn borer populations sampled in Spain<sup>216</sup>. However, the researchers argue for the need to maintain systematic monitoring for longer periods.

#### *Economic significance of micropropagation of plants<sup>217</sup>*

Micropropagation has been applied with variable success to the different agricultural and horticultural fields. The commercial uptake of micropropagation has been highest in ornamental plants (e.g. flowers, foliage plants, woody ornamentals, etc.), followed by vegetable plants and fruit plants. Certain plants can only be propagated profitably by means of micropropagation; for example in the case of orchids this technique allows the production of large and uniform plant stocks in a short time, allowing the price of orchids to fall. The huge demand for some ornamental plants such as orchids can only be fulfilled by applying micropropagation. Consumer demand is a strong driver in selecting the types of plants produced. Current production techniques for micropropagation have enabled strong and

continued growth in the micropropagation industry.

The main actors in micropropagation are specialised commercial laboratories and laboratory units of young plant producing companies. The activity of a company may be limited to the production and sale of young/mother plants, or may also involve the grow-out phases (open land or in greenhouses) up to final retail sale. Some companies are simultaneously involved in the micropropagation of several different plant types (e.g. ornamentals, vegetables) and in plant breeding. As a result, the economic activity of micropropagation is spread over several different sectors, which results in a lack of relevant statistical information.

The annual value of “nursery flowers and plants” and “adult ornamental plants and flowers” (end products) in the EU has been estimated at EUR 6.4 and 8.3 billion, respectively (2003 data)<sup>218</sup>. EU production is characterised by the highest production intensity, achieved mainly through the use of modern technologies. The value of production is stable for adult ornamental flowers and plants but is increasing for nursery flowers and plants. The EU is a net exporter of nursery flowers and plants and a net importer of adult ornamental flowers and plants, but the overall balance is positive because EU domestic production is the main source of internal consumption. The Netherlands, Germany and Italy are the top producers of nursery and adult plants and flowers. Overall, nursery and adult flower and plant production is a very competitive sector, the main advantages of EU producers compared to their competitors (mainly in developing countries) being capital availability linked to modern technology use, logistics and a large home market. To this end, micropropagation seems to be one tool that enables some EU producers to remain competitive.

216 De la Poza, M. et al (2005). *Crop Protection* 24(7): 677-684.

217 Non-referenced information is based on expert opinion (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

218 All sector information based on: Working Document of the Commission staff on the situation of the flowers and ornamental plants sector (DG AGRI, 2006).



Interviews with different horticulture/breeding companies (for which micropropagation plays a role) producing orchids, pot plants, strawberries and ornamental woods revealed that most companies use micropropagation for at least 80% of their activities, indicating a high adoption rate of this technique in these companies. A conservative estimate puts micropropagation-related turnover at about EUR 39-313 million, or 0.6%-5% of the total value of the annual production of nursery plants<sup>219</sup>. In the production of adult ornamental plants and flowers derived from micropropagated young plants and mother stock, micropropagation is indirectly related to a turnover of EUR 50-390 million, or 0.004%-0.033% of the agro-food sector turnover.

Micropropagation is a labour intensive technique, with labour costs representing 65%-85% of production costs, more than for conventional propagation techniques. This is one reason for moving micropropagation activities to lower wage countries. Micropropagation companies have a comparatively high proportion of skilled staff (11%) due to the large proportion of laboratory work (academics, engineers, technical assistants, gardeners). However, at the same time, a large number are unskilled and seasonal workers. From the companies interviewed it was estimated that about 75% of employees are involved in micropropagation.

#### *Environmental implications of micropropagation in plants*

Micropropagation has rather marginal environmental implications compared to molecular marker technologies and genetic modification as it does not affect the breeding value of the crop in question; it is merely involved in the multiplication step of the

breeding process. Nevertheless, the following environmental implications may be considered, even if in absolute terms the impacts are likely to be small<sup>220</sup>: i) micropropagation will indirectly improve the efficiency of the breeding process through the multiplication of desirable genotypes, and therefore it will have some share in the change that the related breeding scheme induces; ii) the field growing periods are shortened compared to conventional seed-based propagation which implies a reduction of the water, fertiliser and pesticides used; iii) micropropagation techniques can ensure propagating material is disease-free, reducing pathogen transfer.

#### *Summary of modern biotechnology applied to plants*

Out of the three main modern biotechnology techniques applied to plants, the use of molecular marker-based technologies<sup>221</sup> seems to have the highest economic significance due to the high adoption rate in breeding of at least one of the major crops in the EU. GM crops, because of low adoption rates, have comparatively little significance on an EU level; however, impacts might be considerable on the farm scale for specific applications. The maize seed companies interviewed suggested that the sector would not remain competitive without the use of molecular markers in the breeding process. Molecular marker-based breeding was reported to increase the costs for the breeding companies in the short term, due to high initial investment costs and the need for qualified employees, but to be profitable in the long term. The high costs might prove to be a challenge for smaller companies which might not be able to remain competitive. However, maize breeding is dominated by large companies in the USA and EU, the main competitors.

219 These estimates are based on the figure of 193 micropropagation laboratories reached in a survey in 1996-97 (<http://www.uwe.ac.uk/fas/cost822>), and the range of turnover of the companies interviewed in this study (EUR 250 000 to EUR 2 000 000) applying the adoption rate of 80%.

220 Expert opinion (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

221 Note, however, that there is some interdependence of the various breeding tools, as modern biotechnology techniques may be applied simultaneously, as well as in combination with “conventional” breeding practices.



The turnover generated from economic activities using modern biotechnologies in the production process has been estimated at EUR 184-730 million, and may rise to EUR 2.38 billion under the assumption that all plant breeding has adopted molecular marker techniques in the breeding process. The use of modern biotechnology-derived products by the user sectors, i.e. the crops and plants produced from seeds and young plants (indirect significance) is relevant to a turnover of about one order of magnitude higher than the direct contributions, amounting to 0.2%-0.7% of the turnover of the agro-food sector. These figures provide an indication for the importance of modern biotechnology to these sectors, and should be used with caution since they are based on a number of assumptions and since modern biotechnologies are not the sole factor responsible for output. Overall, modern biotechnology is being applied to plant breeding and propagation to a significant extent in the EU for specific applications, while the respective sectors are important players in the world market.

The environmental implications of the application of modern biotechnologies to the breeding and propagation of plants are mainly indirect (i.e. through resource efficiency improvements), but may also be direct (trait-specific) as in the case of some GM crops. While, overall, the environmental implications seem to be positive, modern biotechnologies may present novel and sometimes indirect environmental risks, necessitating robust case-by-case evaluation and monitoring.

#### 2.2.1.2 Breeding and propagation of livestock

The value of livestock production at farm level represents about 40% of overall agricultural primary production in 2004 (EUR 127 billion<sup>222</sup>).

Additionally, some crop production is used for animal feed; the EU feed industry has a turnover of about EUR 35 billion. Cattle, mainly dairy cattle, and pigs are major livestock segments (56% and 20% of agricultural output, respectively), and globally important. For example, after China, the EU is the largest producer of pig meat worldwide with production of about 22 million tonnes/year. According to a preliminary estimate by FABRE<sup>223</sup>, breeding efforts are responsible for an economic gain from improved production of EUR 1.83 billion annually. Cattle account for 27% (EUR 500 million), pigs for about the same, poultry for 33%, and fish for 4%.

Information from livestock breeding companies indicates that about 20%-30% of their turnover is related to the use of modern biotechnology<sup>224</sup>. This includes mainly molecular marker-supported breeding and embryo transfer techniques (ET). Genetic modification of livestock for food production has not yet reached the commercial scale.

#### *Economic significance of molecular markers used in livestock breeding<sup>225</sup>*

Molecular markers are applied in animal breeding in the same way as in plants. However, no definitive data are available on the extent to which molecular markers are used in livestock breeding. Breeding companies/organisations do not usually distinguish nor record their molecular markers-related activities separately from conventional breeding practices. Moreover, there is an intellectual property rights issue specific to animal breeding in that, while genetic markers may be patented, there is no animal equivalent to the plant breeder's rights, which may hamper both development and documentation of the use of molecular markers in livestock breeding<sup>226</sup>.

222 All statistical information from Eurostat, 2003 data.

223 FABRE (2006). Sustainable farm animal breeding and reproduction: a vision for 2025. FABRE Technology Platform, Oosterbeek.

224 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

225 Non-referenced information is based on expert opinion (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

226 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications. Working Group 'FABRE Technology Platform' (2006). Sustainable farm animal breeding and reproduction: a vision for 2025. <http://www.fabretp.org/content/view/21/43/>.



Examples for the use of molecular marker-based technologies in livestock breeding can be found in pig breeding. Since the 1990s, pig breeding has made use of genetic information. A targeted trait for molecular marker-based pig breeding is for example, the absence of the halothane gene<sup>227</sup>, which is responsible for pale, soft and exudative (PSE) pig meat and stress sensitivity<sup>228,229</sup>. Other targeted traits include increased litter size<sup>230</sup> and disease resistance<sup>231</sup>. One publicly reported example is the use of seven meat quality genetic markers to identify pigs with improved meat quality. Based on an agreement between a breeding company and a German retailer a pig meat quality programme to supply branded meat was set up<sup>232</sup>. Under this scheme, pig producers were offered around EUR 0.02 per kg premium if they used boars selected for the programme.

The livestock breeding sector is heterogeneous in structure, comprising cooperatives or companies organised nationally that have relatively high domestic market shares. For example, no single organisation among pig breeders has an EU market share of more than 25%. There seems to be one big pig breeding company (PIC/Sygen/Genus, UK/USA), and about 3 to 6 medium-sized breeding organisations (in Denmark, Netherlands, France, Belgium and the UK), and numerous smaller organisations and national schemes. Conditions are similar in the cattle breeding sector, although

cooperatives tend to be more important and private companies less so.

Data gathered from a survey of major EU livestock breeders<sup>233</sup> (mainly cattle and pig breeders) indicate that molecular marker-related turnover accounts for about 14%-28%<sup>234</sup> of the breeding sector's turnover or EUR 207-411 million. This translates into 0.02%-0.03% of the overall agro-food sector turnover. Sales outside the EU accounted for more than half, corroborating the strong competitive position of EU livestock breeders and the relative importance of the technology.

Extrapolating the estimated adoption rates to total EU livestock production (as EU breeders have major shares in EU farm-gate production), provides an indication of the indirect relevance of molecular marker based technologies in livestock; it is estimated that molecular marker-assisted breeding indirectly affects the generation of turnover of EUR 17.8-35.7 billion (which is 14%-28% of overall livestock production at EUR 127 billion), or 1.5%-3% of agro-food sector turnover.

#### *Environmental implications of molecular markers in livestock breeding*

The implications of molecular markers in the livestock breeding sector are similar to those for

227 The gene is called the halothane gene because pigs carrying two copies of the gene are prone to physiological stress and die when subject to halothane anaesthesia. Pigs with one copy of the gene produce leaner meat.  
 228 McLaren and Rohl, personal communication quoted in [http://dbgenome.iastate.edu/max/Reviews/1998\\_review/implic.html](http://dbgenome.iastate.edu/max/Reviews/1998_review/implic.html).  
 229 Otto, R. et al. quoted in Primetiva, L., R. Klont, O. Southwood and G. Plastow (2006). "The influence of ultimate pH on meat quality and the role of marker assisted selection." In: Rehout, V. (ed.) *Biotechnology 2006*. Scientific Pedagogical Publishing, Č. Budějovice, p. 41-44.  
 230 Unpublished results of Short, Wilson, McLaren and Plastow, quoted in: Rothschild, M.F. and G.S. Plastow (1998). Current advances in pig genomics and industry applications. Department of Animal Science, Iowa State University, Ames, I.A. [http://db.genome.iastate.edu/%7Emax/Reviews/1998\\_review/](http://db.genome.iastate.edu/%7Emax/Reviews/1998_review/).  
 231 Van der Steen, H.A.M., G.F.W. Prall and G.S. Plastow (2005). *J.Anim.Sci* **83**:E1-E8.  
 232 ThePigSite (2005). "EDEKA Südwest and PIC Deutschland sign technology contract for meat quality," 28 June. 5M Enterprises Ltd., Sheffield. <http://www.thepigsite.com/swinenews/9611/>. And expert opinion (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.  
 233 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.  
 234 Breeding organisations answering the survey (in total 16 organisations) stated that a share of 28% of their turnover relates to MAS. This is assumed to be the maximum value for MAS contribution to overall breeding activity (if applied to the whole breeding sector), as companies active in MAS are more likely to answer the survey. The minimum contribution is assumed to be the share of the turnover value declared by these organisations over the total breeding sector turnover, which comes to 14%.





plants. In general<sup>235</sup>, there are no examples of use of molecular marker that provide direct benefits to the environment, but the indirect impact may be considerable, and similar to what is achieved through traditional genetics. For example, improving the growth rate and food conversion ratio reduces the amount of emissions and resource use per unit output. Similarly, molecular markers used to improve the reproductive rate may reduce the number of breeding animals that need to be kept in order to produce a slaughter generation animal, and hence the amount of pollution from keeping such breeding animals, although the implications at the breeding stage are far fewer compared to the grow-out phases.

#### *Social implications of molecular markers in livestock breeding*

The social implications of modern biotechnologies currently applied in animal breeding and propagation are mainly in animal health and welfare, and the discussion will therefore be limited to these aspects.<sup>236</sup> A baseline animal welfare concern for some is that modern biotechnologies are artificial, compared with natural selection and reproduction, but this is a common feature with more conventional agricultural practices. The impact on animal welfare of assisted breeding using molecular markers has also been discussed, although to a lesser extent compared to other applications. Marker-assisted breeding is not considered to be different in qualitative terms from traditional quantitative genetics-based breeding, as the means and targets are similar. The major difference that molecular marker information makes is that it improves efficiency in driving genetic selection.

Direct impacts on animal welfare will depend on the trait targeted: conventional breeding through quantitative genetics has already been criticised for selecting for production traits without due concern for specific animal welfare issues<sup>237</sup>; the relevance of molecular markers to animal welfare therefore depends more on the trait targeted than on the technology itself. One advantage for animal welfare is that molecular marker-assisted breeding may also be geared more to disease resistance and product quality-related attributes, which have positive public health implications, than to clearly productivity-related ones. A look at the traits targeted in pig breeding<sup>238</sup> indicates that molecular marker-assisted breeding has already been directly applied to traits with positive animal welfare implications: an example, which experts say has already been extensively applied in pig production, is selection against the ‘Halothane’ gene, which has reduced pre-slaughter mortality in pigs from between 4-16 per 1000 pigs to nearly zero<sup>239</sup>. Similarly, a survey of two Spanish commercial abattoirs suggested that pre-slaughter deaths (during transport and lairage) could be reduced from 0.22%-0.02% through selection against the “Halothane” gene<sup>240</sup>. However, some of the traits targeted, such as increased litter size, would also require the consideration of potential indirect negative animal welfare effects<sup>241</sup>.

#### *Economic significance of embryo transfer in livestock<sup>242</sup>*

Embryo transfer (ET) is a propagation technique aiming to increase the productivity of selected females, and to multiply animals with a favourable genetic make-up at a faster pace, and

235 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

236 A number of emerging applications, however, are now aiming at other “social” objectives, such as targeting the development of zoonotic disease-resistant animals (e.g. BSE-resistant cattle developed via genetic modification) or selection for nutritional quality traits (e.g. through MAS).

237 See for example “The welfare of chickens kept for meat production (broilers),” SCAHAW report, European Commission, 2000.

238 For references and expert opinion see ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

239 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

240 Fàbrega, E. et al. (2002). *Animal Welfare* **11**(4): 449-452.

241 See for example Weary, D.M. et al. (1998). *Applied Animal Behaviour Science* **61**: 103-111.

242 Non-referenced information is based on expert opinion (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

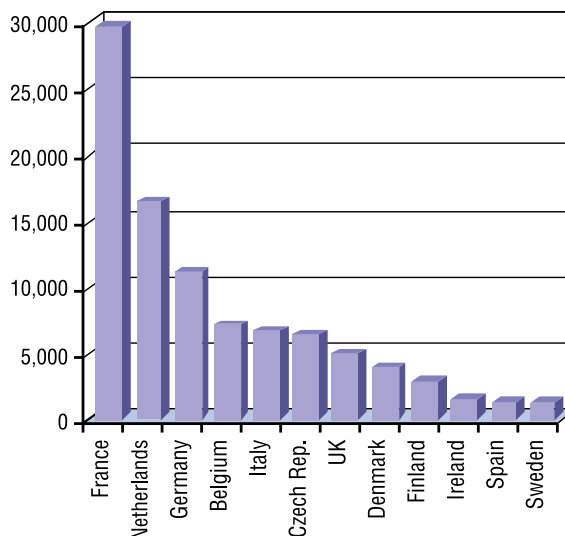


as such supports breeding efforts. It is currently widely used only in cattle, where it is limited to the top of the breeding pyramid due to the high cost. ET is estimated to be about 15 times more expensive than artificial insemination (AI) in on-farm costs. Only approximately 0.5% of calf production results from ET. Expert opinion indicates that at least 75% of bulls used as donors for AI are derived from ET in those countries with the largest numbers of cattle. It has also been reported that the use of ET has increased the rate of genetic improvement by 30% (as measured by productivity) compared to conventional breeding schemes without ET<sup>243</sup>.

In cattle there is a large international trade in semen and embryos, meaning that livestock genetic evaluation can occur across borders. The EU is an important player in the international cattle breeding sector as five of the ten largest cattle breeding companies are based in the EU. There are a number of different companies/organisations involved in cattle breeding, such as large privately owned companies and cooperatives operating on an international scale, significant national schemes (e.g. in Denmark, France and Italy) and numerous smaller organisations, such as individual breed societies or AI associations (e.g. in Germany several of the AI associations have their own breeding programmes).

In the top 12 EU countries for ET (Figure 2-12) about 94 000 embryos were transferred in 2004. The three most active countries, France, the Netherlands and Germany, account for about 60% of all embryos transferred. From survey data, the value of ET transfer activities in the EU has been estimated at EUR 190 million<sup>244</sup>.

■ Figure 2-12 Total transfers of cattle embryos, by top EU countries



Source: ETEPS<sup>245</sup>.

Given the pyramid structure of cattle production and the estimate that 75% of bulls used for breeding, i.e. AI, are derived from ET, we can take it that the use of ET indirectly supports 75% of the total turnover of cattle farm-gate output, which produces a figure of EUR 55.2 billion, representing 4.6% of agro-food sector turnover.

#### *Environmental implications of embryo transfer in livestock*

As ET is not directly involved in altering breeding value but only in the propagation (and therefore faster dissemination) of desired genotypes, the main environmental impact is through assisting the rapid and cost-effective dissemination of improved resource productivity based on genetic improvements. For example,

243 Villanueva, B, G. Simm and J.A Wooliams (1995). *Animal Science* **61**: 231-239.

244 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

245 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.



the number of cattle in the EU is declining whilst output is steady or increasing. This is particularly obvious for milk production, which has been the focus of selection for the last fifty years. In the EU-15, cattle numbers decreased from 1994 to 2001 (with the exception of Sweden) by approximately 11%. In the same period the average milk yield per head increased by 17%<sup>246</sup>.

#### *Social implications of embryo transfer in livestock*<sup>247</sup>

One technique used in ET, ovum pick-up (OPU), is an invasive method and therefore may have negative implications for the welfare of individual animals that need to be balanced by the benefits obtained from the technology. Kolar and Rusche reviewed the acceptance of these technologies (by animal welfare organisations)<sup>248</sup>. Two organisations (of the six surveyed) did not accept ET or in vitro production (IVP) (however, only two of the organisations generally accepted AI). These results suggest that there are consumer concerns (raised by welfare groups) about the impact of these procedures on animal welfare. Public perception of reproduction techniques was also considered for France and the UK in the SEFABAR project<sup>249</sup>. It was found that AI was unanimously accepted in these two countries, with the author interpreting this to be a consequence of both its usefulness amongst humans and its length of service. In both countries, IVF and ET were represented as displaying some of the same features but some of the participants viewed them negatively in terms of animal production. Education, labelling and minimum standards were suggested as means of addressing concerns.

On the other hand, ET is considered a very safe method of disseminating genetics in terms of infectious disease (under regulations laid down by IETS<sup>250</sup> and OIE<sup>251</sup>). Thus, internationally it is thought of by some as contributing to animal welfare in terms of animal health.

#### *Summary of modern biotechnology applied to livestock breeding and propagation*

Molecular marker-based technologies and ET are the main modern biotechnology techniques applied to livestock breeding and propagation, and together they directly account for EUR 397-600 million of the turnover of the breeding sector<sup>252</sup>. While it is clear that the application of molecular markers and ET are not the only factors in the success of breeding efforts, but rather supplement breeding efforts based on conventional quantitative genetics, their application and diffusion seems to be significant. Given the use of modern biotechnology-derived animals further down the chain, all the way to the farm gate, it is estimated that modern biotechnology indirectly affects 58-72% of animal production, which in turnover terms represents EUR 73.4-91.4 billion of the EU annual animal output, or 6.1%-7.6% of EU agro-food sector turnover.

In general, modern biotechnologies such as molecular marker technologies and ET lead to improvements in the eco-efficiency of the primary sector, which, in combination with the comparatively stable economic activity of EU livestock production in recent years, should result in a relative decrease in livestock-related environmental pressure. However,

246 Table 4.1 in: Liinamo, A.-E. and A.vM. Neeteson-van Nieuwenhoven (2003). Economic value of livestock production in the EU – 2003. Farm Animal Industrial Platform, Oosterbeek.

247 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

248 Kolar, R. and B. Rusche (2003). "Animal welfare aspects of farm animal breeding and reproduction: chances for a sustainable future?" In: Liinamo, A.E. and A.M. Neeteson-van Nieuwenhoven (eds). Sustainable farm animal breeding and reproduction. Final Workshop Proceedings. SEFABAR, Oosterbeek, pp. 17-35.

249 Ouédraogo, A.P. (2003). "Symbolic goods in the market place: public perceptions of farm animal breeding and reproduction in France and UK" In: Liinamo, A.E. and A.M. Neeteson-van Nieuwenhoven (eds). Sustainable farm animal breeding and reproduction. Final Workshop Proceedings. SEFABAR, Oosterbeek, p36-46.

250 IETS: International Embryo Transfer Society.

251 OIE: World Organisation for Animal Health.

252 Including turnover from embryo transfer activities and from molecular marker-related breeding activities.



animals are sentient beings, and there are also potential risks in terms of animal health and welfare that need to be carefully accounted for in selection programmes in general and the use of biotechnologies in particular, along with the focus on enhanced productivity.

### 2.2.1.3 Breeding of fish

The main modern biotechnologies currently used in aquaculture are polyploidy induction and sex reversal. The use of molecular markers to optimise breeding strategies is increasing. Molecular markers in fisheries management (harvest fisheries) is still at a rather experimental/pilot phase. Harvest fisheries and aquaculture are of less economic significance than agriculture. However, regionally they can be very important.

#### *Economic significance of modern biotechnology in breeding fish*

In 2004, the EU aquaculture sector produced a total of 1.4 million tonnes of fishery products with a value of some EUR 2.8 billion. Production has been relatively stable since 1999, after a considerable increase between 1993 and 1999 (46%). The EU accounts for about 2.5% of worldwide production by volume and 4.6% by value, being the world production leader for some species such as trout and mussels. Within EU fisheries production, aquaculture represents 19% by volume, but 30% by value. Spain (26%), France (18%) and the UK (15%) are the largest producers in the EU. The largest world producers are Asian countries, with China producing nearly 30 times as much as the EU<sup>253</sup>.

In the EU, Atlantic salmon, rainbow trout, and oysters are among the five major species farmed. A survey of salmon, trout and oyster breeders and experts provided an indication of the adoption

of modern biotechnologies in aquaculture<sup>254</sup>. It stated that molecular markers have been mainly used in salmon and trout breeding for parentage assignment supporting breeding efforts (e.g. via microsatellites) and accounted for 30% of the revenues of salmon and trout breeders (EUR 10 and 11 million, respectively), and 10% (EUR 2 million) for oyster breeders<sup>255</sup>. Sex reversal and ploidy induction techniques have mainly been applied to trout and oyster breeding, accounting for about 50% (EUR 18 million) and 20% (EUR 4 million) of total turnover, respectively. Applying these adoption rates to farm-level production provides an indication of the indirect relevance of modern biotechnologies. It was estimated that approximately 15% of EU-wide fish farming turnover was produced through the use of seed fish produced with the aid of modern biotechnologies (EUR 432 million), representing 0.04% of overall agro-food turnover.

Overall, available information indicates that modern biotechnologies are important for particular sectors, namely sex-reversal and ploidy induction in trout and oyster production and molecular markers in assisting genetic selection (almost exclusively through pedigree identification and related technologies and not through markers for specific traits) for salmon and trout, as a relatively large share of seed fish are produced using these technologies. Expert opinion indicates that sex and ploidy-related technologies may have reached the limits of potential benefit where applied (i.e. trout and oysters) and that, therefore, adoption is not likely to increase in the future. Nevertheless, these techniques have not been adopted to the same extent by all EU Member States, and thus EU-wide adoption can be expected to increase in the future. The highest increase in adoption is, however, expected for the use of molecular markers in breeding of all relevant species. Overall, an increase in the use

253 European Commission (2006) Fact and figures on the CFP; European Commission (2006), Statistics in focus 23/2006 Aquaculture.

254 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

255 Referring to shares and absolute values of the companies that responded to the survey and not the whole sector.



and importance of modern biotechnologies in fish farming can be expected. Currently, however, the economic significance of breeding activities and aquaculture production is marginal in relation to the agro-food sector as a whole.

Regarding employment, the survey indicates that about 5% of employees in breeding companies/hatcheries have biotechnology-related jobs. However, no employment statistics are available for this sector. For fish farming, based on modern biotechnology adoption rates, it is estimated that about 10 000 jobs (out of 65 000) are related to modern biotechnology products.

#### *Environmental implications of modern biotechnology in fish breeding and propagation*

The environmental implications of the use of molecular markers in fish breeding have not been recorded. Nevertheless, the basic principles behind the potential environmental relevance of this technology are the same in all applications (fish, plants, and livestock). In relative terms, the expected improvements may be larger as fish breeding is more recent compared to plant and livestock breeding and therefore the genetic improvements to be made are larger; in absolute terms, however, the impacts are likely to be smaller, as the technology is used to a smaller extent in fish farming than in plants and livestock, and as the overall aquaculture output is much smaller. As far as ploidy and sex manipulation are concerned, the producers' survey<sup>256</sup> revealed benefits associated with the adoption of the technology, related to improved production efficiency, and reduced need for chemical treatment following secondary infections due to aggressiveness and stress.

#### *Social implications of modern biotechnology in the breeding and propagation of fish*

As far as ploidy induction and sex reversal in fish are concerned, both favourable and unfavourable views on their impacts on animal welfare have been expressed<sup>257</sup>. All-female trout production has been associated with a general increase in animal welfare as it is claimed to help alleviate up to 50% of secondary infections caused by early maturation, and its associated characteristics, such as reducing the need for chemotherapeutics. The induction of triploidy has been associated with increased deformity and susceptibility to disease (low stress tolerance) but also with the beneficial avoidance of maturity-related stressors.

### **2.2.2 Modern biotechnology in feed and food production, animal health and agro-food diagnostics**

#### 2.2.2.1 Modern biotechnology in feed and food production

##### *Economic significance of modern biotechnology in feed additives*

Feed additives have been gaining in importance as the consumption of animal products is increasing globally. The role of feed additives is mainly to complement the nutritional profile<sup>258</sup> of feeds in several ways. Feed enzymes mainly function as digestibility enhancers, whereas vitamins, amino acids and minerals directly complement the nutritional profile of feeds. Modern biotechnology has been applied in the production of a large number of feed additives, mainly feed enzymes (e.g. phytases), amino acids (e.g. lysine) and vitamins (e.g. riboflavin). The European Feed Manufacturers

256 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

257 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

258 Feed additives also target physical performance, but this is not relevant for biotechnology-based feed additives.



Federation (FEFAC) estimates that approximately 3% of feed material consumption comprises feed additives (out of the approximately 143 million tonnes of EU feed production in 2005)<sup>259</sup>, while it has been estimated that 65% of poultry and 10% of swine feed already contain enzymes such as carbohydrases or phytase<sup>260</sup>. Moreover, the EU and the USA are currently the global leaders in compound feed production, at 143 million tonnes (24% share) and 150 million tonnes (25% share), respectively, while the annual turnover of the EU compound feed industry in 2004 was estimated at approximately EUR 36 billion.

Feed enzymes are developed to function as digestibility enhancers for a variety of nutrients, such as phytases for plant phytate degradation and release of phosphorus content, carbohydrases for carbohydrate degradation, etc. The production of enzymes is described in greater detail in Chapter 2.3.1.1. The use of enzymes in feed may result in a variety of changes, mainly related to feed formulation and ingredient composition as well as to nutrient utilisation at the animal production stage. Feed formulation has been traditionally driven by least-cost objectives, but lately environmental and food quality aspects have been gaining importance. For example, the use of phytase may allow a higher share of plant ingredients or different types of plant ingredients in feed for monogastric animals (such as pigs, poultry and some fish) and a reduction in the use of inorganic mineral supplements. The use of enzymes affects the whole chain from feed ingredient producers, through the feed manufacturer, to the animal producer.

Phytate is an organic molecule containing high levels of phosphorus, which is a natural constituent of many plant ingredients used in animal feeds. 50%-80% of the total phosphorus in pig and poultry diets is bound in the largely unavailable form of phytate, as monogastric animals lack sufficient quantities of the enzyme phytase that naturally catalyses the degradation. Modern biotechnology has enabled the cost-effective production and use of phytase products for animal production, through the use of recombinant DNA techniques with selected microbial strains. The use of phytase in animal feeds leads to better phosphorus utilisation, and also improves the utilisation of protein and other minerals<sup>261</sup>. Besides the benefits in terms of animal performance, phytase addition also has important environmental implications, as it can reduce phosphorus emissions by animal facilities. Moreover, emerging modern biotechnology applications offer novel solutions here: new plant varieties of low phytate content have been developed using chemical mutagenesis techniques<sup>262,263</sup>, GM plant varieties expressing phytase have been developed<sup>264,265</sup>, and a GM pig (EnviroPig<sup>TM</sup><sup>266,267</sup>) developed by researchers in Canada expresses phytase that is secreted in the saliva, all of which provide promising alternatives for tackling the same problem.

259 <http://www.fefac.org/statistics>.

260 van Beilen, J.B. and Z. Li (2002). *Current Opinion in Biotechnology* **13**: 338-344.

261 Kornegay, E.T. (2001). Digestion of phosphorus and other nutrients. In: Bedford, M.R. and G.G. Partridge (eds). *Enzymes in farm animal nutrition*. CABI Publishing, Marlborough, pp. 237-271.

262 Raboy, V. et al. (2000). *Plant Physiol.* **124**: 355-368.

263 Sands, J.S. et al. (2001). *J. Anim. Sci.* **79**: 2134-2142.

264 Zhang, Z.B. et al. (2000). *Journal of Animal Science* **78**(11): 2868-2878.

265 Koegel, R.G. et al. (1999). Alfalfa produced phytase for supplementation of poultry and swine rations. ASAE Paper 996127 (St. Joseph, M.I.).

266 Golovan, S.P. et al. (2001). *Nat. Biotechnol* **19**: 741-745.

267 <http://www.uoguelph.ca/enviropig/>.



Amino acids and vitamins are supplements that provide essential nutrients lacking in the macro ingredients used in feed. An illustrative example is the case of the amino acid lysine<sup>268</sup> (see also Chapter 2.3.1.6): modern biotechnology has facilitated the industrial-scale production of lysine, which is used in a large proportion of prepared animal feeds, mainly for monogastric animals (pigs, poultry and carnivorous farmed fish). This means for example that soy-derived ingredients can be partly substituted by wheat and corn-derived ingredients (which have a lower lysine content compared to soy) in pig feed, and fishmeal can be partly replaced with wheat and corn-derived ingredients for carnivorous farmed fish. This substitution may also have impacts on the EU crop-growing sector and trade flows, as soybean meal is largely imported by the EU<sup>269</sup>. Another example is the biotechnological production of the vitamin riboflavin: 70% of global production is used for animal feed (see also Chapter 2.3.1.6). The production of riboflavin using modern biotechnology has apparently resulted in cost reductions of 40%-50% compared to the conventional chemical production process<sup>270</sup>, thus potentially facilitating its use as a feed additive.

In general, modern biotechnology enables the production of feed additives at lower costs, making their use by the feed industry (and livestock producers) more attractive. However, the share of feed containing modern biotechnology-derived amino acids and vitamins in their formulation is not known. The worldwide feed additives market is estimated at about EUR 4.8 billion<sup>271</sup>, including amino acids, vitamins, minerals, antibiotics, enzymes and acidifiers. Modern biotechnology plays a major role in the production of additives,

whereby amino acids, all of which are produced using modern biotechnology, represent about 36% of the feed additives market. Several vitamins and organic acids used in animal feed are also produced using modern biotechnology (see also Table 2.6). No data were available regarding the EU market for feed additives, but based on the data for lysine production, the EU share of feed additive production is estimated at about 20% or EUR 960 million. Of this, nearly 90% is estimated to be modern biotechnology-derived (EUR 860 million), representing 0.067% of the turnover of the agro-food sector.

#### *Environmental implications of modern biotechnology in feed additives*

Feed additives (whether biotechnology-based or not) in general optimise nutrient utilisation, thereby improving the environmental performance of animal production. Some feed additives have a direct environmental impact, such as most of the feed enzymes. Phytase addition, for example, has been reported to significantly reduce phosphorus emissions in pig and poultry production. On the other hand, many feed additives result in indirect environmental benefits by optimising nutrient metabolism and utilisation, such as in the case of lysine, which may reduce nitrogen excretion in pig production<sup>272</sup>. Moreover, as the addition of lysine to pig feeds is accompanied by the replacement of soybean by wheat or maize, and as the area needed to grow soybeans is larger than the corresponding area for maize or wheat, the use of lysine may also considerably reduce the agricultural area needed per unit output<sup>273</sup>. In general, as low protein and low phosphorus diets are increasingly used in animal production,

268 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

269 <http://www.fefac.org/statistics>.

270 EuropaBio (2003). White biotechnology: gateway to a more sustainable future. EuropaBio, Brussels.

271 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

272 Gâtel F. and E. Porcheron (2003). "The role of cereals in the European protein supply." In: FEFANA workshop proceedings, Protein supply for European pigs 2010, Brussels, 18 March, p. 23-27.

273 Toride, Y. (2002). "Lysine and other amino acids for feed: production and contribution to protein utilization in animal feeding." In: Protein sources for the animal feed industry: FAO Expert Consultation and Workshop, 29 April - 3 May, Bangkok. Food and Agriculture Organization, Rome, p. 161-166.



partially due to stricter environmental regulations, the importance of these two feed additives can also be expected to increase.

#### *Economic significance of modern biotechnology in food processing*

The use of enzymes in food processing is described in detail in Chapter 2.3.1. The direct economic significance mainly relates to the turnover realised by the enzyme producers relevant to food applications (EUR 390-585 million); the production of modern biotechnology-based food additives would add more to this estimate. The use of enzymes by the food and beverage processing sector provides an estimate of the indirect economic contributions (EUR 304 billion).

#### 2.2.2.2 Modern biotechnology in animal health

##### *Economic significance of modern biotechnology in animal health*

The veterinary pharmaceutical market represents only a small share of the global pharmaceutical market<sup>274</sup>, accounting for about 3% (EUR 13 billion). The market is further divided into products for companion animals and products for farm animals. The latter segment is mainly influenced by cost considerations and an emphasis on prevention rather than treatment of diseases. Products for farm animals account for about 60% of the sales of animal health products (including vaccines). Major product groups are vaccines and immunostimulants, antibiotics and anti-parasitics<sup>275</sup>. Modern biotechnology is used in the development and production of vaccines and antibiotics.

Antibiotics, partly produced using modern biotechnology, accounted for about 28% of the veterinary pharmaceutical market in 2004<sup>276</sup>. Their use for prophylactic, therapeutic and growth promotion reasons has been reduced due to food safety concerns and the development of bacterial resistance to antibiotics. The use of antibiotics in feed as growth promoters (apart from coccidiostats<sup>277</sup>) is banned in the EU<sup>278</sup>.

Bovine somatotropin (bST) is a hormone naturally produced by dairy cows which regulates milk production. A recombinant bST product (rbST) was commercialised by Monsanto in the USA in 1994, under the name POSILAC, as a treatment to enhance milk production. The use of rbST has been controversial, and while it has been approved in a number of countries, it was banned in the EU, as well as Canada, Australia, New Zealand and Japan, on the grounds of harm to animal health and welfare. While the EU has not approved the commercialisation of the product within its borders, it allows the import of dairy products derived from cows treated with rbST. The adoption of rbST by the US dairy cattle sector has been estimated at an average of 30% of the national dairy cow population, but with considerable variation (15-45%) depending on the region and the herd size<sup>279</sup>. Most ex-post economic assessments of rbST adoption in the USA have reported significant increases in milk output and numerically positive but non-statistically significant increases in profitability, mainly due to the large variability among farms. The numerical increase in profitability for adopters has been estimated at around US\$100 (EUR 78) per

274 ETEPS (2006). Bio4EU Task 2 Main report.

275 Based on the 64 veterinary products approved by the European Medicines Agency (EMA) 1995-2006 (biotechnology derived products, performance enhancers and vaccines for EU-wide prophylactic programmes).

276 ETEPS (2006). Bio4EU Task 2 Main report.

277 Coccidiostats prevent and treat coccidiosis in poultry, a disease caused by protozoa and resulting in damage to the intestines of the infected animal. Infections can spread rapidly and often are fatal.

278 Regulation (EC) 1831/2003 of the European Parliament and of the Council on additives for use in animal nutrition. OJ L 268/29, 18.10.2003.

279 Barham, B.L., J.D. Foltz, S. Moon and D. Jackson-Smith (2004). *Review of Agricultural Economics* 26: 32-44.





Table 2.5 Major veterinary pharmaceutical producers (source ETEPS<sup>282</sup>)

Company*	Country	Turnover in veterinary products (2005, € million)	Employees
Pfizer Animal Health	USA	1600	
Merial	France	1500	5000
Intervet	Netherlands	1094	4800
Bayer	Germany	700	
Fort Dodge	USA	693	
Elanco	USA	680	
Schering Plough AH	USA	672	
Novartis	Switzerland	622	2300
Adisseo	France	512	1200
Idexx	USA	500	3000
Virbac	France	372	2230
Boehringer Ingelheim	Germany	361	
CEVA	France	271	1732
Alpharma	USA	248	
Phibro Animal Health	USA	220	992
Vetoquinol	France	197	1140

\*Additional companies for which turnover or employment information was not available are: BASF (Germany), Dainippon/Sumitomo (Japan), Degussa (Germany), and DSM (Netherlands).

year per cow. A recent study has also reported a significant decrease in the production cost of milk following rbST adoption, with an estimated cost saving of US\$46-104 (EUR 36-81) per cow<sup>280</sup>.

Modern biotechnology is mainly applied in vaccine development and production. Vaccines represent about 20% of the global veterinary pharmaceutical market. About 50% of the products approved by the European Medicines Agency (EMA) between 1995 and 2006 belonged to this group. Of these, about 75% were modern biotechnology-derived, mainly using genetic engineering (see also Chapter 2.1.2 on vaccines for human health). The global turnover on animal vaccines has been estimated at EUR 2.6 billion<sup>281</sup>. The EU share is assumed to be 50% (based on Table 2.5), or EUR 1260 million. About 75% are

modern biotechnology-based, corresponding to EUR 920 million (0.016%-0.12% of turnover in the agro-food sector). The vaccine market for farm animals is highly dependent on official vaccination programmes and disease status in the individual EU Member States. Once eradication has been achieved, the vaccine is prohibited for further use.

The above turnover estimate for vaccines is a conservative estimation, since several major veterinary pharmaceutical companies are EU companies. Of the top sixteen veterinary pharmaceutical companies, eight are located in the EU (5 in France, 2 in Germany and 1 in the Netherlands). Three specialise in veterinary products, while the others are pharmaceutical companies that produce veterinary products alongside other health products (Table 2.5). The

280 Tauer, L.W. (2006). *AgBioForum* 9: 79-83.

281 ETEPS (2006). Bio4EU Task 2 Main report.

282 ETEPS (2006). Bio4EU Task 2 Main report.



share of modern biotechnology-based activities could not be determined for these companies. However, as with human pharmaceutical products, it can be assumed that most use modern biotechnology in product development and production.

Diagnostics using modern biotechnology are mainly applied for the detection and monitoring of notifiable diseases in the context of animal health. These applications will be described in the following chapter dealing with diagnostics in the food chain in general.

#### *Social implications of modern biotechnology in animal health*

Prevention of disease in farm animals plays an important role both in economic terms and as regards animal welfare and public health (zoonoses) issues. Vaccination is one approach to disease prevention and has proven to be effective in the eradication of diseases in the EU Member States. Vaccination potentially decreases animal suffering from diseases and avoids the need for pharmaceutical treatment. Modern biotechnology is increasingly used to develop vaccines, in particular 'marker' vaccines, which allow a distinction to be made between vaccinated and infected animals. This in turn allows disease monitoring and targeted animal culling before symptoms appear, limiting the spreading of the disease. The vaccine against pseudorabies or Aujeszky's disease is one example<sup>283</sup>, and was also the first GMO authorised in the EU.

Aujeszky's disease, also called pseudorabies, is a notifiable disease primarily affecting pigs, a major livestock in the EU. It is caused by a virus and results in nervous disorders in affected animals, increased

mortality of piglets and reduced fertility. The disease had not existed widely outside Eastern Europe before the 1960s, but by 1989 it had a worldwide distribution affecting 43 countries<sup>284</sup>. Prior to vaccine development and administration, the only options were either to allow the disease to remain endemic in the population or to try and control it through animal culling. This resulted in substantial animal and economic losses, as Aujeszky's disease is one of the most dangerous diseases in domestic pigs<sup>285</sup>. Currently, there are 10 EU Member States where the disease is still endemic, while 10 of the 13 EU Member States for which relevant information was available are disease-free with or without continuing vaccination and 3 are currently vaccinating the endemically affected population<sup>286</sup>.

The biotechnology vaccine against pseudorabies was developed at the beginning of the 1980s with two main objectives: to develop a live vaccine (known to be more effective than inactivated viruses) and to develop a vaccine to allow a distinction to be made between vaccinated and infected animals, thus facilitating the eradication of the disease. Genetic engineering was used to produce a modified virus, approved in 1989, which is not infectious and allows, due to the deletion of a specific surface protein, vaccinated pigs to be distinguished serologically from pigs infected with the natural virus. The vaccine (the only type authorised in the EU) provided the basis for the EU programme for the eradication of pseudorabies disease.

283 See ETEPS (2006) for more information. (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.)

284 <http://www.defra.gov.uk/animalh/diseases/notifiable/aujeszkys/>.

285 Müller, T., et al. (2003). *Journal of Veterinary Medicine B* **50**: 207-213.

286 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.



### *Environmental implications of modern biotechnology in animal health*

The environmental impacts of modern biotechnologies applied in the production of animal health products are in general positive: firstly, there is a general trend towards increasing prevention (vaccination and other immunostimulation/disease-resistance methods based on pre- and pro-biotics, all of which are increasingly biotechnology-based), which leads to a decrease in the use of less desirable chemical treatments (e.g. antibiotics). The prevention of disease and subsequent disease eradication inherently bring about improvements in production efficiency associated with a healthy stock. Moreover, a decrease in the use of antibiotics will diminish the negative impacts of microbial resistance to antibiotics, while marker vaccines make eradication programmes more effective, therefore reducing the number of animals that need to be culled.

#### 2.2.2.3 Modern biotechnology in diagnostics in the food chain

##### *Economic significance of modern biotechnology in diagnostics in the food chain*

Diagnostics are applied throughout the food chain: in livestock production for animal health purposes (e.g. foot-and-mouth disease detection), in food safety and public health (e.g. salmonella testing or bovine spongiform encephalopathy (BSE) detection), and for traceability purposes (e.g. GM food and feed detection and quantification, end product and origin identification). Modern biotechnology

is mainly used for DNA-based diagnostic tests and immunoassays (see also Chapter 2.1.4 on diagnostics in human health). Diagnostics are far less used for veterinary purposes in comparison to human medicine. This is also reflected in the comparatively marginal turnover on veterinary diagnostics, estimated at about EUR 400 million in 2003<sup>287</sup>, compared to EUR 22 billion for the overall in-vitro diagnostics (IVD) market. Half of the largest veterinary pharmaceutical companies are located in the EU, so the EU share is assumed, due to the lack of statistical data, to be 50%, or EUR 200 million. Additionally, diagnostics for food safety and traceability purposes are valued at EUR 500 million<sup>288</sup>, 20% (EUR 87 million) of the total for rapid, biotechnology-based methods. The economic value of modern biotechnology diagnostics can be roughly estimated at EUR 300 million, which represents 0.03% of turnover in the EU's agro-food sector. Laboratory-related turnover in modern biotechnology diagnostics for food safety and veterinary health may be conservatively estimated at EUR 1.5 billion<sup>289</sup>, accounting for 0.23% of agro-food turnover in the EU.

Farm animal disease outbreaks can have serious economic consequences, so fast and accurate diagnosis is an important tool in their prevention and/or monitoring. In the case of bovine spongiform encephalopathy (BSE), the UK lost beef export markets, sales of beef went down by 40% and the price of beef fell by 25%, resulting in an economic loss for the UK of about 0.1%-0.2% of GDP<sup>290</sup> in the year following the outbreak. Losses of the same order of magnitude were calculated for the more recent outbreak of foot-and-mouth disease in the UK.

287 ETEPS (2006). Bio4EU Task 2 Main report.

288 No data are available at sector level, so a best estimate was taken from the data provided by: Blankenfeld-Enkvist, G., and M. Brännback (2002). Technological trends and needs in food diagnostics. Technology Review 132/2002, National Technology Agency, Helsinki. The report covers the food chain from raw material to end products (turnover of EUR 491 million). Furthermore, GMO diagnostics were included (estimated at EUR 3 million for 1999 with predicted annual growth rates of 100%; a more conservative estimate was taken).

289 DNA-based tests and immunoassays for GMO detection cost EUR 6-150 per test while laboratory analysis costs €100-570). For BSE testing (immunoassay), laboratory analysis was estimated at EUR 40-50. (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications). A fivefold greater laboratory turnover is thus a conservative estimate.

290 ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.



Modern biotechnology-related diagnostics are generally faster than conventional methods and at least as accurate, and may be the only option in some cases (e.g. for BSE monitoring or GMO traceability). Overall turnover on modern biotechnology kits (test kit sales) is about EUR 300 million. The indirect use of these test kits by laboratories generates an estimated additional turnover of EUR 1.5 billion, contributing only marginally to agro-food sector turnover (0.15%).

### *Social implications of modern biotechnology in diagnostics*<sup>291</sup>

Diagnostics are essential for assuring the functioning of the food chain through early and quick identification of pathogens, thus avoiding animal suffering from diseases and ensuring food safety as well as enabling compliance with regulatory obligations and consumer choice, e.g. in the case of GMO traceability. Contagious diseases such as foot-and-mouth disease (FMD) are of minor danger to humans but, if not controlled, spread rapidly and involve the suffering of many animals, apart from significant economic losses. In a recent outbreak in the EU in 2001 (mainly in the UK, but also in Ireland, France and the Netherlands), about 4 million animals were culled. Rapid and specific diagnostic tests could facilitate detection and control of the disease.

In the case of BSE, modern biotechnology provides the only method for the rapid processing of samples and diagnosis, thus enabling the level of surveillance required by EU legislation<sup>292</sup>. Thirteen different immunoassays have been approved by the EU for BSE testing of slaughtered animals before they enter the food chain, reducing the risk of contamination and increasing consumer trust in beef. However, food safety and

consumer confidence come at a price. Between 2001 and 2004, around 44.7 million cattle were tested at a cost of EUR 1835 million. About EUR 1.56 million were spent for every BSE case identified in healthy animals, and EUR 70 000 for every BSE case in at-risk animals.

Bovine spongiform encephalopathy (BSE) is a zoonotic disease affecting cattle, first confirmed in the UK in 1985. BSE is a neurological disease the symptoms of which may last several weeks, are progressive and fatal. The disease belongs to the family of Transmissible Spongiform Encephalopathies (TSEs), which also appear in other mammals, including humans. Most recorded BSE cases have occurred in the UK, peaking at 37 301 in 1992 and falling to 561 in 2005 (EU-wide data)<sup>293</sup>. The risk of nvCJD (new-variant Creutzfeldt-Jakob Disease) from the consumption of BSE-infected meat was identified in 1996, and so far approximately 162 cases of nvCJD have been found in the UK and 36 in the rest of the world (of which 30 in the EU). The impact of the disease is multifaceted and, besides human and animal losses, has also brought with it a loss of consumer confidence, trade implications, and the large and long-term costs associated with control measures, the drop in the value of beef animals, the safe disposal of waste material, animal testing and extra procedures in the slaughtering industry. The cost of the epidemic to the EU has been calculated at 10% of the annual value of the EU beef sector, while the discounted present value has been estimated at EUR 92 billion<sup>294</sup>.

A new generation of modern-biotechnology diagnostic methods could also enable faster

291 For details on the case studies see: ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.  
292 Regulation (EC) No 999/2001 of the European Parliament and of the Council laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. OJ L147/1, 31.5.2001.  
293 Report on the monitoring and testing of ruminants for the presence of Transmissible Spongiform Encephalopathy (TSE) in the EU in 2005. European Commission, DG Health and Consumer Protection, 2006.  
294 Cunningham, E.P. (ed.) (2003). After BSE: a future for the European livestock sector. EAAP Series no. 108, Wageningen Academic Publishers, Wageningen.



detection of the food pathogen salmonella. Salmonella causes food poisoning and is the second most prevalent pathogen in food and the most frequent cause of food-borne bacterial gastroenteritis in the EU. In 2004, an average 42.2 cases per 100 000 inhabitants were registered in the EU. Early and quick identification of contaminated raw material and food could help avoid or control such cases.

Modern biotechnology also enables the identification and quantification of genetically modified (GM) ingredients in raw material and food. It thus facilitates compliance with EU regulation regarding traceability and the labelling of food<sup>295</sup> and also increases transparency and consumer choice regarding GM food.

### **Environmental implications of modern biotechnology in diagnostics**

In environmental terms, the adoption of modern biotechnology-based diagnostics brings about improvements (efficiency and/or accuracy) in avoiding potential environmental contamination (e.g. Salmonella) and/or animal culling in the case of outbreaks (e.g. BSE, FMD). Moreover, modern biotechnology-based diagnostics for tracing GMOs in the food chain also permit the long-term monitoring of GMOs in the environment, which is crucial for the post-marketing environmental monitoring and general surveillance that supplement the environmental risk assessments of GMOs under current EU legislation.

### **2.2.3 Emerging biotechnology applications in primary production and agro-food**

Emerging applications in plants

*The production of plants as raw material for non-food purposes*

An emerging issue in agriculture and forestry is the increasing emphasis on the development and use of plants for non-food purposes, mainly for industrial applications, such as the production of energy, biofuels and other bio-based materials (such as bio-polymers, plant oils, etc.)<sup>296</sup>. These developments are relevant for the primary sector providing the raw material, but also for the industrial sector involved in processing it into the various final product forms, and may also have consequences for the agro-food sector in that resources (such as arable land or even the final raw material produced) may need to be shared among different users. The potential of bio-based resources to provide alternative raw materials has been recognised in the EU and globally<sup>297</sup>. Modern biotechnology plays a dual role in this context: i) industrial biotechnologies are important for transforming the raw material into the final product (e.g. in bio-refineries), and ii) modern biotechnologies applied in plant breeding are important for the development of plants optimised for industrial purposes. In the latter case, modern biotechnologies such as molecular markers and/or GM-based technologies are already being explored for the development of plants with traits optimised for industrial applications. Examples include a higher yield from plants suitable as feedstock

295 Regulation (EC) No 1829/2003 of the European Parliament and of the Council on genetically modified food and feed, OJ L 268/1, 18.10.2003; Regulation (EC) No 1830/2003 of the European Parliament and of the Council concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC. OJ L268/24, 18.10.2003.

296 For example, see <http://www.epobio.net/overview.htm>, <http://www.biofuelstp.eu/overview.html> or <http://www.epsoweb.org/Catalog/TP/index.htm>.

297 For example, see [http://ec.europa.eu/research/biotechnology/ec-us/docs/ec-us\\_tfws\\_2004\\_april\\_albany\\_proceedings.pdf](http://ec.europa.eu/research/biotechnology/ec-us/docs/ec-us_tfws_2004_april_albany_proceedings.pdf).



in industrial applications, plants with optimal composition, plants with novel traits, etc.<sup>298</sup>. In general, modern biotechnology is considered a critical factor for the future development of plant production for industrial purposes<sup>299</sup>, with considerable economic (knowledge-based bio-economy), environmental (especially in terms of energy saving and GHG emissions) and social (e.g. in terms of energy security or alternative activities for farmers) implications<sup>300</sup>.

### Genetically modified plants

Currently commercially available genetically modified (GM) crops are mainly “first-generation” GM plants, i.e. with modified agronomic input (production) traits. Emerging GM crops (second- and third-generation GM plants) mainly involve<sup>301</sup>:

- i) the insertion of more than one trait in a plant (stacked traits),
- ii) the insertion of novel and/or more complex traits, such as output traits (i.e. improved quality) and abiotic stress-resistance traits (e.g. drought or salt tolerance), and
- iii) the production of novel products through molecular farming.

Overall, there are a large number of products in the pipeline, given that the period from 1991 to 2006 saw 2121 notifications of deliberate field

trials<sup>302</sup>, many of which concern novel traits<sup>303</sup>. Also of particular interest is the production of GM plants through metabolic engineering (engineering the metabolism of organisms) to express complex traits<sup>304</sup>.

The most recent developments target plant molecular farming, i.e. the production of pharmaceuticals, functional proteins and industrial enzymes in plants. Over the last decade, plants have emerged as convenient and economic alternative expression systems, and plant molecular farming is expected by some to challenge established production technologies that currently use bacteria, yeast or cultured mammalian cells. To date, over 20 plant-derived pharmaceuticals have been submitted for clinical trials, including recombinant antibodies, human- and animal-edible vaccines (in 2006 FDA authorised the first plant-derived animal vaccine), and other proteins such as gastric lipase for the treatment of cystic fibrosis. Additionally, six plant-derived technical proteins are already available (avidin, trypsin,  $\beta$ -glucuronidase, aprotinin, lactoferrin, and lysozyme). R&D is currently dominated by not-for profit research organisations. Patent analyses for the years 2000-2003 have revealed the strong position of the USA in the field, with EU organisations holding 70% fewer patents than the USA<sup>305</sup>.

The major technological challenge to be addressed by researchers is to ensure that the

298 For example, Syngenta is developing a genetically modified strain of corn that expresses high levels of a Diversa alpha amylase enzyme, called internally amylase-T, to increase the cost-effectiveness of ethanol production from corn starch. <http://www.diversa.com/Pages/Products/AlternativeFuels/AltFuelsAmylaseT.html>.

299 For example, see <http://www.biomatnet.org/publications/us-ec0605strategy.pdf>.

300 For example, see <http://ec.europa.eu/research/conferences/2005/kbb/>.

301 It should be noted, however, that there are no strict borderlines between current and emerging applications, nor among 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation GM plants.

302 <http://biotech.jrc.it/deliberate/dbcountries.asp>.

303 Two products expressing novel traits are in the pipeline for authorisation, namely potato with altered starch composition and fodder maize with increased lysine content ([http://efsa.europa.eu/science/gmo/gm\\_ff\\_applications/catindex\\_en.html](http://efsa.europa.eu/science/gmo/gm_ff_applications/catindex_en.html)). Moreover, several products that combine herbicide resistance with pest resistance or different types of pest resistance (stacked traits) have already been authorised. (For example see [http://gmoinfo.jrc.it/gmc\\_browse.asp](http://gmoinfo.jrc.it/gmc_browse.asp) and [http://ec.europa.eu/food/dyna/gm\\_register/index\\_en.cfm](http://ec.europa.eu/food/dyna/gm_register/index_en.cfm)).

304 Examples of such products under development include “golden” rice (Paine J.A. et al. (2005). *Nature Biotechnol.* **23**: 482-487), which contains two transgenes to produce pro-vitamin A ( $\beta$ -carotene) and which has already undergone the first field trials in the USA, or leaf mustard (Brassica juncea), which has been engineered with three to nine structural genes to express high levels of  $\omega$ -3 poly unsaturated fatty acids (PUFAs) (Wu, G. et al. (2005). *Nature Biotechnol.* **23**: 1013-1017). These applications are among the first of their kind, with prospects for providing nutritional solutions for both developing and developed countries.

305 Arcand, F. and P.G. Arnison (2005). Development of novel protein-production systems and economic opportunities & regulatory challenges for Canada. Discussion paper. <http://www.cpmp2005.org/Plant-factories.aspx>.



structure of the engineered protein results in a functionality equivalent to that of the native form. However, the cost-efficiency of plant production is controversial. Other factors that add to the uncertainty are limited clinical data, public debate on transgenic technology, and the uncertainty as to regulatory approval for such plant-produced drugs.

#### Emerging biotechnology applications in animals<sup>306</sup>

##### *Genetically modified animals*

While genetic modification (GM) technology has so far mainly been applied to microorganisms and plants, GM animals, including fish, have been receiving increasing interest in recent years. The first GM mammal was produced in 1985 and GM pigs, sheep, cattle, goats, rabbits, chickens and fish have all been reported. Currently, the majority of GM mammals are mice used for R&D purposes. In the UK, for example, the number of GM animals increased from 50 000 in 1990 to 900 000 in 2004<sup>307</sup>.

There are several possible applications of GM animals (though so far relatively little commercial activity):

*Production of novel compounds (mainly pharmaceuticals) in the milk, eggs and blood of animals (molecular farming):* between 5–10 products produced in GM animals are progressing through human clinical trials as part of the regulatory procedures required for pharmaceutical products. The production of proteins in animals has several advantages over various other methods that are currently used for the industrial production of proteins. ATryn® (GTC Biotherapeutics, Inc), a human antithrombin product produced in the milk of genetically modified goats, became the first product to receive market authorisation by the European Commission in August 2006.

*Food production (including fish):* The lead product is probably GM fish, including faster-growing GM salmon developed in North America, which is awaiting regulatory approval for use in the food chain. Other applications are at the experimental stage, but it seems unlikely that any will be in general use before 2010. No companies developing GM animals for food were identified in the EU.

*Production of organs for transplant into humans (xenotransplantation):* The production of GM pigs to supply organs for human transplants has been the subject of considerable research. However, no examples of xenotransplantation products from GM livestock are currently on the market or available for treatments. Various degrees of optimism are expressed about the prospects for xenotransplantation, but most proponents suggest that it will be 10 years or more before GM pig organ transplants become available.

*Production of specific types of pets:* GM ornamental fish have been available commercially in the USA since late 2003. Research is reportedly also being conducted to produce GM cats with reduced allergenicity for humans. However, reduced-allergenicity cats have just recently been produced by Allerca (USA) through the use of a patented technology based on directed evolution and not GM.

The most contentious issues with regard to the use of GM animals are welfare and ethical issues. As there may be adverse animal welfare effects related to GM animal production, GM animal welfare may need a case-by-case assessment. The extensive ethical discussion has shown that there is no universal agreement on the ethical considerations. Other issues raised by some in the animal welfare and ethical debate as regards both cloning and GM include the potential to interfere with “animal integrity”, which refers to the naturalness, wholesomeness, and independence

306 The information herein is mainly based on a study developed and coordinated by the JRC/IPTS and carried out through the European Science and Technology Observatory (ESTO): “Animal cloning and genetic modification: a prospective study”. Publication in preparation.

307 Home Office, Statistics of Scientific Procedures on Living Animals, Great Britain (1990-2004).



of animals, and the potential increase in the perception of animals as commodities, such as research tools or units of production.

#### *Animal cloning*<sup>308</sup>

The first mammalian species cloned using somatic cell nuclear transfer (SCNT) was sheep, in 1996. Since then several species have been cloned, including cattle, goat, pig, horse, cat and most recently dog.

Animal cloning may be used in a variety of commercial contexts including:

*Food production*<sup>309</sup>: Cloned livestock (especially pigs and cattle) are currently being developed for use in the food chain, the main barriers being regulatory approval and public acceptance. At least in the beginning, cloned animals are likely to be used just for breeding purposes, as it will not be economic to use them directly for food or milk production. Cloned animals for the food sector are being developed primarily in the USA, Australia/New Zealand and Asia. No company was found in the EU to be developing this technology for use in the food chain.

*Pets and sports animals*: Commercial services for cloning cats were available in the USA<sup>310</sup>. Similar services exist for various sports animals in the USA and there is a company offering a commercial service to clone horses in France. Dogs have been cloned on an experimental basis in South Korea. The total number of cloned pets or sports animals worldwide is currently very small.

*Endangered species*: Commercial companies offering to clone endangered species exist in

the USA, Brazil and France. Cloning to preserve endangered species offers a chance to regain genes lost through the death of an animal but will not increase the amount of genetic diversity and does not address other issues such as loss of habitat. Individuals from some endangered species have been cloned, e.g. the mouflon, banteng and African wildcat, and cloning technology has been used to restore endangered breeds of cattle.

The welfare of cloned animals and the ethics of cloning, particularly where the benefits perceived by citizens are small, are likely to be controversial. Many cloned animals display a range of physiological disorders (collectively known as Large Offspring Syndrome), which in some cases can have a severe impact on welfare. Some claim that these welfare problems have been overcome, but others remain sceptical.

#### Nutrigenomics - Nutrigenetics

The basic goal of both nutrigenomics and nutrigenetics<sup>311</sup> is to match nutrition to individual human genotypes (looking at genes and/or other biological measurements) in order to delay the onset of disease or to optimise and maintain human health (i.e. personalised nutrition). In commercial terms, this involves the provision of a new service in the form of nutritional advice tailored to the needs and particular characteristics of individuals (or populations). Similarly, the technology may be applied to animals to improve livestock production and companion animal nutrition. The genetic testing companies with or without nutritional expertise (e.g. through hospitals and dieticians) are the main players currently involved in the provision of personalised

308 Animal cloning refers to the production of genetically identical “copies” of an animal through Somatic Cell Nuclear Transfer (SCNT) technology. This involves the production of animals through transfer of the genetic material from one donor somatic cell to a recipient unfertilised oocyte that has had its nuclear DNA removed (enucleation). Through the use of several individual cells from a given unique source and an equivalent number of recipient oocytes, several cloned animals can be produced. SCNT can also be used as a tool in the production of GM animals.

309 Suk, J. et al. (2007). *Nature Biotechnology* 25: 47-53.

310 The only company offering this service has closed.

311 As a scientific endeavour, nutrigenomics is the study of the response of organisms to food and food components using genomics, proteomics and metabolomics approaches. Nutrigenetics, in turn, refers to genetically determined differences in how individuals react to specific foods.





nutrition advice. GeneWatch UK<sup>312</sup> identified 12 mainly small biotech companies operating (or in the planning phase) worldwide, most of them with their headquarters in the USA, although some also claim to be marketing in the EU<sup>313</sup>.

Genetic testing followed by dietary advice for monogenic nutrient-related diseases may be considered as an elementary application of nutrigenomics. This is the case for phenylketonuria and haemochromatosis testing and for another approximately 50 genetic diseases in humans caused by variants in enzymes, where changing the substrate (nutrient) concentration may be the general approach for dietary intervention<sup>314</sup>. While today almost 1 000 human disease genes have been identified and partially characterised, 97% of which are known to cause monogenic diseases<sup>315</sup>, most chronic diseases are due to complex interactions between several genes and environmental factors, which makes directed dietary intervention more challenging. Nutrigenomics is expected to have an impact primarily in the prevention (but also mitigation and curing) of chronic diseases such as obesity, diabetes type II, cardiovascular diseases (CVD) and cancers, and is therefore expected to have a beneficial effect on human health and wellness.

While nutrigenomics is considered promising by some, it is still in its infancy and the benefits are not expected to be realised in the short term. A number of concerns regarding the commercialisation of nutrigenomics and personalised nutrition have been raised<sup>316</sup>, questioning the potential of the commercial application of nutrigenomics.

## Nanobiotechnologies in agriculture and food

Nanotechnology may converge with biotechnology and enable new and/or improved applications not only in primary production, but also throughout processing, packaging, distribution and preparation processes, such as<sup>317</sup>:

*Improved diagnostics, biosensors and surveillance/monitoring systems*, e.g.: improved microarrays based on nano-scale materials (e.g. silica-based chips); nanosensors utilising nanotubes or nano-cantilevers that are small enough to trap and measure individual proteins or other small molecules; nanoparticles or nanosurfaces that can be engineered to trigger an electrical or chemical signal in the presence of a contaminant such as bacteria; other nanosensors that work by triggering an enzymatic reaction or by using nano-engineered branching molecules (dendrimers) to bind target chemicals and molecules. For example, BioMerieux launched the first high-density DNA multi-detection test for food and animal feed testing (FoodExpert-ID) in 2004<sup>318</sup>. Other improved sensors are currently being developed for sensing and signalling microbiological and biochemical changes, e.g. those relevant to food safety and quality during packaging and storage and relevant to improving food appearance (such as colour, flavour and consistency).

*Improved delivery systems*, e.g.: encapsulation and controlled release methods for the precise and targeted delivery of fertilisers, pesticides and herbicides in crop farming, of veterinary treatments to animals, as well as of nutrients to animals and humans. For example, Syngenta is

312 Wallace, H. (2006). Your diet tailored to your genes: preventing diseases or misleading marketing? GeneWatch, Buxton.

313 Besides these biotech companies, larger food manufacturing companies, such as Nestlé, Unilever, Kraft and Cargill seem to have expressed interest in investing in research on nutrigenomics applications, while the International Life Sciences Institute (ILSI) has also engaged in related activities (From footnote 312).

314 Kaput J. and R.L. Rodriguez (2004). *Physiological Genomics* **16**: 166-177.

315 Jimenez-Sanchez, G., B. Childs and D. Valle (2001). *Nature* **409**: 853-855.

316 Wallace, H. (2006). Your diet tailored to your genes: preventing diseases or misleading marketing? GeneWatch, Buxton.

317 Joseph T. and M. Morrison (2006). Nanotechnology in agriculture and food. Nanoforum Report. nanoforum.org, Düsseldorf.

318 [http://industry.biomerieux-usa.com/news/pressreleases/food\\_expert\\_id\\_pr.htm](http://industry.biomerieux-usa.com/news/pressreleases/food_expert_id_pr.htm).



using nanoemulsions in its pesticide products, has marketed a quick-release microencapsulated insecticide under the name Karate ZEON, which breaks open on contact with leaves<sup>319</sup>, and holds a patent for a “gutbuster” insecticide that breaks open to release its contents when it comes into contact with alkaline environments, such as the stomach of insects<sup>320</sup>. In the food sector, an example is “Tip Top Up” bread, on sale in Australia, which has incorporated  $\omega$ -3 fatty acids in nanocapsules designed to break up only upon reaching the stomach, thus avoiding the unpleasant taste of fish oil<sup>321</sup>.

The application of nanotechnology in the agriculture and food sectors was first addressed in the USA by the USDA<sup>322</sup>. The European Commission published a Nanosciences and Nanotechnologies Action Plan in June 2005, in support of its Nanotechnology Strategy for Europe<sup>323</sup>. Claims of potential benefits from the application of nanotechnology have been coupled with concerns, which include potential risks to human health and the environment. Under the Nanosciences and Nanotechnologies Action Plan, the Commission will aim to identify and address safety concerns associated with the application of nanotechnology, become involved in the development of terminology, guidelines, models and standards for risk assessment and, where appropriate, propose adaptations of EU regulations in relevant sectors.

#### 2.2.4 Summary

##### Economic significance

Modern biotechnology is applied in most areas of primary production and the food chain,

ranging from applications in breeding to the provision of diagnostic tools for food safety and food ingredient identification. The combined economic contribution of the application of modern biotechnology in the input sectors has been estimated at between EUR 3-5.6 billion or 13%-23% of turnover in these sectors. This represents only a small share of the overall agro-food sector (0.26%-0.47%) or total EU gross value added (GVA) (0.01%-0.02%<sup>324</sup>). Overall, and based on a conservative estimate, the largest turnover share among the various applications is held by veterinary products (30%), followed by feed additives (28%), food enzymes (13%), and diagnostics (10%), while breeding and propagation-related activities altogether (plants, livestock and fish) account for the remaining 19% (Figure 2-13). An estimation based on the upper limits of the turnover values calculated for these applications indicates a larger relative economic significance for molecular marker-based technologies in plants.<sup>325</sup> This reflects the large uncertainty in the actual adoption of molecular marker-based technologies in plant breeding. The role of modern biotechnologies in the different applications may differ as well, and so may their relative importance for the turnover obtained with these applications. For example, modern biotechnologies may have a core or a supporting role in production processes. From the product perspective, modern biotechnology may be the only technology available for reaching a certain objective (e.g. in diagnostics applications), may provide a more cost-effective option (e.g. riboflavin production) or may provide better-quality though more expensive products for optimising benefits in downstream uses (e.g. breeding).

319 <http://www.syngentacropprotection-us.com/prod/insecticide/Karate/>.

320 Syngenta's US Patent No 6,544,540: Base-Triggered Release Microcapsules.

321 <http://www.tiptop.com.au/driver.asp?page=main/products/bread/up+white+omega+3+dha>.

322 Nanoscale science and engineering for agriculture and food systems, Department of Agriculture, US, 2003.

323 'Nanosciences and nanotechnologies: An action plan for Europe 2005-2009' (COM(2005) 243).

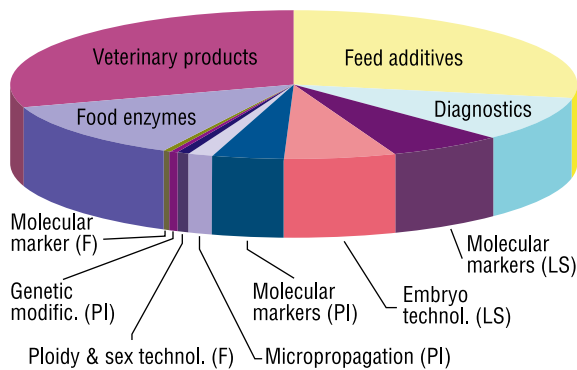
[http://europa.eu.int/comm/research/industrial\\_technologies/lists/list\\_108\\_en.html](http://europa.eu.int/comm/research/industrial_technologies/lists/list_108_en.html).

324 The turnover values were multiplied by 0.3 to obtain an estimate in GVA terms.

325 For example, assuming that 100% of maize seed is derived from molecular marker-assisted breeding increases the relative share of this application to 10%, while the assumption that 1/3 of all plant breeding uses molecular markers further increases its share to 37% of the total.



■ *Figure 2-13: Relative economic values of biotechnology applications in input sectors (conservative estimate)*

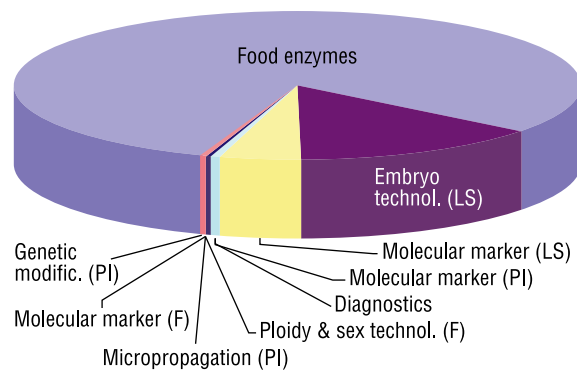


Note: LS = livestock, PI = plants, F = fish.

The use of biotechnology-derived products provided by the input sectors, mainly in primary production and food processing, also contributes to the economic performance of these “user” sectors. The turnover of the sectors using modern biotechnology-derived products has been estimated at EUR 382-453 billion<sup>326</sup>, which accounts for 32%-38% of agro-food sector turnover and 1.3%-1.55% of total EU GVA<sup>327</sup>. Based on a conservative estimate, the largest turnover share is accounted for by the use of modern biotechnology-derived products in the food processing sector (80%), followed by the livestock sector (19%) and the plant sector (1%) (Figure 2-14). However, an estimation based on the upper limits of the turnover values calculated for these applications indicates a higher relative economic significance for molecular marker-based technologies in plants<sup>328</sup>. Thus modern biotechnology indirectly has economic implications for at least a third of the agro-food sector. The economic scale of these indirect

effects is approximately two orders of magnitude larger than the direct contributions of the input sectors. This estimate is not, however, an absolute measure of the indirect impacts per se: modern biotechnology-derived products provide varying economic advantages to the user sectors, generally related to improvements in productivity, production efficiency, and therefore overall competitiveness.

■ *Figure 2-14: Relative economic values of applications of biotechnology-derived products in primary production and food processing (conservative estimate)*



Note: LS = livestock, PI = plants, F = fish.

As far as global competitiveness in concerned, apart from the production of GM seeds and the cultivation of GM crops, where the EU lags behind, the EU has an important share in the markets where biotechnology-based products play a role. This can be seen from its considerable share in the export market for breeding and propagation material as well as in the markets for veterinary products, diagnostics and feed additives.

326 Not including the indirect impacts of feed additives and veterinary products, although as the indirect impacts will relate mainly to livestock production, they are already partially covered by other applications relating to livestock (as the users of the various inputs may overlap).

327 The turnover values were multiplied by 0.3 to obtain an estimate in GVA terms.

328 For example, assuming that 100% of maize production is derived from seeds produced via molecular marker-assisted breeding increases the relative share of this application to 2%, while the assumption that 1/3 of all plant breeding uses molecular markers further increases its share to 12% of the total.



### Contribution to employment

Data on employment are largely missing, while complex interactions and unknown substitution effects limit any attempt to arrive at a comprehensive assessment. In general, the contribution of modern biotechnology is seen mainly in the creation of “more qualified jobs” in sectors that use modern biotechnologies directly. Moreover, the share of direct employment that may be attributed to modern biotechnology probably corresponds to that calculated for the adoption of biotechnology applications in general. As with biotechnology applications overall, a proportion of the newly generated jobs can be assumed to replace existing employment. Results along these lines were obtained in a previous study<sup>329</sup> focusing on seed biotechnology, which also indicated that most of the future growth potential for direct employment lies in the success of EU companies on foreign markets (where the future growth in “users” lies) and that indirect employment opportunities in the agro-food chain are much greater than the direct prospects, not least because of the large differences in current employment numbers (e.g. while the EU seed sector has more than 30 000 employees, total employment in food processing alone is over 3 million).

### Social implications

The social implications of modern biotechnology in the agro-food sector mainly relate to public health issues, including animal health and welfare. As with biotechnology in the health field, the public health benefits of modern biotechnology applications in the agro-food sector derive from the availability of new and better diagnostics and vaccines. In particular, the monitoring and control of some of the most important zoonoses and food safety concerns (e.g. Salmonella and BSE) help in ensuring EU-wide food safety and consumer confidence in the food chain. The cost-effectiveness of modern biotechnology applications is also

relevant for applications in the agro-food sector with a potential indirect impact on public health. It has been reported, for example, that the use of the modern biotechnology-based vaccine for Aujeszky's disease in pigs is the most cost-effective option for eradication of the disease. Similarly, modern biotechnology-based diagnostics are crucial for the surveillance of several of the major communicable livestock diseases in the EU, though achieved at a high monetary cost. Yet a general assessment is not feasible, especially if social and ethical costs are taken into account. Ensuring optimal animal health and welfare is important both from a social and an economic perspective. Modern biotechnology may have contrasting implications for animal health and welfare. On the one hand, some modern biotechnologies present new issues in terms of animal welfare, necessitating a case-by-case assessment of the potential adverse effects and perceived benefits. This is especially the case with what are perceived as intrusive techniques or techniques that may involve novel risks for animal welfare, such as pain, suffering or distress in the short or long term. On the other hand, modern biotechnology provides solutions that improve animal health and welfare in a variety of ways, for example by replacing the use of animals in chemical safety testing or through the provision of novel animal health management tools that decrease animal suffering.

### Environmental implications

The agro-food sector is a major contributor to a number of environmental pressures, such as the use of natural resources (e.g. land, water) as well as emissions of harmful substances (e.g. nutrients, pesticides). Therefore, improvements in the environmental performance of the agro-food sector may be very important from a global perspective. A quantitative analysis of the environmental implications of biotechnology was hampered by the lack of data, so a more qualitative approach was

329 Tait, J., J. Chataway and D. Wield (2001). PITA project: Policy influences on technology for agriculture: chemicals, biotechnology and seeds. Final report. Scottish Universities Policy Research and Advice Network (SUPRA), Edinburgh.



followed, except in cases where data were available. Modern biotechnology applications in the agro-food sector may affect both the eco-efficiency of manufacturing-related activities (e.g. food processing) as well as activities in the primary sector. The use of modern biotechnologies by the manufacturing sector in general leads to eco-efficiency improvements, mainly in energy use and associated greenhouse gas emissions, but also in water use and waste generation (see also Chapter 2.3.1). In the primary sector, modern biotechnologies supplement other technological innovations that predominantly target improvements in production efficiency, thereby reducing resource use or emissions of harmful substances per unit output. Yet, while these impacts are mostly of an indirect nature, there are direct impacts as well, for example the replacement of drug and antibiotic treatments with the use of vaccines in animal production, many of which are produced using modern biotechnology, and the reduction of harmful emissions due to the use of improved crop varieties or biotechnology-based feed additives. However, some modern biotechnology applications may also raise new challenges, requiring a case-by-case evaluation to consider specific aspects or potential risks. To this end, the EU has put in place specific legislation making it obligatory to carry out comprehensive risk assessments before placing such products on the EU market.



## 2.3 Modern biotechnology in industrial production processes, energy and environment

### 2.3.1 Modern biotechnology in industrial production processes

Many industrial manufacturing sectors have long-standing traditions in using biotechnology, e.g. pancreas extracts containing an enzyme

mix were used in detergents at the beginning of the 20th century. The use of isolated enzymes or microorganisms in industrial production processes is also referred to as industrial biotechnology. The term biocatalysis<sup>330</sup> is mainly used to describe the application of isolated enzymes in production processes, but also covers non-growing whole-cell systems. For processes using growing microorganisms, the term fermentation is used.

Industrial biotechnology is nowadays used to manufacture a wide range of products in many different industrial sectors, including those that traditionally did not use biotechnological processes. It often replaces chemical processes because of several advantages:

- Improved process efficiency through highly substrate- and reaction-specific activity. Enzymes and microorganisms have the ability to catalyse reactions with a high selectivity, including stereoselective reactions<sup>331</sup>. Biotechnological production yields purer products (fewer by-products) and consequently requires less extensive purification steps compared to complex chemical production. This is for example important in the production of pharmaceutical intermediates.
- Reduced energy consumption through the ability of most enzymes to work at room temperature. The discovery of extremophilic microorganisms, which find optimal living conditions in comparatively harsh surroundings (high-pressure, very hot, very cold, alkaline or acidic environments), has broadened the application areas of enzymes.
- Less waste production, because the use of microorganisms in fermentation processes often replaces several chemical production steps with one biotechnological production step (e.g. production of riboflavin).

330 Catalysts increase the rate of a chemical reaction without being consumed, i.e. without becoming part of the product.

331 Stereoselective reaction refers to the preference for one 3-D form of a specific molecule out of the different forms this molecule can have.

- Manufacturing of products with improved or novel characteristics, e.g. biologically degradable biotechnology-based polymers or detergents with better performance.

Modern biotechnology widens the application of industrial biotechnology, for example by enabling the identification of new enzymes using modern screening techniques, the large-scale production of enzymes using improved fermentation processes and more efficient microbial producer strains, the tailoring of enzymes to specific reactions and environments through directed evolution and genetic modification, and the conversion of microorganisms into “cell factories” using metabolic engineering. More than 50% of all enzymes currently in commercial use are produced by genetically modified organisms<sup>332</sup>.

Industrial biotechnology is applied in a variety of industrial manufacturing sectors, ranging from chemicals to pulp and paper production (see below under enzyme production). Furthermore, it is used to produce a large variety of different

products, including bulk chemicals such as bioethanol or citric acid, which are produced in large quantities at low prices, but also fine chemicals such as Vitamin B12 or the amino acid methionine, which are high-price products with comparatively low production volumes. Table 2.6 gives an overview of some of these products.

### 2.3.1.1 Enzyme production

Enzyme production can be considered a subsector of the chemical manufacturing sector. It uses modern biotechnology in production processes and produces the biotechnological products, i.e. enzymes, needed for applications in other industrial sectors. As such, it plays a crucial role for the latter, described in this chapter as users of biotechnological processes. In Table 2.7 the main enzyme groups are shown together with the reactions catalysed and the user industries. Enzymes are very versatile tools, each of which can be applied in different industrial processes. Users range from the pharmaceutical industry to food producers.

Table 2.6 Examples of biotechnology-based products, annual global production volumes and prices

Product	Annual production (tonnes)	World market prices (€/kg)
<b>Bulk chemical</b>		
Bioethanol	>18.5 million	0.40
<b>Amino acids</b>		
L-Glutamic acid	1 500 000	1.20
L-Lysine	700 000	2
L-Threonine	10 000	6
L-Methionine	400	20
<b>Acids</b>		
Citric acid	1 000 000	0.80
Lactic acid	150 000	1.80
Gluconic acid	100 000	1.50
<b>Vitamins</b>		
Vitamin C	80 000	8
Vitamin B12	20	25 000
Riboflavin	30 000	NA
<b>Antibiotic derivatives</b>		
6-aminopenicillanic acid	10 000	NA
D-p-hydroxyphenylglycine	7 000	NA
7-Aminocephalosporinic acid	4 000	NA

Source: DECHEMA.<sup>333</sup>; NA: not available

332 Gavrilescu, M. and Y. Chisti (2005). *Biotechnology Advances* 23: 471-499.

333 DECHEMA (2004). *Weißer Biotechnologie: Chancen für Deutschland*. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M.



Table 2.7 Different groups of enzymes and reactions

Type of enzyme	Substrate	Reaction catalysed by the enzyme	User sectors
Proteases (proteolytic enzymes)	Proteins	Hydrolysis of proteins into shorter fragments, peptides and amino acids	Detergents, food, pharmaceuticals, chemical synthesis
Carbohydrases	Carbohydrates	Hydrolysis of carbohydrates into sugar	Food, feed, pulp and paper, textiles, detergents
Lipases	Fats (triglycerides)	Hydrolysis of fats into fatty acid and glycerol molecules	Food, effluent treatment, detergents, pharma
Pectinases	Pectins	Mix of enzymes to degrade pectin, a complex polysaccharide present in fruits	Food, beverages (clarification of fruit juices)
Cellulases	Cellulose	Hydrolysis of cellulose into sugar	Pulp, textiles, feed, detergents, energy
Amylases	Poly-saccharides	Hydrolysis of starch into smaller carbohydrate molecules such as glucose and maltose	Food, textiles

Source Lievonen<sup>334</sup>, adapted by IPTS.

Most of these enzymes are used in the food sector (30%-45%) and the detergents sector (33%). The textile and pulp and paper industries account for about 8%-14% and 1%-3%, respectively. Enzymes for fine chemical production account for another 5% of the world market<sup>335</sup>.

#### Economic significance

In this study, about 117 enzyme-producing companies were identified worldwide. 75 (64%) are located in the EU, with France, Spain and Germany having more than 10 companies each, representing more than 50% of all EU enzyme companies (Figure 2-15). 18% of the companies are situated in the USA. However, the main enzyme producers by volume can be found

in Denmark, with 47% of worldwide enzyme production in 2001. Since the acquisition of one of the major US enzyme producers (Genencor) by Danisco (Denmark) in 2005, this share has most probably increased even further. The most important companies in terms of production volumes are Novozymes (Denmark), Chr. Hansen (Denmark), DSM (Netherlands), AB Enzymes GmbH (Germany), and DIREVO Biotech AG (Germany). Other major producers in volume terms are in the USA (Genencor – part of Danisco since 2005) and Japan. World production volume was estimated at 53 000 tonnes per year in 2001, with the EU's share being about three quarters. With an estimated 5% growth for the enzyme market, a production volume of around 65 000 tonnes for 2005 can be assumed<sup>336,337</sup>.

334 Lievonen, J. (1999). Technological opportunities in biotechnology. VTT Group of Technological studies, Espoo, p. 24.

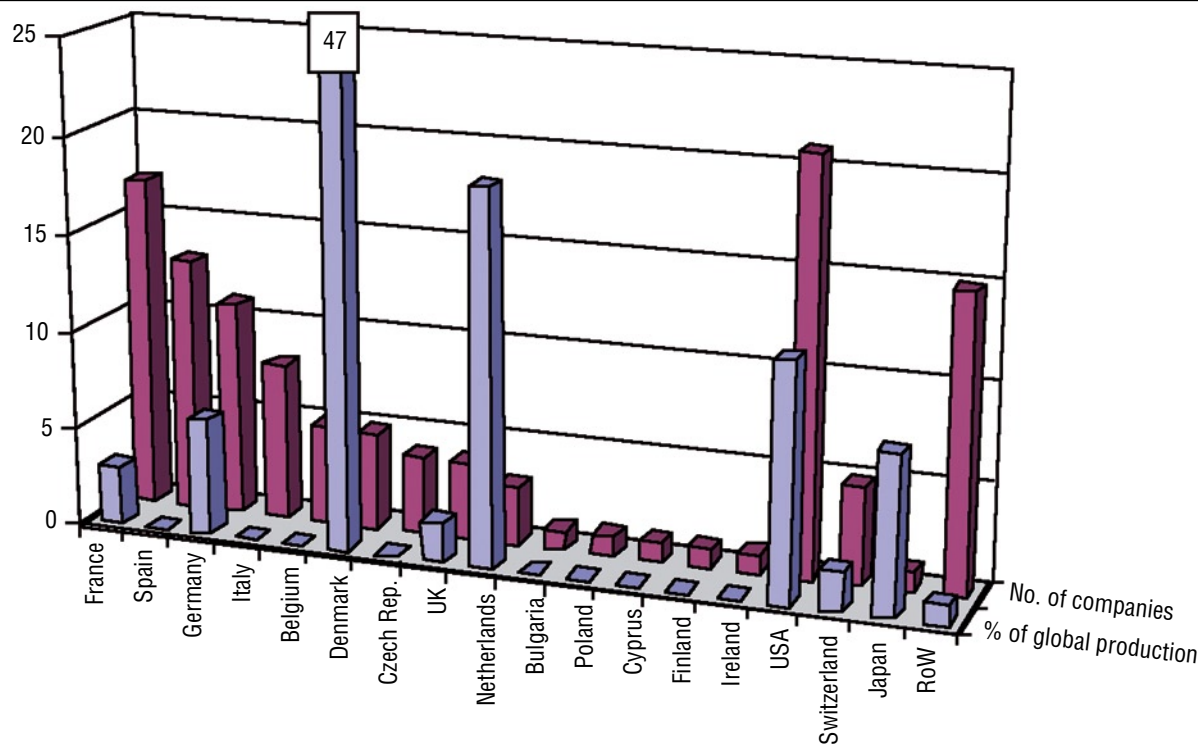
335 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications. And DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M.

336 DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M.

337 Gavrilescu, M. and Y. Chisti (2005). *Biotechnology Advances* **23**: 471-499.



Figure 2-15 Enzyme-producing companies and worldwide production shares in 2001, by country



RoW: rest of the world  
Source: ETEPS.<sup>338</sup>

The market value of the global enzyme market for 2004/2005 was estimated at around EUR 1.8 billion<sup>339</sup>. Assuming an EU share of 75% in enzyme production and an even distribution of enzyme price levels, it can be concluded that EU companies earned around EUR 1.3 billion from enzymes in 2005. Based on the gross value added (GVA) share that the biggest enzyme producer Novozymes (Denmark) declares for its activities (57%<sup>340</sup>), EU enzyme production created a GVA of EUR 684 million, which represents 0.05% of the GVA produced by the EU manufacturing sector in 2002.

It is estimated that the sector employs between 4000 and 6000 staff<sup>341</sup>, representing 0.015%-0.02% of all employees in EU manufacturing. Its GVA/employment ratio (share of all economic activity in the EU compared with the share of

EU employment) reveals a labour productivity of 2.8-4 (0.0084% of EU GVA is created by 0.002%-0.003% of EU employment). Enzyme production thus has a higher labour productivity than the chemical sector (2.0) and the average for EU economic activities (1.0), indicating a mature industry with a high degree of automation.

#### Environmental implications

The production of enzymes as an intermediate chemical product has environmental implications in terms of energy use and process-related greenhouse gas and other emissions. Generally, little information is available on these aspects of enzyme production. However, environmental assessments of individual products carried out by one of the main enzyme-producing companies (Novozymes) provide an indication. A lifecycle

338 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

339 DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.43. And: Novozymes (2005). The Novozymes report 2005. Novozymes, Bagsværd, p. 11 (conversion: 1 DKK = 0.135 Euro).

340 Novozymes (2005). The Novozymes report 2005. Novozymes, Bagsværd, p. 22 (turnover DKK 6024m, GVA DKK 3424m).

341 Estimation based on data from a fruit juice enzyme business (200 employees) and the share of fruit juice enzymes in all enzyme production (3.5%), and on information from the Novozymes homepage, which indicate 2 250 EU based employees, with Novozymes holding 60% of the enzymes market.





assessment comparing phytase<sup>342</sup> production with the production of the feed additive monocalcium phosphate (replaced by phytase) revealed that the production of the enzyme consumes about 90% less energy, which also leads to reductions in greenhouse gas emissions<sup>343</sup>. A comparison of enzyme production processes using conventional or genetically modified microbial production strains revealed that the use of genetically modified organisms has environmental benefits along all the environmental dimensions analysed, such as global warming, energy consumption and others<sup>344</sup>.

In the following, the application of industrial biotechnology, in particular biocatalysis, in different sectors will be described and analysed: detergents, food processing, textile finishing, pulp and paper processing, and fine chemicals. Bioethanol fuel production will be described in Chapter 2.3.2 under energy. There are also other sectors applying industrial biotechnology, such as mining (bioleaching), which however have only minor significance in the EU and therefore will not be taken into account in this analysis.

### 2.3.1.2 Biocatalysis in detergents

Biocatalysis in detergents is different from enzyme applications in other sectors, because the biocatalysts, i.e. enzymes, form part of the end product, the detergent, to improve its performance when used by the consumer. Hence, biotechnology is not used here to improve the manufacturing process of detergents. Enzymes have been used in detergents since the beginning of the 20th century, when crude pancreatic enzymes were added to laundry detergents.

Commercial large-scale utilisation of enzymes produced by microorganisms in detergents began in the 1960s, and the range of enzymes used nowadays includes different proteases, amylases, cellulases and lipases (see Table 2.7). By 1968, a few years later, 80% of all laundry detergents in Germany contained enzymes<sup>345</sup>. Advantages are the ability to reduce washing time and temperature, thus reducing energy consumption, improving cleaning performance, and reducing the environmental impact due to biodegradability. Accordingly, the improved quality of the product and environmental considerations, rather than lower production costs, are the driving factor for the application of enzymes in detergents<sup>346</sup>. Today, enzymes are mainly used in detergents for washing machines and dishwashers.

#### *Economic significance*

Detergent enzyme sales in 2005 were about EUR 592 million, 33% of the world enzyme market. The leading detergent enzyme producers are Novozymes (Denmark) and Danisco/Genencor (Denmark), with 50% and 20% of the world market, respectively. Two thirds of enzyme detergents are sold in the EU (32%), the USA (23%) and Japan (10%). The market grows by about 4.5% per year, due to growing enzyme markets for dishwasher and liquid detergents. The high share of detergent enzymes among industrial enzymes and the continuous growth along with low volatility indicate a well-established market. It represents a considerable share of the business of the world market leaders: 32% of Novozymes' sales in 2005 (EUR 273 million) and 47% of Genencor's sales in 2004 (EUR 142 million<sup>347</sup>; since 2005 part of Danisco, Denmark)<sup>348</sup>.

342 Phytase is an enzyme degrading phytate, a phosphorus-rich plant ingredient not digestible for monogastric animals. It is a feed additive. See also box in Chapter 2.2.1.1

343 Nielsen, P.H. and H. Wenzel (2006). *International Journal of Life Cycle Assessment*, online first, <http://dx.doi.org/10.1065/lca2006.08.265.2>.

344 Nielsen, P.H., K.M. Oxenbøll and H. Wenzel (2006). *International Journal of Life Cycle Assessment*, online first, <http://dx.doi.org/10.1065/lca2006.08.265.1>.

345 Braun, M., O. Teichert and A. Zweck (2006). *Übersichtsstudie: Biokatalyse in der industriellen Produktion*. VDI Technologiezentrum, Düsseldorf.

346 ETEPS (2006). *Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications*.

347 Conversion: 1 U.S. Dollar = 0.776 Euro.

348 ETEPS (2006). *Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications*.



Overall sales of soap, detergents, and maintenance products in the EU (here including Norway, Iceland and Switzerland) amounted to about EUR 30 billion in 2005<sup>349</sup>. About 30%-50% of all detergents sold in 2005 contained enzymes, equivalent to about EUR 9 to 15 billion. Based on the GVA of the relevant industrial manufacturing sector (Manufacture of soap, detergents, cleaning and polishing — NACE DG 24.51) in 2003 and the market share of 30%-50%, the contribution of enzyme-containing detergents to GVA in the EU is estimated at EUR 2.5 to 4.0 billion, or 0.03%-0.05% of overall EU GVA (see Table 2.15 at the end of this chapter).

Following the same approach, it is estimated that about 36 000 to 60 000 employees work in the manufacturing of enzyme-containing detergents. The contribution to overall EU employment is 0.02%-0.03%. Labour productivity is similar for all detergent manufacturing, and at 1.5-1.7 is higher than the average labour productivity for the EU (1.0).

#### *Environmental implications*

The environmental impact of enzymes in detergents can only be qualitatively described due to the lack of data. The use of enzymes in household detergents results in lower washing temperatures, reduced water consumption, reduced washing times, and a reduced load of toxic substances in waste water (enzymes replace chemical substances in detergents). Reducing the washing temperature from 95°C to 40°C reduces energy consumption by 70%. However,

it is not possible to quantify this effect as the overall energy used by the washing process is not known. The amount of toxic substances such as benzoapyrene, lead, cadmium, or sulphur oxide can be reduced by 5%-60%. However, exposure to enzymes can result in allergic reactions. This used to be the case for workers handling the enzyme powders for detergent production and inhaling air with enzyme particles. Today, enzymes are encapsulated to avoid allergic reactions. Still, because of risk of inhalation and allergic reactions, enzyme-based detergents are not used for cleaning open surfaces in either households or industry.

#### 2.3.1.3 Biocatalysis in food production

Biotechnology in food production has a long history, e.g. in beer, wine, bread and cheese production. The significance of modern biotechnology (i.e. the use of biocatalysis) in food processing nowadays is illustrated by the large share of food enzymes in the enzyme market: 30%-45%<sup>350,351</sup>. Table 2.8 provides some examples of enzyme applications in food processing and illustrates the diversity of the processes involved. Since the early 1960s, all glucose production based on starch has been carried out by enzymatic rather than acid hydrolysis, reducing steam cost by 30%, ash by 50% and by-products by 90%<sup>352</sup>. Laccases are used in the clarification of juices as well as in baking for the treatment of dough<sup>353</sup>. Amylases, proteases and xylanases also play important roles in baking, cheese production, sweetener production and other food production processes.

349 AISE (2005). Market data. International Association for Soaps, Detergents, and Maintenance Products, Brussels. [http://www.aise-net.org/go\\_withsub.php?pid=14&topics=4](http://www.aise-net.org/go_withsub.php?pid=14&topics=4).

350 DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p. 30.

351 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

352 Novozymes (2004). Enzymes at work. Novozymes, Bagsværd, p. 27.

353 Rodríguez Couto, S. and J.L. Toca Herrera (2006). *Journal of Biotechnology Advances* **24**: 500-513.



Table 2.8 Examples of enzymes used in food processing

Food processing	Enzyme	Effect
<b>Dairy</b>	Protease (chymosin)	Milk clotting
	Lipase	Cheese flavour
	Lactase	Lactose removal (milk)
<b>Bakery</b>	Amylase	Bread softness and volume, flour adjustment
	Xylanase	Dough conditioning
	Lipase	Dough stability and conditioning (in situ emulsifier)
	Phospholipase	Dough stability and conditioning(in situ emulsifier)
	Glucose oxidase	Dough strengthening
	Lipooxygenase	Dough strengthening, bread whitening
<b>Beverage</b>	Pectinase	De-pectinisation, mashing
	Amylase	Juice treatment, low calorie beer
	Beta-Glucanase	Mashing
	Acetolactate decarboxylase	Maturation (beer)
	Laccase	Clarification (juice), flavour (beer), cork stopper treatment
<b>Starch</b>	Amylase, Amyloglucosidase, Pullulanase	Starch liquefaction, saccharification
	Glucose isomerase	Glucose to fructose conversion

Source: Kirk et al<sup>354</sup>, adapted by IPTS.

Enzymes are used in food production to improve the production processes and the product quality. In juice production, for example, the application of enzymes such as pectinases, amylases and proteases, which also occur naturally in the fruit ripening process, helps to soften the fruit cell walls and to reduce the viscosity of the material. This results in

- Increased juice yield (fruits 15%-20%)
- Decreased filtration times, up to 50%,
- Clarification and cloud stabilisation of juice and juice concentrates,
- Decreased risk of jellification.

The treatment is supposed to improve taste, colour stabilisation and oxidative stability<sup>355</sup>.

#### *Economic significance*

The dairy, starch and sugar, and bakery segments are the main users of enzymes in food processing, each representing about a quarter of enzyme sales in 2006 (Table 2.9). Fruit juice, wine and brewing together represent about 20%, and supplements about 5%. The analysis will thus concentrate on these food manufacturing segments<sup>356</sup>, which represented about 40% of the overall GVA of the food manufacturing sector (NACE DA 15) in 2002 according to Eurostat data<sup>357</sup>.

354 Kirk, O., T.V. Borchert and C.C. Fuglsang (2002). *Current Opinion in Biotechnology* **13**: 345-351.

355 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

356 NACE codes: DA15.3 Fruit and vegetables, DA 15.4 Vegetable and animal oils and fats, DA15.5 Dairy products, DA 15.62 Starch and starch products, DA 15.7 Prepared animal feed, DA 15.81 Bread, pastry, cake, DA 15.83 Manufacture of sugar, DA 15.93 Wine making, DA 15.94 Cider and fruit wines, DA 15.96 Manufacture of beer.

357 The calculations focus on industrial food production. In the bakery segment, therefore, the figures have been adjusted to take only large-scale industrial bread manufacturing into account, disregarding the large share of family owned businesses. They thus cover about 18% of the employees in this food manufacturing segment (224 000), producing 32% of its GVA (EUR 8.5 billion). See Table 2.15 at the end of this chapter.



Table 2.9 Share of enzyme sales per application area in the food sector<sup>358</sup>

Food application area	Enzyme sales in 2006
Dairy	26%
Starch and sugar	25%
Bakery	24%
Fruit juice	7%
Wine making	7%
Brewing	6%
Nutrition and dietary supplements	5%
<b>Total</b>	<b>100%</b>

Many enzymatic processes have been universally taken up by the industry and are state-of-the-art technology, which makes a comparison with conventional alternatives impossible. The entire output of the food production processes concerned is therefore considered for calculating the impact of modern biotechnology. The contribution of the segments listed above to EU GVA is 0.8% (EUR 70 billion, 2002), or 4.8% of manufacturing sector GVA (2002). With 1 375 082 employees, these segments also account for 0.69% of overall EU employment and 4.2% of employment in the manufacturing sector. Labour productivity in the food sectors applying enzymes is 1.2, or about 30% higher than the average for the overall food sector (0.9) and 20% higher than the EU average for all economic activities (1.0).

#### *Environmental implications*

The analysis of the environmental impacts of biocatalysis in food processing faces challenges similar to those posed by the measurement of economic impacts. As most enzymatic processes have a diffusion of 100% in the sector, no other process is available for comparison. The only conclusion that can be drawn is that about 50% of the food processing segments apply enzymes to a large extent, and that the contribution of

food and feed manufacturing to CO<sub>2</sub> emissions of all manufacturing sectors is about 7% (excluding agriculture) and 0.35% to overall greenhouse gas emissions. The potential for reducing greenhouse gas emissions, water and energy use and chemical inputs by using enzymes in other food segments might be limited as biocatalysis is already widespread in food production.

#### 2.3.1.4 Biocatalysis in pulp and paper

Paper and board are made of cellulose sourced from wood. In the production process, there are several steps in which enzymes are applied (Figure 2-16). However, enzyme application has not been taken up on a large scale in pulp and paper production since its first introduction in the 1980s. Some processes are now established, but others have only recently entered production scale.

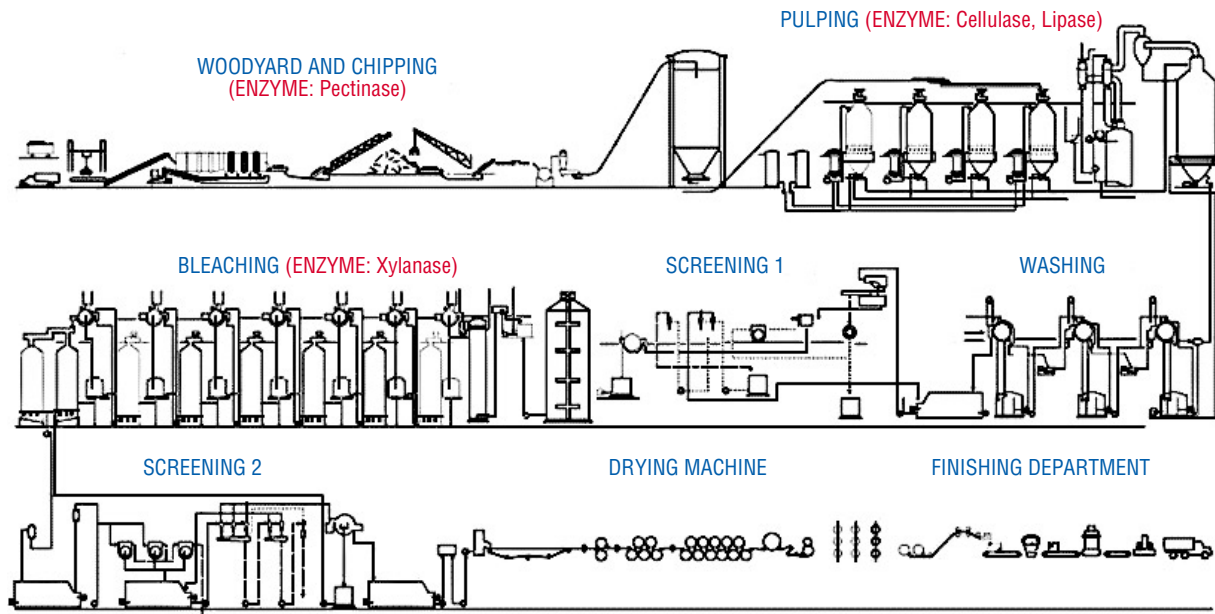
Xylanases are the major enzyme class used in pulp and paper production. They are used in the pulp bleaching process to enhance the extractability of lignin. According to expert estimates, xylanases are applied in about 20 mills throughout Scandinavia, North America and Russia, where about 10% of kraft pulp is manufactured using xylanase treatment with cost savings of 5%-6%<sup>359</sup>. Kraft pulp (chemical

358 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

359 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.



Figure 2-16 Enzymes used in an integrated mill (chemical pulping, bleaching and paper production)



Source: EPA<sup>360</sup>, modified by IPTS.

pulp) has a share of about 60% of all the pulp manufactured in the EU<sup>361</sup>.

Apart from xylanases, the use of other enzymes such as pectinases in raw material treatment or cellulases and lipases in the pulping process has become established in the pulp and paper industry.

The recycling rate of paper in the EU was 55% in 2004<sup>362</sup>. Pulp from recycled paper needs to be cleaned of dirt and ink. Cellulases and hemi-cellulases can be used in enzyme-aided de-inking. This process is already used in mills but is not yet widespread.

Wood contains esters of fatty acids (“pitch”) that can lead to sticky depositions in paper-making machines, thus disturbing the production

process. These substances are usually removed using chemicals. Enzymes such as lipases can be used in mechanical pulps to reduce pitch problems. Mechanical and semi-chemical pulp represents about 34% of all pulp manufactured in EU countries in 2005<sup>363</sup>.

Paper making is a water-intensive process. The prevailing conditions (temperature, nutrients, pH) favour the growth of microorganisms and the development of biofilms on surfaces. The application of biocides, together with biodispersants, and enzymes to remove and prevent biofilms is common practice. Another biotechnology application in paper making is the enzyme-aided removal of fines and polysaccharides on fibres to improve the drainage of water, thus increasing the efficiency of pressing

360 US Environmental Protection Agency EPA Office of Compliance Sector Notebook Project (2002), Profile of the pulp and paper industry, 2nd edition, p.17. Washington DC.

361 CEPI (2006). Annual statistics 2005. Confederation of European Paper Industries, Brussels. (Covering 17 EU countries and Norway and Switzerland.)

362 CEPI (2006). Annual statistics 2005. Confederation of European Paper Industries, Brussels.

363 CEPI (2006). Annual statistics 2005. Confederation of European Paper Industries, Brussels.



and drying processes<sup>364</sup>. No data on the actual uptake of these processes or their impact were available. Paper making will therefore not be considered in the following analysis.

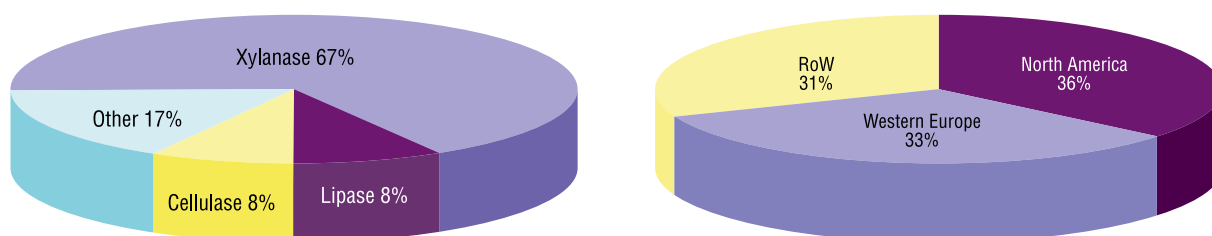
#### *Economic significance*

Overall, the adoption rate of enzyme-aided processes in pulp manufacture, including bleaching, de-inking, and pitch reduction, was assumed to be 15%. Sales figure for pulp enzymes show that xylanases used for pulp bleaching dominate (67%), followed by lipases (8%) for pitch control and cellulases (8%) for de-inking and fibre modification (Figure 2-17). The overall pulp enzyme market was about EUR 46.6 million in 2004, or about 2.6% of the overall enzyme market. Sales in Northern America and Western

Europe are similar, representing 36% and 33% of the world market, respectively.

The main pulp producers worldwide in 2004 were the EU (23%), the USA (30%), and Canada (15%), with Finland (8%) and Sweden (7%) being the largest producers within the EU (Figure 2-18). Russia, China and Japan have comparatively small production volumes. In 2005, pulp and paper was produced in the EU by about 214 pulp mills and 1005 paper mills. The number of mills decreased between 1991 and 2005 by 20%–24%<sup>366</sup>. Comparing the regional distribution of the sales of the enzymes mainly used in the pulping process with the regional distribution of pulp manufacturing, it seems that the use of enzymes in pulp manufacturing is greater in the EU (23% of pulp manufacturing and 33% of enzymes) than in North America (45% of pulp manufacturing and 36% of enzymes).

Figure 2-17 Distribution of pulp enzymes, by value (left panel) and regional sales (right panel) in 2004



Data: ETEPS<sup>365</sup>; RoW: rest of the world.

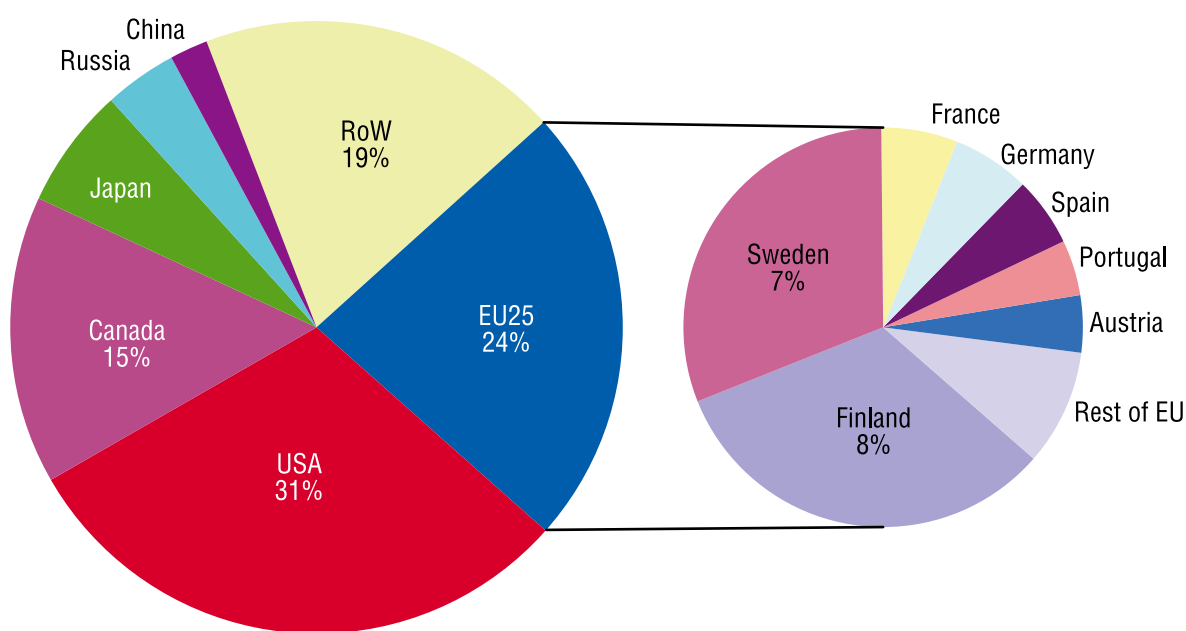
364 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

365 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

366 CEPI (2006). Annual statistics 2005. Confederation of European Paper Industries, Brussels.



Figure 2-18 Share of pulp production in 2004, by country



RoW: rest of the world

Source: Verband Deutscher Papierfabriken<sup>367</sup>.

The EU pulp, paper and paperboard sector (NACE sector DE 21.1) generated a turnover of EUR 75 billion in 2002. Of that figure, the turnover on pulp production was about EUR 6.8 billion (9%). Assuming a GVA rate of 29% (based on data from the pulp, paper and paperboard manufacturing sector), the GVA is estimated at EUR 2 billion or 0.13% of the GVA of overall manufacturing. Assuming furthermore that 15% of all pulp is processed using enzymes, the GVA of pulp manufacturing using enzymes would be around EUR 300 million or 0.02% of all manufacturing (0.0034% of EU GVA). Following the same approach, it is estimated that the 22 000 employees in pulp manufacturing include about 3000 active in enzyme-aided pulp production, only a small share (0.0015%) of EU employment. The labour productivity of enzyme-aided pulp manufacturing is 2.3, or about 10% higher than conventional production (2.1). In total, pulp manufacturing as such seems to be a

comparatively efficient, automated process, with a labour productivity well above the EU average for all economic activity (1.0).

#### Environmental implications

The pulp and paper industry produces emissions to air and water as well as solid waste as a by-product. The main air pollutants are NO<sub>x</sub>, SO<sub>2</sub>, CO, CO<sub>2</sub> and particulate matter. Wastewater contains adsorbable, organically bound halogens (AOX) and is characterised by high biological and chemical oxygen demand (BOD and COD<sup>368</sup>). Chlorine emissions from bleaching processes have been reduced over the past decades: today, most pulp and paper production uses elementary-chlorine-free (ECF) or totally chlorine-free (TCF) processes.

A recent study using model processes<sup>369</sup> identified the following environmental benefits

367 Verband Deutscher Papierfabriken, Papier Kompass 2006, Bonn.

368 BOD: biochemical (biological) oxygen demand is a test used to measure the concentration of biodegradable organic matter present in a sample of water. COD: chemical oxygen demand is a test commonly used to indirectly measure the amount of organic compounds in water. Both tests are used to determine water quality.

369 Kvistgaard, M. and O. Wolf. (eds) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, DG JRC/IPTS, EUR 20407, p. 24.



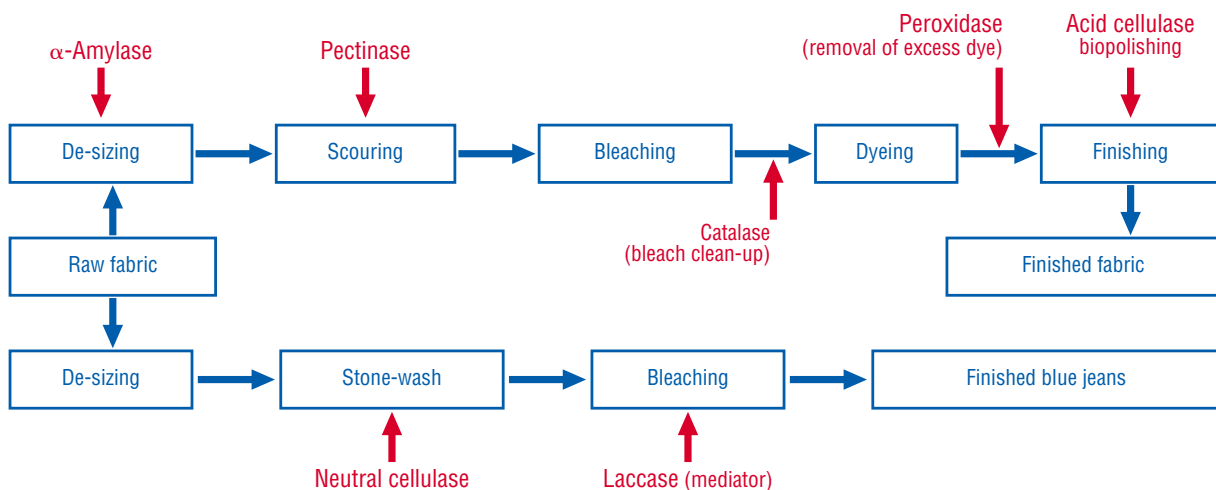
of enzyme applications: xylanase application in chemical pulping reduces the need for elemental chlorine by 90% and thus the AOX content in wastewater streams by 15%-20%. Cellulase (and fungi) applications in mechanical pulping, an energy- and water-intensive process, reduce energy use by about 32% and indirectly lead to savings in greenhouse gas emissions. Direct average greenhouse gas emission savings are around 5%. Furthermore, the use of enzymes in de-inking and pitch control results in less use of additives, surface-active chemicals, and other chemicals. However, no quantitative data are available. Overall, it can be assumed that enzyme application leads to reductions in CO<sub>2</sub> emissions and the pollutant load of wastewater streams.

### 2.3.1.5 Biocatalysis in textile finishing

The textile sector in the EU includes the production of fibres and yarns, the production

of knitted and woven fabrics, and finishing activities such as bleaching, printing, dyeing, etc. Biocatalysis is applied in the last step, in textile finishing, in particular for cotton fabrics. The use of amylases to remove starch from cotton fabric after weaving<sup>370</sup> (de-sizing) is the oldest process, in use for about 100 years (Figure 2-19). This enzymatic process is used in almost all textile manufacturing. “Bioscouring” (the removal of remaining cell-wall components such as waxes and oils in the cotton fabric by pectinases) is a comparatively new process. This application could replace an alkaline cooking process but is most probably not yet widely used. Catalases are applied to remove superfluous hydrogen peroxide used in the bleaching step, replacing repeated rinsing of the fabric in hot water. The take-up of this enzyme application, available since the 1980s, is about 40%-50%<sup>371</sup>. In the biopolishing process, the aim of which is to improve the quality of the fabric, cellulases

Figure 2-19 Enzymes used in cotton fabric processing



Source: Kirk et al.<sup>372</sup>

370 Cotton threads are covered with starch to make them more resistant to mechanical stress during weaving.  
 371 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.  
 372 Kirk, O., T.V. Borchert and C.C. Fuglsang (2002). *Current Opinion in Biotechnology* **13**: 345-351.





modify the surface of the fibres to prevent pilling and increase softness and smoothness. Cellulases are also used in the finishing of denim garments to create a washed-out appearance by replacing the stone wash process by “biostoning”. This process was applied to 80% of jeans trousers in the 1990s<sup>373</sup>. Cellulases account for about 2/3 of textile enzyme sales.

#### *Economic significance*

Enzymes applied in the textile industry represent about 8% of the worldwide enzyme market (EUR 140 million). The Western European market accounts for about 33%, while North America represents 36% of the textile enzyme market. Other countries including China and India account for about 31%, reflecting the importance of these regions in terms of textile manufacturing<sup>374</sup>. The growth rates of the enzyme markets in non-EU regions, e.g. 3.9% in Asia compared to 2.7% in the EU, indicates the growing importance of these regions in textile manufacturing<sup>375</sup>.

The textile sector in the EU comprises about 70 000 companies (EU15, 2002), mainly small and medium-sized enterprises<sup>376</sup>. The sector has been shrinking continuously in recent years, with the contribution to EU GVA decreasing by 35% between 1995 and 2005<sup>377</sup>. Textile finishing contributed 12% to the GVA of EU textile manufacturing in 2002 (EUR 4.3 billion) and 0.05% to overall EU GVA. Assuming an average adoption rate of 40% for enzymes in textile

finishing processes, enzyme applications thus contributed EUR 2 billion or 0.02% of EU GVA. Furthermore, they reduced costs on average by about 25% based on model calculations<sup>378</sup>.

Again based on the share of 40% of enzymatic processes in textile finishing, about 48 480 employees (out of 121 200) can be assumed to have biotechnology-related jobs. Overall labour productivity in textile finishing is low (0.8) compared to the EU average (1.0). Enzyme-based textile finishing processes have a slightly higher labour productivity of 0.9, indicating some technological optimisation through the application of enzymes.

#### *Environmental implications*

The textile industry is known for its energy- and water-intensive processes, resulting in wastewater streams with high and diverse pollutant loads. In textile wetting, 100 litres of water are used for every kilogram of textile fabric. Processes often require high temperatures, and cleaning, bleaching, dyeing and other finishing processes generate a variety of pollutants. The effects of enzyme applications in different textile finishing steps are summarised in Table 2.10. However, quantitative information is scarce.

Overall, it can be concluded that enzymatic processes in textile finishing reduce water and energy usage (and thus the emission of greenhouse gases) and the chemical load in wastewater as well as ensure increased biodegradability.

373 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

374 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

375 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

376 European Commission SEC(2003) 1345 Commission staff working paper: Economic and competitiveness analysis of the European textile and clothing sector in support of the Communication “The future of the textiles and clothing sector in the enlarged Europe”.

377 Eurostat data.

378 Kvistgaard, M. and O. Wolf. (eds) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, DG JRC/IPTS, EUR 20407, p. 46.



Table 2.10 Overview of the effects of enzyme applications in textile finishing

Textile finishing step	Chemical use	Water use	Energy consumption	Time consumption
De-sizing (starch)	Reduction	NA	NA	NA
Bioscouring <sup>379</sup>	Reduction	Reduction	Reduction (lower temperature of 60°C instead of 100°C)	Reduction
Bleach clean-up <sup>380</sup>	Reduction of 80%	Reduction of 50%	Reduction of 20%	Reduction of 33%
Denim bleaching	NA	Reduction of 17%	Reduction of 9%-14%	Reduction of 10%

NA: Not available.

### 2.3.1.6 Industrial biotechnology in the production of chemicals

Modern biotechnology is applied in the production of many chemical substances (for examples, see Table 2.6), using either microorganisms or enzymes, or a combination of both. Often several chemical production steps are replaced by one biotechnological step, with potential advantages ranging from less material input to fewer by-products and reduced waste and energy use. Further below, the biotechnological production of specific intermediates in antibiotic production, vitamins, amino acids and biotechnology-based polymers will be described as examples for bulk and fine chemical production.

#### *Economic significance of industrial biotechnology for the chemical industry*

The chemical industry in the EU comprises about 60 000 companies, of which 56 can be identified as producers of biotechnology-based chemicals<sup>381</sup>. Disregarding bioethanol producers, about 38 companies (0.1%) produce biotechnology-based chemicals. In the USA and Japan, the share seems to be significantly

higher: 1.7% of US chemical companies use biotechnological processes (266 out of 16 000), and 2.5% in Japan (127 out of 5000)<sup>382</sup>. The EU chemical sector has a strong position compared to other countries. In 2003, 16 out of the top 30 chemical companies by sales worldwide (without pharmaceuticals) were EU companies, 7 were situated in Japan and 5 in the USA (3 of those within the top 10). Overall, the manufacturing of chemicals and chemical products (including pharmaceuticals) accounted for 11% of the GVA of the manufacturing sector in 2002, and nearly 2% of overall EU GVA.

No data are available regarding production volumes and sales of biotechnology-based chemicals or regarding employment. Due to the lack of information, a quantitative analysis of the economic relevance of these products is not meaningful. Nevertheless, a selection of case studies can illustrate the nature and magnitude of their environmental and economic impacts.

#### *Example: Biotechnological production of 7-ACA, a cephalosporin antibiotic intermediate*

Naturally occurring antibiotics are mostly produced by fermentation: due to their complex

379 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

380 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

381 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

382 ETEPS (2006). Bio4EU Task 2 Main report.



structure, chemical production is not as efficient. This group includes the broad-spectrum beta-lactam antibiotics penicillin and cephalosporin. However, the natural form is often not sufficiently potent or not orally stable, so what are known as semi-synthetic antibiotics have been developed. They are chemically or, more recently, biotechnologically modified versions of the naturally occurring form. In 1999/2000, beta-lactam antibiotics accounted for about 65% of the world antibiotic market of around EUR 12 billion<sup>383</sup>.

Cephalosporin C, produced by the fungus *Acromonium chrysogenum* on a commercial scale, is the starting point of semi-synthetic cephalosporin production. The removal of a side chain results in the compound 7-ACA<sup>384</sup>, which is the nucleus for further modification and production of different types of cephalosporin antibiotics. In all, two thirds of commercial cephalosporin antibiotics are derived from 7-ACA<sup>385</sup>. The conversion can be carried out chemically, which is the conventional process, or, more recently, using two recombinant enzymes. In particular, recombinant enzyme production has cut the costs of the biotechnological production step and made it economically competitive<sup>386</sup>. The production volume of 7-ACA is about 4000-5000 tonnes/year, while cephalosporin antibiotics amount to about 30 000 tonnes/year for human and veterinary uses<sup>387</sup>. About 20% of 7-ACA is produced using enzymatic conversion<sup>388</sup>, i.e. about 1250 tonnes. Major producers are Sandoz (Switzerland, but with its production facilities in Germany), Antibioticos (Italy), and DSM (Netherlands). Sandoz and Antibioticos account

for about 60-70% of biotechnology-based 7-ACA and 14%-17% of global 7-ACA production. Overall, about 35% of 7-ACA is produced in the EU.

One third of cephalosporin antibiotics are derived from another precursor, 7-ADCA. 7-ADCA can be produced chemically, based on penicillin G as a precursor, or directly in a one-step fermentation process using genetically modified microorganisms<sup>389</sup>. Recently, DSM (Netherlands) has introduced a fully biotechnological production process for Cephalexin, a cephalosporin-based antibiotic, including one fermentation step and 2 enzymatic steps, replacing a 10-step conventional production process and reducing costs by about 50%<sup>390</sup>. DSM is the world's largest producer of 7-ADCA with a production capacity of several 100 tonnes. According to expert opinion, the share of the EU in production and sales is around 50%<sup>391</sup>.

In the case of 7-ADCA, the switch from chemical to biotechnological synthesis has reduced wastewater by 90%. Emissions of CO<sub>2</sub> have decreased by 75% and substantial energy savings have been made (37% less electricity and 92% less steam)<sup>392</sup>. In 7-ACA production, the biotechnological process has reduced by almost 100% the use of solvents and the production of waste needing to be incinerated, and has cut the amount of wastewater by 10%.

Compared internationally, the EU is competitive in the production of 7-ACA and 7-ADCA in terms of production volumes. This is true both for market volume as a whole and for the share of biotechnological processes.

383 Elander, R.P. (2003), *Appl. Microbiol. Biotechnol.* **61**(5-6): 385-392.

384 7-aminocephalosporanic acid.

385 Elander, R.P. (2003), *Appl. Microbiol. Biotechnol.* **61**(5-6): 385-392.

386 Bayer, T. and D. Wullbrandt (1999). Enzymatische Herstellung von 7-Aminocephalosporansäure. In: Heiden, S., C. Bock and G. Antranikian (eds). Industrielle Nutzung von Biokatalysatoren: Ein Betrag zur Nachhaltigkeit. 15. Osnabrücker Umweltgespräche. Initiativen zum Umweltschutz, vol. 14, Erich Schmidt Verlag, Berlin.

387 DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p. 51.

388 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

389 OECD (2001). The application of biotechnology to industrial biotechnology. OECD, Paris

390 DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p. 34.

391 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

392 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.



Worldwide, only a few producers are active. The uncertain factor here is the rapid development of production capacity in China. The North China Pharmaceutical Corporation NCPG and the Harbin Pharmaceutical Group (8000 employees) produce several 1000 tonnes of antibiotics, including 7-ACA and 7-ADCA. It is known that NCPG is developing biotechnological production routes for future production processes. It cannot be predicted how this will influence the current world market structure.

*Example: Biotechnological production of riboflavin*

Riboflavin (Vitamin B2) is a water-soluble vitamin that is an essential nutritional ingredient for humans and animals. Deficiency can lead to skin disorder, retarded growth, diarrhoea, and, in animals, to poor feed utilisation and impaired reproduction. Commercial riboflavin is primarily used as a feed additive (70%), rather than for dietary purposes (30%). The worldwide production volume is about 4000 tonnes/year (2000<sup>393</sup>). The biotechnological production process (fermentation processes partly using genetically modified microorganisms) has now largely replaced the intensive, multi-step chemical production process since it was first introduced in 1990 (accounting for more than 75% of production in 2002)<sup>394</sup>. According to the industry experts interviewed, about 3000 tonnes are produced using a fermentation process (30% in the EU and 70% in Asia). On average, the fermentation process yields 80% pure riboflavin, which is sufficient for feed applications, while

the chemical process yields 96% pure riboflavin, which corresponds better to the purity needs for food applications, in particular for baby food with its particularly high purity standards<sup>395</sup>.

In the EU, two companies produce riboflavin by fermentation processes. BASF in Germany produces about 1000 tonnes or 25% of the world market. However, the production site was moved to South Korea in 2003. DSM, Netherlands, has a production capacity of about 2000 tonnes. Recently, other major producers have been emerging in China. The world market for riboflavin is estimated at about EUR 55-60 million, which indicates an average price of EUR 15/kg riboflavin<sup>396</sup>. Asia accounts for about 30% of the market, North America and Mexico for about 50%, and the EU for about 20%<sup>397</sup>. Chinese manufacturers seem to have increased their production and exports of riboflavin and increased their share of the EU market, from 4% in 1999 to about 24% in 2003<sup>398</sup>.

The substitution of the conventional chemical process by the fermentation process seems to have resulted in significant cost reductions of between 40% and 50%<sup>399</sup>, due to higher efficiency, lower material input costs and less waste production.

*Example: Biotechnological production of the amino acid lysine*

In contrast to riboflavin, the amino acid lysine, also a feed additive, is produced in much larger quantities: yearly production is estimated at about 1 million tonnes in 2006, up from 850 000 tonnes in 2005<sup>400</sup>. Lysine is an essential amino acid

393 Schmid, R.D. (2002). Taschenatlas der Biotechnologie und Gentechnik. Wiley-VCH, Weinheim.

394 BIO (2004). New biotech tools for a cleaner environment. Biotechnology Industry Organization, Washington, D.C., p. 48.

395 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

396 Producers did not disclose current prices, and prices also seem to be rather volatile. Other sources give a range between EUR 14/kg and EUR 32/kg (<http://www.feedinfo.com/>).

397 According to industry experts interviewed; other sources give a range between 27-35% (ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications).

398 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

399 OECD (2001). The application of biotechnology to industrial biotechnology. OECD, Paris. EuropaBio (2003). White biotechnology: gateway to a more sustainable future. EuropaBio, Brussels.

400 Ajinomoto (2005). FY2005 market and other information. Materials for the analysts' meeting for the interim period ended September 30. Ajinomoto, Tokyo. [http://www.ajinomoto.com/ar/i\\_r/ir\\_event.html](http://www.ajinomoto.com/ar/i_r/ir_event.html).



that has to be taken with food or feed in sufficient amounts to meet the nutritional requirements of animals and humans. The limited availability in cereal-based feed requires the addition of lysine rich-soy beans or pure lysine to the feed. Livestock would otherwise have to ingest more feed to satisfy their lysine needs, resulting in less efficient overall feed use. Lysine nowadays is produced exclusively by fermentation processes, which have now completely replaced chemical production.

The world market for lysine is about EUR 1.0–1.2 billion (based on a product price of EUR 1.2/kg<sup>401</sup>). Lysine is an important product in the feed sector, representing about 80% (by value) of all amino acids produced for feed (approx. EUR 1.5 billion) and 26% of the feed additives market (EUR 4.8 billion, including amino acids, vitamins, acidifiers, antibiotics, enzymes, and minerals). More than one third of the feed additives market, even if only amino acids are considered, is based on modern biotechnology. Vitamins, enzymes, and antibiotics add to that share.

Four companies in the EU represent about 40% of world production, although the production itself takes place to a large extent in non-EU countries (South Korea, USA). Only three factories produce lysine within the EU, in France, Italy and Denmark, with an output of 130 000 tonnes (13% of world production). As with riboflavin, Asia seems to be an important market and production location for feed additives with about 43% of world production in Indonesia, South Korea and China, the latter alone accounting for 25%.

Based on feed consumption data for Western Europe, it is estimated that the EU requires about 268 000 tonnes of lysine. This is twice the amount of EU production. While the EU is the largest market (27%), EU companies are however

moving production to low-cost countries (with low wage and/or raw material costs) and turning to higher-value products such as the amino acids threonine or tryptophane<sup>402</sup>.

#### *Production of biotechnology-based polymers*

Plastics or polymers are currently the most used materials worldwide, in packaging materials (37% of the plastics market), in building and construction (20%), in the electrical industry (8%), for automotive uses (8%), in furniture (4%), in household goods (9%), or in agriculture (2%)<sup>403</sup>. The worldwide production volume in 2004 was 224 million tonnes. However, production is based on petrochemicals, i.e. non-renewable resources, and the raw materials and products are mostly not biodegradable (although biodegradable polymers can also be produced using fossil sources). In contrast, the production and use of biotechnology-based polymers could reduce the use of oil-based products and waste. The analysis here focuses on polymers whose production includes a biotechnological step. Starch- and cellulose-based polymers developed from plant material, already known and used for several decades, are not included<sup>404</sup>. In contrast to the other biotechnology processes described above, the production of biotechnology-based polymers is still in an early development phase.

There are several types of biotechnology-based polymers:

- Lactic-acid based: Starch or sugar is fermented to produce lactic acid, which can be dried and extruded to obtain thermoplastic properties, e.g. Solanyl®, based on potato waste, produced by Rodenburg Biopolymers, the Netherlands (40 000 tonnes/year). Other

401 Ajinomoto (2005). FY2005 market and other information. Materials for the analysts' meeting for the interim period ended September 30. Ajinomoto, Tokyo. [http://www.ajinomoto.com/ar/i\\_r/ir\\_event.html](http://www.ajinomoto.com/ar/i_r/ir_event.html).

402 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

403 PlasticsEurope (2007). Plastic demand by end-use application sector 2004 (W. Europe). PlasticsEurope, Brussels. <http://www.plasticseurope.org/content/default.asp?PageID=103>.

404 A comprehensive overview of biobased polymers including all types of products is given in: Patel, M., M. Crank and O. Wolf (eds) (2005). Techno-economic feasibility of large-scale-production of bio-based polymers in Europe. European Commission, DG JRC/IPTS, EUR 22103, pp. 35-36.



EU producers are: PURAC, the Netherlands (80 000 tonnes/year) and Galactic, Belgium (25 000 tonnes/year). Lactic acid can also be chemically polymerised to form poly-lactic acid (PLA), which can be further used to make fibres, films, etc. (e.g. Nature Works®, using maize starch — Nature Works LLC, USA, 140 000 tonnes/year<sup>405</sup>). Applications include food packages, carpets, or PC body components.

- Polyhydroxyalkanoates (PHA) are natural polymers produced by bacteria through fermentation from sugar or lipids as feed stock. The company Metabolix (USA) has developed an enzyme-catalysed polymerisation process for the production of very pure PHA for medical applications. Further process development includes the use of whole-cell biocatalysis to reduce production costs and improve purification<sup>406</sup>. Metabolix currently produces about 1000 tonnes per year in a pilot plant (Biopol®). Procter&Gamble (USA) reports production capacities of about 250 tonnes/year of PHA<sup>407</sup>.
- Bio-PDO (1,3-propanediol) produced via fermentation of maize-derived sugar is used for the production of polytrimethylene terephthalate (PTT), a new type of polyester fibre (Sorona®), which is not biodegradable. The fibre can be used e.g. for carpet and clothing manufacturing. A genetically modified bacterium is used for the fermentation process. In a joint venture with Tate&Lyle (UK), DuPont (USA) will increase production in the USA in 2006 to about 23 000-45 000 tonnes.
- The oldest process using biocatalysts in polymer production is the conversion of

acrylonitrile to acrylamide with the help of a recombinant enzyme. Acrylamide can be further polymerised to polyacrylamide. This is one of the first large-scale biotechnological applications of enzymes in bulk chemical production. Mitsubishi Rayon Co. LTD (Japan, formerly Nitto Chemical Industry) is the largest producer of acrylamide (about 20 000 tonnes/year). Overall worldwide production of biotechnology-based acrylamide is about 100 000 tonnes/year, produced mainly in Japan.

#### *Economic significance*

In the EU, eight companies were identified as active in bio-based polymer production (Table 2.11). Overall production volumes of biotechnology-based polymers have been estimated to be around 148 000 tonnes per year in the EU. Compared to 32.5 million tonnes of oil-based polymers, this is a marginal share of 0.13%<sup>408</sup>. EU producers are still few in number, and are mostly operating on a pilot scale. The market value is estimated at about EUR 55.3 million, 7% of the world production of biotechnology-based polymers<sup>409</sup>. The GVA is estimated at about EUR 11.3 million, or 0.0001% of EU GVA.

The world production of biotechnology-based polymers is estimated to be around at least 390 000 tonnes/year (148 000/year tonnes in the EU, 140 000 tonnes/year NatureWorks® in the USA, 100 000 tonnes/year biotechnology-based acrylamide mainly in Japan). Compared to the combined plastics output in the EU, the USA and Japan of 98 million tonnes/year, this amounts to a share of 0.45%, indicating a higher share of biotechnology-based polymers in Japan

405 Natureworks maintains two production facilities in Blair, Nebraska (US). One produces lactic acid, which is used in different food and non-food applications. Most of the output feeds into the second plant, which produces 140kt PLA/year.

406 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

407 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

408 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

409 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.



Table 2.11 EU companies producing biotechnology-based polymers

Company	Product	Production volume
Rodenburg BioPolymers, The Netherlands	Solanyl® (lactic-acid based polymer)	40 000 tonnes/year
Tate & Lyle, UK	1,3 Propanediol	Joint venture with DuPont, USA; planned production in the USA 23 000 to 45 000 tonnes/year
Hycail (taken over by Tate & Lyle in 2006), The Netherlands/UK	Poly-lactic acid	Pilot plant
Uhde Inventa-Fisher, Germany	Poly-lactic acid	Pilot plant
PURAC, Netherlands	Poly-lactic acid	80 000 tonnes/year
Galactic, Belgium	Poly-lactic acid	25 000 tonnes/year
Biomer, Germany	Biomer® (Poly-hydroxy-butyrate)	
Boehringer Ingelheim, Germany	Poly-lactic acid (Resomer®)	

and the USA. This is partly due to national policy initiatives to support non-petrochemical-based product development.

While biotechnology-based polymers are still more expensive than their oil-based counterparts, the competitiveness threshold also depends on technical requirements and the end-user market and thus might differ strongly between different applications. Due to low production volumes the current impact of biotechnology-based polymers is marginal in the EU. However, production capacities are growing worldwide, and price reductions are expected for nearly all biotechnology-based polymers in the near and mid-term future. The average price of oil-based polymers today is around EUR 0.75/kg. It seems that Solanyl®, with a relatively high current production volume, is the only biotechnology-based polymer that comes near the price of oil-based polymers (EUR 1.13/kg<sup>410</sup>).

The competitiveness gap is expected to shrink in the future with increasing production volumes,

but in the coming five years biotechnology-based polymers are not expected to contribute massively to the market for primary plastics, apart from highly specialised applications.

No evidence is available on the employment effects of biotechnology-based polymers, but based on current production volumes, the employment effects can be regarded as negligible.

#### *Environmental implications*

The production of biotechnology-based polymers could lead to reductions in energy consumption and greenhouse gas production (CO<sub>2</sub>) (Table 2.12). The impact depends on the polymer in question and the polymer it is compared to. A PLA-based polymer such as Solanyl® or NatureWorks® uses 20%-50% less energy compared to polyethylene or other bulk plastics, and has about 50%-70% lower CO<sub>2</sub> emissions (in the case of NatureWorks®).



■ Table 2.12: Environmental impacts of biotechnology-based polymers: energy consumption and CO<sub>2</sub> emissions<sup>412</sup>

Polymer	Energy consumption	Direct CO <sub>2</sub> emissions
Production of Solanyl® compared to conventional oil-based plastics	40% less than bulk plastics such as polyethylene	No data available
Production of NatureWorks® compared to conventional oil-based plastics	20%-50% less than other plastics (PET, HDPE, Nylon-6)	50%-70% less
Production of BioPDO-based polytrimethylene terephthalate compared to conventional oil-based plastics	16% less than polyethylene terephthalate	No difference (indirect effects not included)

Additionally, an indirect reduction in CO<sub>2</sub> emissions can be expected from the lower energy consumption. In the case of acrylamide production, the enzymatic process yields a 30% reduction in energy consumption and a 25% reduction in CO<sub>2</sub> emissions<sup>411</sup>. For Bio-PDO, energy savings of about 16% have been identified, thus also indirectly reducing CO<sub>2</sub> emissions. There is no difference in the CO<sub>2</sub> emissions of the production process.

Ongoing research will influence the environmental impacts of biotechnology-based polymer production. The use of plants to produce PHA could replace the current fermentation process with potentially positive effects on energy use and CO<sub>2</sub> emissions. The use of lignocellulosic biomass as a raw material for PLA production instead of maize starch is expected to reduce the fossil energy requirements for production by 80%<sup>413</sup>.

The advantage of biotechnology-based polymers such as PLA is that they can be composted, incinerated, or re-used in pre-

consumer recycling or post-consumer recycling/recovery. In the case of composting, tests have shown that PLA polymers can be composted in full compliance with DIN, ISO, CEN and ASTM<sup>414</sup> regulations. When incinerated, PLA produces fewer by-products than traditional polymers and also has a lower energy content. Pre-consumer recycling studies show that PLA can be used in thermoforming like any other polymer. In post-consumer recycling, a separate collection system needs to be put in place<sup>415</sup>, which implies that these polymers need to be distinguishable from oil-based polymers. Normally, however, end consumers cannot be expected to tell the difference, so they will not be in a position to collect biotechnology-based polymers separately. As a result, oil- and biotechnology-based polymers could enter the same waste streams. Biotechnology-based polymers are not compatible with the existing oil-based polymer recycling system and could negatively impact on the product quality of recycled polymers.

411 OECD (2001). The application of biotechnology to industrial sustainability. OECD, Paris, p. 74.

412 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

413 OECD (2001). The application of biotechnology to industrial sustainability. OECD, Paris, p. 88.

414 DIN: Deutsches Institut für Normung, Germany; ISO: International Organization for Standardization; CEN: European Committee for Standardisation; ASTM: American Society for Testing and Materials.

415 OECD (2001). The application of biotechnology to industrial sustainability. OECD, Paris, p. 89.





### 2.3.2 Modern biotechnology in the production of biofuel - bioethanol

Rising oil prices, dwindling fossil fuel reserves and concerns about climate change due to increasing CO<sub>2</sub> levels in the atmosphere have put renewable energy sources on the agenda worldwide. One important alternative energy source is biomass, and bio-based fuels in particular have received wide attention recently. Bioethanol, which is produced by conversion of plant biomass into ethanol by biocatalysis and can be used as a transport fuel, is the most important application of modern biotechnology. For all energy production from biomass, modern biotechnology could also play a role on the biomass production side, with an impact on development of energy crops. However, this analysis will focus on the biomass processing side.

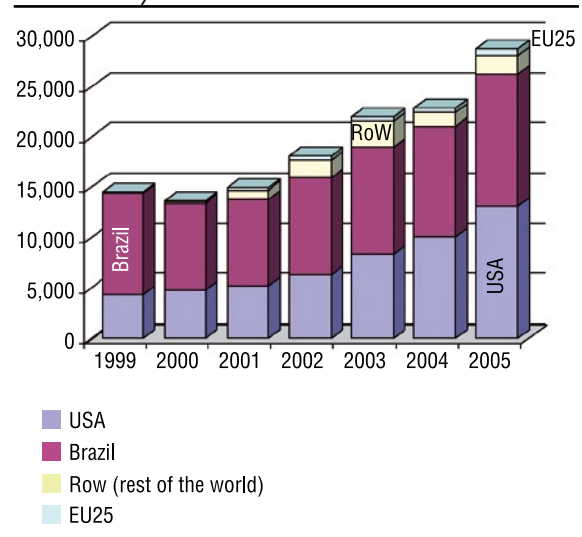
Bioethanol is the product of a fermentation process usually using yeasts, with glucose sugar as a substrate. In the EU bioethanol is produced mostly from wheat, sugar beet and grapes. Wheat is the most important raw material. Conversion of wheat starch into glucose requires enzymatic hydrolysis. The enzymes – recombinant amylases – account for only a small fraction of the costs of bioethanol production.<sup>416</sup> R&D efforts are focusing on improving the fermentation process in order to be able to use other raw materials, such as wood, straw or grass (lignocellulosic material) (see also Chapter 2.3.4)<sup>417</sup>. In the USA bioethanol is produced from maize by means of a similar process as in the EU. In Brazil, currently the largest bioethanol producer in the world, sugar cane is used, which requires no enzymatic pre-treatment.

#### Economic significance

Worldwide, 79% of the bioethanol produced is used as transport fuel.<sup>418</sup> Between 1975 and 2005 world fuel ethanol production increased

steadily. It has more than doubled in the last five years. Up until now Brazil has been the largest bioethanol producer; it has by far the highest share of bioethanol in national liquid transport fuel consumption (14%). The USA has increased its production considerably over the last six years and now has a worldwide share of 45% (see Figure 2-20). The EU's share of worldwide production in 2005 was 2.6%, making it a small international player compared with China, for example, which increased its share from 1.2%-5.5% of world production in three years. Japan does not produce bioethanol as a transport fuel, but imported around 400 000 tonnes in 2004 and 2005.

Figure 2-20 Global bioethanol fuel production (thousand tonnes) by year and country



RoW: rest of the world.

Source: ETEPS, BMELV and IEA<sup>419</sup>.

In contrast to fossil fuel production, bioethanol production is a young industry which is undergoing rapid economic and, in particular, technological development. Table 2.13 shows basic figures on the economic impact of

416 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

417 Herrera, S. (2006). *Nature Biotechnology* 24(7): 755-760.

418 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

419 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications, Report prepared by the Worldwatch Institute for the German Federal Ministry of Food, Agriculture and Consumer Protection (2006), Biofuels for transportation, Washington D.C., and International Energy Agency (2004), Biofuels for transport-An international perspective. Paris.

bioethanol production in comparison with fossil fuel production. By volume, in 2005 bioethanol production was equivalent to about 0.1% of fossil fuel production. Large-scale fossil fuel production facilities produce, on average, 60 times more than biofuel production plants. In 2005, 525 people were employed directly (and around 5 000 indirectly) in fuel ethanol production, which corresponds to around 0.015% of all EU employment in manufacturing or 0.0003% of EU employment.

Table 2.13 also shows that the average production costs of bioethanol exceeded fossil fuel production costs by 60% in 2005.<sup>420</sup> Due to the lower energy content of bioethanol, the production costs per unit energy equivalent were about 130% higher than for fossil fuel in 2005. However, compared with 2004, the cost differences have narrowed (in 2004 production costs per litre of bioethanol were 150% higher and production costs per unit energy equivalent 270% higher). Future cost trends for biofuels can be predicted, on the basis of past experience,

only within certain limits. Growth of production volumes from individual crops is limited due to geographical dependence on raw material supplies (biomass). And, related to that, large-scale production of biofuels has repercussions for the raw material price itself, which might offset any cost reductions as a result of efficiency gains.

Bioethanol production in the EU shows large differences in output from year to year, but overall strong growth, by more than 100% between 2002 and 2005. This is reflected in the increase in the number of biofuel refineries in the EU, from 16 in 2004 to 23 in 2005, with eight more planned. There are several reasons for this development, such as technological progress, recent changes in the market price for crude oil and, in reaction to that, a changing legal framework at both national and EU levels. The EU set a target of 5.75% for biofuel's share of all road transportation fuel in the EU,<sup>421</sup> which was recently increased to 10% by 2020.<sup>422</sup> Some Member States are already designing their national policies accordingly, such as the Netherlands or Germany, which recently

Table 2.13 Comparison of the contribution of fossil fuel and bioethanol to the EU economy

	Fossil fuel in the EU	Bioethanol in the EU
Share of GVA	0.25%	0.0002%*
Share in manufacturing (NACE D)	1.10%	0.00231%
Employment: direct	40 000	525
indirect	approximately 100 000	approximately 5 000
Contribution to employment in Europe (based on direct employment)	0.05%	0.0003%
Turnover per employee	€5 300 000	€800 000
Production cost per litre	€0.33	€0.53
Production cost per litre gasoline equivalent	€0.33	€0.76
Total production	600 000 000 t*	750 000 t
Average output per plant	6 000 000 t/year	100 000 t/year*
Number of refineries	104 (2005)	16 (2005), 23 (2006)
Sales	€139 billion	€192 million
Imports		13%

Data from the most recent year available in each case (i.e. 2002-2006). \*Estimate.

420 The price per unit for biofuel is indicative and differs slightly, depending on the raw material and production pathways. The cost comparison with fossil fuel should, however, give an idea of the approximate range.

421 Directive 2003/30/EC of the European Parliament and of the Council on the promotion of the use of biofuels or other renewable fuels for transport, OJ L 123, 17.5.2003, p. 42.

422 Brussels European Council, 8 and 9 March 2007, Presidency conclusions.



announced an obligatory share of 10% for biofuel by 2014.<sup>423</sup> The USA has announced that biofuels will cover 30% of its national fuel supply by 2030.<sup>424</sup> Availability of a bioethanol production process based on lignocellulose instead of sugar is the precondition for reaching the US target of 30%. Accordingly, research funds and other subsidies are being made available for that area in particular. Total subsidies for bioethanol in the USA have reached USD 5.1 billion to 6.8 billion a year and are expected to rise further during the next five years.<sup>425</sup> As a result, companies such as Novozymes (enzyme development) and Broin (the largest dry mill ethanol producer in the USA) have announced that they are collaborating to speed up development of cellulosic ethanol.<sup>426</sup>

#### Environmental implications

Production of bioethanol and substitution of fossil transport fuels have an impact on several dimensions of the environment, mainly less depletion of non-renewable fossil fuel resources

and a reduction of greenhouse gas (GHG) emissions. The environmental impact differs in scale, depending on the production path chosen. Further factors influencing the environmental impact are the share of imports from non-EU regions, the mix between diesel and gasoline, the blending and the (future) shift from first-generation to second-generation fuel, i.e. to lignocellulosic biomass.

Table 2.14 shows that, for both diesel and gasoline (petrol) alike, substitution by biofuels reduces GHG emissions. As biodiesel production does not involve modern biotechnology, only the implications of bioethanol production are taken into consideration here. Bioethanol produced from wheat reduces GHG emissions by about 50%, from 3.62 tCO<sub>2</sub>eq/toe to 1.85 tCO<sub>2</sub>eq/toe. Wheat is the main raw material used for bioethanol production in the EU. The table also shows that biofuel production from lignocellulosic biomass (straw or wood) reduces GHG emissions by up to 90%.

**Table 2.14 GHG emissions from different biofuels<sup>427</sup>**

	<b>Greenhouse gas emissions (tCO<sub>2</sub>eq/toe)</b>	<b>Savings (%)</b>
Diesel	(3.65)	
Biodiesel from rape*	1.79	51
Biodiesel from soy*	2.60	29
Biodiesel from palm*	1.73	53
BTL from straw	NA	NA
BTL from farmed wood	0.27	93
Petrol	(3.62)	
Ethanol from sugar beet	2.17	40
Ethanol from wheat	1.85	49
Ethanol from sugar cane	0.41	89
Cellulosic ethanol from straw	0.333	91

BTL: biomass to liquid; toe: tonne of oil equivalent; NA: not available; \*chemical transformation.

- 423 FTD (2006). "Koalition zwingt Ölkonzernen zehn Prozent Biosprit auf." *Financial Times Deutschland* (Hamburg), online version 24 October.
- 424 DOE (2006). DOE publishes roadmap for developing cleaner fuels. Press release, 7 July. U.S. Department of Energy, Washington, D.C. <http://www.doe.gov/news/3804.htm>.
- 425 Koplow, D. (2006). Biofuels – at what cost? Government support for ethanol and biodiesel in the United States. The Global Subsidies Initiative, International Institute for Sustainable Development, Geneva.
- 426 Novozymes (2006). Broin and Novozymes to collaborate on development of ethanol from cellulosic biomass. Press release, 26 October. Novozymes, Bagsværd. <http://www.novozymes.com/en/MainStructure/PressAndPublications/PressRelease/2006/NzBroinBiomass.htm>.
- 427 European Commission SEC (2006) 1721/2: Commission Staff Working Document Review of economic and environmental data for the biofuels progress report, p. 20.



The EU has set out to replace 5.75% of fossil transport fuels by biofuels or renewable fuels by 2010 and 10% by 2020.<sup>428</sup> Currently 7.9% of GHG emissions are generated by oil-based gasoline. Hypothetical substitution of 100% of gasoline by ethanol from wheat would lead to a 4% reduction in all GHG emissions, given the 50% CO<sub>2</sub> reduction achievable with bioethanol (assuming unchanged demand for transport fuel). In all, applying a share of only 5.75% for bioethanol produced from wheat would lead to a reduction in GHG emissions of about 0.23%. This calculation takes into account the whole lifecycle. There are other production pathways, one of which is estimated to lead to higher GHG emissions than the fossil fuel it replaces. In absolute terms, real CO<sub>2</sub> savings in the EU due to ethanol were 0.7 MtCO<sub>2</sub>eq in 2005.<sup>429</sup>

However, the potential GHG reduction depends on several factors. As discussed above, savings of CO<sub>2</sub> emissions can be offset if raw materials for biofuels are grown on inappropriate land, for example if wetlands are chosen. The CO<sub>2</sub> balance could be neutralised or even reversed to negative. Another relevant environmental issue to be considered is biodiversity, which might be threatened by large-scale growth of raw materials for biofuels. However, according to the European Environment Agency, enough biomass can be produced in the EU to cover even high demand for biofuel production.<sup>430</sup> Accordingly, the challenge seems not to be a bottleneck in land availability, but to identify appropriate land for growing raw materials for biofuels.

### 2.3.3 Modern biotechnology in bioremediation

Bioremediation is the collective term for treatment of contaminated water, soil, air and

solid waste with living organisms, mostly micro-organisms, to degrade or transform hazardous organic contaminants. These end-of-pipe applications of biotechnology were developed from the 1970s and 1980s onwards.

Amongst the different applications, biotechnological waste water treatment has the longest tradition, whereas biotechnological air filters and specific waste treatments are more recent. The mechanism is similar in all these applications, in that microorganisms adapted to degradation of specific pollutants are used to decontaminate environmental media. This can be done on-site, which is usually the more economic solution, or off-site, which entails transporting contaminated material to a decontamination site. Often the most suitable microorganisms are found in the direct environment of the contaminated material.

Bioremediation has been thoroughly reviewed by the OECD, which collected a number of examples.<sup>431</sup> For air and off-gases, microorganisms in peat and compost beds are able to break down simple volatile organic compounds and reduce odours; at the same time these processes are often simpler and cheaper than the alternative chemical approach. Contaminated soils can be treated “in situ” by injecting nutrient solutions and/or air to support microbial activity (“biostimulation”). Bioaugmentation – introduction of specific strains or consortia of microorganisms on the contaminated site to improve the capacity for pollutant degradation – is at a comparatively early stage of development.<sup>432</sup> Another biological soil remediation method is “ex situ”, which ranges from simple composting to soil-flushing techniques. Solid waste treatment is similar to soil clean-up techniques. Solid organic waste can be degraded in the presence of oxygen in landfills

428 Directive 2003/30/EC of the European Parliament and of the Council on the promotion of the use of biofuels or other renewable fuels for transport, OJ L 123, 17.5.2003, p. 42; Brussels European Council, 8 and 9 March 2007, Presidency conclusions.

429 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

430 EEA (2005). How much biomass can Europe use without harming the environment? Briefing, European Environment Agency, Copenhagen.

431 OECD (1994). Biotechnology for a clean environment. OECD, Paris.

432 El Fantroussi, S. and S.N. Agathos (2005). *Current Opinion in Microbiology* 8: 268-275.



and during composting. Degradation in an oxygen-depleted environment produces usable methane. Waste water treatment has the longest record of applying microorganisms for clean-up purposes with several different technologies.<sup>433</sup>

Currently, limited use is made of modern biotechnology in bioremediation. It is used, for example, to support efficient production of enzymes,<sup>434</sup> which are employed, inter alia, to clean up pesticide residues. In this case, the enzyme is isolated from bacteria in the environment of the pollutants, cloned into a common bacterium, produced by industrial-scale fermentation and then applied in decontamination.<sup>435</sup>

The fact that microorganisms are able to adapt to degradation of a wide range of problem pollutants, such as chlorinated solvents, sparked expectations in the 1980s that modern biotechnology would make it possible to modify microorganisms in a way which would increase their degradation capacity, both by improving the degrading rate, i.e. enabling them to clean material faster, and also by making them applicable to a larger variety of pollutants. Steps have been taken in that direction, resulting in the first-ever patenting of a living organism, a *Pseudomonas* strain able to degrade a series of recalcitrant compounds.<sup>436</sup>

Use of modified microorganisms in bioremediation technologies, however, faced several challenges. With the exception of a few cases, modified microorganisms have performed poorly in degrading pollutants compared with their naturally occurring counterparts. One exception are transgenic plants for decontamination of soil, for example modified tobacco plants for phytodetoxification

of explosives (TNT) in soil.<sup>437</sup> However, this application is not actually being used to remove explosives residues from soil. In addition, the interaction of modified microorganisms with the natural environment is difficult to predict, and newly introduced microorganisms have often turned out to be less fit than their competitors and been eliminated.<sup>438</sup> The potential risks associated with uncontrolled growth and proliferation of the GMOs in the environment and gene transfer to other organisms have limited the applications of GMOs in bioremediation up to now.

Another example of use of modern biotechnology in environmental applications is development of biosensors. Biosensors are analytical devices incorporating biological material, such as microorganisms, enzymes, antibodies, etc., which are associated with or integrated into a physicochemical transducer system, which may be optical, electrochemical, etc.<sup>439</sup> The system is introduced into environmental media, e.g. water, and gives a signal once it detects a specific pollutant. However, no evidence could be found that biosensor systems which do not need additional physical translation of signals are currently on the market – an additional readout system is still attached to biological systems.

#### **2.3.4 Emerging biotechnology applications in industrial processes and energy**

Recent developments, such as rising oil prices and growing concerns about environmental pollution and global warming, are turning increasing attention to industrial biotechnology, in view of the potential environmental and energy-related benefits. The availability of advanced modern biotechnology tools, such as high-

433 Gaugitsch H. and M. Schneider (1997). "Einleitung, Zusammenfassung und Bewertung." In: Umweltbiotechnologie in Österreich, Schwerpunkt: Nachsorge, Monographien Band 85B, Bundesministerium für Umwelt, Jugend und Familie, Vienna, p. 501-510.

434 Alcalde, M. et al. (2006). *Trends in Biotechnology* **24**(6): 281-287.

435 Sutherland, T. and R. Russell (2002). *Pesticide Outlook* **13**: 149-151.

436 Cases I. and V. de Lorenzo (2005). *International Microbiology* **8**: 213-222.

437 Hannink, N. et al. (2001). *Nature Biotechnology* **19**: 1168-1172.

438 Cases I. and V. de Lorenzo (2005). *International Microbiology* **8**: 213-222.

439 ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.



throughput screening, metabolic engineering, metagenomics and synthetic biology, combined with genome sequence information for a growing number of organisms, are supporting development of better or new applications of industrial biotechnology. The main targets of research activities are identification of new biocatalysts or microorganisms for production processes and optimisation of enzymes and production strains for certain tasks, including development of new biocatalytic pathways in microorganisms.

### New and improved approaches to industrial biotechnology

Currently more than 35 000 enzyme reactions are known<sup>440</sup>. Adding the vast number of microorganisms that cannot be isolated with current culturing techniques (it is estimated that only 1% of bacteria can be cultured<sup>441</sup>) and which are likely sources of as yet unknown enzymes, this provides a potentially large pool of enzymes for industrial purposes. Access to unculturable microorganisms can be opened up by metagenomics, i.e. isolating genetic material from natural sources such as soil or seawater and introducing it in well-known organisms such as *Escherichia coli*<sup>442</sup>.

One of the main fields for biocatalysis are fine chemicals, including pharmaceutical compounds. The high selectivity of enzymes facilitates synthesis of these compounds, which is otherwise difficult to achieve due to the highly complex functional groups and their localisation within the molecule<sup>443</sup>. Metabolic pathway engineering allows production not only of different complex compounds (e.g. polyketide, isoprenoide and

alkaloide) but also of compounds that would otherwise be inaccessible because the organisms cannot be cultured (e.g. the cytotoxic substance patellamide). Modification of biosynthetic pathways also facilitates production of compound analogues and promising drug candidates (e.g. analogues of the substance rapamycin)<sup>444</sup>. Further research efforts are looking into biotechnological production of small molecule drug precursors. One example is production by recombinant bacteria of shikimic acid, an intermediate of the antiviral product Tamiflu (targeting avian flu), which is mostly extracted from plants<sup>445</sup>.

Wider availability of new classes of enzymes for industrial purposes (e.g. transaminases, monooxygenases and nitrilases), in addition to the currently most used enzymes (e.g. esterases, proteases and lipases), will have an impact on use of biocatalysis in industrial production<sup>446</sup>. The enzymes will catalyse reactions impossible to achieve by other methodologies as key steps in multi-step syntheses of new drugs and other fine chemicals. Apart from the availability of sufficient and inexpensive enzyme stocks, the enzyme activity and its robustness and adaptation to process conditions play a major role in biocatalysis. Hence, enzymes are subjected to optimisation processes using modern biotechnology tools, for example to increase thermostability, to reduce the optimum temperature or to increase their activity<sup>447</sup>. Enzymes from extremophilic microorganisms (extremozymes) are expected to play a significant role in industrial biotechnology due to their unique stability at high or low temperatures, high pressure, high salt concentrations and extreme pH, plus their high organic solvent and metal

440 Straathof, A.J.J. et al. (2002). *Current Opinion in Biotechnology* **13**: 548-556.

441 Tringe, S.G. and E.M. Rubin (2005). *Nature Reviews Genetics* **6**: 805-814.

442 Gewin, V. (2006). *Nature* **439**: 384-386.

443 Pollard, D.J. and J.M. Woodley (2007). *Trends in Biotechnology* **25**(2): 66-73.

444 Wilkinson, B. and B.O. Bachmann (2006). *Current Opinion in Chemical Biology* **10**: 169-176.

445 Panke, S. and M. Wubbolts (2005). *Current Opinion in Chemical Biology* **9**: 188-194.

446 Pollard, D.J. and J.M. Woodley (2007). *Trends in Biotechnology* **25**(2): 66-73. Faber, K. and W. Kroutil. (2005). *Current Opinion in Chemical Biology* **9**: 181-187.

447 Cherry, J.R. and A.L. Fidantsef (2003). *Current Opinion in Biotechnology* **14**: 438-443.



tolerance<sup>448</sup>. New “natural” biopolymers (e.g. poly-lactic acid analogues) will be made available by appropriate engineering of microorganisms, while enzymes will be employed to produce and modify “non-natural polymers”.<sup>449</sup>

### Bioethanol production

Biofuels, notably bioethanol, are the focus of efforts to diversify energy sources, increase the share of renewable energy sources and reduce greenhouse gas emissions. The current bioethanol production process, based mainly on sugar and starch, will most probably not be able to produce the required quantities of bioethanol in the long term and has limitations in terms of reduction of greenhouse gas emissions<sup>450</sup>. Research is therefore focusing on “second generation” bioethanol, based on non-food lignocellulosic feedstock or biomass, e.g. agricultural residues, wood, municipal solid waste or dedicated energy crops. The compactness and complexity of lignocelluloses poses technical and economic challenges with, among others, depolymerisation of cellulose and hemicellulose and fermentation of the resulting mix of sugars<sup>451</sup>.

Cellulose and hemicellulose are degradable by enzymes (cellulases and hemicellulases). New cellulases and hemicellulases have been isolated from microorganisms in recent years. These cellulases are still comparatively costly and show low catalytic activity.<sup>452</sup> An alternative approach is focusing on plants (see also Chapter 2.2.3). Genetic engineering is attempting to develop plants that produce less lignin. This would

reduce the need to pretreat biomass to facilitate cellulose depolymerisation. Another approach has developed cellulase- and ligninase-producing plant varieties as biofactories for cost-efficient production of these enzymes or as direct input into the process with the biomass. Yet another approach is targeted at increasing the biomass yield from dedicated energy crops<sup>453</sup>.

For fermentation of sugar to ethanol, yeast (*Saccharomyces cerevisiae*) is usually used. However, lignocellulose depolymerisation results in a mix of sugars, mainly glucose (hexose sugar) and xylose (pentose sugar). The latter is not metabolised by most strains of *S. cerevisiae*. Therefore, using genetic engineering, current research efforts are focusing on introducing new pentose metabolic pathways into yeast and other ethanologenic microorganisms or on improving ethanol yields in microorganisms that can metabolise the sugar mix<sup>454</sup>. The recent sequencing of the genome of a xylose fermenting yeast will feed into these developments<sup>455</sup>.

Currently only a few pilot plants are producing bioethanol from lignocellulosic feedstock using an enzymatic hydrolysis process<sup>456</sup>. In the long term, development of integrated biorefineries is envisaged, combining production of biofuels and co-products such as commodity chemicals and materials, thereby making the biofuel production process more efficient and competitive<sup>457</sup>.

Apart from bioethanol, efforts are also being made to apply biotechnology to production of other biofuels. In the case of biodiesel production, research is being carried out to replace the

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- 448 Egorova, K. and G. Antranikian (2005). *Current Opinion in Microbiology* **8**: 649-655. Van den Burg, B. (2003). *Current Opinion in Microbiology* **6**: 213-218.
- 449 Gross, R.A. et al. (2001). *Applied Microbiology and Biotechnology* **55**(6): 655-660.
- 450 Hahn-Hägerdal, B. et al. (2006). *Trends in Biotechnology* **24**(12): 549-556.
- 451 Schubert, C. (2006). *Nature Biotechnology* **24**(7): 777-784.
- 452 Hahn-Hägerdal, B. et al. (2006). *Trends in Biotechnology* **24**(12): 549-556. Gray, K.A. et al. (2006). *Current Opinion in Chemical Biology* **10**: 141-146.
- 453 Sticklen, M. (2006). *Current Opinion in Biotechnology* **17**, 315-319.
- 454 Gray, K.A. et al. (2006). *Current Opinion in Chemical Biology* **10**: 141-146.
- 455 Jeffries, T.W. et al. (2007). *Nature Biotechnology* **3**: 319-326.
- 456 Lin, Y. and S. Tanaka (2006). *Applied Microbiology and Biotechnology* **69**: 627-642. Hahn-Hägerdal, B. et al. (2006). *Trends in Biotechnology* **24**(12): 549-556.
- 457 Biofuels in the European Union: A vision for 2030 and beyond. Final draft report of the Biofuels Research Advisory Council, 14 March 2006. See also European Technology Platforms on Sustainable Chemistry and on Biofuels ([http://www.europabio.org/ne\\_WBTP.htm](http://www.europabio.org/ne_WBTP.htm); <http://www.biofuelstp.eu>).



alkali-catalysed transesterification step with a biocatalytic step using lipases<sup>458</sup>. Biobutanol is the target of another initiative with sugar beet as a feedstock. Again the long-term objective is to use lignocellulosic feedstock<sup>459</sup>.

### Synthetic biology

Another recently emerging approach, making use of the increased knowledge on genes and genome organisation and modern biotechnology tools such as DNA synthesis and genetic engineering, is synthetic biology. Synthetic biology is defined as “the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems, rather than on the understanding of natural biology”<sup>460</sup>.

Synthetic biology is considered to have great potential for creating organisms to carry out specific tasks and reaching beyond current genetic engineering of existing organisms. However, synthetic biology is still at an early stage of development and largely coincides with recombinant DNA technology<sup>461</sup>. Related research activities are focusing on building living organisms from scratch (e.g. assembly of the infectious genome of a bacteriophage from synthetic oligonucleotides<sup>462</sup>) or on creating a minimal microorganism, currently through a top-down approach identifying the set of essential genes<sup>463</sup>.

The first building blocks for synthetic biology have been developed. These are DNA strands with certain functions and universal connectors at each end so that they can be linked to and integrated in a cell's DNA<sup>464</sup>. Construction of a minimal cell based on small molecules is expected to facilitate the production of new proteins difficult to express by standard approaches and creation of useful microorganisms<sup>465</sup>. For example, use of non-natural amino acids for development of proteins with new properties could lead to new drugs<sup>466</sup>.

Other potential applications of synthetic biology envisaged include molecular devices for tissue repair or regeneration, smart drugs, *in vivo* synthesis of small-molecule pharmaceuticals (e.g. complex natural products such as antibiotics), bulk chemical production, bioremediation, energy production, smart materials, biomaterials and in sensor and detection systems, e.g. for detection of chemicals or for diagnostic purposes<sup>467</sup>. One of the first applications considered as an example of synthetic biology is creation in yeast of the metabolic pathway for a precursor of the malaria drug artemisinin, which is in short supply and unaffordable for many malaria patients.<sup>468</sup>

The possibility of creating artificial life forms raises several concerns. Apart from the potentially negative environmental impact, contamination of the natural genome pool and the risk that the approach could be used for bioterrorism attacks, creation of new life forms also raises ethical issues<sup>469</sup>. While the scientific community is discussing these issues and a self-regulating

458 Shah, S. and M.N. Gupta (2007). *Process Biochemistry* **42**: 409-414.

459 Sanderson, K. (2006). *Nature* **444**: 673-676. Hatti-Kaul, R. et al. (2007). *Trends in Biotechnology* **25**(3): 119-124.

460 SynBiology (2006). An analysis of synthetic biology research in Europe and North America. <http://www2.spi.pt/synbiology/documents.asp>.

461 Brenner, S.A. and A.M. Sismour (2005). *Nature Review Genetics* **6**: 533-543.

462 Smith, H.O. et al. (2003). *PNAS* **100**(26): 15440-15445.

463 Glass, J.I. et al. (2006). *PNAS* **103**(2): 425-430.

464 E.g. <http://www.biobricks.org/> and: The Economist (2006). Life 2.0. *The Economist* (London), 31 August.

465 Forster, A.C. and G.M. Church (2006). *Molecular Systems Biology* **2**: 45-.

466 Synthetic Biology – Applying Engineering to Biology. Report of a NEST High-Level Expert Group (2005). European Commission, DG Research, EUR 21796.

467 Synthetic Biology – Applying Engineering to Biology. Report of a NEST High-Level Expert Group (2005). European Commission, DG Research, EUR 21796.

468 Ro, D.K. et al. (2006): *Nature* **440**(7086): 940-943.

469 ETC (2007). Extreme genetic engineering: an introduction to synthetic biology. ETC Group, Ottawa, O.N. Bhutkar, A. (2005). *Journal of Biolaw & Business* **8**: 2. Brenner, S.A. and A.M. Sismour (2005). *Nature Review Genetics* **6**: 533-543.





Table 2.15 Contribution of modern biotechnology in industrial processes to EU gross value added and to employment<sup>472</sup>

Year: 2002	Share of EU GVA (%)	Share of EU employment (%)	Labour productivity
<b>EU gross value added (all economic activity)</b>	<b>100.00</b>	100.00	1.0
<b>Manufacturing total</b>	<b>17.41</b>	16.50	1.1
DG 24.66 Manufacture of other chemical products**	0.09	0.06	1.5
<b>Enzyme production*</b>	<b>0.0084</b>	<b>0.0030</b>	<b>2.8</b>
DG 24.51 Manufacture of soap, detergents, cleaning and polishing**	0.09	0,06	1.5
<b>Enzyme-containing detergents*</b>	<b>0.05</b>	<b>0.03</b>	<b>1.7</b>
DA 15 Manufacture of food products**	2.06	2.22	0.9
<b>Enzyme-using food production segments***</b>	<b>0.8</b>	<b>0.69</b>	<b>1.2</b>
DE 21.11 Manufacture of pulp*	0.02	0.01	2.1
<b>Manufacture of pulp-using enzymes*</b>	<b>0.0034</b>	<b>0.0015</b>	<b>2.3</b>
DB 17.3 Finishing of textiles	0.05	0.06	0.8
<b>Textile finishing with enzymes*</b>	<b>0.02</b>	<b>0.02</b>	<b>0.9</b>
DF 23.2 Refined petroleum products (calculated with 0.8 ratio to focus on fuel)	0.20	0.33	3.7
<b>Bioethanol****</b>	<b>0.0002</b>	<b>0.0003</b>	<b>0.7</b>
<b>Total sectors</b>	<b>2.51</b>	<b>2.46</b>	<b>1.0</b>
<b>Total of enzyme-based processes</b>	<b>0.88</b>	<b>0.75</b>	<b>1.2</b>

\* Estimate: Upper employment estimate used for calculation of labour productivity.

\*\* 2003 data.

\*\*\* In the NACE sector "bread, pastry cakes" only industrial production has been included.

\*\*\*\* 2005 data, only direct employment counted.

approach<sup>470</sup>, a coalition of 35 non-governmental organisations is calling for an inclusive public debate<sup>471</sup>.

### 2.3.5 Summary

Economic significance and contribution to employment

Modern biotechnology has found its way into many different industrial manufacturing processes. Measured in terms of contribution to the EU's GVA, about 45% of all manufacturing

sectors use modern biotechnology. The subsectors where modern biotechnology is actually applied (excluding pharmaceuticals) account for 14.4% of GVA in manufacturing industry and 2.51% of EU GVA (see Table 2.15). Uptake of modern biotechnology in these subsectors differs, as does their economic contribution. Food processing (0.8% of EU GVA), detergents (0.05%) and textile finishing (0.02%) are the three subsectors considered to make the highest economic contribution. This also reflects comparatively high (and early) uptake of modern biotechnology

470 Check, E. (2006). *Nature* **441**: 388-389. Voigt, C.A. and J.D. Keasling (2005). *Nature Chemical Biology* **6**: 304-307.

471 Genewatch press release, 19 May 2006. <http://www.genewatch.org/>.

472 Eurostat and IPTS calculation.



(between 40% and 100%). Although the EU is the market leader in enzyme production, this field contributes comparatively little to the EU's economic performance (0.008%). Bioethanol, because it is still at an early stage of development, takes a marginal share of the EU's GVA (0.0002%) in economic terms. Overall, modern biotechnology contributes 33% to the GVA of the subsectors concerned and about 0.88% to EU GVA. This is comparable to other sectors of manufacturing, such as rubber and plastic products (NACE DH 25: 0.86%) or textile and textile products (NACE DB 17/18: 0.77% of EU GVA).

The share of employees active in manufacturing processes based on modern biotechnology (without pharmaceutical production and chemical production) can be estimated at about 30% (1.5 million out of 4.9 million employees) (see Table 2.15). Food processing, detergents and textile finishing contribute most, with the highest uptake of modern biotechnology. Food processing, in particular, accounts for 90% of biotechnology-related jobs. Overall, modern biotechnology in industrial processes contributes about 0.75% to employment in the EU.

A look at the relation between employment and value added – labour productivity – reveals that, on average, biotechnological processes need one unit of labour input to generate 1.2 units of GVA. The corresponding value for total EU manufacturing is 1.1. This indicates that modern industrial biotechnological processes are technologically superior to conventional methods. Regarding the individual subsectors, enzyme production seems to be the most advanced sector with labour productivity of about 2.6. In the comparable fine chemicals sector labour productivity is substantially lower on about 1.5. Bioethanol, with labour productivity of about 0.7, is far below the EU average of 1.0. This shows

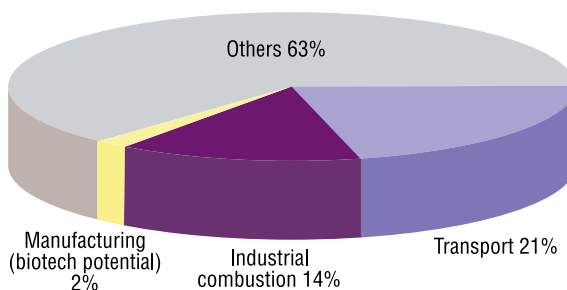
that this application is still at a rather early stage of development. By comparison, fuel production is a mature industry with a labour productivity value of 3.7, far above the EU average.

#### Environmental implications

In the context of modern biotechnology in manufacturing, energy and the environment, the most important environmental aspects to consider seem to be resource and energy use, greenhouse gas (GHG) emissions, other emissions and waste generation.

In the EU anthropogenic GHG emissions consist mainly of carbon dioxide (CO<sub>2</sub>: 83%), methane (CH<sub>4</sub>: 7.5%), nitrous oxide (N<sub>2</sub>O: 8%), and others (1.5%). Industrial manufacturing processes contribute 8% directly to GHG emissions (5% CO<sub>2</sub>, 1.1% N<sub>2</sub>O and only a negligible amount of CH<sub>4</sub>), plus an additional 14% via industrial combustion processes (see Figure 2-21). Transport contributes 21% to overall GHG emissions; more than 90% of that is due to combustion of road transport fuel, of which 37%, or 7.9% of all GHG emissions, is due to gasoline combustion. Energy generation is another major contributor to GHG emissions with 29%. Fuel combustion in sectors other than manufacturing industry contributes an additional 17%.<sup>473</sup>

Figure 2-21 Sectors with GHG (CO<sub>2</sub>, CH<sub>4</sub>, N<sub>2</sub>O) reduction potential by means of modern biotechnology



473 Based on: European Commission (2006). Progress report by the EU to the Intergovernmental Panel on Climate Change (IPCC). Submission 2006, v. 1.4. European Commission, Brussels.



Based on 2001 data for four EU Member States (Denmark, Germany, Italy and the UK),<sup>474</sup> GHG emissions from manufacturing industry were analysed. Out of the total of 5% of all GHG emissions generated by industrial processes emitting CO<sub>2</sub>, about 27% (1.3% of CO<sub>2</sub>) can be attributed to branches of industry applying biotechnological processes (the chemical industry, food and feed processing, pulp and paper production and the textile industry) and could potentially be further influenced by application of modern biotechnology. CH<sub>4</sub> emissions are negligible. N<sub>2</sub>O (1.1%) is produced almost exclusively by the chemical industry, in particular in production of nitric and adipic acid. For both substances no large-scale use is being made of biotechnological production, so the direct impact of modern biotechnology on N<sub>2</sub>O emissions can be assumed to be zero.

Modern biotechnology in industrial processes generally leads to a decrease in energy use, which in turn decreases CO<sub>2</sub> emissions. The degree of reduction depends on the specific application and on the characteristics of the specific process. In the examples given it ranges from about 10% (biobleaching in textile finishing) to 70% (detergents). The potential for further reductions due to increased use of modern biotechnology also varies from sector to sector. In food processing take-up of modern biotechnology is already comparatively high, whereas bio-based polymer production is still an emerging sector.

About one third of the GHG emissions from transport, or 7.9% of total GHG emissions, are caused by gasoline combustion. Blending transport fuels with bioethanol can help to improve the environmental impact of this sector. The environmental impact of bioethanol compared with fossil fuel depends on a variety of factors, such as import share (and origin of imports), type of biomass used and production pathway. First-generation biofuels, produced in the EU using the most economically attractive

production method, result in greenhouse gas emissions 35%-50% lower than the conventional fuels they replace. Applied to gasoline's 7.9% share in overall GHG emissions, this means that 100% replacement of gasoline with bioethanol would lower GHG emissions by around 4%. Accordingly, compliance with the European Commission's 5.75% target will lead to a reduction of around 0.23% in GHG emissions. This calculation takes into account the whole lifecycle. There are other production pathways, one of which is estimated to lead to higher GHG emissions than the fossil fuel it replaces.

Power generation, including energy generation (21%), industrial fuel combustion (13%) and fuel combustion in other non-energy and non-industrial sectors, e.g. the residential sector or agriculture (17%), is the largest GHG emitter. GHG emissions from industrial fuel combustion are more than 50% higher than GHG emissions from industrial processes (8%). Application of modern biotechnology in power generation produces a dual environmental impact: a direct impact, due to the switch from non-renewable resources such as oil to renewable resources such as biomass as input material, and an indirect impact as a result of lower energy demand from industrial processes. This unquantifiable indirect effect emerges because as a general rule application of enzymatic processes in industrial production reduces energy use in the process concerned.

Overall, modern biotechnology contributes to sustainable production and consumption by reducing the necessary inputs, e.g. chemicals and energy, and also emissions into the air (GHG) or water and consumption of water.

Modern industrial biotechnology seems to be applied primarily in individual stages of specific production processes. Take-up of modern biotechnology in industrial applications appears to proceed at a slow pace, despite the cost-effectiveness of biotechnological processes (including increased labour productivity) and

474 Data from Eurostat.



supporting regulatory measures (e.g. biofuels). One factor could be that industrial biotechnology is often targeted at sectors where mainly chemical approaches are used (e.g. textiles or pulp production). Hence, awareness of alternative biotechnological approaches is often lacking, as is the necessary expertise.<sup>475</sup> In addition, introduction of biotechnological processes requires investment in R&D, infrastructure and staff, which creates a bottleneck, in particular for small and medium-sized companies.<sup>476</sup> The increasing awareness of the need for energy- and resource-efficient processes and sustainable, low-carbon technologies might add to the interest in industrial biotechnology.

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475 Wolf O. and P. Sørup (eds.) (2000). The introduction of process-integrated biocatalysts in companies. European Commission, DG JRC/IPTS EUR 19582, p. 57.  
476 Wolf O. and P. Sørup (2000). The introduction of process-integrated biocatalysts in companies. European Commission, DG JRC/IPTS EUR 19582, p. 57.

# 3

Consequences, Opportunities  
and Challenges of Modern  
Biotechnology for Europe

## 3. Modern biotechnology R&D in the EU and worldwide



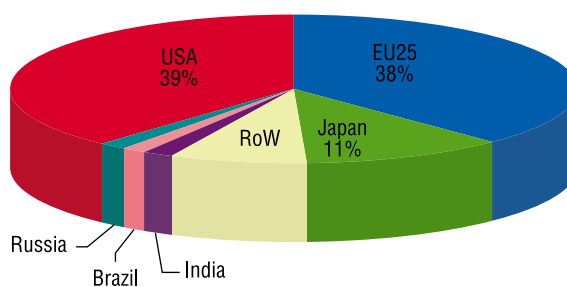
## ■ 3 Modern biotechnology R&D in the EU and worldwide

The competitiveness of the EU in developing modern biotechnology applications depends on the EU's capacity for conducting research, generating new knowledge and converting it into new products and processes. Stimulating research, but also promoting take-up of innovations and encouraging entrepreneurship in biotechnology to reap the economic returns that can be generated from the research results, have been identified as challenges for the EU.<sup>477</sup> This chapter will describe the current situation with modern biotechnology R&D in the EU and worldwide in terms of research publications, patent applications and dedicated biotechnology firms.

### 3.1 Bibliometric analysis

Worldwide, the absolute number of biotechnology publications increased by 24% between 1995-1997 and 2002-2004, with the EU accounting for about 38% of the publications in 2002-2004, a similar share to the USA (see Figure 3-1). Considering population size, however, the USA is more productive with 469 biotechnology publications per million inhabitants, followed by Japan with 316 publications per million and the EU with 297 per million. This relative success of the USA in terms of publication output is further underlined by the fact that in the USA there were only 17 holders of a PhD in life sciences per million inhabitants in 2003/2004, compared with 27 per million in the EU.<sup>478</sup>

■ Figure 3-1 Distribution of biotechnology publications in the period 2002-2004 by country/region



Source: ETEPS,<sup>479</sup> IPTS calculations.  
RoW: rest of the world.

Nevertheless, between 1995-1997 and 2002-2004 the share of biotechnology publications out of all scientific publications increased (from 12%-14% in the EU, from 15%-17% in the USA and from 11%-13% worldwide), indicating the growing importance of biotechnology research. The distribution by sectors of application highlights the significance of health-related biotechnology (see Figure 3-2). Worldwide, health biotechnology accounted for over 50% of all biotechnology publications over the period 1995 to 2004. Out of the countries analysed, only Brazil, India and Russia publish considerably less on health biotechnology (from 25%-35% of all biotechnology publications). Globally, agro-food biotechnology generates around 17% of all biotechnology publications, with Brazil and India showing higher research activity in this area (29% and 32% respectively). Publications focusing

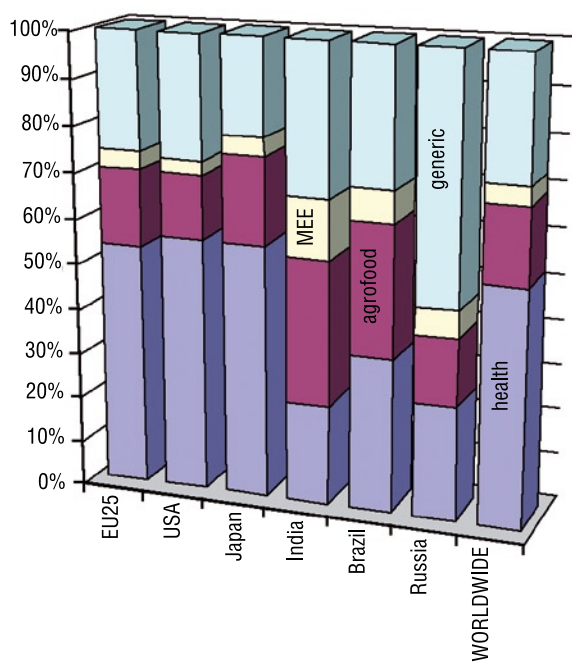
477 European Commission (2006). 2006 Report from the Competitiveness in Biotechnology Advisory Group (CBAG). DG Enterprise and Industry, European Commission, Brussels. [http://ec.europa.eu/enterprise/phabiocom/comp\\_biotech\\_commit.htm](http://ec.europa.eu/enterprise/phabiocom/comp_biotech_commit.htm).

478 ETEPS (2006) Bio4EU: Task 2 Main report.

479 ETEPS (2006) Bio4EU: Task 2 Main report.

on manufacturing, energy and the environment are a minor field of research with only 4% of all biotechnology publications worldwide in 2002-2004, up from 2% in 1995-1997. Only India shows comparatively higher activity in this field, with 13%. Russia focuses strongly on publications covering generic biotechnology topics, which are addressed by more than 50% of its biotechnology publications.<sup>480</sup>

■ Figure 3-2 Distribution of biotechnology publications in the period 2002-2004 by sector



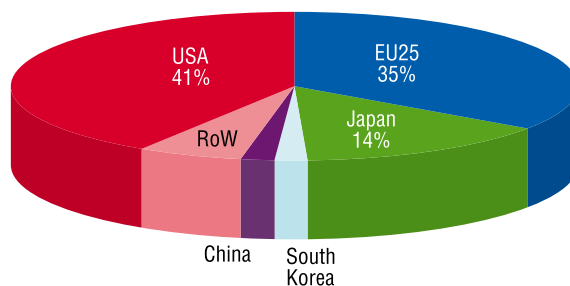
Source: ETEPS.<sup>481</sup>  
MEE: manufacturing, energy and environment.

### 3.2 Analysis of patent applications

Looking at biotechnology patent applications to the European Patent Office (EPO),<sup>482</sup> between 1995 and 2004 the absolute number of

biotechnology patent applications per three-year period fluctuated between 18 657 and 33 189. Over the period 2002-2004 the EU accounted for 35% of all biotechnology patent applications, whereas 41% could be attributed to the USA (see Figure 3-3). Hence, while the EU generates as many biotechnology publications as the USA in absolute terms, it seems to be less successful at converting this scientific knowledge into practical and economically promising inventions. Although the US share of biotechnology patent applications decreased between 1995 and 2004, other countries, such as Japan, China, Singapore and South Korea, increased their patenting activities, and the EU's share remained stable.<sup>483</sup>

■ Figure 3-3 Share of biotechnology patent applications in the period 2002-2004 per country/region



RoW: rest of the world.  
Source: ETEPS.<sup>484</sup>, IPTS calculations.

When it comes to the relative importance of the different fields of use, the distribution of biotechnology patent applications mirrors the results of the bibliometric analysis: health is the most important sector, accounting for 50% of all biotechnology patent applications from the

480 ETEPS (2006) Bio4EU: Task 2 Main report

481 ETEPS (2006) Bio4EU: Task 2 Main report

482 Patent applications to the EPO were taken as the basis for the patent analysis because recent data are available and because patent applications to the EPO are considered comparatively costly, i.e. it can be assumed that applications are filed only for commercially attractive and economically sustainable inventions. However, by leaving out, for example, patent applications to the United States Patent and Trademark Office (USPTO), this analysis could be biased in favour of the EU. A separate analysis by Fraunhofer ISI revealed that about 80% to 90% of the patent applications are granted, i.e. applications can be taken as a proxy for patents granted.

483 ETEPS (2006) Bio4EU: Task 2 Main report.

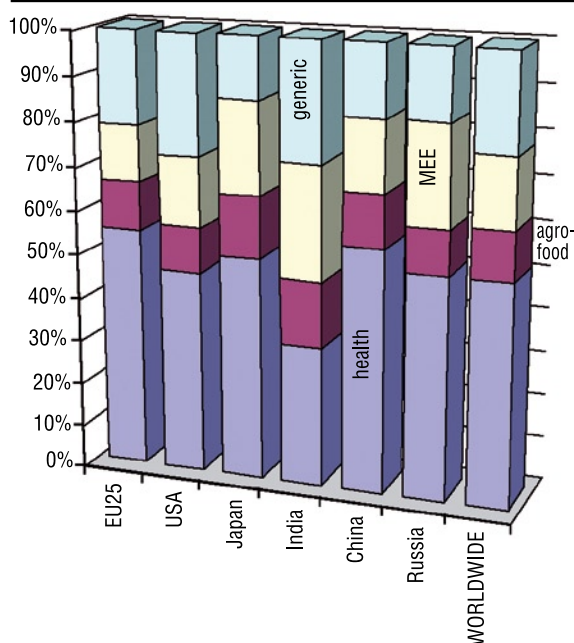
484 ETEPS (2006) Bio4EU: Task 2 Main report



different countries, the only exception being India (see Figure 3-4). The second largest class are generic biotechnology patents, whose share has been increasing since 1995 to reach 22% of all biotechnology patent applications to the EPO in 2002-2004. Agro-food biotechnology patents account for about 10% of all patent applications with little variation across countries. Biotechnology in manufacturing, energy and the environment, in contrast to its share of biotechnology publications, generates about 13% of all biotechnology patent applications in the EU.<sup>485</sup> This suggests that scientific progress in manufacturing (measured by publications) is more readily converted into relevant practical inventions.

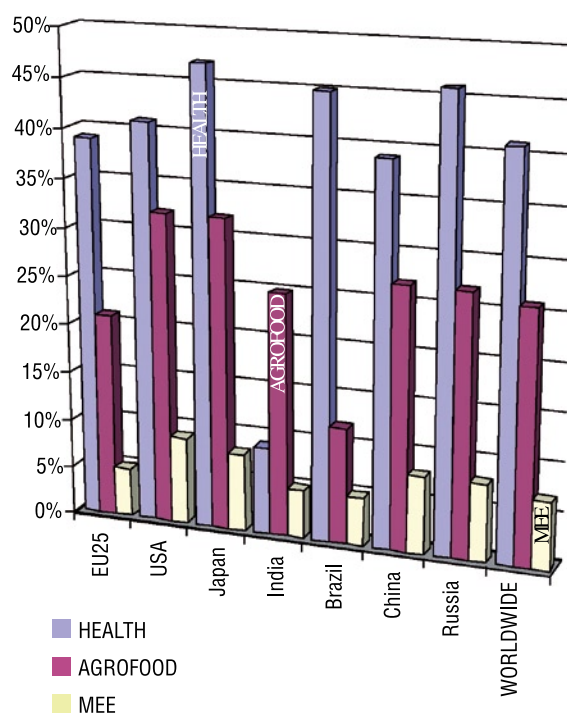
Looking at the role of modern biotechnology in R&D and inventiveness in each sector, the share of biotechnology patent applications out of all patent applications confirms, in particular, the significance of biotechnology for the health sector, where about 40% of all patent applications to the EPO relate to biotechnology (see Figure 3-5). But in the agro-food sector too biotechnology plays an important role in applied R&D, where it generates about 20%-30% of all patent applications. By contrast, for manufacturing, energy and the environment, biotechnology seems to play a comparatively small role, with under 10% of all patent applications relating to biotechnology.<sup>486</sup> However, in this sector modern biotechnology is even less relevant in the EU than it is in the USA or in other countries – despite the EU doing quite well according to the bibliometric analysis.

■ Figure 3-4 Distribution of biotechnology patent applications in the period 2002-2004 by sector



Source: ETEPS.<sup>487</sup>

■ Figure 3-5 Share of biotechnology patent applications out of patent applications from all sectors in the period 2002-2004 by country/region



Source: ETEPS.<sup>488</sup>

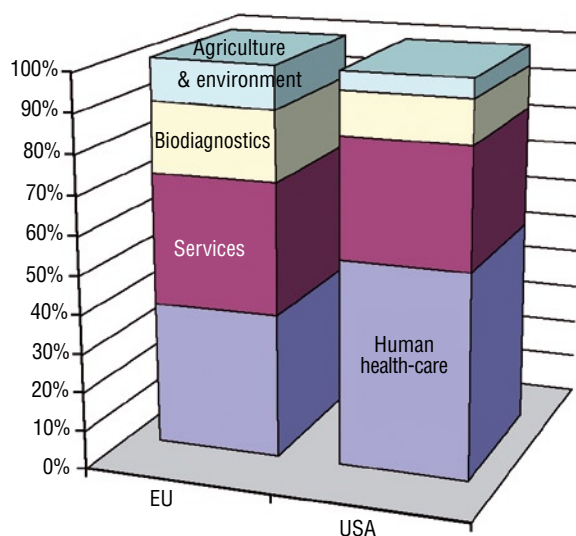
MEE: manufacturing, energy and environment.

485 ETEPS (2006) Bio4EU: Task 2 Main report.  
 486 ETEPS (2006) Bio4EU: Task 2 Main report.  
 487 ETEPS (2006) Bio4EU: Task 2 Main report.  
 488 ETEPS (2006) Bio4EU: Task 2 Main report.

### 3.3 Biotechnology in the private sector

The predominance of the health sector in modern biotechnology is also visible from the distribution of dedicated biotechnology firms (DBF) by sector. According to Critical I (2006), 37% of biotechnology companies in 18 European countries (including Norway and Switzerland) were active in the human health care sector (see Figure 3-6); another 18% were classified as active in biodiagnostics, which also includes health care diagnostics. Companies active in agricultural and environmental biotechnology make up 11% of all DBFs, and 34% of the biotechnology companies provide services such as bioprocessing and screening. The distribution in the USA is even more focused on health care (53% of all DBFs there are active in this sector), with only 5% of companies active in agriculture and the environment.

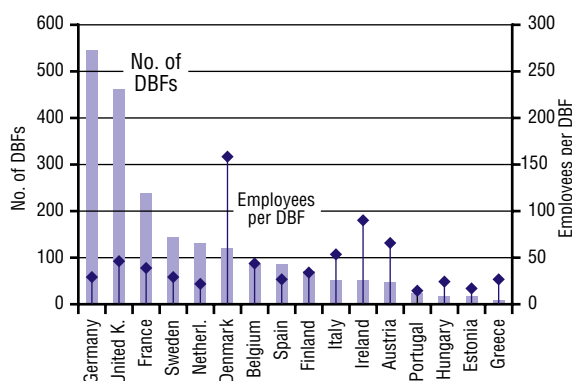
Figure 3-6 Distribution of biotechnology companies in 2004 by sector



Source: Critical I<sup>489</sup>.

In contrast to biotechnology patent applications, where the USA was in the lead, 2032 DBFs were identified in the EU in 2004 (based on 16 EU Member States), similar to the USA with 1991 DBFs.<sup>490</sup> Within the EU, most of the companies are located in Germany, the UK, France, the Netherlands and the Scandinavian countries (see Figure 3-7). However, DBFs are defined as companies whose *primary* activity depends on biotechnology. Hence, for example, large pharmaceutical companies for which biotechnology is a *comparatively* minor part of their business are not included in this definition, even though their biotechnology business may be bigger than that of many DBFs. Allowing for population size, the USA has a higher number of DBFs per million inhabitants (seven) than the EU with five DBFs per million (see Figure 3-8).<sup>491</sup>

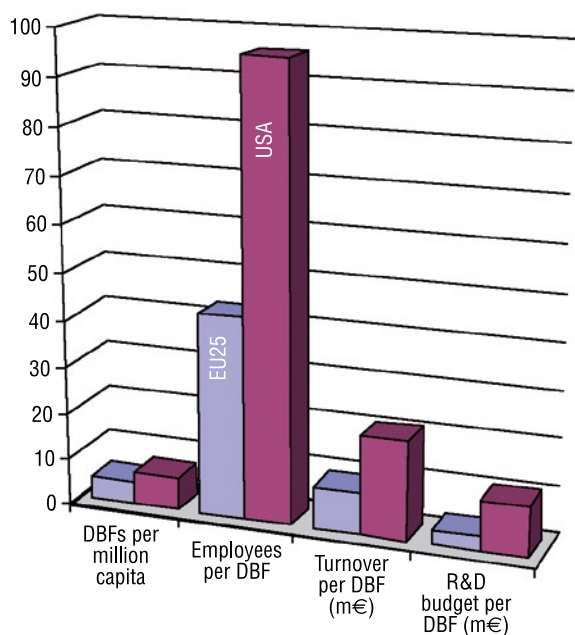
Figure 3-7 Number of dedicated biotechnology firms (DBFs) and average number of employees by country



Source: Critical I<sup>492</sup>.

489 Critical I (2006): Biotechnology in Europe: 2006 comparative study. Critical I, Banbury  
 490 Critical I (2006): Biotechnology in Europe: 2006 comparative study. Critical I, Banbury.  
 491 ETEPS (2006) Bio4EU: Task 2 Main report.  
 492 Critical I (2006): Biotechnology in Europe: 2006 comparative study. Critical I, Banbury

■ Figure 3-8 Dedicated biotechnology firms in the EU and the USA in 2004



Data Source: Critical I<sup>493</sup>, ETEPS<sup>494</sup>.

Therefore, the number of DBFs in a given region is in itself only a weak indicator of the capacity of the region to create new companies and derive economic returns from the scientific knowledge it generates. Moreover, looking in more detail at these companies reveals that European DBFs employ, on average, about 43 staff, while DBFs in the USA have about 2.2 times more employees (see Figure 3-8). Big companies, such as Novo Nordisk in Denmark, may inflate the national averages considerably (see Figure 3-7). And while the share of R&D staff in both regions is similar, accounting for about 42% of all staff, turnover and R&D expenditure indicate that the US biotechnology sector is both economically more successful and investing more in development of new products: on average, the turnover of US DBFs is about twice as high as the average turnover of their EU counterparts and US companies spend a larger share of their

revenue on R&D than DBFs in the EU (50% vs. 35%). Given the higher revenue of DBFs in the USA, this results in absolute R&D spending three times higher. This stronger position of US DBFs may also explain why they are able to raise about five times more equity capital per company than European DBFs (EUR 4 830 000 vs. EUR 874 000). Consequently, in the case of private-sector biotechnology, the capacity to apply this technology to practical and commercial ends seems to be higher in the USA than in the EU.

Analysis of the global modern biotechnology R&D landscape, with particular focus on the EU, and of the performance of the EU and the USA in converting new scientific knowledge into economically viable products and businesses has shown that even though the EU is doing well in terms of researchers and public biotechnology research centres, its output in terms of scientific publications is relatively lower than the output in the USA. And while this output is still on a par with the US output in absolute terms, the EU's capacity to apply this knowledge to generate novel products, to encourage entrepreneurship and to create new and competitive companies is lower than the USA's. Consequently, the EU still faces the challenge identified by the Competitiveness in Biotechnology Advisory Group (CBAG),<sup>495</sup> namely promoting biotechnology entrepreneurship based on the knowledge created by scientific research.

493 Critical I (2006): Biotechnology in Europe: 2006 comparative study. Critical I, Banbury

494 ETEPS (2006) Bio4EU: Task 2 Main report

495 European Commission (2006). 2006 Report from the Competitiveness in Biotechnology Advisory Group (CBAG). DG Enterprise and Industry, European Commission, Brussels, cf above.



# 4

Consequences, Opportunities  
and Challenges of Modern  
Biotechnology for Europe

## 4. Contribution of modern biotechnology to European policy objectives



## ■ 4 Contribution of modern biotechnology to European policy objectives

In this chapter the economic, social and environmental implications of modern biotechnology will be summarised and discussed in the context of two horizontal European strategies, namely the Lisbon Strategy and the Sustainable Development Strategy. In the following, these EU strategies will be briefly described and the contributions of modern biotechnology to the achievement of the respective objectives will be presented.

### The policy context

#### *The Lisbon Strategy*

In March 2000, the Lisbon European Council committed the EU to becoming the world's most competitive and dynamic knowledge-based economy within ten years, capable of sustainable economic growth, with more and better jobs and greater social cohesion<sup>496</sup>. This initiative, called the Lisbon Strategy, was launched against the background of high unemployment and economic challenges, not only from the USA but also from Asian countries. Biotechnology was considered to be one of the new technologies with the potential to support the Lisbon Strategy<sup>497</sup>. Consequently, the Commission was requested to examine measures to harness the full potential of biotechnology and to strengthen the biotechnology sector's competitiveness. The Strategy for Life Sciences and Biotechnology was developed in 2002<sup>498</sup>, together with an Action Plan.

An assessment of the achievements of the Lisbon Strategy in 2004 revealed that progress in meeting the goals was too slow<sup>499</sup>. As a result, the strategy was revised in 2005, with the focus on "stronger, lasting growth and more and better jobs" while striving for high social and environmental standards<sup>500</sup>. A mid-term review of the Strategy on Life Sciences and Biotechnology was also considered in this context, to which this Bio4EU study provides a major input<sup>501</sup>.

#### *The Sustainable Development Strategy*

In 2001, the Lisbon Strategy was complemented by the Sustainable Development Strategy (SDS), strengthening the environmental dimension<sup>502</sup>. Sustainable development means meeting the needs of the present generation without compromising the ability of future generations to meet their own needs<sup>503</sup>. The SDS is broader in scope and takes a longer-term perspective than the Lisbon Strategy. It was reviewed in 2005 and the key issues refocused. These are climate change and clean energy, public health (handling health threats, health promotion and disease prevention), management of natural resources (biodiversity and resource efficiency), sustainable transport, and global poverty and development challenges.

The SDS, like the Lisbon Strategy, is also implemented through other, more sector-

496 Presidency conclusions, Lisbon European Council, 23 and 24 March 2000.

497 Presidency conclusions, Stockholm European Council, 23 and 24 March 2001.

498 European Commission COM(2002)27: Communication of the Commission to the European Parliament, the Council, the Economic and Social Committee and the Committee of the Regions - Life sciences and biotechnology – a Strategy for Europe.

499 European Commission (2004). Facing the challenge: the Lisbon strategy for growth and employment. Report from the High Level Group chaired by Wim Kok. European Commission, Brussels.

500 European Commission (2005). Growth and jobs: working together for Europe's future. Communication to the Spring European Council. European Commission, Brussels.

501 European Commission COM(2005)286 final: Sciences and biotechnology – a strategy for Europe. Third progress report and future orientations.

502 Presidency Conclusions, Gothenburg European Council, 15 and 16 June 2001.

503 World Commission on Environment and Development (1987). Our common future. Oxford University Press, Oxford.

specific policy initiatives, such as the 6th environment action programme<sup>504</sup> and the Environmental Technology Action Plan<sup>505</sup>, while the EU's Common Agricultural and Common Fisheries Policies include Lisbon and SDS policy objectives.

Due to recent increases in oil prices and high import dependency, energy supply security receives more attention, over and above the environmental and climate change aspects of using fossil energy sources. Alternative energy sources such as biofuels are gaining in importance, as reflected in several policy initiatives<sup>506</sup>.

EU policy objectives regarding public health are also described in the programme of Community action in the field of public health<sup>507</sup><sup>508</sup>. In addition to addressing SDS objectives, this programme goes hand in hand with the Lisbon strategy, as good health is crucial to economic growth. Moreover, the general principles and requirements of food law must also be considered in the context of "health and food safety"<sup>509</sup>, as should the protection of animal health and welfare, and the European Environment and Health Strategy.<sup>510</sup>

The prerequisite for any contribution of modern biotechnology to the achievement of EU policy objectives is the availability and uptake of modern biotechnology applications. The Bio4EU study confirms the considerable uptake of modern biotechnology within the EU economy in three main areas: medicine and

health care, primary production and agro-food, and industrial production processes, energy and the environment. Modern biotechnology products and processes are used, for example, in the cultivation of crops and animal husbandry, in food processing, in the manufacturing of textiles, paper and chemicals, in fuel production, in the production of pharmaceuticals and in health care. In the following, the implications of modern biotechnology are described in terms of major EU policy objectives.

### Contributions of modern biotechnology to the Lisbon Agenda

In the context of the Lisbon Strategy, the analysis focused on:

- economic significance of modern biotechnology products and processes,
- employment related to modern biotechnology and quality of jobs, and
- labour productivity and international competitiveness.

### Economic significance of modern biotechnology applications

The analysis confirmed that modern biotechnology applications are important contributors to the EU economy. Taking the production and use of modern biotechnology applications in medicine and health care, primary production and agro-food, industrial production

504 European Commission COM(2001)31 final. Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions on the sixth environment action programme of the European Community 'Environment 2010: Our future, Our choice' - The Sixth Environment Action Programme.

505 European Commission (COM(2004)38): Communication from the Commission to the Council and the European Parliament - Stimulating Technologies for Sustainable Development: An Environmental Technologies Action Plan for the European Union.

506 European Commission (2005). Doing more with less: green paper on energy efficiency. European Commission, Brussels. Directive 2003/30/EC of the European Parliament and of the Council on the promotion of the use of biofuels or other renewable fuels for transport, OJ L 123/42, 17.5.2003.

507 Decision No 1786/2002/EC of the European Parliament and of the Council adopting a Community programme in the field of public health (2003-2008), OJ L 271/1, 9.10.2002.

508 Amended proposal for a decision of the European Parliament and of the Council establishing a Programme of Community action in the field of Health 2007-2013 - COM(2006)234 final.

509 Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures of food safety, OJ L 31/1, 1.2.2002.

510 European Commission COM(2003)338 final: Communication from the Commission to the Council and the European Parliament and the European Social and Economic Committee - A European Environment and Health Strategy.



processes, energy and the environment, modern biotechnology contributes to about 1.43%-1.69% of the EU's gross value added (based on 2002 GVA data). Further induced economic effects, such as improved health status and applications not included (modern biotechnology in R&D of small molecule drugs or in chemical production), would add to this estimate. This is in the range of entire economic sectors such as agriculture (1.79%) or chemicals (1.95%).

Yet, within the EU, the adoption rates of biotechnology-based products and processes in the various sectors and fields of application vary considerably. In the area of medicine and health care, where biotechnology is widely applied, biotechnology applications contribute about 30% to the overall turnover of *in vitro* diagnostics in the EU, whereas biopharmaceuticals have a share of 9% in the total turnover of pharmaceuticals. In the field of industrial manufacturing, modern biotechnology adoption is even more divergent: turnover shares of individual applications range from less than 1% in the case of biotechnology-based polymers, 10% in pulp and paper, 30% in detergents and to up to 100% in the production of specific fine chemicals. Finally, in the agro-food sector modern biotechnology is estimated to directly contribute 13%-23% to the overall turnover of the input sectors, such as breeding or feed additive production, while the use of these biotechnology-based inputs affects about 32%-38% of the agro-food sector's total turnover.

However, given the different degrees of adoption of individual applications, there is further growth potential insofar as modern biotechnology enables the provision of new or improved products or enhances efficiency. For instance, dynamic developments of this kind can be seen in health biotechnology, where the EU market for biopharmaceuticals has grown twice as fast as the overall EU pharmaceuticals market. Patent data also highlight the significance of modern biotechnology for medical and agro-food-related developments: in the time period 2002-2004, 39% and 21%, respectively, of all sector patent applications were biotechnology-related.

### ***Effects of modern biotechnology on employment***

The contribution of modern biotechnology to employment is mainly seen in the creation of "better jobs" (i.e. more higher qualified jobs), due to the higher level of training often necessary to develop and deal with biotechnology products and processes. Measuring the quantitative impact (i.e. "more jobs") is hampered by limited data availability and the difficulties of integrating indirect employment effects. Nevertheless, the order of magnitude of direct employment effects is probably in line with the overall uptake of biotechnology applications, although some of the newly generated jobs can be assumed to substitute existing ones.

### ***Effects of modern biotechnology on competitiveness***

Modern biotechnology may improve competitiveness through efficiency gains that lead to higher labour productivity. For instance, labour productivity in industrial manufacturing processes where modern biotechnology is applied is estimated to be 10% to 20% higher than conventional processes. However, other countries, especially the USA, were often quicker or more pro-active in adopting modern biotechnology applications and they did so more comprehensively, i.e. they were able to increase their competitiveness vis-à-vis the EU. While the USA had embarked late on the production of bioethanol, for example, they provided policy support that helped its enterprises to gain a large share of world production within a few years' time. Similarly, developments in China and India indicate that, at least in terms of market size, these countries may soon outpace the EU, too. In the field of health biotechnology, only 15% of the biopharmaceuticals on the market were developed by EU companies, compared to over 50% developed by US companies. That said, in the agro-food sector – if GM seeds and GM crops are disregarded – the EU has significant shares in the markets for which biotechnology-based products are relevant.

The predominance of the USA in modern biotechnology is also visible in terms of R&D activities, namely scientific publications and patent applications. Although the EU has a similar number of scientific publications in absolute terms, the output of the USA is about 60% higher per million capita. In addition, as regards patent applications, the EU is doing less well in translating the scientific knowledge that it has gained into patents.

### Contributions of modern biotechnology to environmental sustainability

In the context of the environmental aspects of the Sustainable Development Strategy, the analysis considered:

- resource productivity,
- emission reduction, including greenhouse gas emissions and waste prevention, and
- energy supply security.

In the agro-food sector, biotechnology applications are mostly aimed at improving production efficiency. Thus, modern biotechnology contributes to reducing the use of resources and the emission of harmful substances per unit output. More direct impacts include, for example, the reduction of drug and antibiotic treatments in animal production due to the use of (recombinant) vaccines. However, some modern biotechnology applications may also raise new challenges, requiring a case-by-case evaluation of specific aspects or potential risks (e.g. in relation to GMOs or feed additives). To this end, the EU has put in place specific legislation making it obligatory to carry out comprehensive risk assessments before placing such products on the market.

In the case of industrial production processes, modern biotechnology applications reduce the use of crucial inputs like energy, water or chemicals in production processes. Consequently, modern biotechnology applications reduce greenhouse gas emissions, waste generation and the use of non-renewable resources. For instance,

given that energy production for industrial use generates over 50% more greenhouse gases than the industrial production processes themselves, reduced energy demand could lead to a substantial decrease in related emissions.

Another, indirect impact of modern biotechnology could emerge from the use of biofuels in the transport sector, which is responsible for 21% of total greenhouse gas emissions. Because more than a third of this share (7.9%) is due to the combustion of gasoline, the blending of gasoline with bioethanol, which results in comparatively lower greenhouse gas emissions, could help to reduce the environmental impact of this sector. In addition, the use of renewable biomass for energy generation could also help to diversify the energy portfolio and improve energy supply security. However, emerging issues such as potentially increasing land use intensity and the large-scale use of food and feed products for non-food purposes, such as maize and wheat in the case of bioethanol, need to be considered.

While the overall contribution of modern biotechnology to the different environmental objectives is impossible to quantify in absolute terms, the fact that modern biotechnology applications lead, in general, to improvements in the eco-efficiency of production processes, while being themselves a new source of economic activity, underscore its role in decoupling economic growth from environmental pressures.

### Contributions of modern biotechnology to public health and food safety

In the context of public health, including food safety, the analysis focused on:

- improved warning, monitoring and control of communicable diseases,
- reduction of disease burden, and
- reduction of health care and social costs.

The analysis was based on case studies of modern biotechnology-based medicinal products and diagnostics. The case studies indicate that

modern biotechnology may provide various benefits, such as better clinical interventions and treatment options, potentially safer products, and a higher quality of life of the individuals concerned. Health biotechnology thus contributes to progress in the monitoring and control of communicable diseases, to increases in the effectiveness of medical intervention, to reductions in the burden of disease and to improvements in the quality of life of those suffering from disease. Seen in this light, modern biotechnology will help to keep an ageing population healthier, thus facilitating active ageing, in the context of other measures, not least disease prevention.

Its contribution to reducing health care and social costs is less clear: in some cases, modern biotechnology applications increase efficiency in the health care sector, thus contributing to the objective of reducing health care costs, while in other cases a new drug puts an overproportional strain on health care resources. While the latter case is not specific to biotechnology-based therapies, and also applies to conventional approaches, it emphasises the ethical question of how to allocate scarce resources in health care. A more general assessment of the cost-effectiveness of health biotechnology applications is still pending, given that in many cases the results of pertinent studies are only preliminary and further studies are needed. Moreover, as the technology matures and generic biopharmaceuticals (biosimilars) reach the market, product prices may come down, thus improving cost-effectiveness.

The public health effects of modern biotechnology applications in the agro-food sector build on the availability of new and better diagnostics and vaccines. In particular, the monitoring and control of some of the most important zoonoses and food safety concerns (e.g. Salmonella and BSE) help to safeguard food EU-wide and to ensure consumer confidence in the food chain. However, as some biotechnology applications may raise new issues relating to animal welfare, a case-by-case assessment may be needed. Nevertheless, modern biotechnology also provides solutions that improve animal

health and welfare in a variety of ways, such as through replacing the use of animals as tools in chemical safety testing or through the provision of novel animal health management tools that decrease animal suffering.



## ■ Annex 1: Modern biotechnologies

The basic technologies used in modern biotechnology (see Table A.1) are described below.

■ *Table A.1 Technologies used in modern biotechnology*

Nucleic-acid (DNA/RNA)-related technologies	<ul style="list-style-type: none"> <li>• High-throughput sequencing of genome, gene, DNA</li> <li>• DNA synthesis and amplification</li> <li>• Genetic engineering</li> <li>• Anti-sense technology</li> <li>• siRNA technology</li> </ul>	Analysis and modification of genetic material
Protein-related technologies	<ul style="list-style-type: none"> <li>• High-throughput protein/peptide identification, quantification and sequencing</li> <li>• Protein/peptide synthesis</li> <li>• Protein engineering and biocatalysis</li> </ul>	Analysis and modification of proteins
Metabolite-related technologies	<ul style="list-style-type: none"> <li>• High-throughput metabolite identification and quantification</li> <li>• Metabolic pathway engineering</li> </ul>	Analysis of metabolites (small molecules)
Cellular-/ subcellular-related technologies	<ul style="list-style-type: none"> <li>• Cell hybridisation/fusion</li> <li>• Tissue engineering</li> <li>• Embryo technology</li> <li>• Stem-cell-related technologies</li> <li>• Gene delivery</li> <li>• Fermentation and downstream processing</li> </ul>	Cell manipulation for various applications
Supporting tools	<ul style="list-style-type: none"> <li>• Bioinformatics</li> </ul>	Application of computational tools in analysis and storage of biological data

### Nucleic-acid-related technologies

Nucleic acids consist of polymerised nucleotides. Two forms of nucleic acids are known: DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). For all higher organisms, including humans, DNA constitutes the genome, which includes all the necessary information for proteins and the functioning of the body. Nucleic acids exist in linear or circular forms, single- or double-stranded (the “double helix”).

**High-throughput sequencing** of nucleic acids (DNA, RNA) is used to determine the sequence of the different individual building blocks of nucleic acids (nucleotides) in the most efficient way, i.e. automatically, quickly and at low cost. Micro-arrays are the basic component in this approach. The time taken to sequence a genome/ gene/certain amount of DNA has decreased since

1995 when traditional sequencing methods were replaced by high-throughput technologies.

Nucleic acid sequencing is used to identify genome structures, compare gene sequences and predict protein structures.

**DNA synthesis and amplification.** Polymerase chain reaction (PCR) is an essential technology for copying and amplifying DNA. It makes use of specific enzymes, namely DNA polymerases that are capable of synthesising new DNA using a DNA template and copying it. If this process is repeated several times, small amounts of DNA can be amplified. PCR was developed in the 1980s and was awarded the Nobel Prize in 1993.

**Genetic fingerprinting or genotyping** is used for identification or distinction between individuals of one species based on their DNA. The technique is often used in forensic analyses,

but also in plant and animal breeding. If PCR is used for amplification, only small amounts of DNA are needed. Restriction enzymes are applied to cut the DNA at specific sequences. The resulting pattern of DNA fragments is specific to an individual.

**Genetic engineering** is used to modify the genome of an organism by adding or deleting a gene or modifying the nucleotide sequences of existing genes. The modified organism thus gains or loses certain abilities, such as producing a specific enzyme. In microorganisms, mainly for use in industrial production processes but also for bioremediation, metabolic pathways are modified or new ones are introduced by genetic engineering, called “metabolic pathway engineering”. Genetic engineering is also called transgenesis, recombinant DNA technology or genetic modification.

**Anti-sense technology** means use of anti-sense RNA to block translation of mRNA into the respective amino acid chain and thus prevent gene expression. It is applied mainly in research to study gene function, but recently this principle has also been applied for therapeutic approaches.

**siRNA technology:** RNA interference (RNAi) is a mechanism invented by nature to protect the genome. In the past few years this field has emerged at a surprisingly rapid pace. The underlying molecular mechanism of gene silencing provides short interfering RNAs (siRNAs), which can target any gene with high specificity and efficiency. Successful knock-downs of disease-related genes indicate that siRNAs open the door for novel therapeutic procedures.

## Protein-related technologies

Proteins consist of varying numbers of polypeptides, which consist of amino acid chains. Genetic information encodes amino acid sequences of proteins.

**High-throughput identification, quantification and sequencing.** High-throughput technologies for proteins are not yet as far advanced as those for nucleic acids due to the complex structure of proteins. Classic technologies, such as gel electrophoresis, mass spectroscopy and nuclear magnetic resonance, are being developed further to produce high-throughput versions.

**Protein/peptide synthesis** is the chemical creation of proteins and peptides. Natural proteins and peptides can be produced this way (particularly if they are difficult to produce using other tools), but modified proteins (using, for example, non-natural amino acids) can also be synthesised. Nowadays, solid-phase synthesis is used. The growing amino acid chain is linked to a bead in a reactant solution. Amino acids are added one by one to the polypeptide backbone. The process can be automated.

**Biocatalysis.** Catalysts are substances which have the ability to increase the speed of a chemical reaction. Enzymes (which are proteins) are natural catalysts and are used in transformations of organic compounds, e.g. natural fibres or food. Enzymes can be used in isolated form or within a cell line or an organism, usually bacteria, yeasts or fungi. The process to optimise enzymes for the desired function is also called protein engineering. The “rational design” approach requires detailed knowledge of the structure and function of the enzyme and its amino acid sequence to introduce targeted changes at DNA level. The “directed evolution” approach uses randomly introduced mutations and a selection system to develop enzymes/organisms with the desired qualities.

## Metabolite-related technologies

Metabolites are compounds of low molecular weight that are intermediate or end-products of metabolism. The metabolome includes the whole set of metabolites of a given organism, tissue or cell under certain conditions.

### **High-throughput technologies for identification, quantification and analysis.**

The metabolome can be analysed by a range of techniques, including high-performance mass spectrometry, high-performance liquid chromatography, liquid chromatography/mass spectrometry, nuclear magnetic resonance spectroscopy and others. High-throughput techniques are attracting increasing attention as an emerging tool for identification of metabolic pathways and of biomarkers associated with diseases.

### **Cellular- and subcellular-related technologies**

Modern biotechnologies are applied in manipulation of cells and microorganisms for various purposes. Cell-based technologies include, for example, tissue engineering, i.e. application of cells to regenerate biological tissue. In addition, cells can be manipulated to generate a specific protein which can be easily extracted. Stem cells are unspecialised cells which have the capacity to differentiate into various cell types under given conditions, providing a promising tool for development of new therapies. So far they have been applied in bone marrow transplantation.

### **Bioinformatics**

Bioinformatics means application (and development) of computational tools and approaches for retrieval, analysis and storage of biological information.<sup>511</sup> Bioinformatics may be applied, for example, in analysis of genomes, protein structures or entire biological systems (e.g. neural networks).

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511 The NIH working definition of bioinformatics and computational biology is available at: <http://www.bisti.nih.gov/CompuBioDef.pdf>.





## Annex 2: Methodology

### Scope

#### **Modern biotechnologies**

Biotechnology can be defined as “the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services”.<sup>512</sup> This definition includes both traditional processes that have been used for a very long time, e.g. in the food and drinks industry, and also modern biotechnological processes. This study focuses on major modern biotechnologies. These encompass DNA-, protein-, metabolite- and cell-based technologies, together with supporting tools, used for modification of living or non-living materials for production of goods and services. This definition does not include traditional biotechnologies, such as fermentation and conventional animal and plant breeding. However, modern biotechnologies used in combination with traditional biotechnologies, e.g. fermentation processes using recombinant organisms, are considered modern biotechnology. Major modern biotechnologies were identified in a preparatory stage of the study (see Annex 1).<sup>513</sup>

#### **Biotechnology applications included**

Modern biotechnology applications were subdivided into three main fields of application:

- Medicine and health care;
- Primary production and agro-food;
- Industrial production processes, energy and the environment.

#### **Geographical area**

The analysis focuses on EU-25 and its competitors, in particular the USA and Japan; for specific applications, additional countries have been included. Companies were allocated to a country or region on the basis of the location of their headquarters.

#### **Assessment**

##### **General approach**

The impact of biotechnology was subdivided into direct or indirect: in the context of this study, direct impact means effects on the users of biotechnology, while indirect impact means the effects resulting from use of products derived from biotechnology (downstream sectors). Therefore, the direct impact (at sector and EU level) covers the various effects arising from the activities of producers of modern biotechnology products, such as pharmaceutical companies, breeders, enzyme manufacturers, etc. The indirect impact relates mainly to the effects arising from use of these products and may affect several links along the production chain.

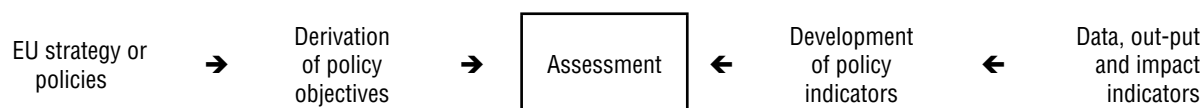
The aim of the analysis was to provide results at the most aggregated level possible in terms of both indicators and sectors. In addition, a representative set of 29 case studies was used to analyse in depth the current economic, social or environmental impact. The case studies were selected to cover all relevant applications of modern biotechnology, particularly those considered to have the greatest impact, whether economic, environmental or social.<sup>514</sup>

512 OECD (2006). Biotechnology Statistics. OECD, Paris.

513 ETEPS (2006) Task 1 – Mapping of modern biotechnology applications and industrial sectors, identification of data needs and development of indicators. Final report. <http://bio4eu.jrc.es/documents/Bio4EU-Task1.pdf>.

514 The case studies cover: therapeutics, preventives and diagnostics in medicine and health care; diagnostics and preventives in animal health; diagnostics, breeding and propagation techniques in primary production and the agro-food chain; and processing of biomass, use of enzymes, production of exemplary fine chemicals and bioremediation systems in industrial processes, energy and the environment.

Figure A-2. Approach for selection of indicators based on policy objectives and the final assessment



The preliminary phase of the study assessed the availability of data for potential indicators.<sup>515</sup> In the second stage, indicators were selected based on their relevance to major EU policy objectives. While there is no standard methodology for linking the indicators to EU policy objectives, a structured approach was developed that first identified the major policy objectives and then related the indicators to these objectives, where possible on a quantitative basis. The approach is illustrated in Figure A-2.<sup>516</sup>

A cost-benefit analysis in the strict sense of the term<sup>517</sup> was not carried out, for a number of several reasons. Firstly, for many modern biotechnology applications there is a significant lack of data regarding adoption and the economic, social and environmental impacts. It was not possible to fill these data gaps within the framework of this study. Thus it is impossible to quantify in a meaningful way costs or benefits of modern biotechnology applications. Secondly, modern biotechnology is a comparatively new technology and so many of the applications identified are fairly recent. Major technologies such as modern biotechnology often develop over long time horizons, and cost-benefit analysis can be very sensitive to when it is performed. Thus for many applications, and for the technology as such it is too early to assess conclusively the costs and benefits. Thirdly, modern biotechnology, due to its enabling character, has effects over wide areas of the EU economy involving a large

number of actors and stakeholders, rendering any cost-benefit analysis a hugely complex task, and unfeasible in the framework of this study.

### Data

Data were obtained from a number of sources. Depending on availability and based on data quality, the following descending order of priority was applied for data compilation purposes: official statistics and reports (provided by public institutions), peer-reviewed publications, surveys and interviews of industrial and technical experts, market reports and other publications and, finally, web-based information from validated sources. This information was obtained either from direct desk research or from the ETEPS network.<sup>518</sup> Overall, data quality was highest for the medicine and health care sector, followed by manufacturing, and lowest for primary production and the agro-food sector. Where no robust data were available, an effort was made to provide estimates for illustrative purposes. In any case, at least a qualitative analysis was performed. All conversions to euro used this rate: 1 Dollar = 0.7765 Euro.

A lack of data on many applications of modern biotechnology limited the quantitative analysis. Future assessments would benefit from improvements in the basic statistics.

515 ETEPS (2006) Task 1 – A preparatory study mapping modern biotechnology applications and industrial sectors, identifying data needs and developing indicators. Final report <http://bio4eu.jrc.es/documents/Bio4EU-Task1.pdf>.

516 For further details and, in particular, a list of the indicators used, see the Analysis Report: DG JRC/IPTS (2007). Analysis Report: contributions of modern biotechnology to European policy objectives, <http://bio4eu.jrc.es/documents.html>.

517 Cost-benefit analysis is an approach to investment appraisal which takes a broad view of locating and quantifying the costs and benefits of a project, including external costs and benefits.

518 See also <http://bio4eu.jrc.es/tasks.html>.

## Methodological remarks

### *Sector classification*

The sectors in which modern biotechnology is known to be applied were identified, based on the NACE classification,<sup>519</sup> where feasible. For primary production and the agro-food sector, the sector classification provided by Eurostat was mainly used. Where needed, sectors were further disaggregated. For each biotechnology application the closest matching sector category was chosen as a benchmark, e.g. “manufacture of soap, detergents, cleaning and polishing” (NACE DG 24.51) for “enzyme-containing detergents”. The data for each individual biotechnology application were then put into context alongside the benchmark data for the sector.

### *Economic and employment indicators*

Gross value added (GVA) for the most recent year (2002, with some exceptions) is the main economic indicator used throughout this analysis. Value added was chosen because it is equally as good as GDP or turnover as an economic measure, but more information is available in public databases. Turnover was used only for the analysis of primary production and the agro-food sector, especially at more disaggregated levels, due to limited availability of GVA data. Where available, other economic indicators were also used, e.g. to show the changes induced by adoption of modern biotechnology in terms of efficiency increases. If no solid estimates could be obtained, the information was omitted. Competitiveness is discussed in qualitative terms throughout the analysis.

The number of direct employees was used as the main employment indicator. If this number is not known for a specific application of biotechnology, but the number of employees and rate of diffusion in the benchmark sector are,

then “number of employees x diffusion rate” is applied to calculate employment numbers for the relevant application.

The figures obtained are linked to the corresponding statistics for the economy as a whole in order to learn (i) the contribution of biotechnology applications to GVA in EU-25 and (ii) the contribution of biotechnology applications to GVA (or turnover) of the various benchmark sectors used.

For the analysis of industry the labour productivity of biotechnology was also estimated as:

This figure was then used to determine (i) how the labour productivity of manufacturing sectors using enzymes relates to labour productivity in the relevant NACE sector and (ii) how their labour productivity relates to overall labour productivity in manufacturing.

This analysis was carried out for both the direct and the indirect impact by calculating the economic output and employment using biotechnology. Therefore, the analysis of the contributions made by modern biotechnology to the EU economy is static in that it does not calculate the change, in economic or employment terms, induced by adoption of modern biotechnology.

Where modern biotechnology (direct) or derived products (indirect) are used at some steps of a production process, the entire output is calculated as the impact of modern biotechnology, even if the modern biotechnology-based process is only one amongst several non-biotechnological steps in production. Therefore the indicator calculated provides a relative measure of the take-up and importance of modern biotechnology in the EU-25 economy rather than an absolute measure of the positive or negative effects on the economy. An additional reason for taking this approach can be found in the basic assumption that modern biotechnology production has

519 NACE is the statistical classification of economic activities in the European Community. In this report version 1.1 of 2002 is used.

been taken up by producers in order to remain competitive on the relevant product market.

### ***Environmental, energy and public health indicators***

The assessment of the contribution made by modern biotechnology to the environment, energy and public health is based on a range of indicators. In the case of the environment and energy these include mainly resource productivity, waste prevention, air/soil/water quality, biodiversity, greenhouse gas emissions and security of supply; in the case of public health they include protection against health risks, disease prevention and health care and social costs. Yet, due to the inherent differences between the individual sectors and applications in the context of the environment and public health, the exact assessment varies between the three sectors. Where necessary, further details of the assessment are provided in the relevant chapters.

## ■ Annex 3: Glossary of terms and acronyms

### A

*acrylamide (acrylic amide)*: readily polymerised → amide derived from acrylic acid used, for example, for manufacturing water-soluble thickeners and dyes, wastewater treatment, papermaking or in synthetic fibres; it is a carcinogen.

*ADR*: adverse drug reaction (can be reduced by → pharmacogenetics).

*agent*: force or substance which has the power to produce an effect (to achieve an end).

*AI*: artificial insemination.

*AMI (acute myocardial infarction)*: heart attack.

*amide*: nitrogen-containing organic compound.

*amylase*: → enzyme that catalyses → hydrolysis of starch, glycogen and dextrin to sugar.

*anthropogenic*: caused or produced by human activities.

*antigen*: substance that stimulates the immune system.

*anti-sense technology*: use of a specific → nucleic acid to inactivate a gene with complimentary sequence (the nucleic acid is called anti-sense and is designed to bind the intermediate à RNA derived from the respective gene).

*autologous cell*: cell that is re-implanted in the same individual as it came from.

### B

*bibliometrics*: the study or measurement of texts and information, e.g. content analysis.

*biocatalysis*: use of → enzymes or → microorganisms to perform chemical transformations on organic compounds (in industrial production processes).

*biocidal agent*: → agent that is destructive to living organisms.

*bioethanol*: ethanol derived from → biomass by fermenting its sugar components, to be used as an alternative to gasoline.

*bioinformatics*: research, development or application of computational tools and approaches for expanding use of biological, medical, behavioural or health data.

*biomass*: renewable organic material (mostly plant matter but also animal or microbial waste) which can be used for fuel or industrial production.

*biomolecule*: chemical compound that naturally occurs in living organisms.

*biopharmaceuticals*: pharmaceuticals derived from biotechnology.

*bioremediation*: process that uses biological → agents (e.g. → microorganisms) to break down, neutralise or remove contaminants (e.g. in polluted soil or water), to overcome environmental problems or to return the environment to its former state.

*biosensor*: device that detects or analyses a physiological change or a chemical or biological substance in the environment; it integrates a biological → agent with a physicochemical detector component.

*biotechnology active firm*: firm engaged in key biotechnology activities, such as application of at least one biotechnology technique to produce goods or services (or perform biotechnology R&D).

*biotechnology*: application of science and technology to living organisms and to parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.

*biotransformation*: → biocatalysis.

*Bt crop*: crop that has been genetically engineered to be resistant to certain types of insects (the gene conferring resistance comes from the soil bacterium *Bacillus thuringiensis*).

## C

*CAGR*: compound annual growth rate.

*catalyst*: substance that accelerates a chemical reaction.

*cell culture*: process by which cells are grown under controlled conditions.

*cell-based therapy*: therapeutic approach (which is in the development phase, e.g. → tissue engineering).

*cellulase*: → enzyme that catalyses → hydrolysis of cellulose (i.e. breaks down fibre to sugar).

*cloning*: reproduction of genetically identical “copies” of an organism.

*corticoid (or corticosteroid)*: steroid → hormone produced by the cortex of the adrenal glands.

*cost-utility analysis*: economic analysis in which the effect of consumption of a good or service is measured in terms of the happiness, satisfaction or gratification gained (by a patient, society, etc.) relative to the cost of provision.

*CVD (cardiovascular disease)*: disease affecting the heart or blood vessels.

## D

*DBF (dedicated biotechnology firm)*: → firm active in biotechnology whose predominant activity involves application of biotechnology techniques to produce goods or services (or perform biotechnology R&D).

*DNA*: → nucleic acid.

## E

*EMA*: European Agency for the Evaluation of Medicinal Products.

*endotoxin or intracellular toxin*: toxic compound within certain microorganisms that is released upon destruction of the microorganism.

*enzyme*: protein that accelerates a chemical reaction (catalyst).

*EPO*: European Patent Office.

*ESA*: European Seed Association.

*ESC (embryonic stem cell)*: → stem cell that is derived from the inner cell mass of embryos at the blastocyst stage; in contrast to somatic (adult) stem cells, ESCs are pluripotent, i.e. they have the capacity to differentiate into any one of the more than 200 cell types found in the body and they can replicate indefinitely in culture.

*ET (embryo transfer) technique*: one of a number of techniques, such as embryo transfer from donor to recipient, embryo sexing (through microsurgery on the embryo), embryo freezing and embryo splitting (to produce identical siblings).

## F

*fermentation*: whole cell → biocatalysis; process that allows cells to obtain energy from molecules anaerobically, by splitting complex organic compounds into simpler substances.

*FMD*: foot and mouth disease.

## G

*gene silencing*: inactivation of genes (at the level of transcription or translation).

*gene therapy*: introduction of a gene into a cell to achieve a therapeutic goal through its product (protein).

*genetic engineering*: modification of the genome of an organism by adding or deleting a gene or modifying the nucleotide sequences of existing genes; the modified organism thus gains or loses certain abilities, such as producing a specific enzyme.

*genetic fingerprinting*: = genotyping.

*genetic modification*: = genetic engineering.

*genetic testing*: in this report genetic testing is defined as DNA-based testing to identify variations in the DNA sequence that correlate with a disease or higher risk of developing a disease. It is often defined more broadly as analysis of human DNA, RNA, chromosomes, proteins and certain metabolites to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes or to establish family relationships.

*genome*: hereditary information of an organism, which is encoded in the → DNA.

*genomics*: study of an organism's genome and the function of the genes.

*genotype*: specific genetic makeup (→ genome) of an organism, which determines its hereditary characteristics.

*genotyping*: identification of or distinction between individuals of the same species based on their DNA.

*GHG (greenhouse gas)*: gaseous component of the atmosphere that contributes to the greenhouse effect (i.e. to a rise of global temperatures); the three main → anthropogenic GHGs are carbon dioxide (CO<sub>2</sub>), methane (CH<sub>4</sub>) and nitrous oxide (N<sub>2</sub>O).

*GM*: genetically modified (→ genetic engineering).

*GMO*: genetically modified organism (→ genetic engineering).

*GVA (gross value added)*: value of all newly generated goods and services minus the value of all goods and services consumed in producing them (i.e. minus the value of intermediate consumption).

## H

*herbicide tolerance (HT)*: ability of a crop to withstand a particular herbicide (which can therefore be used for weed management); HT is achieved by selective breeding, mutagenesis and → genetic engineering.

*high-throughput technology*: large-scale analysis (including identification, quantification and sequencing) of → nucleic acids, proteins or → metabolites.

*hormone*: chemical substance that controls and regulates the activity of certain cells or organs.

*hybrid vigour (heterosis, outbreeding enhancement)*: superior qualities in → hybrids or increase in their performance over that of purebreds, most noticeably in → traits like fertility and sterility.

*hybrid*: plants or animals resulting from a cross between two genetically dissimilar parents

*hybrid*: plants or animals resulting from a cross between two genetically dissimilar parents

(→ hybrid vigour).

*hydrolysis*: chemical reaction of a compound with water, in which one or more new compounds are formed through an exchange of functional groups.

## I

*IETS*: International Embryo Transfer Society.

*immunoassay*: biochemical test that uses antibodies to measure the level of a specific protein in a sample.

*immunochemistry testing*: detection of immune reactions by measuring the body's reaction to foreign → agents.

*immunostimulant*: → agent that enhances the response of the immune system.

*interferon*: protein produced by cells of the immune system.

*IVD (in vitro diagnostic)*: reagents and instruments for testing specimens taken from the body and intended for use in a broad spectrum of health care applications, including evaluation of an individual's risk of developing specific diseases, their early detection, identification and monitoring of treatment, etc.

*IVF*: in-vitro fertilisation.

*IVP*: in-vitro embryo production (part of → ET techniques).

## L

*labour intensity*: the degree to which labour is used relative to capital (and land) in the production of a good or service.

*labour productivity*: measure for the amount of output (here → GVA) produced per unit of labour used.

*lignocellulose*: strengthening substance found in woody plant cells, composed of lignin and cellulose.

*lipase*: → enzyme that catalyses → hydrolysis of fats into glycerol and fatty acids (e.g. in the digestive tract it breaks down fats into individual fatty acids, which can then be absorbed).

*lysine*: amino acid that is needed for the growth of protein molecules but not produced by animals themselves; it can be found in other protein sources or is given as feed additive.

## M

*MAS (marker-assisted selection)*: use of molecular markers (certain DNA regions linked directly or indirectly to specific traits) to facilitate the incorporation of desirable → traits into selection schemes for plant or animal breeding.

*MEE*: manufacturing, energy and the environment.

*metabolic engineering*: modification of genetic and regulatory processes within cells to produce desired substances.

*metabolism*: biochemical modification of chemical compounds in living organisms and cells that produces energy and basic materials that are necessary for life.

*metabolite*: compounds of low molecular weight that are intermediates or end-products of metabolism.

*metabolome*: set of metabolites of a given organism, tissue or cell under certain conditions.

*micro-array*: collection of segments immobilised on a solid surface (e.g. glass, plastic or silicon chip) that allows → high-throughput analyses through hybridisation with a set of specific probes.

*microbe*: = microorganism.



*microorganism*: any organism of microscopic size (i.e. too small to be seen with the naked eye).

*micropropagation*: use of tissue culture techniques for plant propagation to produce a large number of progeny plants.

*molecular farming*: cultivation of plants for the production of pharmaceuticals, functional proteins and industrial enzymes.

*molecular marker*: fragment of DNA sequence that is associated with a part of the genome.

*molecular testing*: investigation of disease association with a specific genotype.

*monoclonal antibody*: protein produced in the laboratory from a single clone of a B cell (the type of cells of the immune system that make antibodies); monoclonal antibodies bind to specific molecules at a specific site, e.g. a disease-causing organism, allowing targeted medication.

*monogenic disease*: inherited disease controlled by a single pair of genes.

*mRNA*: messenger → RNA.

## N

*NACE (Nomenclature générale des activités économiques dans les communautés européennes)*: general industrial classification of economic activities in the European Communities.

*nanomedicine*: application of → nanotechnology in treatment and in disease diagnosis and monitoring.

*nanoparticle*: microscopic particle below 100 nanometres in size.

*nanotechnology*: engineering of atoms, molecules or materials (on a scale below 100 nanometres) to produce new features.

*NDDS*: nano drug delivery systems.

*nucleic acid*: two forms of nucleic acids are known, DNA (deoxyribonucleic acid) and RNA (ribonucleic acid); for all higher organisms DNA constitutes the genetic material responsible for all heritable traits; RNA is an intermediate for the synthesis of proteins.

*nutrigenetics*: study of the effect of genetic variation on the interaction between diet and disease.

*nutrigenomics*: study of the response of organisms to food and food components using → genomics, → proteomics and metabolomics approaches.

## O

*OIE (Office International des Epizooties)*: World Organisation for Animal Health.

*OPU*: ovum pick-up (part of → ET techniques).

*orphan drug*: medicinal product to diagnose, prevent or treat a life-threatening, seriously debilitating or serious and chronic condition affecting fewer than five in every 10 000 persons, of which the development and marketing cost is not expected to be recouped from sales of the product under normal market conditions because of the very low incidence of the underlying condition.

## P

*pathogen*: → agent that can cause disease or illness.

*PCR (polymerase chain reaction)*: technology for copying and amplifying DNA by using enzymes.

*peptide synthesis*: chemical creation of peptides.

*PHA (polyhydroxyalkanoate)*: natural polymer produced by bacterial fermentation of sugar or lipids and synthesised and accumulated as an energy storage substance in cells; used as animal feed.

*pharmacogenetics*: study of the influence of genetic variation on differences in how people respond to medicines with the aim of tailoring therapy to individual genetic make-up.

*ploidy manipulation*: increase of sets of chromosomes from two to three by giving embryos a shock (heat, cold or pressure) shortly after fertilisation; in aquaculture triploid fish are expected to perform better than their conventional diploid counterparts.

*polymer*: material composed of large molecules that are constructed of smaller, simpler molecules, which usually has a high molecular weight; polymers are essential material for almost every industry.

*protein engineering*: modification of a protein to achieve a desired function.

*protein synthesis*: chemical creation of protein.

*proteomics*: analysis of protein expression under different conditions, including separation, identification and characterisation of the proteins in a cell, to explain biological processes.

*PSE*: pale, soft and exudative (pig meat).

*PUFA (polyunsaturated fatty acid)*: fatty acid that contains more than one double bond.

## Q

*QALY (quality-adjusted life year)*: weighted equivalent of one healthy life year.

## R

*recombinant DNA technology*: = genetic engineering.

*riboflavin*: vitamin B2; used in food processing as a colorant or for fortification.

*RNA*: → nucleic acid.

*RNAi (RNA interference)*: use of double-stranded → RNA to inactivate a specific gene.

*RoW*: rest of the world.

## S

*SCID*: severe combined immunodeficiency.

*SCNT (somatic cell nuclear transfer)*: production of animals by transfer of genetic material from one donor somatic cell to a recipient unfertilised oocyte from which the nuclear → DNA has been removed (enucleation).

*sex manipulation*: creation of monosex populations by hormonal treatment and appropriate breeding techniques; in aquaculture this results in increased productivity due to faster growth, reduced aggression and later maturation.

*siRNA technology*: = RNAi.

*stacked trait*: insertion of more than one → trait in a GMO.

*stem cell*: unspecialised cell that has the capacity for self-renewal and the ability to differentiate under certain physiological or experimental conditions into various types of specialised cells.

## T

*tissue engineering*: regeneration of diseased tissues and organs by use of cells and with the aid of supporting structures or biomolecules.

*toe (tonne of oil equivalent)*: unit of energy; the amount of energy released by burning one tonne of crude oil.

*trait*: one of the many characteristics that define an organism.

*transgene*: genetic material that has been transferred by → genetic engineering from one organism to another.

*transgenesis*: = genetic engineering.

## X

*xenotransplantation*: transplantation of cells, tissues or whole organs from one species to another.

## Z

*zoonose*: infectious disease that can be transmitted from animals to humans or vice versa.

Note: These definitions are partly based on online sources: <http://www.accessscience.com/>, <http://wordnet.princeton.edu/>, <http://www.bartleby.com/>, <http://www.fao.org/biotech/>, etc.

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**Abstract**

Modern biotechnology is considered as one of the key enabling technologies of the 21<sup>st</sup> century to support the sustainable development of the European Union. *The Biotechnology for Europe Study* (Bio4EU) provides the first comprehensive evaluation of the contributions that modern biotechnology is making in the context of major European Union policy goals. The present report, the Bio4EU synthesis report, sets out the main findings of the study.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, whether private or national.

