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Consequences, Opportunities and Challenges of Modern Biotechnology for Europe

- The Analysis Report -

Contributions of modern biotechnology
to European policy objectives

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

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THE Bio4EU STUDY

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Preface

The Biotechnology for Europe (Bio4EU) study was carried out in 2005-2007, responding to a request from the European Parliament, to provide information on the contribution of modern biotechnology to achieve major policy goals of the European Union (EU), and on its economic, social and environmental consequences.

The study was developed and led by the European Commission Joint Research Centre's (JRC) Institute for Prospective Technological Studies (IPTS). Much of the data providing the basis for the analysis presented in this report was collected by the European Techno-Economic Policy Support Network (ETEPS), which also contributed to the analysis. Furthermore, European stakeholder organisations provided input to the study.

These contributions as well as other relevant reports and information are available on the Bio4EU website (http://bio4eu.jrc.ec.europa.eu/).

The present document, the Bio4EU Analysis Report, complements the Bio4EU synthesis report[1], providing more detailed data and analysis focussing on the contribution of modern biotechnology to the Lisbon Strategy and the Sustainable Development Strategy as the overarching EU policy goals.

[1] Zika, E., Papatryfon, I., Wolf, O., Gómez-Barbero, M., Stein, AJ., Bock, AK. (2007). Consequences, opportunities and challenges of modern biotechnology for Europe. European Commission, IPTS, EUR 22728. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1470.

Executive Summary

Biotechnology is generally considered one of the key technologies of the 21st century, with a potentially wide range of applications in e.g. healthcare, agriculture, and industrial production processes. However, the diversity of sectors in which biotechnology is applied makes it difficult to investigate its actual degree of diffusion. Against this background and following a request from the European Parliament, the European Commission initiated the Biotechnology for Europe Study (Bio4EU Study). The study's objectives are to assess the contributions of modern biotechnology to the achievement of major European policy goals, and to increase public awareness and understanding of modern biotechnology[2]. Furthermore, the study provides input to the ongoing discussion of the respective roles of biotechnology and life sciences in the renewed Lisbon Strategy. The Bio4EU study was carried out between autumn 2005 and spring 2007[3] under the leadership of the European Commission's Joint Research Centre (JRC), particularly by the Institute for Prospective Technological Studies (IPTS).

This report presents an analysis of the collected data structured in accordance with the major EU policy goals economic growth and job creation (Lisbon Strategy), and environmental sustainability and public health (Sustainable Development Strategy). It is thus a background document for the Bio4EU synthesis report, which sets out the main findings of the study[4].

Application areas of modern biotechnology

According to the statistical industrial sector classification[5], the main biotechnology application areas are in the manufacturing sector (which represents approximately 17% of the EU's Gross Value-added, GVA), the agriculture and forestry sectors (2%), and fisheries (0.04%). Within manufacturing, a number of different subsectors apply modern biotechnology, e.g. the chemical sector (including pharmaceuticals), textile, pulp and paper, and food. The major applications that target human and animal health are biopharmaceuticals, recombinant vaccines and diagnostics. Modern biotechnology can also be found in primary production (agriculture, forestry and fisheries) and agro-food, for example, in breeding activities, feed additives, veterinary products, diagnostics, and enzymes for food production. Furthermore, biocatalysis, the application of enzymes or whole cells in industrial production processes, is applied to fine and bulk chemicals, fuel, textiles, and pulp and paper, although its adoption varies greatly between sectors and individual processes.

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[2] 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. http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=en&DosId=193071

[3] The European Techno-Economic Policy Support network (ETEPS, http://www.eteps.net) carried out a large part of the data gathering and provided input to the analysis, whereas IPTS was responsible for the design and coordination of the study, as well as overall data analysis. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1470.

[4] Zika, E., Papatryfon, I., Wolf, O., Gómez-Barbero, M., Stein, AJ., Bock, AK. (2007). Consequences, opportunities and challenges of modern biotechnology for Europe. European Commission, IPTS, EUR 22728. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1470.

[5] NACE is the statistical classification of economic activities in the European Community. Version 1.1 from 2002 is used in this report. http://ec.europa.eu/eurostat/ramon/nomenclatures/.

Contribution of modern biotechnology applications to the Lisbon Strategy[6]

Regarding human health applications of modern biotechnology, biopharmaceuticals are the most important application in economic terms, with about 140 products available worldwide; this represents a turnover share of 9% of the EU pharmaceutical market, or EUR 11 billion. Average growth rates of the biopharmaceutical market are twice as high compared to the pharmaceutical market, and in the EU, the number of biopharmaceuticals on the market has more than doubled in the last ten years. Recombinant vaccines play a smaller role, delivering approximately 17% (EUR 259 million) of the vaccine sector's turnover. Modern biotechnology-based diagnostics mainly relate to immunoassays and DNA-based tests, which represent about 30% (EUR 1.7 billion) of the *in vitro* diagnostics sector.

The pharmaceutical and *in vitro* diagnostic markets[7] are dominated by the US, which have a market share of 65% and 51% respectively, compared to an EU share of 30% and 26%. Furthermore, only 15% of the currently available biopharmaceuticals were developed by EU companies, compared to a share of more than 50% developed by US companies. The biopharmaceutical pipeline further consolidates the picture: in 2005, EU companies had only about 50% of candidates in clinical trials compared with their US counterparts. However, the EU position is better regarding recombinant vaccines, with 26% of available products having originated from EU companies.

Overall, modern biotechnology contributes about 5% of the EU pharmaceutical market's GVA, and 0.04% to the EU's GVA. This contribution is in the same order of magnitude as, for example, the contributions of the agrochemical or man-made fibre sectors, which indicates the high value of the comparatively low number of products. Indirect economic contributions via the sale and use of products in, e.g. pharmacies, hospitals, and the effects of using modern biotechnology in pharmaceutical R&D have not been calculated, but would add to this contribution.

The agro-food sector (including the input sectors, primary production and food processing) is another major sector where modern biotechnology is applied. This refers primarily to the sectors that provide input to crop, livestock and fish production in the form of new varieties and breeds, feed additives, veterinary products and diagnostics, and to food production in the form of enzymes and diagnostics. Between 13% and 23% of the relevant input sector's turnover is related to modern biotechnology, but adoption differs widely between applications. The use of modern biotechnology-derived products further downstream by the EU agro-food sector, e.g. in crop and livestock production, contributes to more than 30% of the sector's turnover. Overall, by enabling new or better products and services and by contributing to the sector's overall competitiveness, modern biotechnology in the agro-food sector is related to the generation of 1.3 - 1.55% of EU GVA.

Manufacturing subsectors applying biocatalysis in industrial production processes, such as the production of fine and bulk chemicals, detergents, textiles, pulp and paper, and bioethanol, on the whole generate about 5.85% of EU GVA (without food processing). Adoption rates of biocatalysis are specific for individual processes and products, and differ between 100% for

[6] Lisbon European Council 23 and 24 March 2000 Presidency conclusions. http://consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/ec/00100-r1.en0.htm. *And:* European Commission COM (2005) 24: Communication to the Spring European Council - Working together for growth and jobs – a new start for the Lisbon Strategy. http://europa.eu/growthandjobs/pdf/COM2005_024_en.pdf.

[7] The markets include the EU, the US and Japan.

individual textile finishing steps and certain fine chemical compounds, and 0.4% for biotechnology-based polymer production. Aside from chemical production, for which no disaggregated data were available, and food processing, which has been included in the agro-food sector, modern biotechnology in industrial production processes is estimated to contribute 0.08% of EU GVA or 14% of the subsectors' GVA, indicating that biocatalysis is applied only to specific manufacturing steps and/or to a limited number of products. However, where applied, biocatalysis seems to increase labour productivity[8] by 10 - 20% of the average value for the relevant sectors.

The EU is the leading producer of enzymes, generating approximately 75% of worldwide production. In the case of the biotechnology-based production of fine chemicals, bioethanol and biotechnology-based polymers, the US, as well as Asian countries such as China, are moving into the market and are outpacing the EU's production capacity growth. This is partly caused by the availability of cheaper raw materials, but is also due to targeted policy support towards the buildup of biomass-based alternatives to fossil fuel-based products.

Considering all application areas, i.e. human and animal health, agro-food, and industrial production processes, the production and use of modern biotechnology-derived products relate to the generation of approximately 1.43 - 1.69% of EU GVA.

In terms of employment, modern biotechnology's contribution is mainly seen in the creation of higher qualified jobs. The quantitative effect of modern biotechnology is difficult to measure, mainly due to limited data availability and the difficulties of integrating indirect employment effects. However, employment effects are likely to correspond to the overall diffusion of modern biotechnology applications. Just as with the diffusion of biotechnology applications, it can be assumed that some of the newly generated jobs replace existing ones.

Contribution of modern biotechnology to environmental sustainability[9]

Modern biotechnology's main contributions to environmental sustainability can be attributed to applications in industrial manufacturing, including bioethanol and the agro-food sector. The application of modern biotechnology in industrial processes (detergents, pulp and paper, textiles and fine chemicals, including antibiotics) leads generally to savings in energy and water usage, while at the same time reducing greenhouse gas (GHG) emissions, usually in the form of carbon dioxide emission reductions and chemical inputs. Generating energy for industrial processes emits twice as much GHG as the industrial processes themselves. Through energy savings generated by biocatalytic applications, these emissions could be reduced.

The transport sector is, with 21%, one of the largest emitters of GHG; petrol, which potentially could be replaced by bioethanol, is responsible for more than one third of these emissions (7.9%). The use of bioethanol, currently manufactured in the EU from wheat, could lead to GHG emission reductions in the transport sector.

[8] Labour productivity is defined as the ratio between labour input and GVA generation.

[9] European Commission (2001). The European Sustainable Development Strategy 2001. http://ec.europa.eu/sustainable/sds2001/index_en.htm. *And:* European Commission (2006). The renewed European Sustainable Development Strategy 2006. http://ec.europa.eu/sustainable/sds2001/index_en.htm.

Modern biotechnology applications in the agro-food sector usually target production efficiency and thus could lead to improvements in resource efficiency and reduced emissions, e.g. as in the case of the enzyme phytase added to animal feed. Also, breeding activities that aim to increase resistance to pathogens and abiotic stress factors are expected to have indirect environmental benefits. However, novel risks that may arise from the use of modern biotechnology also need to be assessed for their potential environmental relevance on a case by case basis.

Contributions of modern biotechnology to public health

Modern biotechnology applications in the human health sector directly affect public health through the provision of effective treatments, unique solutions for treatment and diagnostics (e.g. enzyme replacement therapy for Gaucher's disease or HIV/AIDS diagnostic tests) or potentially safer available treatments that do not require animal or human sources (e.g. human recombinant insulin or recombinant hepatitis B vaccine). In addition, modern biotechnology enables the further development of drugs, with the aim of increasing patients' quality for life (e.g. human insulin analogues).

Analysing the cost-effectiveness studies of several modern biotechnology products provides a mixed picture. While some applications seem to be cost-effective (e.g. HIV testing for monitoring drug resistance or monoclonal antibodies against non-Hodgkin's lymphoma), for other applications, conclusive studies are missing or analysis indicates that they provide no additional health benefit compared to their conventional counterparts (recombinant human insulin or recombinant hepatitis B vaccine), or the treatments are clearly not cost-effective but offer the only treatment available (enzyme replacement therapy for Gaucher's disease).

In the agro-food sector, modern biotechnology diagnostics and veterinary products – mainly vaccines – play a role in monitoring and controlling some of the most important zoonoses and food safety concerns (e.g. salmonella and BSE). Besides the direct impact on food safety and thus public health, these applications also have implications regarding the assurance of consumer confidence in the food chain and international commerce.

Opportunities and challenges

The Bio4EU study shows that modern biotechnology has been adopted to a considerable extent by many sectors. While some applications are not visible to the general public (e.g. marker assisted selection, MAS, inbreeding), others are in daily use (e.g. enzymes in detergents, bio-stonewashed jeans), and others have become the subject of controversy (e.g. genetically modified organisms, GMOs). Adoption rates differ between applications, and range from emerging applications such as biotechnology-based polymers, to well established processes such as biocatalysis in food processing.

The economic and environmental benefits of modern biotechnology products and processes, as well as the potential to provide unique solutions, in particular in the field of human health, provide opportunities that have not yet been fully exploited. Applications currently under development, such as the use of ribonucleic acid molecules for therapies, or new biocatalysts, indicate that the potential of modern biotechnology is greater than the applications currently available.

However, modern biotechnology applications also pose challenges. The development of these applications entails high development and infrastructure costs which might pose a problem, e.g. for small and medium sized enterprises that lack the financial resources to carry out R&D, hire sufficiently skilled staff and invest in new infrastructure and equipment to introduce biocatalytic processes. In the agro-food sector as well, the return on comparatively expensive applications and related up-front investments in terms of staff and equipment, such as for breeders' MAS, might materialise rather slowly. Regarding health applications, the generally high costs of biotechnology-based products might place economic strain on healthcare systems, thus stressing the importance of cost-effectiveness evaluations.

Modern biotechnology applications raise new ethical questions, as well as environmental, socio-economic and legal issues. Examples include potential discrimination due to the misuse of personal genetic information, and the quality assurance of genetic testing. Consumers' negative perception of GM foods raises the need for new regulatory initiatives such as those related to traceability and co-existence requirements. The EU has enacted specific legislation that requires comprehensive risk assessments to be carried out before putting products on the market, and is currently active in the further development of animal welfare-related guidelines and legislation.

Another general issue concerns the limited availability of statistical data regarding modern biotechnology applications, their adoption rates and their relevant impacts, in particular for agro-food and industrial manufacturing applications. To facilitate monitoring modern biotechnology's development and adoption, as well as their impacts, e.g. for evidence-based policy making, a comprehensive database needs to be developed.

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1 Introduction

Modern biotechnology is considered one of the key enabling technologies of the 21st century with a potentially wide range of applications, in e.g. healthcare, agriculture, and industrial processes. At the same time modern biotechnology has contributed to major advances in basic science. In its simplest sense, modern biotechnology can be defined as the use of cellular, molecular and genetic processes in the production of goods and services, and its beginning dates 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 is associated with a different set of technologies including the industrial use of recombinant DNA, cell fusion, tissue engineering and others.

In healthcare, modern biotechnology techniques have opened new avenues for the development of innovative and more accurate diagnostics, and for the discovery of novel drugs (e.g. genetic tests, monoclonal antibodies). Additionally, modern biotechnology techniques are now being applied to plant breeding (e.g. development of cereal crops with increased protein yield or pest-resistant crops), and to the production of industrial goods (e.g. chemicals or textiles). It is evident that modern biotechnology offers unique opportunities to address many needs and could consequently serve as a major contributor in achieving European Union (EU) policy goals on economic growth and job creation, public health, environmental protection and sustainable development[10].

In spite of these observations, recent data on the economic performance as well as on R&D activities of the European biotechnology industry indicate that 2004 was a year of consolidation rather than growth[11]. Moreover, recent reports[12] suggest that the actual adoption of modern biotechnologies by various European sectors may be lower than anticipated (e.g. genetically modified crops are hardly grown in Europe, stem cell-related applications are still in R&D phases, and gene therapy is currently not available outside clinical trials). In fact, it appears that modern biotechnology might have been successful primarily in niches where economically competitive alternatives do not exist (e.g. antibody-based pharmaceuticals). However, modern biotechnology today is still a developing, immature technology and extensive research and development programmes are under way to generate new products and new applications. Additionally, data on the actual uptake by various sectors (e.g. health, agriculture, and environment) and its socio-economic consequences in Europe are still scarce.

Against this background, and following a request of the European Parliament, the European Commission announced in the Third Commission Biotechnology Progress Report[13] that it will

[10] European Commission COM (2002) 27: Communication form 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. http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=en&DosId=171079.

[11] Critical I (2005). Biotechnology in Europe: 2005 comparative study. Critical I, Banbury. http://www.europabio.org/CriticalI2006/Critical2006.pdf. *And:* van Beuzekom, B. (2004). Biotechnology statistics in OECD member countries: an inventory. OECD STI working paper 2004/8. OECD, Paris. http://dx.doi.org/10.1787/304575100848.

[12] Arundel, A. (2003). Biotechnology indicators and public policy. OECD STI working paper 2003/5. OECD, Paris. http://dx.doi.org/10.1787/262776281580.

[13] 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

'*carry out a study into, and conduct a cost-benefit analysis of, biotechnology and genetic engineering, including genetically modified organisms, in the light of major European policy goals formulated in the Lisbon strategy, Agenda 21, and sustainable development*'.

It has also announced that '*The purpose of this study is twofold. 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 their understanding of life sciences and biotechnology.*'

On this basis the Biotechnology for Europe (Bio4EU) study was developed by the European Commission's Joint Research Centre (JRC), in particular by the Institute for Prospective Technological Studies (IPTS). The study is designed in a way that allows identifying and quantifying, as far as possible, contributions of modern biotechnology to the achievement of major European policy objectives formulated in the Lisbon Strategy and in the Sustainable Development Strategy, in particular concerning economic growth and job creation, public health and food safety, food production and environment and energy.

The study focuses on existing modern biotechnology[14] applications including, for example, biopharmaceuticals, diagnostics and recombinant vaccines, marker assisted selection, propagation, biocatalysis and bioremediation. Modern biotechnology applications were studied in the three major application areas: human and animal health; primary production and agro-food; and industrial processes, energy and environment.

Data gathering has been structured along different sets of indicators developed for the study to support the analysis of impacts, costs and benefits of biotechnology applications and to illustrate i) the high expectations of biotechnology in terms of public and private investments in the technology (input indicators), ii) the output of the investment in terms of modern biotechnology products and services (output indicators) and iii) the impact of the uptake of modern biotechnology in terms of support to achieving major EU policy goals (impact indicators) (see Annex 1 – Methodology).

Data were collected mainly between April and October 2006 by the European Techno-Economic Policy Support Network (ETEPS)[15] and the IPTS. Twenty-nine case studies covering applications of modern biotechnology considered to have the highest current impact in economic, social and environmental terms were selected for in-depth analysis. The selected case studies comprise representative examples of modern biotechnology applications in human and animal health, primary production and agro-food and industrial processes, energy and environment (see Table 63 in Annex 1 – Methodology), and they were studied in-depth

biotechnology – a strategy for Europe. Third progress report and future orientations. http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=en&DosId=193071

[14] Modern biotechnology includes: biotechnologies covering DNA, proteins and other molecules, cell and tissue culture and engineering, process biotechnologies, and sub-cellular organisms, but excludes traditional biotechnology processes used, for example, in the food industry or for bioremediation. However, modern biotechnology used in combination with traditional biotechnology is included.

[15] European Techno-Economic Policy Support Network (ETEPS, http://www.eteps.net/). Institutes which participated in the Bio4EU study are listed at the beginning of the report. References to ETEPS reports either refer to the main report or to the application-specific case study reports in which 28 case studies are presented in detail (available on the Bio4EU study web site: http://bio4eu.jrc.ec.europa.eu/).

with the aim of quantifying, as far as possible, their economic, social and environmental impacts.

This report provides the results of the analysis of the data with a view to evaluating the contributions of modern biotechnology to major EU policy objectives formulated in the Lisbon Strategy[16] and in the Sustainable Development Strategy[17], in particular concerning economic growth and job creation, public health and food safety, and environment and energy. A mixed quantitative/qualitative methodology based on indicators is employed for the assessment of the economic, social, and environmental consequences of modern biotechnology applications (see also Annex 1 – Methodology). The quantitative approach is used wherever feasible but is further complemented by qualitative analyses, focusing on factors shaping costs and benefits.

The contribution of modern biotechnology to economic growth, competitiveness and employment is presented in Chapter 2, whereas contributions to environment and energy, and public health and food safety are analysed in Chapters 3 and 4, respectively.

[16] Lisbon European Council 23 and 24 March 2000 Presidency conclusions. http://consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/ec/00100-r1.en0.htm. *And:* European Commission COM (2005) 24: Communication to the Spring European Council - Working together for growth and jobs – a new start for the Lisbon Strategy. http://europa.eu/growthandjobs/pdf/COM2005_024_en.pdf.

[17] European Commission (2001). The European Sustainable Development Strategy 2001. http://ec.europa.eu/sustainable/sds2001/index_en.htm. *And:* European Commission (2006). The renewed European Sustainable Development Strategy 2006. http://ec.europa.eu/sustainable/sds2001/index_en.htm.

2 Contribution of modern biotechnology to economic growth, competitiveness and employment

2.1 General outline and overall contribution of modern biotechnology

Since 2000, the overriding EU policy strategy has been the Lisbon Strategy, aiming at a leading position of the EU in several areas such as innovation, research, economic growth and employment[18]. The revision of the Strategy in 2005 has put more emphasis on growth and employment[19], without neglecting other policy fields and the need for balanced progress in the sense of the different pillars of sustainable development[20] (see Chapters 3 and 4). Biotechnology is one of the few explicitly mentioned high technology areas that is monitored closely by the Commission because of 'its potential to create growth and new jobs and benefit a wide range of sectors, while at the same time contributing to our broader goals, such as sustainable development'[21].

From the underlying policy themes of *economic growth*, *competitiveness* and *employment*, the policy objectives of i) economic growth, ii) improved international competitiveness, iii) more and better employment and iv) higher labour productivity were derived. In the following analysis these objectives are matched with concrete policy indicators that have been developed to facilitate the measurement of the contribution of modern biotechnology to their achievement (see Annex 1 – Methodology).

With regard to *economic growth*, the analysis confirmed that modern biotechnology applications are important contributors. Modern biotechnology enables the provision of new or improved products, thereby directly generating additional economic benefits. In the field of human and animal health, novel modern biotechnology products have become mainstream, contributing as much as 10 - 30% to the turnover of the respective market segments and partially growing at higher average rates than the respective non-biotechnology markets. Modern biotechnology additionally provides tools that enhance the efficiency of production processes, and thereby is an important factor in ensuring the *competitiveness* of the various sectors of application. This is a significant role of modern biotechnology in the agro-food and industrial manufacturing sectors, although to varying extents among the different applications: in the agro-food sector, modern biotechnology is estimated to directly contribute to 13 - 23% of the overall turnover of the relevant input sectors, such as breeding or feed additive production, and the use of these biotechnology-based inputs affects about 32 - 38% of the agro-food sector's total turnover. In the field of industrial manufacturing, the

[18] Lisbon European Council 23 and 24 March 2000 Presidency conclusions. http://consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/ec/00100-r1.en0.htm.

[19] European Commission COM (2005) 24: Communication to the Spring European Council - Working together for growth and jobs – a new start for the Lisbon Strategy. http://europa.eu/growthandjobs/pdf/COM2005_024_en.pdf.

[20] European Commission COM (2001) 264 final: Communication from the Commission A Sustainable Europe for a Better World: A European Union Strategy for Sustainable Development. http://europa.eu/eur-lex/en/com/cnc/2001/com2001_0264en01.pdf; *AND*: Council of the European Union (2006) DOC 10917/06: Renewed EU Sustainable Development Strategy. http://register.consilium.europa.eu/pdf/en/06/st10/st10917.en06.pdf.

[21] European Commission COM (2003) 96: Communication from the Commission to the European Parliament, to the Council and to the European Economic and Social Committee - Life sciences and biotechnology – a strategy for Europe. Progress report and future orientations, p. 2. http://ec.europa.eu/biotechnology/pdf/com2003-96_en.pdf.

importance of modern biotechnology is reflected in the turnover shares of individual applications that range from less than 1% in the case of biotechnology-based polymers, to 10% in pulp and paper and 30% in detergents, and up to 100% in some food production processes (e.g. fruit juice). Moreover, the overall contribution of modern biotechnology to economic growth will also be reflected in the indirect impacts on the economic performance of the specific sectors, all along the production and services chain: for example, modern biotechnology-based diagnostics are instrumental in ensuring consumer confidence in the food chain and in the safeguarding of related trade activities.

Dynamic developments provide additional insights on the contribution of modern biotechnology to economic growth. While the diffusion of some modern biotechnology applications is thought to have reached a plateau, the expectations in most cases are for increases in adoption and the emergence of novel applications. Moreover, some economic benefits are cumulative in time, such as those realised with the aid of modern biotechnology applied in selective breeding (e.g. embryo transfer and marker assisted selection). Similarly, in health biotechnology, the EU market for biopharmaceuticals grows on average at 23% annually, which is twice as much as the overall EU pharmaceuticals market average growth rate (11%). Given the different degrees of adoption, there is a potential for future modern biotechnology related turnover growth as far as modern biotechnology enables the provision of new or improved products or enhances efficiency.

When it comes to the EU's economic *competitiveness*, modern biotechnology brings direct benefits to the sectors concerned. However, an additional issue is the comparison with the competitive position of other global players, as in other countries several applications of modern biotechnology have experienced a more comprehensive and quicker adoption. There are some fields (such as the production of enzymes) where the EU holds a strong position, but from a global perspective on modern biotechnology, the US can be considered the leader in the field, with other countries like China, India, or Brazil catching up in one field of application or another.

Quantifying the contribution of modern biotechnology to *employment* and *labour productivity* is hampered by the lack of data and cross-sectorial effects. In particular it is difficult to assess if job creation through modern biotechnology applications leads to additional jobs or has substitution effects. Yet, it is assumed that modern biotechnology related employment roughly corresponds to its overall diffusion rate in the various fields of application. Furthermore, the jobs that are created represent higher qualified jobs, i.e. the contribution of biotechnology in this context is more qualitative in nature. This is also reflected in a seemingly higher labour productivity per employee as compared to productivity when no modern biotechnology is used. Industrial manufacturing processes applying modern biotechnology are estimated to have on average a 10 - 20% higher labour productivity, which in turn may potentially improve competitiveness.

2.2 Human health biotechnology

The contribution of health and healthcare towards the achievement of the Lisbon Strategy objectives is well recognised. A healthy and well educated working population is an essential prerequisite for economic growth. People in the EU live in better health and longer than ever before[22]. Life expectancy has increased to between 75 and 79 years in all Member States and infant mortality has fallen sharply in recent years[23]. This is an important development considering that increased life expectancy may also lead to an increase in economic growth (e.g. the World Health Organisation WHO predicts that a 10% increase in global life expectancy can increase economic growth by 0.35% a year[24]). A recent study investigating the link between health and the economy in the EU indicates four main channels through which health may influence economy: higher productivity, greater supply of labour, higher skills, and more savings available for more capital formation (e.g. in anticipation of a longer life expectancy after retirement)[25]. However, apart from these potential effects on economic growth, which is only a means in itself, better healthcare, better therapies and more prevention contribute to an improvement in the quality of life and to overall welfare.

Modern biotechnology impacts human health by facilitating the development of novel and improved therapies and preventives, as well as better and more accurate diagnostics. Apart from indirectly acting through health improvements on economic growth, biotechnology also has a direct impact on the pharmaceutical sector (NACE[26] DG 24.4[27]), which in 2002 employed 579 500 persons and created EUR 58 billion of value-added[28], and represents a share of about 4% of the total value-added of the manufacturing sector (NACE D).

The analysis of the economic relevance of modern biotechnology applications in the area of human health is primarily based on the assessment of direct impacts (see Annex 1 – Methodology) that arise from the use of modern biotechnology in the private sector, e.g. by the pharmaceutical industry (NACE DG 24.4) for the development of medical products. The analysis considers direct impacts of health-related biotechnology adoption in the context of the pharmaceutical sector at a disaggregated level (i.e. biopharmaceuticals and vaccines, and diagnostics). The indicators that were selected for measuring modern biotechnology uptake and its direct economic impact are the following:

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[22] Byrne, D. (2004). Enabling good health for all: a reflection process for a new EU health strategy. Paper by the Commissioner for health and consumer protection. European Communities, Luxembourg. http://ec.europa.eu/health/ph_overview/Documents/pub_good_health_en.pdf.

[23] European Commission COM (2000) 285 final: Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions on the health strategy of the European Community. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0285:FIN:EN:PDF.

[24] Sachs, J.D. (2001). Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health, World Health Organisation, Geneva. http://whqlibdoc.who.int/publications/2001/924154550X.pdf.

[25] Suhrcke, M. et al. (2005). The contribution of health to the economy in the European Union. European Commission, DG Health and Consumer Protection. http://ec.europa.eu/health/ph_overview/Documents/health_economy_en.pdf.

[26] NACE is the statistical classification of economic activities in the European Community. Version 1.1 of 2002 is used in this report. http://ec.europa.eu/eurostat/ramon/nomenclatures/

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

[28] Eurostat. http://epp.eurostat.ec.europa.eu/

- number (and share) of biotechnology-based products
- number of companies active in biotechnology
- economic share(s) of modern biotechnology applications (e.g. in terms of turnover, gross value added - GVA).

Indirect impacts resulting, for example, from the end-use of biotechnology-based products for health are discussed only qualitatively, due to the limited availability of quantitative data.

Relevant data were obtained from official statistics, databases and market reports of commercial origin (biopharmaceuticals, vaccines). Additional data were obtained through specific case studies on biopharmaceuticals (recombinant insulin, interferon-beta for the treatment of multiple sclerosis, glucocerebrosidase for Gaucher's disease, CD20 monoclonal antibodies for non-Hodgkin's lymphoma), recombinant vaccines (hepatitis B vaccine), and modern biotechnology-based diagnostics (cardiac diagnostic assays, HIV testing, and genetic testing).

2.2.1 Adoption of modern biotechnology applications

Modern biotechnology applications in health encompass therapeutic products and preventives, but also diagnostics. Recombinant DNA technology (i.e. the ability to insert a specific DNA sequence into bacteria or mammalian cells allowing the expression of the corresponding protein) has been a milestone for the development and production of specific therapeutics, and has led to the launch of the first true biotechnology drug, recombinant human insulin, in 1982. Since then, about 165 biotechnology-based products, including vaccines and nucleic acid products, have reached the market in the US and the EU for the treatment of a range of conditions including rheumatoid arthritis, hepatitis and various cancers[29], representing a market that has been constantly growing over the last decade. In addition, biotechnology provides a combination of enabling techniques utilised not only in identifying and validating putative targets and drug candidates, but throughout the whole drug development process.

In spite of these observations, a clear picture of the significance of modern biotechnology applications in the pharmaceutical sector is lacking. A first indication for its importance can be derived by the degree of adoption as measured by i) the numbers and shares of biopharmaceuticals and recombinant vaccines, and ii) the numbers and shares of biopharmaceutical companies[30]. It is noted that, although biotechnology-derived vaccines (i.e. recombinant vaccines) are also often regarded as biopharmaceuticals, in this analysis, they are considered separately as they represent a distinct application (prevention). In a later section (Section 2.2.1.3), the adoption of modern biotechnology in diagnostics is also discussed, although for this area it has been difficult to retrieve disaggregated data.

[29] Walsh, G. (2006). Nature Biotechnology **24**: 769-776. http://dx.doi.org/10.1038/nbt0706-769.
[30] See Section 2.2.2 for a definition.

2.2.1.1 Number and share of biopharmaceuticals

The number of available human health products based on modern biotechnology was analysed through the pharmaprojects[31] database according to originating country (see Table 1). These fell into three main categories: biopharmaceuticals[32], recombinant vaccines, and other products such as gene therapy vectors. Biopharmaceuticals represent the largest group of biotechnology-based pharmaceuticals both worldwide, and in individual regions (e.g. 78% of all biotechnology products that originated from the EU are biopharmaceuticals). In total, 142 biopharmaceuticals are now available, the majority of which (54%) originated from the US, whereas 15% originated from the EU[33]. The complete list of biopharmaceuticals that originated in EU companies (as determined by headquarters) can be found in Table 65 of Annex 2 – Human Health. These products fall into four main groups: i) recombinant hormones (a total of five including two insulin products), ii) four monoclonal antibodies, iii) two recombinant interferons, and iv) recombinant growth factors (one product, erythropoietin). The remaining nine products varied from anticoagulants to enzymes, and also included one orphan drug, the enzyme replacement therapy for the Anderson-Fabry disease (an X chromosome-linked disorder caused by a genetic deficiency of the lysosomal enzyme α-galactosidase)[34].

Table 1: Biotechnology-based products marketed worldwide according to originating country (total available, 2005)

	Total	Originating in the US	Originating in the EU	Originating in Japan	Originating in Switzerland	Originating in other countries (Australia, South Korea, India)
Biotechnology products	183	88	27	11	19	7
Biopharmaceuticals	142	76	21	8	15	5
Recombinant vaccines	23	4	6	3	4	2
Others (gene therapy vectors; cellular, DNA, RNA products)	18	7	1	0	0	0

Another indication for the degree of modern biotechnology uptake by the pharmaceutical industry comes from the number of new biotechnology-based products launched. An analysis based on the pharmaprojects database indicates that the number of new biopharmaceuticals

[31] 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.

[32] Biopharmaceuticals include: recombinant interferon, interleukin, growth factors, hormones, monoclonal antibodies, immunotoxins, immunoconjugates.

[33] In the pharmaprojects database an originator company is defined as 'that company, academic institution or other non-industrial organisation responsible for discovering the drug.'

[34] For one of these drugs (Scintimun) an application for marketing authorisation was pending at the EMEA but was recently withdrawn (http://www.emea.eu.int/humandocs/PDFs/EPAR/scintimun/18999206en.pdf).

launched in the EU has varied over the last 10 years from a maximum of 11 new products in 1999 to a minimum of two in 2005. On average six new biopharmaceuticals per year are launched into the EU market (since 1996), representing a share of 9% out of all new pharmaceuticals launched per year (see Figure 1).

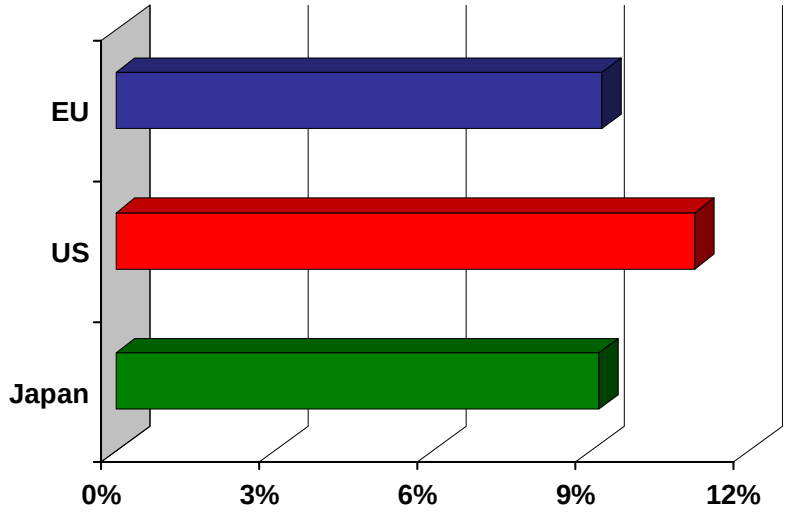

Figure 1: Share of biopharmaceuticals in all pharmaceuticals launched between 1996 and 2005
Source: ETEPS[35], IPTS calculations

Based on these data, the number of available biopharmaceutical products on the market may be derived. In 2005, 85 biopharmaceuticals were available on the EU market, more than twice as many as in 1996 (see Figure 2).

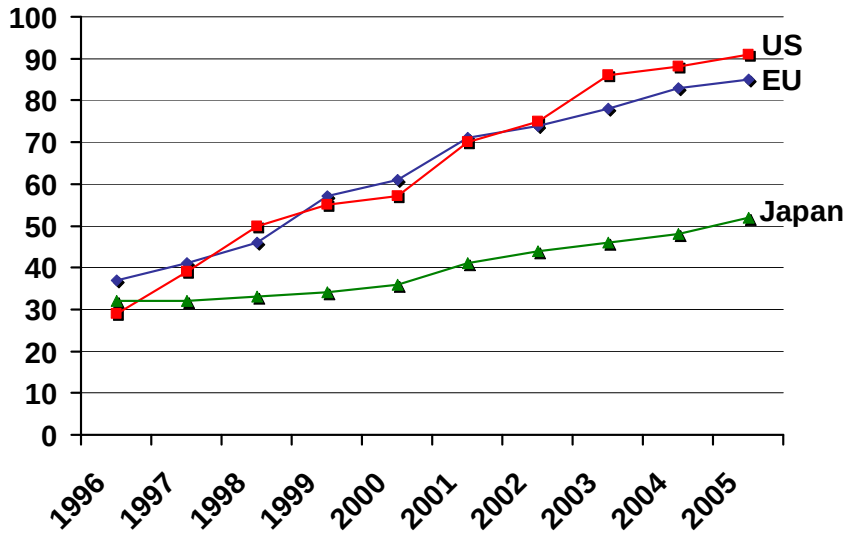

Figure 2: Number of biopharmaceuticals available on the market
Source: ETEPS[35], IPTS calculations

[35] ETEPS (2006). Bio4EU Task 2, main report.

Since the launch of human recombinant insulin, biopharmaceuticals have amplified over the last years to encompass recombinant forms of several natural proteins. The main types are

- blood factors and thrombolytics
- hormones (e.g. insulin, somatotropin)
- interferons and interleukins, and growth factors (e.g. erythropoietin) and
- therapeutics based on monoclonal antibodies, targeting a broad range of conditions.

A closer analysis of the indications of the currently available biopharmaceuticals identified through the pharmaprojects database, shows that cancer (24 biopharmaceuticals), metabolic (22 biopharmaceuticals), musculoskeletal and immune disorders (16 and 15 biopharmaceuticals, respectively) are the predominant therapeutic fields.

2.2.1.2 Number and share of recombinant vaccines

A major group of preventive products is vaccines. Recent advances in biotechnology have made an impact on the development of new and improved vaccines. This includes the development of better delivery methods (e.g. viral vectors) and the identification of novel immunogens. In addition, the application of recombinant DNA technology led to the development of the recombinant hepatitis B vaccine, which has contributed to the reduction of infections[36] (more detailed information on the public health impact of this vaccine is discussed in Chapter 4). Currently, there is growing interest in DNA vaccines which activate an immune response utilising DNA instead of proteins (several are in phase I clinical trials for AIDS, malaria and influenza).

To date, recombinant vaccines represent a much smaller share of biotechnology-based products (12.5%) available worldwide, as compared to biopharmaceuticals (see Table 1). The majority of the currently available recombinant vaccines are targeting hepatitis B. One vaccine available on the market includes the recombinant cholera toxin B subunit, and recently a vaccine against diseases caused by the human papillomavirus, including cervical cancer, was approved in the US and the EU.

After an initial phase of a growing number of recombinant vaccines that were available in the EU, their number seems to have stabilised over the last five years. In the US, the number of recombinant vaccines has increased by only two in the same period (see Figure 3). In general, there is a more dynamic development in the EU vaccines market overall, where more vaccines are available on the market from year to year. Due to this positive development in the overall market, the share of recombinant vaccines in all available vaccines in the EU fell from 25% to under 14% over the last ten years.

[36] Chang, M.H. (2006). Journal of Clinical Virology **36**: S45-S50. http://dx.doi.org/10.1016/S1386-6532(06)80008-9.

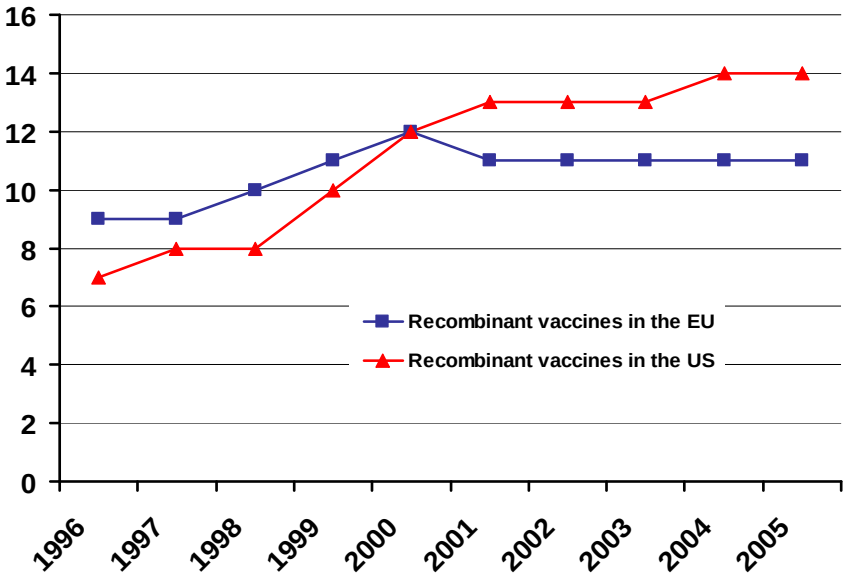

Figure 3: Number of recombinant vaccines available on the market
Source: ETEPS[37]

2.2.1.3 The role of modern biotechnology in diagnostics

In vitro diagnostics[38] (IVDs) are tools (e.g. reagents, chips) for testing specimens taken from the body and intended for use in a broad spectrum of healthcare applications, including evaluation of an individual's risk for developing specific diseases or conditions, their early detection and/or diagnosis, identification or quantification of treatment, monitoring of treatment effectiveness, etc. These diagnostics are grouped in five main categories (see Table 2), which may vary depending on both the application of the test and the technology that is utilised[39].

Modern biotechnology diagnostics can be distinguished in two main groups: protein-based and 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, cancer). In addition, protein-based assays have been developed to identify foreign proteins during an infection (e.g. HIV tests). In general, this involves the detection of 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 higher risk for developing a disease.

[37] ETEPS (2006). Bio4EU Task 2, main report.
[38] The US Food and Drug Administration (FDA) defines *in vitro* diagnostics as: reagents, instruments and systems intended for use in the 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.
[39] The Lewin Group (2005). The value of diagnostics, innovation, adoption and diffusion into healthcare. AdvaMed, Washington, DC. http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf.

Table 2: Categories and examples of *in vitro* diagnostic products
Source: The Lewin Group 2005[40], adapted by IPTS

Clinical segment	Purpose	Examples
Immunochemistry	Match antigen-antibody- response to detect presence or level of a protein (point of care testing, blood banking)	• Immunoassay tests for troponin • HIV antibody testing • Tumour markers
General (clinical) chemistry	Measurements of base compounds in the body (often performed during patient entry into a hospital)	• Calcium level testing • Cholesterol tests • Serum iron studies
Haematology/cytology	Study of the blood and blood-producing organs. The most frequently ordered tests in clinical labs	• Blood counts • CD4 cell counts • Papanicolaou (Pap) smear
Microbiology/infectious disease	Detection of disease-causing agents	• SARS blood screening • Antibiotic susceptibility testing • West Nile Virus blood screening
Molecular: genomic, proteomic, metabolomic	Study of DNA and RNA to detect genetic sequences that may indicate presence or susceptibility to disease	• *BRCA1* and *BRCA2* testing • Polymerase chain reaction • Pharmacogenetic testing using microarrays • Genomic disease management tests

Diagnostics based on modern biotechnology are found in all categories described in Table 2. However, their most prominent application is in the area of immunochemistry and molecular testing. Immunochemistry tests are utilised in the detection of immune reactions by measuring the body's antigen-antibody reaction to foreign agents. The main components of such tests are recombinant antibodies and these can be used to test for a broad range of conditions including cancer, allergies, and infectious diseases.

The category 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. tests used to identify a predisposition to breast cancer based on the genes *BRCA1* and *BRCA2*), and infectious diseases (e.g. HIV testing). Genetic tests performed for diagnostic, confirmatory or predictive purposes were recently estimated likely to be above 700 000 per year in the EU with an economic dimension of around EUR 500 million[41]. Emerging applications of DNA-based tests include the investigation of genetic variation affecting drug response (with the aim of, e.g. adjusting drug dosage or selecting a specific

[40] The Lewin Group (2005). The value of diagnostics, innovation, adoption and diffusion into healthcare. AdvaMed, Washington, DC. http://www.advamed.org/NR/rdonlyres/61EB858F-EC9E-4FAB-9547-09DABF7D2A72/0/thevalueofdiagnostics.pdf.

[41] Ibarreta, D. et al. (2003). Towards quality assurance and harmonisation of genetic testing services in the EU. European Commission, IPTS, EUR 20977. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1124 .

treatment). This application is known as pharmacogenetics/pharmacogenomics and is expected to impact tailor-made medicine.

IVDs constitute a diverse group of products ranging from antibodies used in different assays to probes used in DNA amplification techniques (PCR) and microarrays[42]. Although these are still a newer technology, DNA microarray products have already reached the market, including a test (AmpliChip, Roche) that predicts drug metabolism by genotype analysis of the cytochrome P450 pathway, and distinguishes individuals who are poor, intermediate, extensive or ultrarapid metabolisers primarily of antidepressants. Based on the test, drug dosing can be adjusted according to the needs of different patient groups, ensuring minimum adverse reactions. Protein and metabolite microarrays are still less developed, although some products are already on the market.

2.2.1.4 The role of modern biotechnology in drug development

Drug development is a lengthy process (it can take up to 10-12 years before a drug reaches the market) consisting of the following two 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)[43]. 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 combination with bioinformatics, have improved our understanding of the genetic contribution to disease, leading to the identification and selection of multiple potential drug targets at the same time (high-throughput/microarray approach). Modern biotechnology has also impacted target validation. One important technology for this process has been the use of genetically modified (transgenic or knockout) animals (more commonly mice) for the validation of the drug targets (further discussed in Section 4.2.4). However, other techniques including antibody-based assays are also applied for this purpose. Finally, modern biotechnology is contributing to drug safety through 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. the identification of the underlying genetic differences in patients' drug responses in order to modulate therapy, is increasing. 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[44]. Additionally, such approaches can be applied in the validation of predictive biomarkers, for example, in cancer treatment[45]. 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

[42] DNA microarrays (or chips) are a collection of DNA segments immobilised on a solid surface (e.g. glass, plastic or silicon chip) which allow the quantitative and high-throughput analysis of several thousands of genes through hybridisation to a set of specific probes.
[43] DiMasi, J.A., et al. (2003). Journal of Health Economics **22**: 151-185. http://dx.doi.org/10.1016/S0167-6296(02)00126-1.
[44] Hopkins, M.H. et al. (2006). Nature Biotechnology **24**: 403-410. http://dx.doi.org/10.1038/nbt0406-403.
[45] Sargent, D. et al. (2005). Journal of Clinical Oncology **23**: 2020-2027. http://dx.doi.org/10.1200/JCO.2005.01.112.

populations and by minimising toxicity effects[46]. In this context, the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) have recently published guidelines for the submission of pharmacogenetic data[47].

In spite of the rapid development in science and the increased use of modern biotechnology in drug production as estimated by experts (see Section 2.2.6), the attrition rate remains high (only about one molecule out of every ten subjected to clinical trials is actually licensed)[48] and the costs associated with drug development have increased (the average cost of developing a new biotechnology drug has recently been estimated at about EUR 1 billion)[49], 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 rather 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 also suggested that the application of new technologies may further increase costs (at least in the short term), as these might lead to the identification of numerous drug targets which are not currently well understood[50]. Thus, it is still unclear as to whether modern biotechnology has significantly improved the R&D process, but it is suggested that this potential can be further harvested through better co-ordinated interdisciplinary research which can also be directly translated in specific therapeutic products[51].

2.2.2 The (bio)pharmaceutical industry

In 2003, the pharmaceutical industry amounted to about 4% of the total EU manufacturing value-added and totalled 4111 companies, with 75% of these situated in six EU countries (see Figure 4). The 2006 EU Industrial R&D Investment Scoreboard[52] demonstrates a similar geographic concentration as the majority of the total 64 pharmaceutical companies ranked in the top 1000 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 continuously grown since 1993, at a higher growth rate than the average in the chemicals

[46] Lesko, L.J. and J. Woodcock (2002). The Pharmacogenomics Journal **2**: 20-24. http://dx.doi.org/10.1038/sj/tpj/6500046.

[47] EMEA (2006). Guideline on pharmacogenetics briefing meetings. European Medicines Agency, London. http://www.emea.eu.int/pdfs/human/pharmacogenetics/2022704en.pdf. *And:* FDA (2005). Guidance for industry: pharmacogenomic data submissions. US Food and Drug Administration, Rockville, M.D. http://www.fda.gov/cber/gdlns/pharmdtasub.htm. *And:* EMEA (2006). Guiding principles processing Joint FDA-EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the confidentiality agreement. European Medicines Agency, London. http://www.emea.eu.int/pdfs/general/direct/pr/FDAEMEA.pdf.

[48] Climbing the helical staircase. A survey of biotechnology. The Economist (London), 29 March 2003, pp. 3-18. http://www.economist.com/surveys/displaystory.cfm?story_id=E1_TGQSVVG.

[49] CSDD (2006). Impact Report **8**(6). Tufts Center for the Study of Drug Development. Tufts University, Boston, M.A. (Conversion: USD 1 = EUR 0.7765; 22 November 2006)

[50] DiMasi, J.A., et al. (2003). Journal of Health Economics **22**: 151-185. http://dx.doi.org/10.1016/S0167-6296(02)00126-1.

[51] Pisano, G.P. (2006). Harvard Business Review **84**(10): 114-125. http://harvardbusinessonline.hbsp.harvard.edu/b02/en/common/item_detail.jhtml?id=R0610H.

[52] http://iri.jrc.es/research/scoreboard_2006.htm.

sector[53], and its trade surplus in 2004 was more than EUR 32 billion, having increased almost five times since 1990[54] (US, Switzerland and Japan are the top three trading partners).

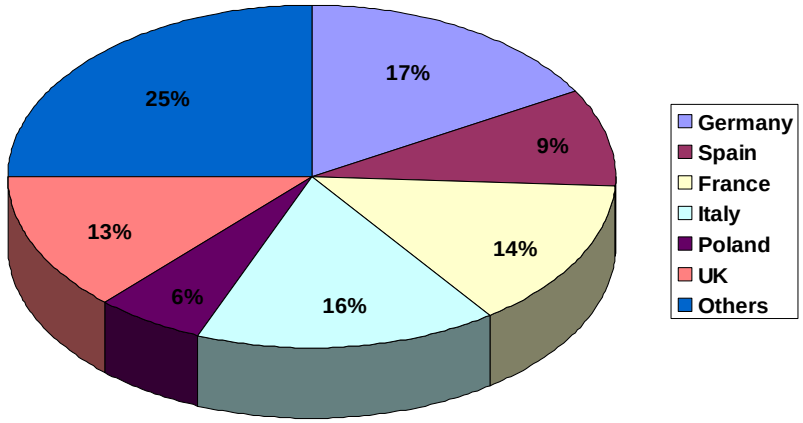

Figure 4: Share of pharmaceutical companies in the EU (2003)
Source: Data from Eurostat[55]

Biopharmaceutical companies (i.e. active in biotechnology) fall in this sector and in this analysis they were identified through the pharmaprojects database[56]. These companies are in their majority focusing on the development of biotechnology-based products for human health whereas only three companies in the EU, two in the US and three in Japan were found to produce recombinant vaccines[57]. The biopharmaceutical sector in the EU has augmented over the last decade (see Table 3), as in 2005 the number of companies was more than double that in 1996. Additionally, biopharmaceutical companies represent a large – and constantly increasing – share of pharmaceutical companies. This observation potentially points to the increasing relevance of biotechnology for the pharmaceutical industry (as more companies opt to develop and produce biotechnology-based drugs) although it should be interpreted with caution as these data have not been weighted for the size of the companies identified (or their turnover).

[53] Eurostat (2006). European business - facts and figures. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-BW-05-001/EN/KS-BW-05-001-EN.PDF.
[54] EFPIA (2006). The pharmaceutical industry in figures. EFPIA, Brussels. http://www.efpia.org/Content/Default.asp?PageID=199. *And:* Eurostat, database.
[55] Eurostat. http://epp.eurostat.ec.europa.eu
[56] This includes all companies that have a minimum of one biotechnological product, i.e. biopharmaceuticals, recombinant vaccines, other (i.e. gene therapy, vectors, cellular products, DNA and RNA products) in clinical trials or launched. Includes both large pharmaceutical companies and biotech companies. Companies are assigned to a country according to their headquarters.
[57] In 2005 these were Sanofi-Aventis (France), Crucell (NL), GlaxoSmithKline (UK) in the EU. In the US two companies were mentioned in the pharmaprojects database (Biogen Idec and Merck & Co). In Japan three companies were listed (Mitsubishi Pharma, Kaketsuken, Research Development Corp).

Table 3: Increase in number of biopharmaceutical companies between 1996 and 2005
Source: ETEPS[58]

	Number of companies in 1996	Number of companies in 2005	Increase (%)
EU	37	143	286
US	102	281	175
Japan	18	22	22

Data on the size and turnover of all EU biopharmaceutical companies are not available. However, some insight may be gained by taking a closer look at the companies responsible for the development of the 21 biopharmaceutical products originating in the EU (the complete list of these can be found in Table 65 of Annex 2 – Human Health). These include both large pharmaceutical firms and small or medium-sized biotechnology companies (see Table 4)[59].

Table 4: Companies that have developed biopharmaceuticals originated in the EU

	Number of products	Country	Pharma	Biotech	Number of employees (2005)	Net sales (EUR billion, 2005)	R&D/Net sales ratio (%, 2005)
Sanofi-Aventis*	4	France	√		97 181	27.3	14.8
Novo-Nordisk	4	Netherlands	√		21 146	4.5	15.1
Bayer	4	Germany	√		61 300**	27.4**	7**
Boehringer-Ingelheim	2	Germany	√		37 406	9.5	14.3
Shire	2	UK	√		2090	1.4	18
GlaxoSmithKline*	1	UK	√		99 503	31.5	14.5
Crucell*	1	Netherlands		√	252	0.033	84.1
AkzoNobel	1	Netherlands	n.a.	n.a.	n.a.	n.a.	n.a.
AstraZeneca	1	UK	√		64 900	20.3	14.1
BTG	1	UK		√	95	0.073	16.2
Total	**21**		**7**	**2**	**383 873**	**153.51**	

*These companies have also developed and market recombinant vaccines. **Data taken from Bayer (http://www.bayer.com/bayer-group/profile-and-organisation/page2351.htm), R&D/net sales ratio calculated by IPTS. n.a.: not available

Together these companies employed 383 873 persons and generated more than EUR 153 billion in net sales, in 2005. This represents a large share of the pharmaceutical sector in the EU, which employed 579 500 people and had a turnover of EUR 171 billion in 2002 (data for 2005 are not available). The share of biotechnology-based product sales in the total sales of these companies may provide an indication of the relevance of biotechnology for the

[58] ETEPS (2006). Bio4EU Task 2, main report.
[59] The classification was taken from the 2006 EU Industrial R&D Investment Scoreboard which ranks 64 pharmaceutical companies and 57 biotechnology companies in the EU top 1000 R&D investors. However, the latter are not specific only for health applications. The classification of these companies has been made on the basis of the ICB (Industry Classification Benchmark) which is in turn based on the company's own classification (i.e. how the company declared itself when it was first introduced in the stock exchange).

economic performance of this industry. Although such information is not available for all biopharmaceuticals originating in the EU, examples can be provided from the case studies. For instance, in 2005, sales of the human insulin analogue glargine reached almost EUR 1.2 billion, accounting for 5.45% of Sanofi-Aventis' total sales[60]. Human insulin sales accounted for over 40% (i.e. EUR 2 billion) of the total sales of Novo-Nordisk.

2.2.3 Economic shares of biopharmaceuticals

In this section the economic shares of biotechnology-based products which are grouped in three main categories, i.e. biopharmaceuticals, vaccines and diagnostics, are analysed. As discussed earlier, biopharmaceuticals represent the most predominant application area in terms of products on the market (see Table 1). The predominance of this group is also reflected in its turnover compared to recombinant vaccines and diagnostics (see Figure 5[61]).

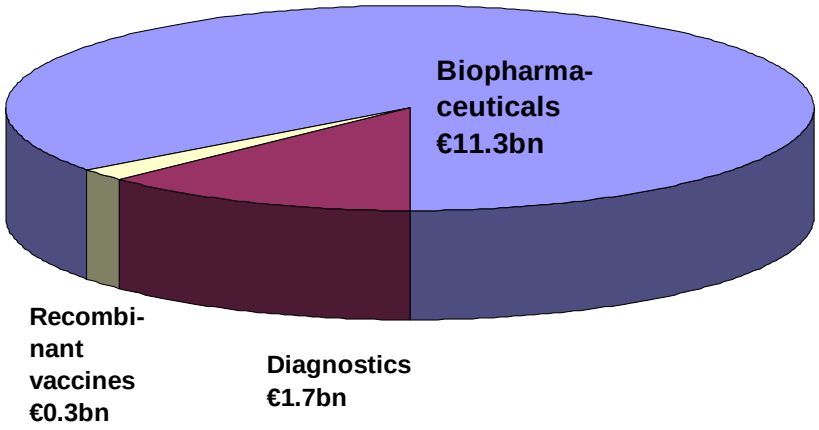

Figure 5: Turnover of modern biotechnology products in the EU (2005)
Source: ETEPS[62], revenues of diagnostics calculated by IPTS

In 2005, the combined turnover[63] of biopharmaceuticals in the EU, the US and Japan (which probably represents about 75% of the world market, similar to pharmaceuticals[64]), was EUR 38.43 billion, representing a 10% share of the combined turnover of the pharmaceutical market of the EU, the US and Japan (see Table 5). The EU share of biopharmaceuticals was 30%.

[60] Sanofi-Aventis is also the originating company for three additional biotechnology drugs (lepirudin, rasburicase and somatropin) but sales data for these drugs individually were not available. Thus the total share of biotechnology drugs in the total sales of this company is likely to be underestimated. A similar issue applies to Novo-Nordisk from which three products originated in addition to insulin aspart biphasic.
[61] Data for diagnostics are for 2004 (estimated by IPTS, based on ETEPS (2006). Bio4EU Task 2, main report).
[62] ETEPS (2006). Bio4EU Task 2, main report.
[63] The analysis of (bio)pharmaceutical revenues on basis of the manufacturer ex-factory prices was carried out in the database IMS MIDAS, owned by IMS Health. All biotherapeutics (biopharmaceuticals without recombinant vaccines) approved by FDA or EMEA as listed by Walsh (see footnote 29) were used by their generic name(s) as basis for biopharmaceuticals. Of this list 16 products (among them 6 monoclonal antibodies, one insulin analogue, two growth hormones and three morphogeneic proteins) could not be found in the database.
[64] EFPIA reports that the worldwide pharmaceutical market was worth about EUR 455 billion in 2005. (http://www.efpia.org/6_publ/infigures2006.pdf). Additionally, the biopharmaceutical market is valued at a range of between EUR 50 billion (EPFIA) and EUR 59 billion (Visiongain (2005). World biotech market 2005. Strategic report VIS020. Piribo, London).

Table 5: Biopharmaceuticals and pharmaceuticals turnover in 2005
Source: ETEPS[65], IPTS calculations

	Turnover of biopharmaceuticals (EUR billion)	Share of total (in %)	Turnover of pharmaceuticals (EUR billion)	Share of total (in %)	Share of biopharmaceuticals out of all pharmaceuticals (in %)
EU	11	30	124	33	9
US	25	65	202	54	12
Japan	2	5	46	12	4
Total	38	100	372	100	10

An analysis of biopharmaceutical turnover in the last ten years (see Figure 6) indicates that their share out of all pharmaceuticals has been constantly growing both in the EU and in the US markets. This observation points to the economic success of biopharmaceuticals, in spite of the lower absolute number of such products on the market (as compared to the numbers of non-biotechnology derived pharmaceuticals), and is further supported when looking at the average turnover per biopharmaceutical available on the market.

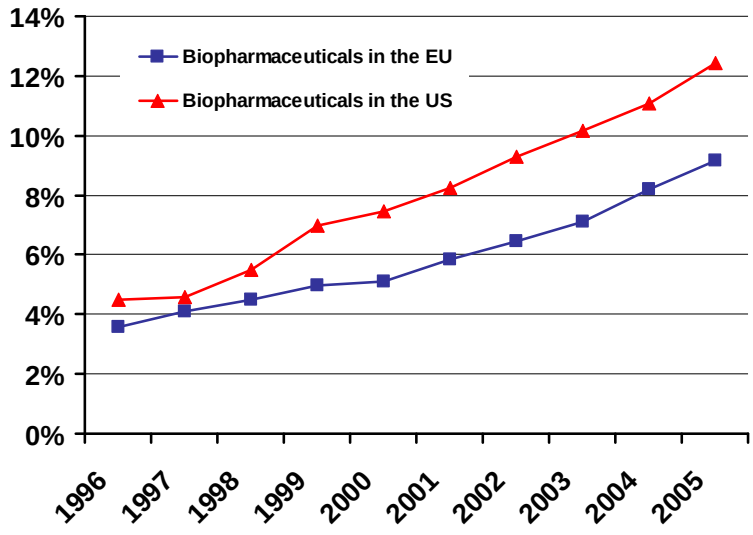

Figure 6: Share of turnover of biopharmaceuticals from all pharmaceuticals
Source: ETEPS[65]

The analysis shows that the average turnover of the EU biopharmaceutical market has almost tripled between 1996 and 2005 (see Figure 7). Nevertheless, the absolute value of turnover per biopharmaceutical in the EU is consistently lower than in the US. This implies that although the numbers of available products in both markets have been comparable over the years (see Figure 2), biopharmaceuticals in the US seem to generate higher turnover. This could be at least partly attributed to differences in the pricing systems applied in the two regions. In the US, pricing follows the free market model and is thus considered a more

[65] ETEPS (2006). Bio4EU Task 2, main report.

lucrative market. In the EU, pharmaceutical prices are regulated, in varying ways, resulting in lower prices paid by EU consumers, when compared with the US[66].

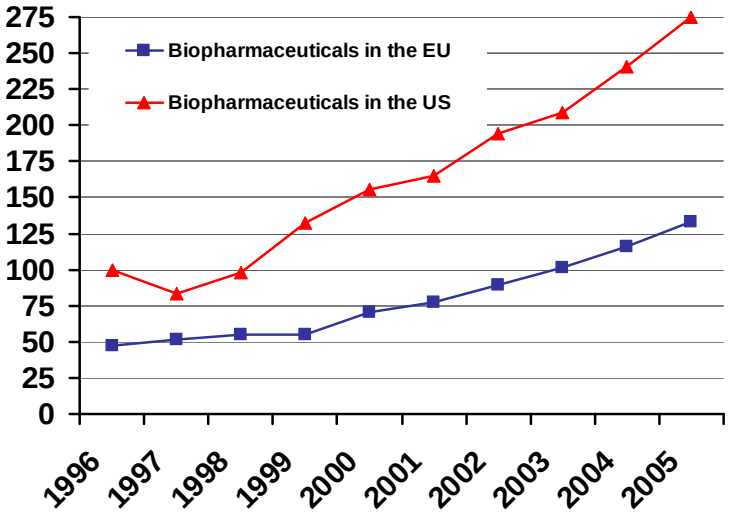

Figure 7: Average turnover per biopharmaceutical on the market (EUR million)
Source: ETEPS[67], IPTS calculations

The growth in turnover from biopharmaceuticals peaked around 2000, and has now reached comparable rates as in previous years, following a trend similar to the pharmaceutical market. However, more notably, the rate of the annual growth of biopharmaceuticals is outpacing that of pharmaceuticals (see Figure 8). In 2005, growth of the biopharmaceutical market in the EU was almost four times higher than that of pharmaceuticals. Moreover, the average annual growth rate of biopharmaceuticals over the last ten years is 23%, as compared to 11% for the EU pharmaceutical market during the same period.

This effect is also observed in the US, where the average annual growth rate of biopharmaceuticals is double (28%) that of pharmaceuticals (14%) (see Figure 9). Thus biopharmaceuticals represent a highly dynamic and fast growing market in spite of its low volume in terms of products.

This rapid increase in the biopharmaceutical market might be at least partly attributed to several blockbuster biotechnology-based drugs. The top 10 selling biopharmaceuticals represented more than half of the entire market value in 2005 having experienced an annual growth of 33.7% (see Table 6). There are two leading product classes: i) erythropoietin (Erypro/Procrit, Aranesp, Epogen) and ii) monoclonal antibodies (Mabthera/Rituxan, Remicade, Herceptin). Interferon (Avonex) and insulin (Lantus) products each represent about 6% of the total sales of these top 10 products.

[66] Golec, J.H. and J.A. Vernon (2006). European pharmaceutical price regulation, firm profitability, and R&D spending. Working paper. Social Science Research Network, Rochester, N.Y. http://ssrn.com/abstract=932989.
[67] ETEPS (2006). Bio4EU Task 2, main report.

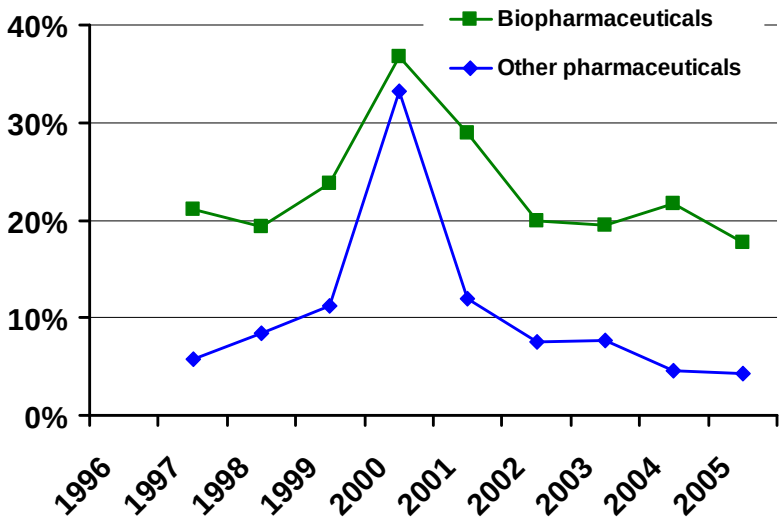

Figure 8: Turnover growth of biopharmaceuticals and pharmaceuticals in the EU 1996 - 2005
Source: ETEPS[68], IPTS calculations

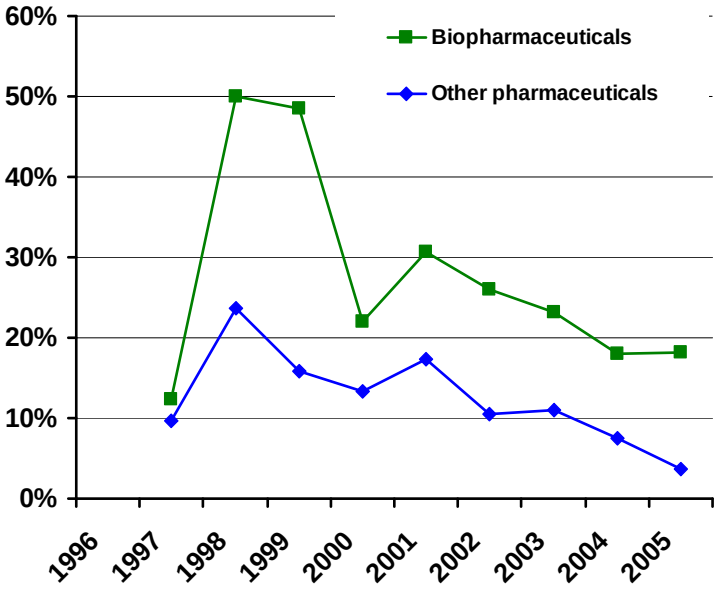

Figure 9: Turnover growth of biopharmaceuticals and pharmaceuticals in the US 1996 - 2005
Source: ETEPS[68], IPTS calculations

From the top 10 selling biopharmaceuticals, only Lantus, an insulin analogue, originated in the EU which might indicate the weaker position of the EU, at least in terms of generating blockbuster drugs. However, biopharmaceuticals produced and marketed in the EU are generating significant turnover. Support for this may be further provided by taking a closer look at the turnover of EU producers of insulin (including analogues) and interferon. Both

[68] ETEPS (2006). Bio4EU Task 2, main report.

product groups are economically important, having generated together a total turnover of about EUR 7 billion[69] (see Table 66 of Annex 2 – Human Health).

Table 6: Top 10 biopharmaceuticals ranked by global sales in 2005
Source: IMS Health, MIDAS, MAT Dec 2005 via EuroBio 2006 Press Kit[70]

Top 10 products	Type	Country	Sales (EUR million, 2005)	Change over 2004 (%)	CAGR 2000 - 2004	Market share 2005 (%)
Global biotech market			**41 175**	17.1	21.4	100
Erypro/Procrit (Johnson & Johnson)	Erythropoietin	US	2897	-8.8	12.8	7
Enbrel (Amgen/Wyeth)	Cytokine	US	2887	40.7	38.9	7
Aranesp (Amgen)	Erythropoietin	US	2800	38	n.a.	7
Remicade (Johnson & Johnson/ Schering-Plough)	Monoclonal antibody	US	2331	17.3	66.7	5.7
Epogen (Amgen)	Erythropoietin	US	2240	-0.8	10.1	5.4
Mabthera/Rituxan (Roche)	Monoclonal antibody	Switzerland	2112	23.6	49.6	5.1
Neulasta (Amgen)	Growth factor	US	1925	31.7	n.a.	4.7
Avonex (Biogen Idec)	Interferon	US	1188	9.6	16.1	2.9
Lantus (Sanofi-Aventis)	Insulin analogue	France	1174	47.5	210.1	2.9
Herceptin (Roche)	Monoclonal antibody	Switzerland	1106	48.2	49.6	2.7
Total (top 10)			**20 661**	**19.4**	**33.7**	**50.2**

CAGR = Compound Annual Growth Rate; n.a.: not available

2.2.4 Economic shares of vaccines

The relative decrease in the number of marketed recombinant vaccines in the EU is also reflected in the development of the share of recombinant vaccines in overall vaccine revenues (see Figure 10). Nevertheless, the turnover in 2005 was still higher than in earlier years. This may be an indication that the (relatively fewer) recombinant vaccines that have been recently marketed in the EU are bigger successes. Indeed, while the average turnover per recombinant vaccine in 1996 was EUR 7.2 million, it more than tripled over the next ten year period and was considered to reach a value of EUR 23.5 million in 2005, similar to the average turnover of vaccines marketed in the US (see Figure 11). In contrast, the average turnover of the other vaccines remained stable at around EUR 17 million. One possible explanation is that recombinant vaccines are increasingly used to prevent infectious diseases, either because they are cheaper, more effective or they are the only vaccine available.

[69] This calculation is based on the turnover of NovoNordisk and Sanofi-Aventis for insulins and Schering and Sanofi-Aventis for interferon-beta.
[70] EuroBIO 2006 Press Kit. http://www.eurobio2006.com/DocBD/press/pdf/18.pdf; all conversions to EUR used this rate: USD 1 = EUR 0.7765 (22 November 2006).

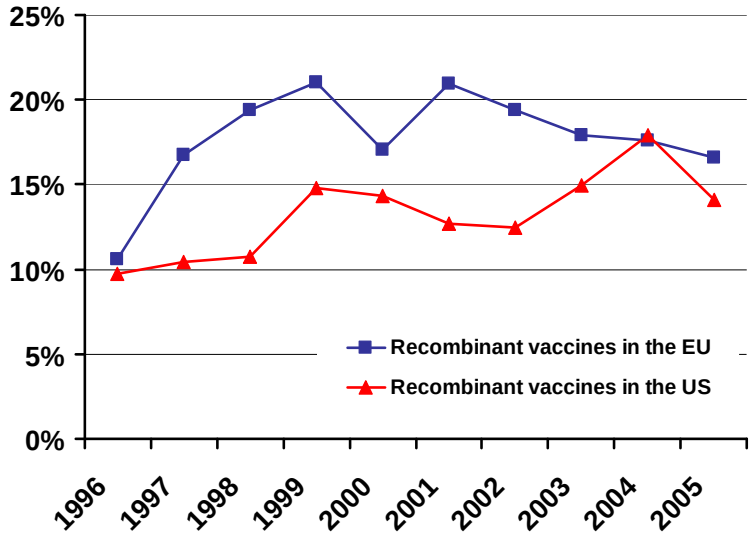

Figure 10: Share of turnover of recombinant vaccines from all vaccines
Source: ETEPS[71]

The growth in turnover from recombinant vaccines relative to overall vaccine turnover shows a more positive growth path than the corresponding development of the recombinant vaccines market in terms of mere product numbers. After an initially strong growth of recombinant vaccine turnover relative to overall vaccine revenues, the growth curve flattens out and the share of recombinant vaccines in the overall vaccines market seems to stabilise at around 17%. In absolute terms, the market value for recombinant vaccines in the EU has almost quadrupled over the last ten years, with revenues growing from EUR 65 million in 1996 to EUR 259 million in 2005. This would correspond to a share of 46% of the total recombinant vaccine market[72], as compared to 54% for the US.

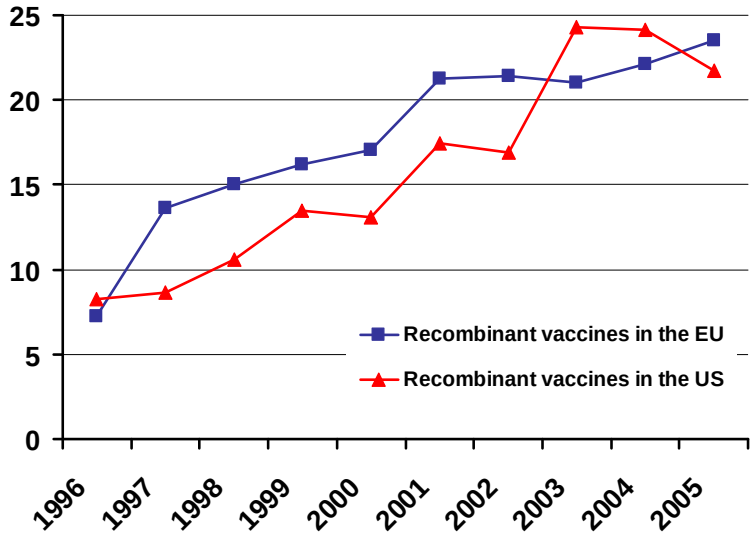

Figure 11: Average turnover per recombinant vaccine on the market (EUR million)
Source: ETEPS[71]; IPTS calculations

[71] ETEPS (2006). Bio4EU Task 2, main report.
[72] Includes the EU, the US and Japan.

Thus recombinant vaccines (which are used as a conservative proxy for analysing the economic impact of modern biotechnology on vaccines) have established themselves on the vaccines market in the EU, where they contribute about 17% of overall revenues. These revenues are generated by relatively fewer recombinant vaccines as compared to all vaccines, potentially indicating that recombinant vaccines tend to be more successful on the market and sell at higher quantities and/or prices than vaccines in general. Given that the economic relevance of vaccines in general for the pharmaceuticals sector is rather small (representing a share of 1.1% in all pharmaceuticals[73]), the economic potential of recombinant vaccines at a more aggregated level may be limited. Still, the over proportionally high revenues these vaccines generate, indicate that recombinant vaccines are sought after and important for disease prevention.

2.2.5 Economic shares of modern biotechnology-based diagnostics

The diagnostics sector is less well defined than the pharmaceutical sector, involving not only companies that develop and/or manufacture these products, but also hospitals and reference laboratories (which can be both service providers and consumers of diagnostic products). Moreover, due to the diversity of these diagnostic tests, it is difficult to obtain information on the absolute numbers of these products (data exist more typically for the types of applications rather than the tests per se). Thus, disaggregated economic data and statistical data specific for modern biotechnology-based diagnostics are scarce. However, data exist on the entire IVD sector[74] and specific application areas. Based on this, the economic share of modern biotechnology in this sector can be estimated.

The global IVD market was estimated to be more than EUR 22 billion in 2004[75] and is predicted to reach over EUR 33 billion in 2010, with an annual growth of 7.1% (see Table 7). This included diagnostic tests in the areas of clinical chemistry, immunochemistry, diabetes, microbiology, haematology, point of care testing, molecular diagnostics, etc[76]. The US had a 42% share in all IVDs, and five EU countries (France, Spain, Germany, Italy and the UK)

[73] Includes the EU, the US and Japan.

[74] This does not include medical device companies or manufacturers of diagnostic equipment.

[75] ETEPS (2006). Bio4EU Task 2, main report.

[76] The following definitions were applied: **Clinical chemistry**: Tests for cardiac enzymes, cholesterol, drugs of abuse (DOA), electrolytes, glucose, hepatic enzymes, lipids, proteins, and therapeutic drug monitoring (TDM) **Diabetes testing**: Lab tests that diagnose diabetes and monitor glucose levels, such as fructosamine and glycohaemoglobin (HB1Ac) tests **Haematology**: Tests for complete blood count (CBC), red blood cell (RBC) count, haemoglobin (Hb), haematocrit (Hct), platelet count, white blood cell (WBC) count, white blood cell differential (3-diff/5-diff), and blood and tissue groups **Haemostasis**: Tests for activated clotting time (ACT), activated partial thromboplastin time (aPTT), factors Xa and Iia (thrombin), low weight molecular heparins (LWMH), and prothrombin time (PT) **Immunochemistry**: Tests for allergies, anaemia markers, cancerous tumour markers, and hormones **Microbiology**: Tests based on culture techniques **Molecular Diagnostics**: Tests for bacteria (chlamydia trachomatis (CT), neisseria gonorrhoeae (GC), mycobacterium tuberculosis (MTB), viruses (HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), including nucleic acid-based amplification tests (NATs)) **Point of Care (POC)**: Tests for cardiology, coagulation, diabetes, drugs of abuse (DOA), **Self-Monitoring Blood Glucose (SMBG)**: Device that obtains a drop of blood to test for blood sugar level. Most often used by diabetics for home testing. **Urine testing**: Tests done on urine in order to monitor the treatment of certain conditions such as diabetes, kidney stones, a urinary tract infection, hypertension, or some types of kidney or liver disease.

represented 26% (EUR 5.8 billion). Another recent report has estimated the value of the total IVD market in Europe to be EUR 8.9 billion in 2004[77].

Table 7: Worldwide IVD market and growth forecasts
Source: ETEPS[78]

Segment	Worldwide IVD market 2004 (EUR billion)	Worldwide IVD market 2010 (EUR billion)	CAGR (%)
Clinical chemistry	5.2	6	2.6
Immunochemistry	5.4	7.2	4.7
Diabetes	0.35	0.48	5.5
Microbiology	1.2	1.8	5.7
Haematology	1.5	1.8	3.9
POC	1.2	2.2	10.9
Haemostasis	0.85	1.6	10.2
Molecular diagnostics	1.2	2.8	15.3
Urine	0.42	0.6	5.3
SMBG	4.4	8.4	11.5
Others	0.42	0.5	3.6
Total	**22.14**	**33.4**	**7.1**

CAGR = Compound Annual Growth Rate

Although data on the share of modern biotechnology-based diagnostics in IVDs are not available, an estimate can be derived based on the information above. As discussed earlier (see Table 2), these products fall mainly in the category of immunochemistry and molecular diagnostics (other categories might also include modern biotechnology-based tests but their shares in these groups are probably much smaller and are thus not included in the following estimates). Thus, in 2004, modern biotechnology diagnostics represented a share of almost 30% in all IVDs, with estimated revenues of EUR 6.6 billion. The five EU countries mentioned above held 26% of this market (i.e. tests in immunochemistry and molecular diagnostics) with EUR 1.7 billion in estimated revenues. The US held a share of 51%. Table 8 summarises these findings.

The two groups of diagnostics where modern biotechnology is mainly applied are expected to experience dynamic growth. Molecular diagnostics are predicted to grow at the fastest rate, when compared with all other groups of IVDs, and is likely driven by the emergence of 'omics' high-throughput technologies (genomics, proteomics, metabolomics) allowing both earlier diagnosis (e.g. based on the correlation of specific biomarkers to a disease) as well as more tailor-made applications such as measuring individual responses to drugs, or predicting the risk of disease recurrence (e.g. Oncotype Dx is a test based on 16 genes used for

[77] ETEPS (2006). Bio4EU Task 2, main report. Extrapolation was based on the following 14 countries: Germany, Italy, France, Spain, the UK, Switzerland, Belgium, the Netherlands, Austria, Portugal, Greece, Finland, Poland, Czech Republic.
[78] ETEPS (2006). Bio4EU Task 2, main report. Includes: US, Canada, Japan, Germany, Italy, France, Spain, the UK, China, Brazil, Russia, Mexico, India, Korea, Taiwan, Indonesia, and the rest of the world.

predicting the risk of recurrent breast cancer)[79]. In addition, immunochemistry tests are predicted to reach EUR 7.2 billion by 2010 at an annual growth of 4.7%.

Table 8: Estimate of modern biotechnology-based diagnostics[80] and IVDs revenues in 2004
Source: ETEPS[81]

	Modern biotechnology-based diagnostics (EUR billion)	Share of total (in %)	IVDs (EUR billion)	Share of total (in %)	Regional share of biotechnology in IVDs (in %)
EU*	1.7	26	5.8	26	29
US	3.4	51	9.3	42	37
Others	1.5	23	7.04	32	24
Total	6.6	100	22.14	100	30

*Includes: the UK, France, Spain, Italy, and Germany

As regards companies, it is difficult to delineate those that are exclusively dedicated to the development of diagnostics based on modern biotechnology. Thus, an evaluation of the economic relevance of such manufacturers is hampered. However, information exists on the leading IVD companies worldwide, based on revenues. The majority of the top 15 companies are based in the US, but two EU companies are also present. These are: i) Bayer Diagnostics (Germany) whose IVD sales of almost EUR 2 billion in 2005 represented 8% of its total sales, and ii) BioMerieux (France) whose total sales in 2005 resulted from IVDs (EUR 0.9 billion). Both of these companies produce molecular diagnostics products and immunodiagnostics (e.g. for HIV, hepatitis), although it is not clear what share out of all their diagnostic activity these represent.

Overall the lack of more precise (disaggregated) information on, e.g. the absolute numbers and origin of diagnostic products based on modern biotechnology and the share of such products in all activity of IVD companies, hampers the detailed analysis of the economic relevance of this modern biotechnology application. Nevertheless, it represents a considerable economic activity in the EU with an estimated share of 29% in all IVDs in the EU and 26% of that worldwide. The contribution of this sector to the EU economy is further estimated in Section 2.2.6 below.

2.2.6 Contribution of modern biotechnology applications to the EU economy

The data presented thus far point to the growing economic significance of modern biotechnology applications (i.e. biopharmaceuticals, recombinant vaccines and diagnostics) for the EU pharmaceutical industry (NACE DG 24.4) which contributes 4% of the value-added in total manufacturing. To assess the overall economic contribution of biopharmaceuticals and vaccines to the pharmaceutical sector, their share of value-added is

[79] Batchelder, K. and P. Miller (2005). Nature Biotechnology **24**: 922-926. http://dx.doi.org/10.1038/nbt0806-922.
[80] Immunochemistry and molecular diagnostics.
[81] ETEPS (2006). Bio4EU Task 2, main report.

evaluated here (see Table 9). The revenues in the pharmaceutical industry totalled EUR 171 billion for the EU in 2002 and the corresponding value-added was EUR 58 billion. Thus, the share of value-added in pharmaceutical revenues was 34%. Making the conservative assumption that the revenue share of value-added through biotechnology applications in the pharmaceuticals industry is the same (despite it being a newer technology that may, e.g. have efficiency advantages), the value-added from biopharmaceuticals and recombinant vaccines can be derived from the revenue these products generated in the same year[82]. A similar approach may be applied to derive the value-added of diagnostics. Modern biotechnology-based diagnostics can be related to the pharmaceutical sector, as these products include reagents (e.g. antibodies) and kits (or their individual components)[83], which are typically produced by the same companies that develop biopharmaceuticals and recombinant vaccines. The estimated revenues of diagnostics based on modern biotechnology in 2004, were EUR 6.6 billion. Hence, an approximation for the overall contribution of biotechnology to the value-added in the pharmaceuticals sector in 2002 would be more than 5% (see Figure 12), and its contribution to the value-added in the overall chemicals sector (NACE DG 24) would be almost 2%.

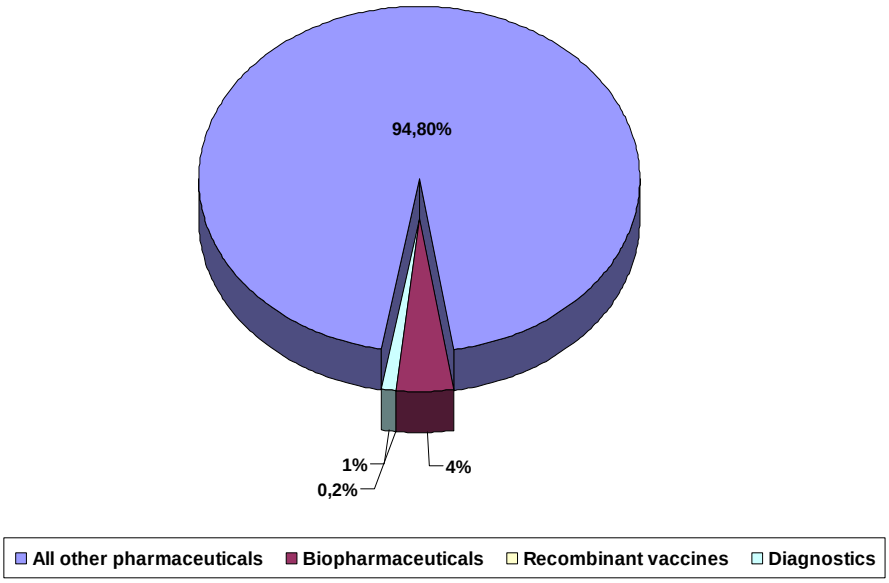

Figure 12: Share of modern biotechnology products in pharmaceuticals gross value-added

Biopharmaceuticals hold the largest share of value-added in the pharmaceuticals sector, which could be partly attributed to the commercial success of blockbuster biotechnology-based drugs such as interferon-beta. In addition, biopharmaceuticals contribute 0.2% to the total manufacturing value-added, which is comparable to two subsectors of chemicals, namely agrochemicals (NACE DG 24.2) and man-made fibres (NACE DG 24.7) (see Table 9). This finding indicates the significant economic value of these products, in spite of their low volume (in terms of products). Collectively, biotechnology-based products in the area of human health, contribute an estimated 0.25% to the total value-added of the manufacturing sector, and in turn about 0.04% to the value-added of the total EU economy.

[82] It is noted that the contribution of biotechnology to the EU economy is estimated based on EU market shares (i.e. the total revenues of all biotechnology-based products marketed in the EU) rather than the revenues of those biotechnology-based products which are manufactured and produced by EU companies.
[83] Diagnostic instruments and testing systems have not been included in this analysis.

It should be noted though that the current analysis may underestimate the economic contribution of biopharmaceuticals, diagnostics and recombinant vaccines as it does not consider indirect economic impacts (i.e. economic impacts that result from their end use, like cost savings in hospitals, etc.). Some of these impacts will be discussed later in a more qualitative manner in Section 4.2.

Table 9: Contribution of modern biotechnology-based applications to the EU economy

EU – 2002	Turnover (EUR billion)	GVA (EUR billion)	Share of chemicals GVA (%)	Share of manufacturing GVA (%)	Share of EU GVA (%)
EU (all economic activity)		8783			100
Manufacturing (NACE D)	5799	1529		100	17.4
Chemicals (NACE DG 24)	601	171	100	11	2
Basic chemicals (NACE DG 24.1)	246	65	0.7	4	0.7
Agrochemicals (NACE DG 24.2)	12	2.5	0.03	0.2	0.03
Paints (NACE DG 24.3)	37	11	0.1	0.8	0.1
Pharmaceuticals (NACE DG 24.4)	**171**	**58**	**34**	**4**	**0.7**
Detergents (NACE DG 24.5)	68	17	0.2	1	0.2
Other chemicals (NACE DG 24.6)	53	15	0.2	1	0.2
Man-made fibres (NACE DG 24.7)	12	3	0.03	0.2	0.03
Biotechnology-based products					
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*
Total biotech	***9***	***3.1***	***1.86***	***0.25***	***0.04***

*EU-19; ** Includes: the UK, France, Spain, Italy, and Germany, 2004; figures in italics are estimates; GVA: gross value-added

Other indirect impacts which could further augment the economic significance of biotechnology for the pharmaceutical sector are related to the application of biotechnology in the development and production of non-biotech drugs, e.g. small molecules. Although no quantitative data measuring this impact exist, the results of experts' interviews[84] indicated that the share of biotechnological processes related to chemical processes applied in production is estimated in a range of between 10% and 15%, and in the future the increase of this share is foreseen. However, the evaluation of the direct economic consequence of the use of biotech in small molecule drug development and production is, at the moment, not possible.

[84] 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. ETEPS (2006). Bio4EU Task 2, main report.

2.2.7 Contribution of modern biotechnology to employment

In 2002, the pharmaceutical sector employed 579 500 persons[85]; data for more recent years are not available. An indication for the size of the EU pharmaceutical sector in terms of employed persons in more recent years may be provided through the 2006 EU Industrial R&D Investment Scoreboard[86]. Based on this, the 62 out of the 64 pharmaceutical companies who ranked in the top 1000 by R&D investment employed 525 492 persons in 2005[87]. In this context, due to limited data availability, it is difficult to evaluate whether and how much employment was created as a result of modern biotechnology adoption in the pharmaceutical sector.

Some estimates may be made for the employment figures related to specific biotechnology-based products on the basis of their sales as a proxy (e.g. for insulin and insulin analogues). However, such estimates would have to be treated with great caution, company personnel are not generally organised by product type. It is difficult to directly relate the staff employed in production, sales, management and administration to one single product. Additionally, it is not clear as to what extent R&D staff (which would be included in the estimates) are involved in work on these established products, or what share of the total employees in each company is actually employed within the EU, as the majority of these companies are present in several countries outside the EU as well. Finally, although biotechnology-based products may be marketed by EU companies, very few of these products have actually originated from the EU, which makes it more difficult to evaluate changes in employment that are associated with the introduction of modern biotechnology. The lack of such data also hampers the assessment of labour productivity (i.e. the relation of value-added to employment) in biotechnology-specific applications in the pharmaceutical industry.

Health biotechnology applications may also indirectly influence employment through its impact on public health (see Section 4.2). Hence, irrespective of the general improvements in social welfare, in as much as better healthcare enables people to stay in their jobs, or to reduce times of absence, it also helps to maintain a productive workforce, which again, is a prerequisite for economic growth. However, the quantification of this indirect impact is also hampered by the lack of relevant statistics.

2.2.8 EU - US comparison

2.2.8.1 Performance of pharmaceutical industries

The performance of the overall pharmaceutical industry in the EU and the US is quite different, not only in terms of value-added but more importantly as regards labour productivity. In 2000, the value-added of the US pharmaceutical industry was 40% higher than the value-added of its counterpart in the EU. At the same time, the EU pharmaceutical industry employed almost twice as many persons as the US, thus resulting in lower apparent

[85] Eurostat, database.
[86] http://iri.jrc.es/research/scoreboard_2006.htm.
[87] Data for the two remaining companies were not available.

labour productivity[88]. Although more recent data for these indicators are not available (at least for the US), similar trends are reported for 2001[89]. The US pharmaceutical companies[90] are leading in worldwide sales, with nine out of the top 20 pharmaceutical companies with the highest sales being US based. The EU compares well in that respect (in total six EU companies are found in the top 20)[91]. However, the US is also leading in terms of innovation, with consistently higher R&D investment in the last ten years, and having generated a higher share of new molecular entities[92].

A similar situation is reflected in the performance of the EU regarding modern biotechnology applications[93]. Although the current analysis indicates that modern biotechnology-based products are an important component of the pharmaceutical sector contributing to the total economy of the EU (discussed in Section 2.2.6), the EU is still lagging behind the US in its overall performance. In absolute numbers, fewer biopharmaceuticals have originated from the EU than the US, but the average number of products launched per year in the two markets is comparable.

However, this corresponds to very different market values (see Table 10). The EU represents 30% of the total[94] turnover of biopharmaceuticals, and the US holds a 65% share (see Table 5). Both markets have been constantly growing since 1996 at comparable average annual growth rates (23% in the EU and 28% in the US). This expansion may be also reflected in the increase of biopharmaceutical companies (see Table 3). In this context, the EU biopharmaceutical industry grew more dramatically than the US, although in absolute terms it still has fewer companies.

As regards recombinant vaccines, the EU compares well with the US, having generated 26% of all the recombinant vaccines available worldwide as compared to 17% from the US. Moreover, the average turnover per recombinant vaccines in the EU has increased significantly over the last decade surpassing that in the US (see Figure 10). A detailed comparison between the EU and the US regarding diagnostics is rather hampered by the lack of disaggregated data, as discussed in Section 2.2.5. Nevertheless, it was estimated that the EU holds a 26% share in all modern biotechnology-based diagnostics, as compared to 51% held by the US (see Table 8).

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[88] Vekeman, G. (2005). Statistics in focus **44**. European Communities, Luxembourg. http://epp.eurostat.ec.europa.eu/pls/portal/url/page/PGP_MISCELLANEOUS/PGE_DOC_DETAIL?p_product_code=KS-NP-05-044.

[89] Pammolli, F. et al. (2004). European competitiveness in pharmaceuticals. European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/docs/eupharma_28102004_1.pdf.

[90] The number of companies of the US pharmaceutical industry is not clear. The Pharmaceutical Research and Manufacturers of America (PhRMA) represents about 48 companies including pharmaceutical and biotech firms (http://www.phrma.org/about_phrma/member_company_list/members/).

[91] The top 20 companies include Pfizer, Johnson & Johnson, Merck & Co., Abbott, Bristol Myers Squibb, Wyeth, Eli Lilly, Amgen, and Schering-Plough from the US, GlaxoSmithKline, Sanofi-Aventis, AstraZeneca, Boehringer Ingelheim, Bayer, and Schering AG from the EU, Novartis and Roche from Switzerland, Takeda and Daiichi Sankyo from Japan and Teva from Israel.

[92] EFPIA (2006). The pharmaceutical industry in figures. EFPIA, Brussels. http://www.efpia.org/Content/Default.asp?PageID=199.

[93] The comparison does not include value-added or labour productivity related specifically to biotechnology applications due to the lack of statistical data.

[94] Includes the EU, US and Japan.

Table 10: Turnover of modern biotechnology-based products in the EU and the US
Source: ETEPS[95], revenues of diagnostics calculated by IPTS

	Turnover modern biotechnology-based products (EUR billion)	
	EU	**US**
Biopharmaceuticals*	11	25
Recombinant vaccines*	0.3	0.3
Diagnostics**	1.7	3.4
Total	**13**	**28.7**

***Data from 2005; ****Estimate; EU includes the UK, France, Spain, Italy and Germany, data from 2004

In summary, the available data indicate the EU is still lagging behind the US regarding the generation of economic gain from biotechnology applications. Additional information also suggests that the future improvement of the EU's position may be hampered by the limited innovativeness of EU companies compared with their US counterparts.

2.2.8.2 Pharmaceutical markets and policies

One reason that is mentioned as being potentially responsible for the different performance of EU and US pharmaceutical (and health biotechnology) companies, regarding, for example, their R&D activities and turnover, as discussed in Section 2.2.8.1, is the difference between the pharmaceutical markets in EU Member States and in the US. First, unlike in the US, within the EU there is no single market for pharmaceuticals; rather, in the EU this market is characterised by a distinction between national and European competences: while nearly every aspect of a drug's development is subject to Community legislation, once the product has been authorised, its control largely falls within the national systems for important issues such as pricing, reimbursement and distribution[96]. Second, while in the US government policies rely more on competition and a less regulated market approach[97], within the EU a broader mix of policies can be found: whether and how pharmaceutical prices are regulated varies from country to country, ranging from free pricing to fixed prices[98].

In the US, the view held is that the development of innovative pharmaceutical products (i.e. the quality aspect) plays a critical role in ensuring future health gains and increasing longevity – and that without economic incentives private companies, which bring the vast majority of new drugs to the market, would be less able to assume the risks and costs of continuing their R&D activities. Therefore incentives that favour innovation are provided through direct and indirect government funding, intellectual property laws and other policies. In this context,

[95] ETEPS (2006). Bio4EU Task 2, main report.
[96] European Commission (2006). Evaluation of the G10 medicines initiative: interim evaluation. Evaluation report. Enterprise and Industry DG. http://ec.europa.eu/dgs/enterprise/pdf/Evaluation_of_approaches.pdf.
[97] US DOC (2004). Pharmaceutical price controls in OECD countries: implications for US consumers, pricing, research and development, and innovation. International Trade Administration, US Department of Commerce, Washington, D.C. http://www.ita.doc.gov/drugpricingstudy.
[98] Mrazek, M.F. (2002). Croatian Medical Journal **43**: 453-461. http://www.cmj.hr/2002/43/4/12187524.pdf.

competitive pressure from a generic pharmaceutical industry is relied upon to lower drug prices[99].

In this context, in many EU Member States the emphasis is put on the importance of affordable drugs for all and on efficient public healthcare systems (i.e. on access and efficiency aspects), as these are fundamental for a widespread realisation of health gains and the achievement of a higher life expectancy. Therefore, in many countries attempts are made to control rising pharmaceutical and healthcare costs by regulating the pharmaceuticals market through different combinations of demand and supply interventions (e.g. price controls, restrictive reimbursement policies or the use of positive and negative lists). Another reason for regulatory interventions to contain drug costs are imperfections in the pharmaceuticals market that may lead to market failure[100].

Given the above-mentioned discussion, the actual outcomes of the healthcare systems in the US and in EU Member States in terms of relative expenditure on pharmaceuticals show a different picture (see Figure 13).

While the US clearly has the most expensive healthcare system of all OECD countries (in 2003 the US spent 15.2% of gross domestic product (GDP) on health, while Switzerland, the second 'most expensive' country, spent 11.5%, with South Korea spending the least on health, namely 5.5% of GDP), in terms of relative expenditure on pharmaceuticals, no clear distinction can be drawn between the various systems. For instance, France and Portugal, where pharmaceuticals are subject to price controls[101], spend 2.0% and 2.2%, respectively, of GDP on pharmaceuticals, while the US, with a less regulated market, spend 1.9% of GDP. On the other hand, for instance the Netherlands and Ireland, where pharmaceuticals are also subject to price controls, spend only 1.0% and 0.8%, respectively, of GDP on pharmaceuticals, but New Zealand, where suppliers are able to market their products with no constraints on pricing[102], spends only 1.1% of GDP as well.

This situation may partly be explained by the fact that each system mixes regulatory components with free market approaches, although to a different extent. For instance, although in the US the federal government does not set or regulate the price pharmaceutical manufacturers can charge for prescription drugs, federal laws ensure that manufacturers extend significant price discounts to federal agencies and selected public sector purchasers[103]. And only recently the US government proposed to intensify the use of reference pricing in its

[99] US DOC (2004). Pharmaceutical price controls in OECD countries: implications for US consumers, pricing, research and development, and innovation. International Trade Administration, US Department of Commerce, Washington, D.C. http://www.ita.doc.gov/drugpricingstudy.

[100] Mrazek, M.F. (2002). Croatian Medical Journal 43: 453-461. http://www.cmj.hr/2002/43/4/12187524.pdf. *And:* Kanavos, P. (2001). Overview of pharmaceutical pricing and reimbursement regulations in Europe. Enterprise and Industry DG, European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/docs/synthesis.pdf.

[101] Kanavos, P. (2001). Overview of pharmaceutical pricing and reimbursement regulation in Europe. Enterprise and Industry DG, European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/docs/synthesis.pdf. *And:* European Commission (2005). LSE study on healthcare in individual countries, G10 Medicines. Country profiles. Enterprise and Industry DG. http://ec.europa.eu/enterprise/phabiocom/p6.htm.

[102] Braee, R. (2005). LSE study on healthcare in individual countries, G10 Medicines. Country profile New Zealand: pharmaceutical pricing and reimbursement policies. Enterprise and Industry DG, European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/p6.htm.

[103] Hansen, J. (2005). LSE study on healthcare in individual countries, G10 Medicines. Country profile United States: prescription drug and reimbursement policies. Enterprise and Industry DG, European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/p6.htm.

Medicaid programme for low income people[104], which is already a well established practice in the US for generically equivalent products (through the use of a 'maximum allowable charge' for reimbursement in managed care programmes)[105].

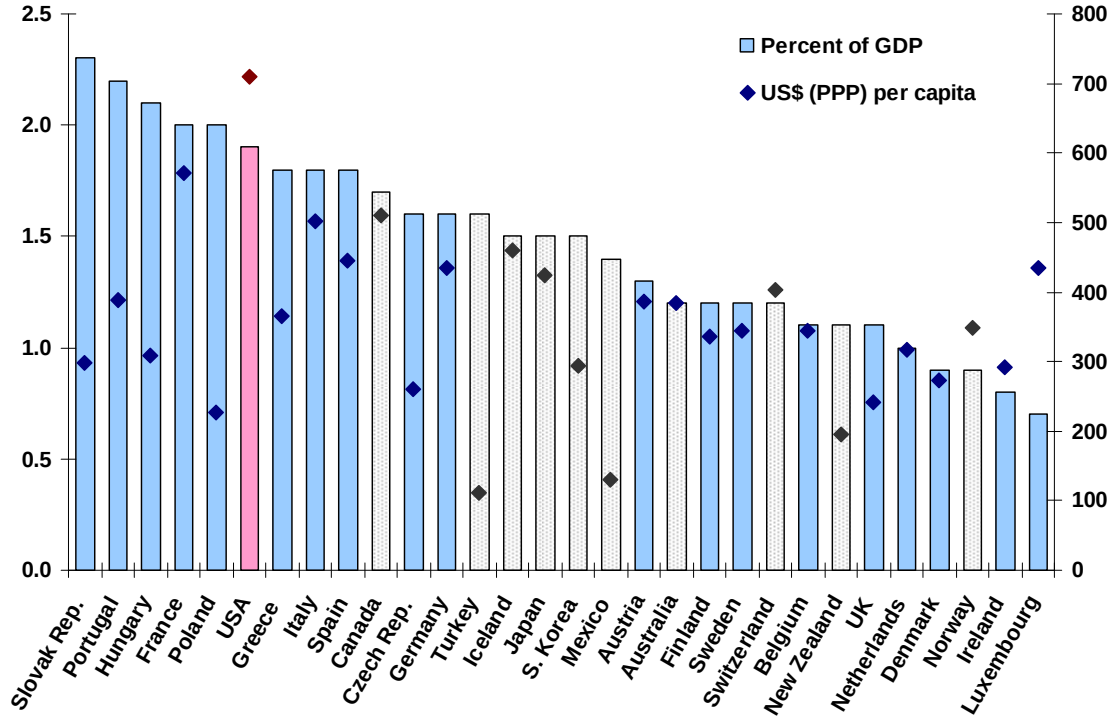

Figure 13. Total expenditure on pharmaceuticals and other medical non-durables (OECD countries, 2003)
Source: OECD (2006)[106]
Note: EU Member States are depicted in blue, the US in red. For Hungary, the Czech Republic, Turkey, New Zealand, the UK and the Netherlands the last available figures (before 2003) were used. US$ (PPP) stands for USD that are expressed as 'purchasing power parity' to make the expenditures more comparable across countries.

Still, the differences between the pharmaceutical pricing and reimbursement policies in different countries, especially between the US and elsewhere, have also given rise to accusations by the US side regarding other countries 'free-riding' on R&D that would be financed by the higher prices that could be charged by pharmaceutical companies in the US[107]. Yet, while the validity of such allegations has been questioned[108], the concern on the EU side is more the increasing competitiveness of US companies in the pharmaceutical

[104]Pear, R. (2006). US is proposing to cut medicaid's drug payments. The New York Times (New York), 18 December. http://www.nytimes.com/2006/12/18/washington/18medicaid.html.
[105] Danzon, P.M. and Ketcham J. D. (2003). Reference pricing of pharmaceuticals for medicare: evidence from Germany, the Netherlands, and New Zealand.NBER Working Paper 10007. http://www.nber.org/papers/w10007.
[106] OECD Health Data 2006. Organisation for Economic Co-operation and Development, Paris. Available online at http://www.oecd.org/document/30/0,2340,en_2649_34631_12968734_1_1_1_1,00. html.
[107] McClellan, M.B. (2003). Speech before the first international colloquium on generic medicine, by the Commissioner of the US Food and Drug Administration, Washington, D.C., on 25 September. http://www.fda.gov/oc/speeches/2003/genericdrug0925.html. *And:* Aldonas, G.D. (2004). Testimony before the joint session of the Senate Finance Committee, Subcommittees on Health and Trade on "International Trade and Pharmaceuticals", by the Under Secretary of Commerce for International Trade of the US Department of Commerce, Washington, D.C., on April 27. http://www.mac.doc.gov/PressMain/Apr2004/27AprTestimony.htm.
[108] Light, D.W. and Lexchin J. (2005). British Medical Journal **331**: 958-960. http://dx.doi.org/10.1136/bmj.331.7522.958; rapid responses http://www.bmj.com/cgi/eletters/331/7522/958.

sector, which historically has been a stronghold of the European industry. This is attributed to structural differences, like lower labour productivity and lower value-added activities in the EU pharmaceutical industry (due to less rationalisation), to slower demand growth in its home markets, to the failure of the EU industry to specialise and integrate vertically, and to inefficiencies that are induced by a lack of competition in the pharmaceutical markets of some EU Member States[109].

2.2.9 Regulatory issues

2.2.9.1 Biosimilars

The emergence of biogeneric drugs or biosimilars will be an important factor in the future economic performance of biopharmaceuticals, especially as several of the available biotechnology-based drugs are facing patent expiration in the next few years or patents have already expired (e.g. for Humulin, Epogen, Procrit)[110]. The introduction of biosimilars into the market is expected to increase competition which could, in turn, help reduce healthcare costs but could also contribute to the improvement of product quality[111]. At the same time, biosimilars (just like generics) appear to influence the emergence of new players in the world pharmaceutical market, such as India[112], China and South Korea.

However, several issues complicate the development and regulatory approval of biosimilars. The manufacturing of a recombinant protein drug is far more complex than that of small molecule drugs involving many steps which could influence its biological properties (e.g. stability, immunogenicity). In this context, some experts argue that two biopharmaceuticals based on the same protein can never be completely identical and therapeutically equivalent. The possibility to demonstrate bioequivalence (including safety and efficacy) is also debated. EMEA has issued recommendations on the approval of biosimilars (or biogenerics), stating that in cases where satisfactory equivalence cannot be demonstrated with existing analytical methods, a full preclinical and clinical data package would be required for approval[113].

Although the FDA has yet to publish recommendations on this, industry experts suggest that full clinical trial data must be required for the approval of biosimilars, as the pharmacokinetic equivalence of two proteins may not be sufficient to predict safety and efficacy. In spite of these uncertainties, the first biogeneric drug, Omnitrope (a recombinant growth hormone) was recently approved in the EU, following a positive evaluation by EMEA. It is also approved in Australia. In the US, Omnitrope received FDA approval as the first follow-on version of a

[109] Gambardella, A., L. Orsenigo and Pammolli F. (2000). Global competitiveness in pharmaceuticals, a European perspective. Report. Enterprise and Industry DG, European Commission, Brussels. http://ec.europa.eu/enterprise/phabiocom/p3.htm.

[110] Schellekens, H. (2005). Nephrology Dialysis Transplantation **20**: iv31-iv36. http://dx.doi.org/10.1093/ndt/gfh1085.

[111] Schellekens, H. (2004). Trends in Biotechnology **22**: 406-410. http://dx.doi.org/10.1016/j.tibtech.2004.06.003.

[112] Jayaraman, K.S. (2003). Nature Biotechnology **21**: 1115-1116. http://dx.doi.org/10.1038/nbt882.

[113] Committee for Proprietary Medicinal Products (2003). Guideline on comparability of medicinal products containing biotechnology derived proteins as active substances: quality issues. CPMP/BWP/3207/00. European Medicines Agency, London. http://www.emea.europa.eu/pdfs/human/bwp/320700en.pdf. *And:* Committee for Medicinal Products for Human Use (2005). Guideline on similar biological medicinal products. CHMP/437/04. European Medicines Agency, London. http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf.

previously approved recombinant drug, although a specific regulatory pathway for the approval of biogenerics in the US remains to be defined.

2.2.9.2 Intellectual property

Modern biotechnology advances have led to the development of new drugs and enabling tools for the diagnosis of diseases. Additionally, the completion of the human genome project has facilitated the association of specific genetic sequences to a disease, thus allowing the identification of novel putative drug targets. Because of their potentially significant economic (and public health) implications, modern biotechnology applications are increasingly being patented (some biotechnology patents are listed in Table 11).

Table 11: Examples of biotechnology patents granted in the US
Source: A. Cohen 2002[114]

Patent	Type	Assignee
Polymerase Chain Reaction (PCR)	Process: automated multiplication of small amounts of DNA	Initially Cetus Corp., now Hoffman La-Roche (four patents in 1987, 1989, 1990)
Oncomouse	Animal model: genetically-modified mouse (through the insertion of an oncogene) for the study of cancer and related drug targets	Harvard University, 1988
Hepatitis B vaccine	Proteins: intermediates triggering production of antibodies against the virus	Biogen, Regents (1987) of the University of California (1988), Institute Pasteur (2000) (one patent each)
HIV protease inhibitors	Molecules inhibiting the action of HIV protease thus blocking viral replication	Merck & Co. Inc. (1995)
Human embryonic stem cells	Isolation and culture process, cell line can differentiate into any type of tissue	Wisconsin Alumni Research Foundation (2001)

Patenting is considered to have a stimulating effect on innovation, by allowing the inventor 'freedom to operate', which may in turn drive investment[115]. However, it is also suggested 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[116]. Drug patents are often under scrutiny especially when the drug in question is targeting a disease with important implications for public health, such as HIV/AIDS. In this context, the use of HIV protease inhibitors in the treatment of HIV/AIDS may cost up to USD 6000/year, but most annual healthcare budgets in developing countries, where the disease prevalence is very high, do not exceed USD 100 per patient[117]. Consequently, limited access to available therapy might have a negative impact on the control of the HIV/AIDS epidemic. To help regulate such situations, the Agreement on Trade-Related

[114] A. Cohen (2002): Copying DNA; Mighty Mouse; Killing Hepatitis; The AIDS drug; Frosh cells; all accessed via http://www.law.com.
[115] Nunnally, A.C. et al. (2005). Community Genetics **8**: 209-216. http://dx.doi.org/10.1159/000087957.
[116] Jensen, K. and Murray, F. (2005). Science **310**: 239-240. http://dx.doi.org/10.1126/science.1120014.
[117] Schmidt, C.W. (2001). Modern Drug Discovery **4**(6): 25-28. http://pubs.acs.org/subscribe/journals/mdd/v04/i06/html/06rules.html.

Aspects of Intellectual Property Rights (TRIPs)[118] allows countries to break a patent under certain emergency conditions (e.g. a national epidemic). In addition, the provision of a 'compulsory license' (with more favourable conditions for the licensee) is also foreseen, although this requires that the production of the patented product takes place in the country to which it is licensed (rather than the country of the patent holder). However, this requirement posed a problem mainly for developing countries lacking the necessary infrastructure for the production of drugs. To address this problem, the Doha declaration (adopted by the World Trade Organisation in 2001)[119] allows that drugs under a compulsory license are manufactured in developed countries on the condition that they are exported to the least developed countries.

With regard to gene patents, 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 licenses) due to the rapid expansion of DNA patents. The scope of DNA patents may now include anything from the therapeutic utility to the application of knowledge related to a specific DNA sequence in a clinical setting and in research[120]. Similarly, the scope of other biotechnology patents may be quite broad. The Oncomouse is a typical example of such a case, where the patent claims not only the oncogene-modified mouse that was developed by the inventors, but any nonhuman mammal that carried an inserted oncogene (i.e. a gene that confers susceptibility to cancer). Such broad claims could inhibit research although a recent study indicates that currently there is not enough evidence to support this notion[121]. However, the future development of patent thickets cannot be ignored. With regard to diagnostics this is 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 patent infringement takes place. This would probably affect the cost of the test, and perhaps its accessibility to services and patients.

Licensing practices regarding genetic patents and diagnostics have varied. One example is that of Myriad Genetics who refused to license its patents on *BRCA1* and *BRCA2* (genes associated with the familial breast cancer) to any other laboratories. However, in the case of the *CFTR* gene (responsible for cystic fibrosis), free access to the gene sequences was granted for their use in mutation analysis (research) but not for their use in commercial tests. Alternative licensing models are seen as one of the best means to alleviate the problems created by the expansion of gene patenting. Two such models are currently attracting the interest of most experts: patent pools and clearing houses[122]. Patent pools are defined as agreements between at least two patent owners who agree to license their patents to one

[118] The TRIPs agreement is a treaty administered by the World Trade Organisation (WTO) which outlines the minimum standards for intellectual property regulation at an international level. The complete text of the agreement can be found at: http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm.

[119] DOHA WTO MINISTERIAL 2001: Ministerial Declaration WT/MIN(01)/DEC/1 20 November 2001. http://www.wto.org/English/thewto_e/minist_e/min01_e/mindecl_e.htm.

[120] Verbeure, B. et al. (2006). European Journal of Human Genetics **14**: 26-33. http://dx.doi.org/10.1038/sj.ejhg.5201503.

[121] National Research Council (2005). Reaping the benefits of genomic and proteomic research: intellectual property rights, innovation, and public health. The National Academies Press, Washington D.C. http://books.nap.edu/catalog.php?record_id=11487.

[122] Van Overwalle, G. et al. (2006). Nature Reviews Genetics **7**: 143-148. http://dx.doi.org/10.1038/nrg1765.

another and then as a package to a third party[123]. Recognised benefits of this approach might include the reduced number of licensing transactions which could also positively influence the number of litigation cases due to patent infringements. One successful example of a patent pool has been observed in the case of Golden Rice[124] and a similar approach has been proposed to facilitate the development of intervention strategies in response to severe acute respiratory syndrome (SARS)[125]. Clearing houses[126] are the second licensing model often proposed as a potential solution to patent thickets allowing information sharing among patent holders. However, these models are not as well explored thus far. A recent study outlining different clearing house models proposes that the 'royalty collection model' (meaning patent holders license their patents to the clearing house which then issues sub-licenses) would be useful in facilitating access to patents on genetic diagnostics[127].

On the EU level, the legal protection of biotechnological inventions is covered by Directive 98/44/EC[128] which came into force in 1998. This Directive allows patenting of gene sequences, but in the course of its transposition into national laws, some differences are observed at Member State level regarding the scope of protection[129]. The patent system is based on the European Patent Convention (EPC)[130], which does not create uniform patents but provides protection in as many member states of the European Patent Organisation[131] as required by the applicant. These patents are granted by the European Patent Office (EPO), but any related litigation must be taken to the national courts. The Community patent, allowing the applicant to obtain one uniform patent throughout the EU, would have an important impact on the reduction in patenting costs (in particular those relating to translation and filing), simplified protection of inventions and the establishment of a single centralised system of litigation, which together could further promote innovation and R&D investment. A proposal was put forward for a Council Regulation in 2000[132], but no decisions have yet been reached.

[123] Verbeure, B. et al. (2006). Trends in Biotechnology **24**: 115-120. http://dx.doi.org/10.1016/j.tibtech.2006.01.002.

[124] Potrykus, I. (2001). Plant Physiology **125**: 1157-1161. http://www.plantphysiol.org/cgi/content/full/125/3/1157. (Golden Rice is a type of genetically modified rice in which the grains are enriched with beta-carotene, a precursor of vitamin A. Due to this modification these rice grains have a yellow hue, hence the name.)

[125] Simon, J.H.M. et al. (2005). Bulletin of the World Health Organisation **83**: 707-710. http://www.who.int/bulletin/volumes/83/9/.

[126] The term refers to any mechanism whereby providers and users of goods, services and/or information are matched.

[127] Van Zimmeren, E. et al. (2006). Bulletin of the World Health Organisation **84**: 337-424. http://www.who.int/bulletin/volumes/84/5/.

[128] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions. OJ 30.7.98 L 213/13. http://europa.eu/eur-lex/pri/en/oj/dat/1998/l_213/l_21319980730en00130021.pdf

[129] European Commission COM (2005) 312: Report from the Commission to the Council and the European Parliament - Development and implications of patent law in the field of biotechnology and genetic engineering. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2005:0312:FIN:EN:PDF.

[130] http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ma1.html.

[131] http://www.epo.org/about-us/epo/member-states.html

[132] European Commission COM (2000) 412 final: Proposal for a Council Regulation on the Community patent. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0412:FIN:EN:PDF.

2.2.10 Summary

The application of modern biotechnology in the development of therapeutics, preventives, and diagnostics has made an overall positive impact on the pharmaceutical sector, representing an estimated total share of 0.04% in the EU's total economic activity. Biopharmaceuticals are the economically most important application of modern biotechnology and they constitute a very dynamic market, experiencing two-digit growth, higher than the growth of other pharmaceuticals. Some biotechnology drugs (for a limited number of indications) have reached blockbuster status but only one of the top ten best selling biotechnology drugs originated in the EU. The economic relevance of biopharmaceuticals for the EU is important, as in 2005, they held a 9% share in all pharmaceuticals in the EU and a 30% turnover share of the EU, US and Japanese pharmaceutical markets combined. In 2002 the biopharmaceuticals' share in the EU's total value-added was 0.03%, comparable to entire subsectors of chemicals (e.g. man-made fibres). Recombinant vaccines have a much smaller share in biotechnology-based products, but represent an area of good performance in the EU: EU companies have developed 26% of all recombinant vaccines currently available. Moreover, diagnostics based on modern biotechnology hold an estimated 30% turnover share in all *in vitro* diagnostics, and are predicted to grow at a higher annual average rate.

2.3 Agro-food biotechnology

2.3.1 The agro-food sector

One of the main areas where biotechnology has been applied traditionally is primary production and the food chain (see Figure 14). This includes the producers of biotechnology products (such as breeders, recombinant vaccine producers, producers of diagnostic test kits, etc.) as well as the downstream users (such as farmers, food processors, diagnostic laboratories, retail chains, etc.). Therefore, and for capturing all the facets of the contribution of biotechnology to primary and agro-food production, the context of this study includes the sectors whose activities are directly involved in the production of food and related products, as well as the sectors which are indirectly involved, such as by providing input and services throughout the production, commercialisation and trade of food products.

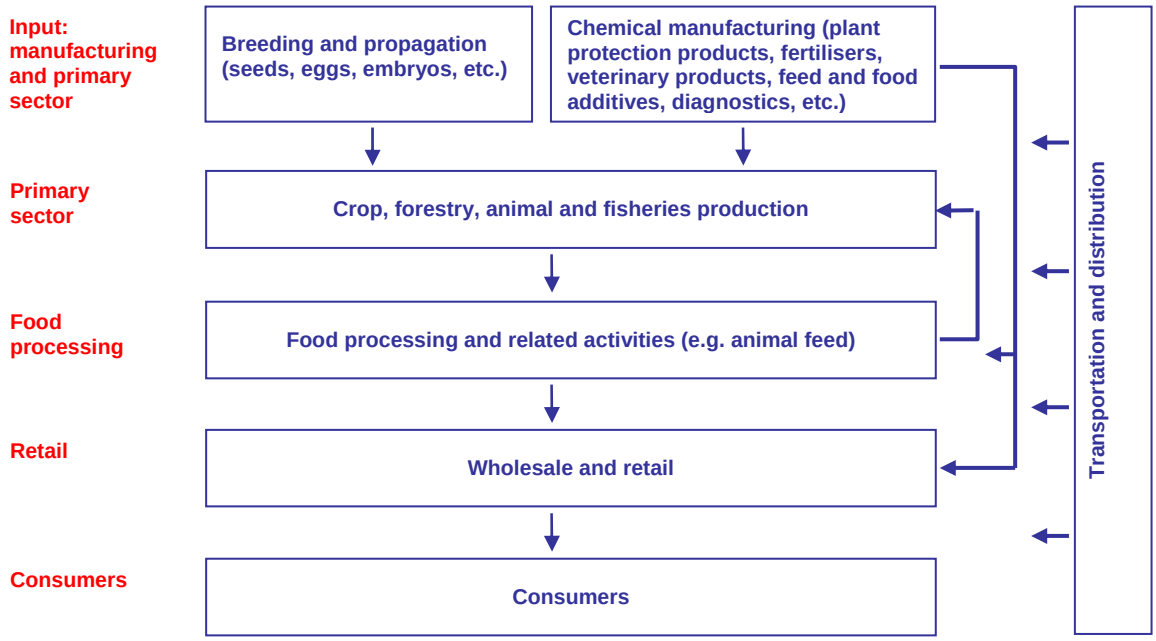

Figure 14: The agro-food chain

There are also other reasons for choosing such a broad scope and for analysing primary production and the agro-food industry together. Firstly, there are complex inter-linkages and a strong interdependence among the various subsectors. Therefore, a change or disruption (e.g. from a technological innovation) in one part of the primary production and agro-food industry will impact on the others. Moreover, almost all biotechnology applications that have an impact on the primary production and food processing sectors are actually used by the input sectors, which then provide biotechnology-derived products to the various downstream users. This interdependence is also reflected in policies that are developed to take into account the complete food chain (farm to fork approach). Finally, another reason for following this approach is that data are often available at an aggregated level only.

The agro-food chain (primary production and agro-food industry) includes the following NACE sectors:

Core production sectors, mainly primary sector and food manufacturing:

- NACE A: Agriculture, hunting and forestry
- NACE B: Fishing
- NACE DA 15: Manufacture of food products and beverages.

Input sectors to the primary sector and the agro-food chain:

- NACE DG 24.15: Manufacture of fertilisers and nitrogen compounds
- NACE DG 24.2: Manufacture of pesticides and other agro-chemical products
- NACE DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products (e.g. as relevant for veterinary products)
- NACE DG 24.66: Manufacture of other chemical products (e.g. as relevant for enzymes, amino acids, etc.)
- NACE KA 74.30: Technical testing and analysis (as relevant for diagnostics in the food chain)
- NACE NA 85.20: Veterinary activities.

The two groups of sectors presented above present the scope of this study, and from now on will be referred to as the 'agro-food' sector for simplicity.

The sectors involved in wholesale and retail services related to the agro-food sector will not be included per se, as they are not directly involved in the production or in the use of biotechnology-derived products. However, as they are important stakeholders in the agro-food chain, frequently influencing the upstream productive activities, due consideration to them will be provided where relevant. These sectors are represented in the NACE classification as follows:

Relevant wholesale and retail services:

- NACE GA 51.2: Wholesale of agricultural raw materials and live animals
- NACE GA 51.3: Wholesale of food, beverages and tobacco (except NACE GA 51.35)
- NACE GA 52.11: Retail sale in non-specialised stores with food, beverages or tobacco predominating
- NACE GA 52.2: Retail sale of food, beverages and tobacco in specialised stores (except NACE GA 52.26)
- NACE HA 55.3 to 55.5: Restaurants, bars, canteens and catering.

2.3.2 The contribution of the agro-food sector to the EU economy

Primary production and the food manufacturing sector contribute an estimated 4.12% to the EU's gross value-added (GVA) (baseline year 2003). The primary sector alone contributes approximately half of this, but its contribution is more important in rural areas, where it rises to 5% of the rural area's GVA[133]; this is even more pronounced in the 10 Member States that joined the EU in 2004, for which the contribution in rural areas rises to 7% of GVA. However, in general, even in rural areas, the majority of the economic activity depends on the

[133] European Commission, DG Agriculture and Rural Development (2006): Rural Development in the European Union – Statistical and Economic Information Report 2006. http://ec.europa.eu/agriculture/agrista/rurdev2006/RD_Report_2006_Foreword_Content.pdf

services sector. Within the primary sector, agriculture is the most important contributor to the EU economy at 1.8% of the EU's GVA (87% of the primary sector GVA), while the remaining 0.2% of the primary sector's contribution to the EU's GVA is provided by forestry and fisheries. The input sectors account for a much smaller share of the EU economy, representing only 0.1% of the EU's GVA. In total, the sectors that are at the focus of this analysis contribute 4.22% of the EU's GVA. In comparison, at 3.36% of total EU's GVA, the food and beverage wholesale and retail sectors are almost as important as the primary sector to the EU economy (see Figure 15).

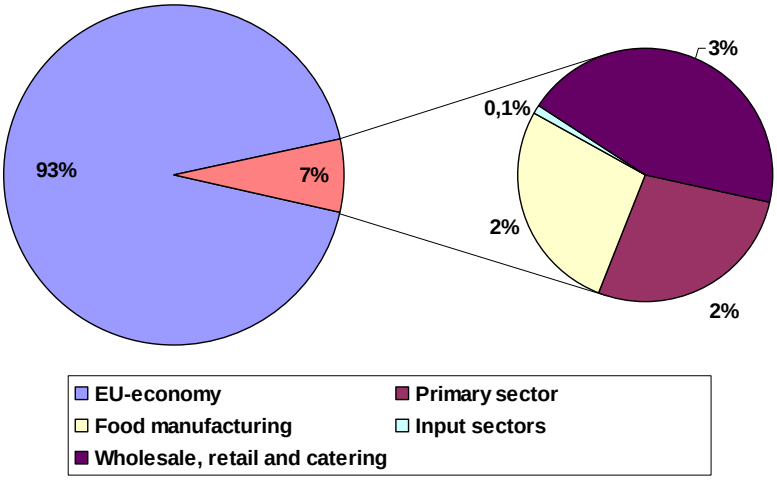

Figure 15: Economic significance of the agro-food sector and the food services sectors to the EU economy (relative to overall GVA)

In terms of employment, the primary sector accounts for approximately 5% of EU employment, while the food processing industry contributes an additional 2.2%. The fisheries sector accounts for a small share of the primary sector, at only 0.13% of overall EU employment. Still, the sector is very important at a regional level, i.e. in fisheries-dependent areas[134]. The input sectors account for 0.5% of EU employment, bringing the total contribution of the agro-food sector to 7.8% of total EU employment. For comparison, the wholesale and retail sectors account for a similar share, at 7% of EU employment.

A more detailed presentation of the relevance of the agro-food sector for the economy and employment in the EU is provided in Annex 3 – Agro-Food .

The EU has traditionally held strong sectorial policies in primary production, mainly through the Common Agricultural Policy (CAP) and the Common Fisheries Policy (CFP). Nevertheless, the sectorial policies have been harmonised with the overarching policies such as the Lisbon Strategy, and therefore, the main policy objectives are the same.

Food manufacturing is very important to the EU economy, as it is among the largest manufacturing sectors in terms of GVA and employment. The European Commission is therefore seeking to ensure the competitiveness of the EU food industries under the Lisbon

[134] Salz, P. et al. (2006). Employment in the fisheries sector: current situation. European Commission, final report FISH/2004/4. http://ec.europa.eu/fisheries/publications/studies/employment_study_2006.pdf.

Strategy goals, in the context of the CAP and the CFP, along with the EU's obligations in the World Trade Organisation.

2.3.3 Modern biotechnology in the agro-food sector

Biotechnology does not appear as a separate sector in the NACE classification. However, modern biotechnology in the agro-food sector as a horizontal enabling technology is applied in different parts of the agro-food sector. A description of agro-food biotechnology applications is provided in Annex 3 – Agro-Food . Their assignment to NACE categories is also described, broken down into two categories: users of modern biotechnology techniques and users of modern biotechnology-derived products. The economic contribution is therefore also separated to direct (users of biotechnology techniques) and indirect (users of modern biotechnology-derived products) impacts.

The direct impact assessment aims to measure the economic impact (to the sector and to the whole economy) arising from the activity of companies applying modern biotechnology (also called modern biotechnology active companies). Examples of modern biotechnology active companies in the agro-food sector include breeding companies employing this technology for the production of seeds, embryos or eggs, diagnostic companies producing modern biotechnology test kits, and pharmaceutical companies producing modern biotechnology-based vaccines. In general, users of modern biotechnology are only found in the input sectors of the agro-food industry, mainly involved in the following activities:

- seeds and planting stock
- nursery plants and flowers
- animal breeding
- fish breeding
- manufacture of chemicals (including enzymes)
- veterinary products and services
- diagnostics in the agro-food sector.

It is possible, therefore, to estimate the maximum direct contributions of modern biotechnology (see Table 12 and Figure 16) by calculating the relevant contributions of the sectors that use modern biotechnology techniques, at the most disaggregated sector level possible (NACE level if applicable).

The direct contribution of biotechnology to the EU economy will be less than 2% of the EU agro-food turnover or less than 0.08% of the total EU-wide GVA. The respective value for employment is not available, but it is likely to be of a similar relative magnitude.

Table 12: Agro-food subsectors using modern biotechnology at the most disaggregated level possible

Sectors	Turnover (EUR million)
Seeds and planting stock [1]	6100
Nursery plants and flowers [2]	6400
Animal breeding [3]	2000
Fish breeding [4]	210
Veterinary products/services [5]	5200
Manufacture of other agro-food chemical products (e.g. enzymes, food/feed additives) [6]	2300
Primary production and food related diagnostics [7]	700
Total of input sectors using biotechnology	22 910
Total EU agro-food sector	1 193 763
Total EU economy (GVA)	8 782 817
Share of modern biotechnology-related input sector turnover in overall agro-food sector turnover of the EU	2%
Share of modern biotechnology-related input sector GVA in overall EU's GVA [9]	0.08%

[1] The data from 2003 provided by the European Seed Association in their submission to the Bio4EU study (http://bio4eu.jrc.ec.europa.eu/documents/ESAsubmission.pdf) is used as the best estimate.

[2] From: Working Document of the Commission staff on the situation of the flowers and ornamental plants sector, European Commission, DG Agriculture and Rural Development, 2006. http://ec.europa.eu/agriculture/markets/fruitveg/flowers/analysis.pdf. This subsector is relevant for using modern biotechnology such as micropropagation and *in vitro* culture.

[3] Estimated from data obtained in the case studies provided by ETEPS; based on the sum of the total turnover of the largest breeding companies in the cattle (total estimated at EUR 600 million) and pig (total estimated at EUR 800 million) sectors; the poultry breeding turnover (estimated at EUR 300 million) was based on the relative shares of livestock production in the EU which was in close agreement with expert opinion; the figure of EUR 1800 million was then rounded up to EUR 2000 million to account for the remaining species, the smaller enterprises, and various other activities.

[4] As no possible breakdown to fish breeding and hatchery related activities is possible, the total of the NACE B 05.02 Fish farming sector turnover (EUR 2770 million) multiplied by a conservative estimate of the share of hatchery costs (8%) is taken as the best estimate.

[5] The value that Eurostat provides (EUR 5187 million in 2003) is used as the best estimate for the economic activity 'Veterinary expenses'. It should be noted that this includes both EU and non-EU sourced products and services; however, as EU companies have important shares in the international veterinary market (estimated at 50%, see Section 2.3.5.3), it is assumed that the trade balance is neutral. This category may also include some animal breeding and animal diagnostic activities (e.g. embryo transfer related services, etc.) as they sometimes form part of veterinary services.

[6] The best estimate is taken as the sum of feed additives (enzymes, amino acids, vitamins, organic acids, etc) and food enzymes; see Section 2.3.5.3).

[7] No data are available at sector level, so a best estimate was taken from the data provided by: Blankenfeld-Enkvist, G. and Brännback M. (2002). Technological trends and needs in food diagnostics. Technology Review 132/2002, National Technology Agency, Helsinki. http://www.tekes.fi/julkaisut/Food_diagnostics.pdf. The report covers the food chain from raw material to end products (turnover of approximately EUR 500 million). Animal health diagnostics were estimated at 50% of the global market (reported at EUR 400 million, based on: BCC (2004). Animal therapeutics and diagnostics. Report HLC034A. BCC Research, Wellesley, M.A. http://www.bccresearch.com/hlc/HLC034A.asp).

[8] This includes the primary sectors, the food manufacturing sectors, and the inputs to the agro-food sectors (all but the wholesale and retail sectors of the total food chain).

[9] The total turnover of the input sectors was multiplied by 0.3 to estimate the GVA (0.3 is the average GVA:turnover ratio of the agro-food sectors involved in production activities, i.e. excluding the wholesale and retail sectors).

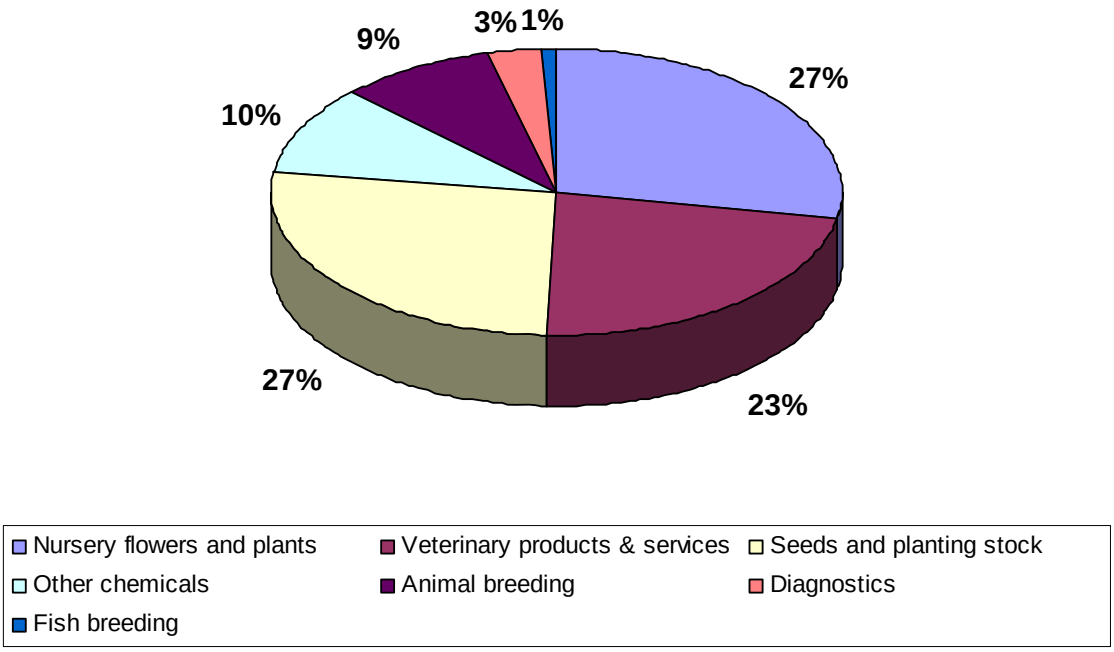

Figure 16: Turnover shares of agro-food input sectors using modern biotechnology

Indirect impacts, on the other hand, mainly relate to the impacts arising from the use of biotechnology-derived products, and it mainly involves tracing the impacts at the farm gate and through food manufacturing, although indirect impacts on the economy may also find their way further downstream, e.g. through final retail sales and catering. As the users of biotechnology-derived products consist of the whole agro-food sector, it follows that the use of modern biotechnology-derived products and services may contribute more to the EU economy in terms of GVA and employment than the application of modern biotechnology to generate these products and services, i.e. the indirect contribution of modern biotechnology to the EU economy is likely to be larger than its direct contribution.

In this study, data were obtained from official statistics and literature in the public domain, as well as from relevant market reports. Because of the lack of data on the agro-food sector, surveys were also conducted within the scope of the Bio4EU study to obtain additional insights for the analysis.

2.3.4 Analysis at an aggregated level

A first estimate of the direct economic and employment contributions of modern biotechnology to the agro-food sector is provided at an aggregated level.

2.3.4.1 Adoption of modern biotechnology applications

As the economic impact of a biotechnology innovation is directly related to its uptake, a first indication of the economic impact is provided by assessing the actual use of modern biotechnology by the agro-food sector. Official statistics and reports were used to derive an estimate of the number of companies in the agro-food sector active in biotechnology (see Table 13). It was only possible to elaborate the corresponding data for nine EU Member States (Belgium, Finland, the UK, Denmark, Ireland, Germany, Poland, Sweden and France) for certain years (mostly 2003). Additionally, data for the US were derived as well.

Table 13: Number of modern biotechnology active companies in the agro-food sector
Source: ETEPS[135], adapted by IPTS

Country (year)	Number of modern biotechnology companies in the agro-food sector
Belgium (2003)	11 [2]
Denmark (2003)	64 [3]
Finland (2003)	22 [2]
France (2003)	78 [2]
Germany (2003)	149 [2]
Ireland (2003)	11 [4]
Poland (2003)	2 [2]
Sweden (2003)	17 [2]
United Kingdom (2003)	34 [2]
Total of individual EU countries	**388**
US (2001)	260 [2]

Definitions of companies active in biotechnology vary and were given in the corresponding reports:
[1] LUC; ULG; Vlerick Management (2004): Report on the national Biopharma innovation system of Belgium. Report to the Federal Science Policy Office.
[2] Van Beuzekom, B.; Arundel, A. (2006): OECD Biotechnology Statistics – 2006.
[3] Biotechnology in Denmark: A Preliminary Report (2004): The Danish Centre for Studies in Research and Research Policy.
[4] InterTradeIreland (2003): Mapping the Bio-Island – A North/South study of the private biotechnology sector.

The sources used do not always differentiate between modern biotechnology and conventional biotechnology. However, most countries whose data are provided (except for Denmark and Sweden) follow the OECD list-based definition or a modern biotechnology definition, both of which are similar to the definition of modern biotechnology used in this study. Moreover, the definition of what constitutes the agro-food sectors and of a biotechnology active company varied among the different countries. It is more probable that the coverage in the statistics has a narrower scope compared to the scope of this study, as in many countries only a company whose core activity is related to biotechnology is counted as a biotechnology active company.

[135] ETEPS (2006). Bio4EU Task 2 Main report.

Most companies active in agro-food related biotechnology in the EU are located in Germany followed by France and Denmark. Compared to these countries, the remaining EU Member States have relatively fewer firms which are active in biotechnology. Furthermore, these data indicate that the EU compares favourably with the US.

2.3.4.2 Economic shares of modern biotechnology applications

The only available information related to an economic measure of the contribution of biotechnology active companies to the agro-food sector is the turnover, mainly from market reports provided by private consultancies, such as Datamonitor. Using as benchmarks i) the total turnover of sectors using modern biotechnology in the area of agro-food, ii) the total agro-food sector turnover, and iii) the total EU GVA, estimates i) of the economic contribution of modern biotechnology to the sectors that use modern biotechnology in the generation of products and services, ii) of the economic contribution of modern biotechnology to the agro-food sector, and iii) of the contribution of modern biotechnology to the EU economy can be obtained (see Table 14).

Table 14: Direct impacts of modern biotechnology in the agro-food sector
Source: ETEPS[136], and IPTS calculations

	Belgium (2004)	France (2004)	Germany (2004)	Italy (2004)	Netherlands (2004)	Spain (2004)	Sweden (2000)	United Kingdom (2004)	Total of listed EU countries
Biotechnology-related turnover (EUR million)[1]	498	103	244	226	47	254	275	724	3022
Total turnover of relevant input sectors of listed EU countries[2] (EUR million)									18 144
Share of biotechnology-related turnover over total turnover of modern biotechnology users (in %)									17
Turnover of agro-food sector of listed EU countries (EUR million)									953 982
Contribution of modern biotechnology to the agro-food sector (in %)									0.3
GVA of listed EU countries (EUR million)									7 026 254
Contribution of modern biotechnology to the EU GVA (in %)[3]									0.01

[1] Data for all countries except Sweden are from Datamonitor (2005); for Sweden, data are from Sandström, A.; Norgren, L. (2003): Swedish Biotechnology – scientific publications, patenting and industrial development. VINNOVA Analysis.
[2] The EU totals were multiplied by 0.8 to estimate the turnovers representative for the eight countries (based on calculations indicating that the turnover of the eight countries is on average 80% of the EU turnover).
[3] The total turnover of the biotechnology producing sectors was multiplied by 0.3 to estimate the GVA (0.3 is the average GVA:turnover ratio of the primary production and agro-food sectors involved in production activities, i.e. excluding the wholesale and retail sectors).

In 2004, the UK had by far the highest total biotechnology-related turnover (around EUR 724 million) of biotechnology active firms in the agro-food sector, followed by Belgium with nearly EUR 500 million (see Table 14). For Germany, Italy and Spain, about EUR 220 million to EUR 250 million in turnover was generated by biotechnology-related applications

[136] ETEPS (2006). Bio4EU Task 2 Main report.

in the agro-food sector, while France and the Netherlands showed the lowest biotechnology-related turnover for the countries covered.

These data provide a first estimate of the economic dimension and the importance of the adoption of modern biotechnology by the relevant agro-food industries. Biotechnology-related turnover represents 17% of the total turnover of the agro-food subsectors that use modern biotechnology in the generation of products and services (relevant input sectors). Expressed in terms of the agro-food turnover and the EU GVA, the direct contribution of modern biotechnology is estimated to be 0.3% and 0.01%, respectively. In comparison, in the US the biotechnology-related turnover of the agro-food sector for 2003 (the most recent available year) was reported to be EUR 76 million, i.e. this equals 0.0007% of the respective US GVA.

It should be noted, however, that these data are only estimates as the definitions used for biotechnology, biotechnology active company and the agro-food sector are not always clear and they may vary among the different countries. Therefore, the comparability among the different countries should be treated with caution.

Table 15: Amount and share of biotechnology-related employment of biotechnology active firms out of total employment in the agro-food sector
Source: ETEPS[137], and IPTS calculations

Country (year)	Number of employees in biotechnology active agro-food firms[1]	Number of employees in country	Direct contribution to overall employment (in %)
Belgium (2000)	1026 [2, 5]	4 195 000 [8]	*0.024*
Ireland (2003)	277 [3, 6]	1 814 000 [8]	*0.015*
Sweden (2003)	607 [4, 7]	4 329 000 [8]	*0.014*
Total of listed EU countries	1910	10 338 000 [8]	0.018

[1] In the statistics/reports it was not clearly mentioned if all employees working in biotechnology active firms in the agro-food sector are meant or all biotechnology active employees working in biotechnology active firms in the agro-food sector. Definitions of employees active in biotechnology companies given in the corresponding reports listed below in notes 5 to 8.
[2] Number of employees active in the 'agro-bio sector' (clear definition not available).
[3] Number of employees active in the 'agro-food sector' (clear definition not available).
[4] Number of employees active in the biotech applications 'agro-biotech' and 'biotech food' (clear definitions not available).
[5] LUC; ULG; Vlerick Management (2004): Report on the national Biopharma innovation system of Belgium. Report to the Federal Science Policy Office.
[6] Inter Trade Ireland (2003): Mapping the Bio-Island – A North/South study of the private biotechnology sector.
[7] Van Beuzekom, B.; Arundel, A. (2006): OECD Biotechnology Statistics – 2006.
[8] Eurostat (2003): http://epp.eurostat.ec.europa.eu.

The same approach, applied to employment, is presented in Table 15. Unfortunately there are no data at a sufficiently disaggregated level for estimating the number of employees of the sectors that include companies using modern biotechnology techniques. However, the direct contribution to the EU employment is estimated at approximately 0.02% (see Table 15), based

[137] ETEPS (2006). Bio4EU Task 2 Main report.

on a very limited number of countries. This is within the same order of magnitude as the relevant economic contribution presented above.

In the following sections, an analysis of the contribution of modern biotechnology at a disaggregated level will be made, using a bottom-up approach, and the findings between the two sets of analyses will be compared.

2.3.5 Analysis at a disaggregated level

The analysis of the contribution of modern biotechnology to the agro-food sector at a disaggregated level follows a bottom-up approach, including the specific sectors in which modern biotechnology has been mostly applied. Modern biotechnology applications were broken down into the following application types by sector classification[138] (see Table 16).

Table 16: Structure of the bottom-up approach for assessing the contributions of modern biotechnology to the agro-food sector

Breeding/propagation in primary production	Plants	Marker assisted selection
		Micropropagation
		Genetic modification
	Livestock	Marker assisted selection
		Embryo technologies
	Fish/shellfish	Marker assisted selection
		Sex/ploidy manipulation
Food processing		Improved enzymes and fermentation processes (recombinant techniques and/or the use of molecular markers)
Other inputs to the agro-food sector		Food/feed additives (vitamins, amino acids, enzymes, etc.)
		Veterinary products (recombinant vaccines, etc.)
Modern biotechnology-based diagnostics		Animal/plant health monitoring
		Food safety monitoring (e.g. salmonella)
		Traceability in the food chain (e.g. GMO traceability)

Data from various sources were used in the analysis. Information that was publicly available was supplemented by targeted surveys and expert opinion[139].

Of importance in the development and adoption of modern biotechnology are the decision maker(s) that influence the adoption of a technology. The decision maker may vary for different applications including the biotechnology producer (e.g. the aim for adoption is to reduce costs), the farmer (e.g. demand for a higher quality input), the processor (e.g. requiring raw material of a specific quality), and the wholesaler or final retailer (e.g. by defining the product specifications). While all these stakeholders may be important in decision making for

[138] Identified earlier as the main application areas of modern biotechnology (ETEPS (2006) Bio4EU Task 1).
[139] Mainly through the ETEPS consortium and IPTS surveys.

the adoption of specific technologies (and therefore for the resulting impacts), a recent trend is the increasing importance of decisions taken downstream in the supply chain (i.e. by the retailer).

Because of the complexity in the structure of the agro-food sector, this impact assessment will mainly be followed to the first user level, i.e. to the farmgate or to the food manufacturing stage, depending on the application; qualitative descriptions of indirect impacts further downstream will be made when such information is available.

2.3.5.1 Breeding and propagation in primary production

The application of modern biotechnology in breeding and propagation in the primary sector is mostly relevant at the top of the breeding pyramid, the aim being to improve and accelerate genetic improvements in the population (plants or animals). Additionally, modern biotechnology may also be used throughout the breeding schemes, for example in parentage identification and lineage traceability. Therefore, the direct impacts of modern biotechnology in this area are expected to occur in the breeding companies or departments and other specialised biotechnology companies supporting the breeding or propagation of plants or animals, rather than at the production and farmer level. However, the use of these biotechnology-derived inputs (as seeds, mother plants, embryos, young animals, breeding animals, etc.) by the farmers will produce indirect impacts up to the farmgate. These impacts may also find their way further downstream, such as through the processing stage, to the wholesale and retail stage.

2.3.5.1.1 Breeding and propagation – plants

The currently used modern biotechnology applications in plant breeding and propagation are mainly related to the use of molecular markers, herein called marker assisted selection (MAS), and tissue culture/micropropagation. These techniques are applied either by breeding/seed companies, or by specialised laboratories involved in the supply of horticultural products and/or young plants. The direct impacts therefore relate to the turnover generated by these activities, whereas the indirect impacts cover the downstream effects to the farmgate.

The EU seed sector provides EU as well as non-EU farmers with the most important input for the realisation of farming activities. Seeds (or any other type of propagating material) provide the germ plasm for the grow-out stage, which is the result of genetic selection over many years. According to the European Seed Association (ESA), the EU seed sector (field and vegetable crops combined) comprises more than 400 seed companies, and while the sector seems to have been following a trend of consolidation, there is still a large number of small and medium sized companies. In general, approximately 10% of the companies generate 40% of the turnover, indicating that a large share of seed production is provided by a smaller number of medium and large sized companies. Moreover, large multinational companies seem to have a lead in major crops (maize, soya, cotton, etc.) while in horticultural crops, small and medium enterprises (SMEs) are competing with larger companies.

The global seed market has been estimated by the International Seed Association (ISA) at approximately EUR 24.4 billion, while the international trade in seeds accounts for approximately 15% of that. The EU turnover from seed sales has been estimated by the ESA

at EUR 6.1 billion. Eurostat provides data on the intermediate consumption of seeds and planting stock (1st generation and certified seeds, allocated to the input industries at about EUR 7.6 billion in 2003), as well as on the value of multiplied seeds (allocated to primary production at EUR 762 million). Data available from the ESA indicate exports of about EUR 2.7 billion while the ISA provides estimates for EU imports at EUR 2.3 billion, which confirms the strong global position of the EU. Moreover, it has also been suggested that EU companies are important players in the US and hold a similar share of the Latin American market to US companies[140], while they are not as strong in the remaining world markets. The ESA also estimates that field crops account for approximately 60% of the total, with horticultural crops making up the rest. According to ESA statistics, the EU seed industry is estimated to employ about 30 000 people. In general, seed breeding is most profitable, in particular for those crops for which farmers use little or no saved seed. This is especially the case for hybrid varieties, and particularly for maize.

Marker Assisted Selection (MAS)

Molecular markers (certain DNA regions linked directly or indirectly to specific traits) are used in several ways: MAS and related techniques make use of them to identify and help incorporate desirable traits into selection schemes. The desired traits may aim to improve agronomic traits (e.g. resistance to physical, chemical or biological stress) or product quality traits (e.g. difference in nutrient content). 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, improve the accuracy of selection and increase the rate of genetic progress (reducing the development time) by identifying organisms carrying desirable genetic variants for a given trait at an earlier age. MAS is applied to maize breeding for the production of feed, food and industrial grade maize. The current available information only allows an analysis to be carried out on MAS used in the broad sense (i.e. the direct and indirect use of molecular markers). MAS is applied on a research basis in almost all plant-related sectors, including crops, vegetables, fruits, and forestry. However, there is very limited information available on the commercial application of MAS.

The maize seed companies surveyed (five companies in France and Germany[141]) suggest that the sector would not remain competitive without the use of molecular markers throughout the breeding process: medium and large sized companies claim that all current maize seed production uses MAS (i.e. adoption rate of 100%) while smaller companies show a smaller adoption rate (as low as 33%). Similar claims have been put forward by the ESA in their contribution submitted within the context of the Bio4EU study[142].

The share of maize in total EU seed production is estimated at EUR 405 million (6.6% of total), based on the maize area cultivated and seed cost information[143]. Using as the MAS adoption rate the expert estimate of 33 - 100% of maize seed turnover, provides an estimate of

[140] Tait et al. (2001). PITA project: Policy influences on technology for agriculture: chemicals, biotechnology and seeds. Final report. Scottish Universities Policy Research and Advice Network (SUPRA), Edinburgh. http://www.supra.ed.ac.uk/Publications/paper22.pdf.
[141] (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).
[142] See http://bio4eu.jrc.ec.europa.eu/submissions.html.
[143] The estimate is based on the maize area cultivated (6 195 000 ha) and the cost of maize seeds (EUR 65.39 per ha), resulting in a EUR 405 million maize seed turnover.

the direct contribution of MAS at a range of EUR 133 - 405 million, which is 2.2 - 6.6% of the total seed-related turnover at EU level or 0.01 - 0.03% of the agro-food sector turnover. The real value is probably closer to the upper estimate as the market share of seeds produced by medium and large companies is likely to be larger.

As molecular markers are claimed to be used throughout the breeding process of other plants, the direct contribution may be significantly larger. Unfortunately, the adoption rate of MAS in all seed and propagating material for crop and horticultural production is not known. A recent publication[144] suggests that maize breeding is more amenable to the application of MAS (in the narrow sense) as compared to wheat, barley and rice, for biological as well as agronomic reasons. Therefore, it is likely that the adoption of MAS is relatively high for maize and lower for other crops/horticultural plants. An estimate of the potentially direct impacts of the adoption of MAS may be obtained by extrapolating the lower value suggested for maize (33%) to the total seed turnover as a high estimate, which results in a total contribution of EUR 2013 million or 0.17% of the total agro-food sector. It should be noted, however, that these estimates are only given to provide benchmarks on the adoption and potential impacts of MAS and should not be taken as robust calculations.

The indirect impacts from MAS adoption relate to the value generated from growing the seeds up to the farmgate, as well as through the use of maize by the manufacturing, wholesale and retail sectors. These calculations add further complexity, due to the difficulty of tracing the biotechnology-derived products throughout the food chain, and due to the additional complexity added by extra-EU trade flows at each stage. While exact data of the share of maize produced in the EU from MAS-derived seeds are not available, it seems reasonable to apply the breeders' adoption rate to maize production[145]. This would imply that a EUR 2429-7360 million turnover from EU maize farming is MAS-derived, accounting for 0.2 - 0.6% of the total agro-food sector and 0.009 - 0.024% of the total EU GVA. When the 33% adoption rate is applied to all plant production, the indirect contributions rise to a turnover of EUR 55.6 billion from crop production, which accounts for 4.7% of the total agro-food turnover and 0.19% of the EU GVA.

The estimates provided here on the economic contribution of MAS do not provide any information on the actual benefits accrued for the adoption of MAS compared to the alternative of non-adoption. However, the fact that the technology is adopted is already an indication of the benefits it provides. These benefits seem to be clear for the breeders, who claim that they would not remain competitive without the use of molecular markers in their development of improved varieties, and are likely to be passed on to the growers, who consciously adopt the improved varieties. It should be noted here that it is impossible to accurately report the share of MAS maize seeds or derived grains that have been marketed, as the companies do not keep separate accounts of conventional or MAS-derived products. This is further complicated by the fact that the introduction of a new variety in the market may take up to 10-15 years from the initial development phase. MAS-based breeding was reported[146] to increase the costs for the breeding companies in the short term (mainly due to the high initial

[144] 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? Turin, http://www.fao.org/Biotech/docs/Koebner.pdf.

[145] Assuming that all main seed providers (e.g. EU, US, etc.) have adopted the technology at similar rates (expert opinion, ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).

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

investment cost, and the need for highly qualified employees), but to be profitable in the long term. The high costs may prove to be a challenge for small companies who may not be able to remain competitive. Supporting programmes, such as through R&D financing and research industry networking, were therefore mentioned as very valuable tools in giving SMEs a chance to benefit from MAS.

The contribution of MAS to employment is less clear as such data are not available. Expert opinion[146] indicates that the share of employees working in the field of MAS in maize breeding is approximately 30% for small companies, and as high as 100% in larger ones (as an indication, altogether the companies interviewed employ between 70 und 600 workers in the field of maize breeding). Moreover, between 4 - 70% of new employment created is said to be dedicated to MAS in maize breeding. These shares do not refer only to technical jobs but also include various supporting jobs (e.g. marketing and sales).

The expectations for MAS use in the EU are in general positive, both because of the expected further developments in genomics research and because MAS may be an alternative to the use of the controversial genetic modification techniques. Furthermore, the interviewees stressed the likely increasing importance of using MAS in the development of varieties towards industrial applications (e.g. the production of plant biomass), and the potential implications this may have in the production of maize and other relevant crops.

Crop breeding in general and maize breeding in particular, is a highly competitive field, the main competitors being the US and the EU, dominated by a small number of large private companies. While there is no information on the extent of the use of MAS in the EU versus the US, the technologies used are comparable.

Genetic modification (GM)

Genetic modification (GM), also known as genetic engineering or recombinant DNA techniques, is one of the newest methods to introduce novel traits to plants. The adoption of GM crops has been progressing at a faster pace than has been the case for 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 a single country (the US). Ten years later (2006) the area under GM crops had expanded to 100 million hectares in 22 countries of which 11 are high-income economies. More than 10 million farmers cultivated GM crops in 2006. During these first years of commercial GM crop cultivation (1996-2006)[147], two agronomic traits were introduced by genetic engineering into a few major crops that 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 global share of the four major agricultural crops for which they are commercially available (maize, canola[148], soya bean and cotton). The number of GM crops authorised for cultivation in the EU is small when compared with other world regions. The EU so far has authorised the cultivation of two Bt maize varieties. These are the transgenic event Bt-176 of the company Syngenta authorised in 1997 and the transgenic event MON-810 of the company Monsanto authorised in 2003. In practice, the only GM crop currently available to EU farmers

[147] James, C. (2006). Global status of commercialised biotech/GM crops in 2006. ISAAA Brief No. 35 (Ithaca, N.Y.). http://www.isaaa.org/resources/publications/briefs/35/.
[148] Canola is a type of oilseed rape.

for cultivation is Bt maize. 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[149]. France, Germany, Portugal and the Czech Republic also grew Bt maize in 2005 and 2006 but reporting very small areas in the order of one thousand hectares or fewer. Slovakia joined this group of EU Bt maize-growing countries in 2006 although the area cultivated is negligible. Before 2005, the adoption in these latter countries can be considered as non-existent. Table 17 shows GM maize adoption rates in the EU and worldwide in 2005, for which figures are more definitive[150].

Table 17: GM maize adoption rates in the EU and worldwide in 2005

Adoption rates (share of GM maize area/total grain maize area, in %)			Source of data
53 225 ha/421 724 ha	in Spain	12.62	Spanish Ministry of Agriculture[1]
500 ha /1 654 000 ha	in France	0.03	Eurostat[2] Clive James[3]
300-500 ha/443 000 ha	in Germany	0.07	
150 ha/ 98 000 ha	in Czech Republic	0.15	
750 ha/110 000 ha	in Portugal	0.68	
54 925ha/6 059 000 ha	in the EU	0.83	
15 649 920 ha/30 096 000 ha	in the US	52	USDA 2005[4]; USDA 2006[5]
289 000ha/1 700 000 ha	in South Africa	17	Clive James[3]
21 200 000 ha/147 000 000 ha	in the World	14	Clive James[3]

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

[1] Spanish Ministry of Agriculture (2006) Superficie en hectáreas de variedades de maíz GM, http://www.mapa.es/agricultura/pags/semillas/estadisticas/serie_maizgm98_06.pdf.

[2] EUROSTAT (2006) Agriculture and fisheries statistics http://epp.eurostat.ec.europa.eu/.

[3] James, C. (2005). Global Status of Commercialised Biotech/GM Crops in 2005. ISAAA Brief No. 34 (Ithaca, N.Y.).

[4] USDA (2005). Acreage in 2005, http://usda.mannlib.cornell.edu/reports/nassr/field/pcp-bba.

[5] USDA (2006). Adoption of genetically engineered crops in the US in 2005: corn varieties. http://www.ers.usda.gov/Data/BiotechCrops/ExtentofAdoptionTable1.htm.

Focusing on Spain, GM seed turnover was estimated to be about EUR 4.1 million in 2002, EUR 6.7 million in 2003, and EUR 11.9 million in 2004[151]. These figures can be considered as the equivalent to the total EU GM seed turnover according to the zero adoption elsewhere in the EU. The annual evolution of the GM maize seed turnover is mainly a consequence of the annual increase of the GM maize area in Spain during the years 2002, 2003 and 2004 (21 004, 32 244 and 58 219 hectares, respectively)[149]. As mentioned in the MAS section above, the EU turnover from seed sales was estimated by the ESA to EUR 6.1 billion in 2003. The EU turnover from GM seed sales had a share of 0.2% of the EU turnover from seed sales

[149] Spanish Ministry of Agriculture (2006), Superficie en hectáreas de variedades de maíz GM, http://mapa.es/agricultura/pags/semillas/estadisticas/serie_maizgm98_06.pdf.

[150] Statistics for 2006 are not yet available for all crop/country combinations.

[151] Turnover figures are calculated as total Bt maize seed cost per hectare multiplied by the area of Bt maize in Spain in each respective year. Total Bt maize seeds cost per hectare are annual averages obtained from a survey of Spanish Bt maize farmers and conducted by IPTS. The average seed costs are available for years 2002, 2003 and 2004 (EUR 197, EUR 209 and EUR 204 per hectare, respectively). More details are found in the Bio4EU GM crops case study (available at http://bio4eu.jrc.ec.europa.eu/documents.html).

in 2004. A more reasonable comparison can be made using the total EU market value of maize seeds as the reference. In this case, the EU turnover from GM maize seeds out of the total EU market value of maize seeds is about 2.9%. Based on these figures, it can be concluded that the direct impact is rather small as a consequence of the low adoption rate of GM crops in the EU (0.9% of GM maize area out of the total EU maize area in 2005).

The indirect impact is defined as the turnover from GM maize grain sold by EU farmers. In 2004 this turnover accounted for EUR 85 million[152]. This figure can also be considered as the equivalent to the indirect impact for the whole EU and represents 1.2% of the total EU maize turnover. Again this small share is a consequence of the small adoption of GM maize in the EU.

A recent study[153] 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 aims to provide a 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 those of the Spanish feed industry 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 requires 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[154]. Positive on-farm and

[152] Average GM maize yields in Spain were 11430 kg per hectare during the three-year period 2002-2004. These yields multiplied by EUR 0.128 per kilogram received by farmers in 2004 yield a revenue of EUR 85 million.
[153] Gómez-Barbero, M., J. Berbel and Rodríguez-Cerezo E. (2008). Adoption and performance of the first GM crop introduced in EU agriculture: Bt maize in Spain. European Commission, IPTS, EUR 22778. http://www.jrc.es/publications/pub.cfm?id=1580.
[154] Gómez-Barbero, M. and Rodríguez-Cerezo E. (2006). Economic impact of dominant GM crops worldwide: a review. European Commission, IPTS, EUR 22547. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1458.

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 genetically modified organisms (GMOs) and derived products that became operative in 2004[155]. 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 EU[156]. 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 seeds. According to the ESA's statistics, the EU seed industry is estimated to employ about 30 000 people. Calculations of how many of these workers are directly related to breeding, producing, conditioning, marketing and distributing GM seeds is rather difficult due to the lack of data. Additionally, GM seeds are mainly not produced in the EU but elsewhere (e.g. the US and Chile), and therefore the employment impact in the EU might be low. Considering an average maize plot area of 12 hectares per farm in Spain and 58 219 hectares of Bt maize grown in 2004 in total, the population of users of the Bt technology is about 4800 farmers. 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[157].

Micropropagation[158]

Micropropagation refers to the *in vitro* asexual propagation of plants based on cell and/or tissue culture. It therefore serves towards multiplying a desirable genotype rather than improving the breeding value of plants. Furthermore, micropropagation refers to a number of techniques that vary depending on the plant types and varieties.

Micropropagation has been adopted where it is cost-effective, as it provides several advantages compared to alternative plant propagation methods (mainly seeds or cuttings-based): rapid and space-saving propagation; uniformity of products; elimination of viral, bacterial or fungal pathogens. This technique also serves conventional, MAS or genetic engineering-based breeding techniques by providing sufficient and high quality starting stock. Therefore, micropropagation is mainly applied for the provision of young and mother plants.

[155] Regulation (EC) No 1830/2003 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.

[156] European Commission (2003). 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.

[157] Gómez-Barbero, M., J. Berbel and Rodríguez-Cerezo E. (2008). Adoption and performance of the first GM crop introduced in EU agriculture: Bt maize in Spain. European Commission, IPTS, EUR 22778. http://www.jrc.es/publications/pub.cfm?id=1580.

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

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

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 (of different types, such as flowers, foliage plants, woody ornamentals, etc.), followed by vegetable and fruit plants. Current production techniques for micropropagation have made a strong and continued growth within the micropropagation industry possible. Furthermore, where micropropagation is applied, demand for most of the ornamental plants exceeds the capability of the commercial laboratories to produce sufficient numbers of plants.

A survey of European micropropagation laboratories conducted in 1996-1997 identified 193 commercial laboratories active in this area[159]. The countries with the highest numbers of companies were the Netherlands (36), Germany (31), the United Kingdom (18), Belgium (14) and Italy (14). However, young plant companies having integrated micropropagation laboratories were not included in the survey, and as there has been build-up of such units recently, this number is likely to be an underestimate.

The adoption of micropropagation depends on its cost-effectiveness compared to other alternatives and varies within the horticultural industry, and even within the ornamental plant industry. As data on the adoption and impact of micropropagation in the EU are not available, interviews were carried out in 11 horticultural breeding or propagation companies. These companies were selected for their activities on those plants where micropropagation plays an important role, namely orchids and pot plants and also strawberries and certain ornamental woods that show high production volumes in Europe[160]. Nine out of the 11 companies were commercial plant propagation laboratories, the other two being young plant companies. The interviewed companies were located in Germany, the Netherlands, Belgium, Austria and the United Kingdom.

The survey revealed that three out of the 11 companies were active in conventional propagation, 10 were active in micropropagation, five were active in breeding and four were involved in R&D activities, which indicates that 91% of these companies are active in micropropagation. Moreover, the companies provided a breakdown of their activity fields as shown in Figure 17.

[159] Ríordáin, F.O. (2000). COST 822 – The Directory of European Plant Tissue Culture — 1996. Acta Hort. (ISHS) 530:33-38. http://www.actahort.org/books/530/530_2.htm
[160] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

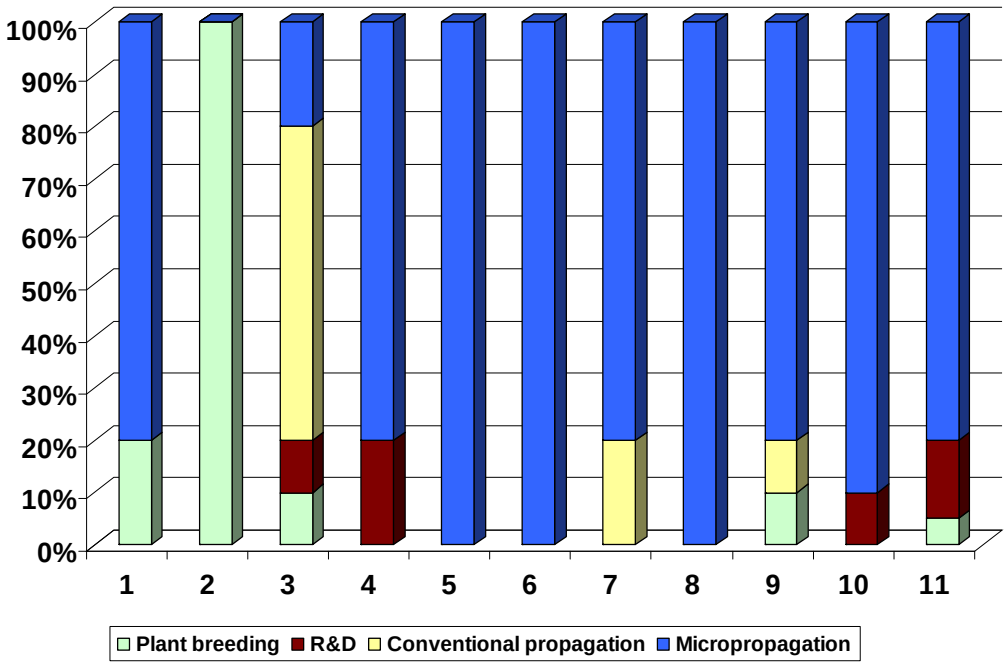

Figure 17: Activity field shares of the interviewed companies
Source: ETEPS[161]

On average, 81% of the overall activity in the adopting companies is related to micropropagation, indicating the dependence of these companies on this technology. When this share is calculated over all 11 companies (including the single non-adopter) the micropropagation-related activity share falls to 74%. The 11 interviewed companies indicated total annual sales of 28 308 000 plants, which, multiplied by the 74% activity rate, provides an estimate of 20 947 920 plants produced through micropropagation. 60% of the plants produced were orchids, followed by fruit plants (16%, mainly small berries and *fragaria*), perennial herbaceous plants (8%), pot plants (8%), ornamental shrubs/trees (4%), cut flowers as mother stock (3%), the remaining being vegetables and forestry plants. The turnover of the interviewed companies ranged from between EUR 250 000 and EUR 2 million per year. Taking this turnover range and multiplying it with the estimated number of companies (193) described above and the estimated micropropagation-related share of the adopters (81%), provides an estimate of the range of the total turnover (direct impact) of specialised micropropagation laboratories in the EU, at EUR 39 - 313 million. This estimate should be treated with caution, as it merely intends to provide an idea of the order of magnitude of the economic contribution of micropropagation in the EU. Using as a benchmark the total value of nursery plants and flowers in the EU (EUR 6.4 billion[162]) provides an indication of the importance of micropropagation to the sector at 0.6 - 4.7%, which is likely to be conservative, as it does not include the turnover of young plant companies using micropropagation. The indirect impacts of micropropagation relate to the production of adult ornamental plants and flowers (EUR 8.3 billion) that are derived from micropropagated young plants and mother stock[162]. The adoption share for the biotechnology producers (0.6 - 4.7%) may be used as the best estimate, which results in EUR 50 - 389 million or 0.004 - 0.033% of the agro-food

[161] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.
[162] All sector information based on: European Commission, DG Agriculture and Rural Development (2006): Working Document of the Commission staff on the situation of the flowers and ornamental plants sector. http://ec.europa.eu/agriculture/markets/fruitveg/flowers/analysis.pdf.

sector[163]. This is probably an underestimate of the true contribution, as the propagation of superior mother stock will probably have a multiplier effect[164].

While the contribution benchmarked to the sector may seem low, certain plants can only be propagated profitably by means of micropropagation. Furthermore, the huge demand for some ornamental plants like orchids can only be fulfilled by applying micropropagation. Therefore, this technique is often described to be complementary to conventional young plant production. One of the first drivers for the adoption of micropropagation was the high demand for cut flowers (e.g. gerbera) in Europe in the eighties. Today the general demand for cut flowers is decreasing, whereas the production of orchids gains ever more significance. Therefore, the extent and success of micropropagation mainly relies on the market demand of end consumers and can change significantly within a few years.

Labour is by far the largest cost item when producing micropropagated plants, which may even reach 60 - 85% of the total costs. For conventional propagation fewer employees are needed. Therefore labour costs have a lower share on the total expenditures than in micropropagating companies. However, the need of land and operating capital is higher in conventionally working firms. The high labour costs have been a driver in seeking low wage countries for the installation of micropropagation activities (both within and outside the EU, such as in Asia).

From the interviewed companies, it was estimated that approximately 75% of the employees are related to micropropagation (a conservative estimate of the total number of employees in the interviewed companies is 400 people). Using a similar approach as the one used for turnover, it is estimated that the number of employees dedicated to micropropagation would fall in the range of 1563 - 15 630 (10 - 100 employees per company, multiplied by the 193 companies and by 81%, the micropropagation-related activity of adopters).

The production of ornamental flowers and plants is of particular importance to the agricultural economy of certain regions of the EU. Furthermore, the EU is a major player in global production with a 12% share by area and a 42% share by value. EU production is characterised for the highest production intensity achieved mainly through the use of modern technologies. The value of production is stable for ornamental flowers and plants but is increasing for nursery flowers and plants. Furthermore, the EU is a net exporter of nursery flowers and plants and a net importer of ornamental flowers and plants, while the total balance is positive. Meanwhile, EU domestic production is the main source of internal consumption. 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) is capital availability linked to modern technology use, logistics and a home market. To this end, micropropagation seems to be one tool that enables some EU producers to remain competitive.

[163] Complications in the calculation include the unknown share of imports and exports of total as well as of micropropagation plants and flowers at the appropriate level of dissagregation.

[164] It should also be noted that some micropropagation companies may have the grow-out phase integrated in their young plant activities, and therefore the direct and indirect impacts will be confounded.

2.3.5.1.2 Breeding and propagation – livestock

Modern biotechnology used in livestock breeding and propagation refers to MAS and embryo technologies used in assisted reproduction. Similar to plants, the biotechnology producers are located upstream from the farmers, and they include livestock breeders and related biotechnology producers, that supply input to farming in the form of embryos, breeding animals, semen, etc. Therefore, the direct impacts relate to the turnover generated by these activities, whereas the indirect impacts cover the downstream effects to the farmgate, processing and final retail sale of the respective products.

The EU animal breeding sector mainly serves the most important livestock species produced in the EU, namely cattle, pigs and poultry[165]. The structure of the respective breeding sectors differs significantly, especially that of poultry breeding, mostly due to differences among the reproductive biology of the different species. In general, animal breeders (as plant breeders) have two main activities: i) genetic selection for improving the desirable characteristics and ii) assisted reproduction for producing large numbers of the desirable genotypes. According to the Sustainable Farm Animal Breeding and Reproduction Technology Platform (FABRE)[166], breeding efforts are responsible for an economic gain through improved production of EUR 1.83 billion. Cattle accounts for 27% (EUR 500 million), similar to pigs, poultry for 33%, and fish for 4%.

Many ruminant breeders are farmers' cooperatives, with a modest turnover and a small number of employees (e.g. fewer than 250); these cooperatives target their activities to their own countries, reaching market shares of 75% or more, while no organisation has more than 25% of the EU market share. In pig breeding, on the other hand, private companies account for approximately 50% of the activity, the rest being cooperatives. Some of the organisations may reach market shares at a national level of 75 - 100%, and in general a few organisations (i.e. three to six) serve each country. As in cattle breeding, no single organisation has more than 25% of the EU market. In contrast, poultry breeding in the EU and globally is characterised by a significant concentration of the market to a handful of private companies. As an example, in laying hens, just three companies serve 80 - 95% of the EU market and over 75% of the global market; while in broilers four breeding companies dominate with 35 - 60% of the market. EU breeding organisations hold, therefore, a very strong position in the EU (accounting virtually for the vast majority of the market) and hold leading positions globally. The EU-wide annual turnover stemming from animal breeding activities was estimated at EUR 2 billion, 40% related to pig breeding, 30% to cattle breeding, 15% to poultry breeding with the remaining related to other livestock (mainly other ruminants, such as sheep and goats, and horses)[167].

[165]Information on the structure of the animal breeding sectors is based on A.M. Neeteson and P. Robinson (2003) Farm animal breeding in Europe – 2003, SEFABAR.

[166] FABRE (2006). Sustainable farm animal breeding and reproduction: a vision for 2025. FABRE Technology Platform, Oosterbeek. http://www.fabretp.org/content/view/19/38/.

[167] IPTS estimate based on information from ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications and expert opinion: EUR 1400 million from the reported activities of major breeding organisations in the surveys for pig (EUR 800 million) and cattle (EUR 600 million) breeding. The EU-wide shares in final animal output were then used to estimate the relevant turnover for poultry (EUR 300 million) and other animal breeding (EUR 300 million).

Embryo technologies[168]

Embryo technologies as part of modern biotechnology refer to a range of techniques, centred around embryo transfer but also including *in vitro* embryo production, embryo and semen sexing, etc. While these techniques have been used to a variable extent with several livestock species (cattle, pigs, equidae, etc.), commercial application at any significant level has only taken place in cattle breeding, and mainly in the dairy sector. Embryo transfer (ET) is used as a means to propagate selected animal genetics throughout the breeding process at a faster pace. Therefore, it does not have an effect on the breeding value of an animal per se, but it aids the faster dissemination of the desirable genetics. The main alternative method is artificial insemination (AI), which is also the main vehicle for propagation in livestock. AI has been used for approximately 60 years and is considerably cheaper than ET, which has limited the use of ET to the top of the breeding pyramid, although ET infers several advantages[169].

The EU cattle herd consists of approximately 40 million cows and heifers. The dairy segment accounts for the majority of gain achieved through genetic improvement in cattle. There is a large international trade in cattle semen and embryos meaning that livestock genetic evaluation can occur across countries. The International Bull Evaluation Service[170] involves nearly 50 countries and is responsible for standardising the international genetic evaluation of bulls. The EU is an important player in the international cattle breeding sector as five out 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 (e.g. Genus in the UK, AltaGenetics in the Netherlands) and cooperatives (e.g. CRV in the Netherlands, Svensk Avel in Sweden) operating on an international scale, as well as 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). ET services are provided either by veterinary specialists or specialist ET companies, but may also be part of the breeding companies themselves. It has been estimated that there are more than 100 such ET 'teams' in the EU[171].

The direct economic impacts of ET may be estimated based on the ET-related turnover realised by the above described companies. While appropriate statistical information is not available, information obtained through a survey of livestock breeding companies and from targeted interviews of cattle breeders and ET companies provide insights into the direct economic contribution of the use of ET. Furthermore, the European Embryo Transfer Association (AETE) provides annual updates on the number of ET globally, for which 2004 data are presented in Table 18.

The proportion of calves resulting from ET is very small (<0.5% of total calf production), as this technology is only meant to be used at the top of the breeding pyramid. The ET activity reported from the survey of nine companies (9000 ET representing a turnover of EUR 20 million) represents around 10% of the ET activity reported for Europe (see Table 18),

[168] Non-referenced information is based on expert opinion and data from (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).
[169] It should be noted that these technologies may be applied in combination, e.g. AI and ET may be used simultaneously in a breeding programme.
[170] http://www-interbull.slu.se/.
[171] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

although the share may be closer to 5% as the reported activity is probably an underestimate of the actual total. The total EU-wide revenue from this activity may therefore be estimated at least at EUR 200 million. Based on these data, the turnover per ET is estimated at EUR 2000, which falls within the range of publicly reported values.

Results from the targeted interviews indicate that the share of ET-related turnover out of total turnover of the companies is very variable (depending on the type of company, e.g. specialist ET company vs. large breeding company) and can be up to 60% in very specialised companies.

Table 18: Top European countries ranked according to total numbers of embryos transferred (*in vivo* plus *in vitro*) in 2004.
Source: European Embryo Transfer Association (2005) via ETEPS (2006)[172], IPTS calculation

Country	Number of embryos transferred	Value in EUR million (IPTS estimate, number of embryos x EUR 2000)
France	29 618	59.2
Netherlands	16 466	32.9
Germany	11 285	22.6
Belgium	7190	14.4
Italy	6755	13.5
Czech Republic	6427	12.9
United Kingdom	5000	10.0
Denmark	3983	8.0
Finland	2985	6.0
Switzerland	1680	3.4
Ireland	1444	2.9
Spain	1329	2.7
Sweden	1300	2.6
Total	95 462	190.9

The indirect contribution of ET relates to the use of ET derived products by the cattle farmers (beef and dairy). Expert opinion from the interviews indicated that the proportion of AI bulls themselves derived from ET is at least 75% in those countries with the largest numbers of cattle. Based on this estimate, it is assumed that 75% of farmgate products have been based on the use of ET, which accounts to EUR 55.2 billion or 4.6% of the agro-food sector. While it is clear that ET is neither the sole parameter and perhaps neither the most crucial one for ensuring the realisation of the economic activity and the farmgate output, its diffusion and application in livestock breeding is considered very important.

[172] European Embryo Transfer Association AETE (2005) 21st Scientific Meeting, Keszthely. http://www.aete.eu/pdf_publication/17.pdf. In ETEPS (2006) Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

As noted by FABRE the strategic importance of animal breeding and reproduction is much greater than one might guess from the size and volume of the sector[173]. Based on the group's estimate of the economic gain achieved through cattle breeding (EUR 500 million) and the experts' estimate that at least 75% of AI bulls are derived from ET (in those countries with the largest numbers of cattle), it is assumed that 75% of the improvements (EUR 375 million annually) would not be feasible without the use of ET. The total ET-related return of genetic improvement assumed at 375 million represents 0.3% of the value of animal production (EUR 127 billion) or 0.5% of the cattle share of animal production (EUR 73.6 billion).

The allocation of 75% of the indirect economic impacts of breeding to ET should be treated with care as genetic improvement also depends on the concomitant application of other breeding techniques, including other biotechnology applications. However, at the same time, it may be argued that it would not have been feasible to disseminate 75% of this genetic improvement without ET. The benefit (indirect impacts) of ET adoption at the farmgate and through to final output is also illustrated by the following examples[174]:

- the company Genus indicates that their ET breeding herd (which is at the top of the pyramid) in the UK averages 14 000 litres of milk per cow per year compared to a UK average of 7000 litres
- the company Cogent illustrates the value of genetic improvement for beef indicating that the difference between the offspring of an average bull and a bull with an outstanding breeding value is EUR 45 as a calf and EUR 105 for the adult animal
- in Denmark between 1984 and 2002, protein production in the first lactation period of dairy cattle increased by approximately 80 kg in 305 days with more than 50% of this increase due to genetic improvement (the rest being the result of management improvements)
- in the Netherlands, the average production per lactation of recorded cows increased by 62% in the 20 years from 1985 (from 5600 to 8900 kg milk).

Marker assisted selection (MAS)

MAS is applied in animals in the same way as in plants. Molecular markers are used to aid the breeding of all livestock species. However, no definitive data are available on the extent to which MAS is used in livestock breeding nor on the extent to which livestock products have been derived from livestock selected through MAS.

As for plants, the impacts of the use of markers in livestock breeding and production are not quantifiable from the data available. The advantage of genetic markers is that they can be assimilated within a general breeding programme but the disadvantage of this is that their contribution cannot be disaggregated from the value of the programme as a whole. Usually, organisations do not distinguish and record their activities in MAS separately from their conventional breeding practices as the two are integrated.

A survey conducted in 2005[175]to cover all major livestock producers provides some relevant insights. More information was also obtained from targeted interviews of major EU pig

[173] FABRE (2006). Sustainable farm animal breeding and reproduction: a vision for 2025. FABRE Technology Platform, Oosterbeek. http://www.fabretp.org/content/view/19/38/.
[174] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.
[175] ETEPS (2006). Bio4EU Task 2 Main report.

breeders[176], but focused on MAS in the narrow sense, i.e. excluding supporting uses of markers in breeding that are not directly involved in the selection of a particular trait.

The MAS specific turnover realised by the 16 breeding companies/organisations that replied to the survey can be used as the minimum direct economic contribution of MAS in livestock breeding, while applying the MAS turnover share to the estimated total livestock breeding related turnover may provide a maximum estimate[177]. The total MAS specific turnover amounted to approximately EUR 207 million (a low estimate of direct economic contribution) which is 28% of the total turnover reported by these companies (EUR 740 million), and 10% of the total estimated turnover of EU livestock breeding (EUR 2 billion). Applying the 28% adoption rate to the total estimated turnover of EU livestock breeding of EUR 2 billion yields the maximum estimate of EUR 560 million[178]. More than half of the MAS turnover was realised from sales outside the EU, corroborating the strong position of EU livestock breeders. Regarding the use of MAS (in the narrow sense) in pig breeding in the EU, and based on very limited quantitative and descriptive data from interviews, the best estimate was that MAS has contributed to the breeding of around 40 - 80% of breeding females[179] in that they or their parents or grandparents had been selected using MAS or testing had been used to ascertain that a specific marker was not useful in the population because a specific gene was not segregated in that population. While this estimate should be used with caution as it is based on a large number of assumptions (due to the lack of firm quantitative data on market share, sales volume or the extent to which markers are used for most of the organisations interviewed), it may be used as an indication for the adoption of MAS by the pig sector.

The indirect contribution of MAS refers to the turnover realised by livestock producers from products that have been derived from livestock selected through MAS. A rough estimate of the indirect contribution is obtained by applying the estimates obtained for the breeding sector to the growing sectors (total animal output of EUR 127.4 billion), which yields EUR 12.74 - 35.67 billion or 1.5 - 3% of the agro-food economy.

Some impacts related to pig production have been described in the general literature and these are summarised in Table 19.

As described in the ET analysis, the value of adopting MAS in the breeding process relates to the fact that breeding provides economic gains to the farmers. Using the estimates provided by FABRE as an illustration, 40 - 80% of the EUR 520 million annual economic gain related to pig production at the farmgate may be due, to some extent, to the use of MAS. The total MAS-related return of genetic improvements assumed to be EUR 208-416 million represents 0.16 - 0.32% of the value of animal production (EUR 132 billion) or 0.8 - 1.6% of the pig share of animal production (EUR 26 billion).

[176] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.
[177] Assuming that the share obtained from the surveyed companies is at the high end, as in general companies involved in biotechnology are more likely to reply to a biotechnology specific survey.
[178] This indicates that the companies replying to the survey covered approximately 50% of the total activity.
[179] Assuming 15 million sows in the EU with 40% being replaced per year and hence a market of 6 million gilts per year. Assumptions were made about market shares of different organisations based on stated sales from organisations which are expected to be broadly similar in size and verbal indications of the use of MAS or indications from marketing literature. Where no data were available, the assumption, based on interviews, was that 25-80% of pigs were produced using MAS. Note that MAS may not be used to the same extent in the production of parent males and females (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.).

Table 19: Impacts of MAS on pig breeding and production
Source: ETEPS[180]

Genetic marker	Impact	Value	Reference
Halothane[1]	Reduced mortality of between 4-16 per 1000 to zero and improved meat quality	Improved public perception and better economic performance	McLaren & Rohl[2], based on PIC data
Halothane	Carriers show 43% more drip loss in meat after two days	Better economic performance and consumer acceptability	Otto *et al.* 2006[3]
ESR (trait affected: litter size)	Increased rate of genetic response in litter size by 30%	Economic performance	Short *et al.*[4]
MC4R (trait affected: appetite – production efficiency)	Increased lean by 1.4% and reduced backfat by 1.1 mm	Economic performance	Plastow 2006[5]
Combination (unspecified)	Reduced drip loss from meat over 7 days from 5% to 3%	Economic performance and consumer acceptability	Primetiva *et al.* 2006[6]
FUT1 (trait affected: resistance to *E. coli* F18 – disease resistance)	Resistance to infection by *E. coli* F18, reducing mortality to zero and improving growth of surviving pigs	Improved public perception and better economic performance	Van der Steen *et al.* 2005[7]
IGF2 (trait affected: higher muscle mass[8])	EUR 2.8/head advantage to positive genotypes in US trial	Improved economic performance	Interview data

[1] RYR1/CRC1 ryanodine receptor gene, trait affected: sudden deaths/meat quality (causal mutation known).
[2] McLaren and Rohl, personal communication quoted in http://db.genome.iastate.edu/%7Emax/Reviews/1998_review/.
[3] Otto, R. et al. quoted in Primetiva, L., R. Klont, O. Southwood and Plastow G. (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, C˘. Bude˘jovice, p. 41-44.
[4] Unpublished results of Short, Wilson, McLaren and Plastow, quoted in: Rothschild, M.F. and Plastow G.S. (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/.
[5] Plastow, G. (2006). Proceedings of the British Society of Animal Science **2006**: 204. http://www.bsas.org.uk/Publications/Annual_Conference_Proceedings/.
[6] Primetiva, L., R. Klont, O. Southwood and Plastow G. (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.
[7] van der Steen, H.A.M. et al. (2005). Journal of Animal Science **83**: E1-E8. http://jas.fass.org/cgi/content/abstract/83/13_suppl/E1.
[8] This marker may also improve uniformity of slaughter animals as only the gene from the male parent is expressed (causal mutation known).

The additional benefits of MAS adoption through to final output may also be illustrated in the following publicly reported example where a pig breeding organisation collaborates with a meat marketing organisation to use genetic markers to identify pigs with improved meat quality. The example is from Germany where a retailer, EDEKA Südwest, and a pig breeding

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

company, PIC Deutschland, have an agreement to use markers in a pig meat quality programme to supply branded meat[181]. A group of boars selected on the basis of a package of seven meat quality genetic markers derived from PIC has been established in (AI) stations for use in the "Gutfleisch-Programm". The EDEKA group is part of the largest food marketing association in Europe. Boars for this programme are not necessarily of PIC origin. Producers are being offered around EUR 0.02 per kg premium if they use boars selected for the programme (interview data). EDEKA requires a supply of around 7000 – 10 000 pigs per week for this programme, at a carcass weight of around 92 - 95 kg.

2.3.5.1.3 Breeding and propagation – fish

Modern biotechnology currently used in fish production is mainly applied in fish farming. Fish breeders have been applying techniques for ploidy and sex manipulation for several years, and are using molecular markers more and more to optimise breeding strategies. As in the other primary production sectors, direct economic impacts refer to the activity of companies in the breeding sector, whereas indirect impacts consist of downstream effects to the farmgate. Molecular markers in fisheries management (harvest fisheries) is still at a rather experimental/pilot phase.

In general, fish breeding resembles poultry breeding in structure, as fish are characterised by a high fecundity and as there are only a small number of dominant companies. For example, only five companies are involved in salmon selection. On the other hand, fish breeding activities are often integrated with other activities in the primary or processing sectors; from the statistical standpoint (Eurostat), hatcheries and breeding activities form part of the primary sector activities specific to fish farming, without separating between the breeding and grow-out stages.

While there are no data on the total turnover realised by the EU fish breeding sector, the best estimate that can be used for illustrative purposes is 8% of the final farmgate output[182] (final farmgate output was EUR 2.77 billion for 2003), and take species specific farmgate output (in value terms) to estimate the species specific relative shares of breeding output. A survey of salmon, trout and oyster breeders and national experts gives an estimate of the adoption of modern biotechnology in aquaculture[183]. The use of markers in the wide sense has been mainly applied in salmon breeding (i.e. mainly used as a tool for genetic selection via fingerprinting and not for assisting in the selection of traits) and based on a conservative estimate seems to contribute to 30% of the salmon's and trout's annual production of eggs (EUR 10 million and 11 million, respectively), and 10% for oyster's annual spat production (EUR 2 million). Sex and ploidy manipulation techniques have been applied since the 70s, mainly in trout and oyster breeding, and based on a conservative estimate contribute 50% (EUR 18 million) and 20% (EUR 4 million) to the total EU turnovers, respectively. Therefore, and based on the species included in the analysis, it can be estimated that approximately 15% of the EU-wide fish farming turnover was produced through the use of seed fish produced

[181] The Pig Site (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.

[182] Conservative expert opinion based on the share of the hatchery costs in the total production costs for different fish species. The shares of the three different species were calculated based on Eurostat data for 2003 at: trout 18%, salmon 16%, and oysters 10%.

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

with the aid of modern biotechnology[184] (modern biotechnology-related turnover of EUR 45 million over a total breeding-related turnover of EUR 277 million). While these adoption rates should be treated with care as indications on the representativeness of these values over the whole industry are not available, they do fall within the range of values reported in the literature and obtained from expert opinion. For a rough estimate of the potential significance of modern biotechnology to the sector, the adoption rates reported above can be used over the total estimated turnover from fish breeding (direct impacts) and fish growing to the farmgate (indirect impacts). On the whole, available information indicates that modern biotechnology is used widely in particular sectors, namely sex and ploidy manipulation in trout and oyster production and MAS fingerprinting for salmon and trout, as a relatively large share of seed fish are produced using these technologies. As the overall sector is relatively small, the significance to the whole EU agro-food sector and the EU economy is, however, relatively small. Applying the 15% adoption rate to the EU-wide fish farmgate turnover provides an estimate of the indirect contributions of biotechnology at EUR 432 million, representing 0.04% of overall agro-food turnover.

Moreover, expert opinion indicates that sex and ploidy manipulation may have reached the limits of potential benefits where applied (i.e. trout and oysters) and therefore, its adoption is not likely to increase any further. Nevertheless, these techniques have not been adopted at the same rate in all EU Member States, and therefore the EU-wide adoption is likely to increase in the future. The highest growth rate in adoption is, however, expected to occur with the use of MAS in the breeding of all species involved. Overall, the outlook is an increase in the use and importance of modern biotechnology in fish farming.

2.3.5.2 Diagnostics

Modern biotechnology-based diagnostics refer here mainly to DNA-based tests and immunoassays. However, modern biotechnology-based diagnostics may involve a wide range of other techniques, the common thread being the detection at the molecular level in combination with rapidity, usually referred to as rapid methods.

Modern biotechnology-based diagnostics have found several applications, the vast majority of which are in the human health sector. However, an important share of diagnostics are developed for the primary production and food sectors, namely in animal, fish and plant health monitoring and in food safety monitoring. Economic information on the diagnostics sector is scarce and, where available, is of a complex nature.

While diagnostics in farm animal health monitoring are used by the farmers themselves in cases of emergency, the major use is for monitoring purposes, especially within the context of notifiable diseases, such as bovine spongiform encephalopathy (BSE), brucellosis, bovine tuberculosis, etc. In the majority of cases, the monitoring is carried out by state and public institutions. Modern biotechnology-based diagnostics in general provide novel or improved diagnostic tools. The improvements may be in terms of accuracy and precision or, most frequently, in terms of the time needed to provide results.

[184] Conservative estimate, as for trout and oysters only the highest turnover estimate was used (i.e. related to sex/ploidy manipulation) in order to avoid double-counting where both sex/ploidy manipulation and MAS are applied together.

The world market for animal health diagnostics has been estimated at EUR 400 million for 2003[185], which is much smaller than for the therapeutics sector and the human health diagnostics sector. However, this estimate mainly considers rapid tests or kits, which in the scope of this study falls in modern biotechnology diagnostics. As approximately half of the largest companies are based in the EU, a simplified estimate is that the EU annual modern biotechnology diagnostics turnover amounts to EUR 200 million[186]. Diagnostics for food safety in the EU have been reported to be EUR 500 million[187], approximately 20% of which is from rapid methods. Therefore, a rough estimate of the size of the direct contribution of modern biotechnology-based diagnostics is provided at EUR 300 million which represents 0.03% of the total EU agro-food sector (also covering diagnostics used in plant health or other agricultural activities).

The indirect contribution of diagnostics to the EU economy relates to the turnover realised by laboratories carrying out the tests as well as downstream impacts such as helping in the assurance of consumer confidence, in the maintenance of trade, and in the avoidance of negative impacts through disease or contamination.

The laboratory related turnover for modern biotechnology-based diagnostics applied in food safety and veterinary health may be conservatively estimated at EUR 1500 million[188], accounting for 0.13% of the EU agro-food economy.

The indirect impacts related to ensuring the continuous functioning of the food chain (food chain actors, regulators, consumers) are very complex to calculate. Farm animal disease outbreaks can have serious economic consequences, with a fast and accurate diagnosis being an important tool in their avoidance and/or monitoring. There are a number of examples where modern biotechnology has been used for the provision of diagnostics in animal health and food safety. Some illustrative examples are provided in the following sections.

Foot and mouth disease (FMD) diagnostics[189]

FMD is one of the most important livestock diseases and is listed in the A list of diseases by the World Organisation for Animal Health (OIE). FMD is difficult to differentiate clinically from several other diseases and so accurate laboratory diagnosis of any suspected case is a matter of urgency. Following the FMD epidemic of 2001, there has been much interest in the development of biotechnological tests for improving the collection of information for use in

[185] BCC (2004). Animal therapeutics and diagnostics. Report HLC034A. BCC Research, Wellesley, M.A. http://www.bccresearch.com/hlc/HLC034A.asp (abstract available online).

[186] BSE tests alone, a large share of which are immunoassays, would account for approximately EUR 100 million annually for the period 2001-2005, assuming a conservative price of EUR 10 per test.

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

[188] DNA-based tests and immunoassays for GMO detection cost EUR 6-150 per test while the laboratory analysis cost EUR 100-570 (ETEPS (2006). Bio4EU Task 2 case studies report – primary production and the agro-food applications.). For BSE testing (immunoassay), a laboratory analysis was estimated at EUR 40 - 50. Therefore a five-fold higher laboratory turnover over the turnover of the test-kits is a conservative estimate.

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

the epidemiology of the disease, in differentiating between the many strains and species which cause confusion in diagnosis and in the early diagnosis of an outbreak. There are at least eleven modern biotechnology firms actively involved in the development and commercialisation of FMD diagnostic tests, four of which are located in the EU. Expert opinion indicates that jobs in inspection and surveillance have already been increasing, in the EU and globally, post 2001.

The indirect impact of the availability of modern biotechnology-based diagnostics for FMD is related to its instrumental role in the avoidance of an outbreak. Following the 2001 outbreaks, Member States have increased their surveillance activities and this may be contributing to the fact that no new cases of FMD have been reported since 2001. However, it is not possible to attribute this fall in incidences to new biotechnological approaches for early diagnosis of FMD. Currently, all EU countries are recognised by the OIE as disease-free without prior vaccination.

The costs incurred following the 2001 outbreak can be used as an example of the potential costs that may be avoided through the use of improved biotechnology-based FMD diagnostics. The UK government alone is estimated to have lost GBP 2.4 billion over two years (mainly from compensation payments and reduced tax returns) without the inclusion of the heavy losses incurred by agricultural export, transport, tourism, hotels and restaurants in the UK. Moreover, the European Commission had also made provisions for EUR 400 million in 2001, and had earmarked a further EUR 400 million towards FMD. Modern biotechnology companies are active in the EU and the US for developing improved diagnostics for FMD, although the most significant impact is expected in the creation of 'pen-side' tests that will be simple for farmers to use, and in the development of marker vaccines, for enabling surveillance rather than post-facto detection. A major challenge to modern biotechnology-based FMD diagnostics relates to the difficulties encountered by the relatively small biotechnology companies to provide the product in adequate numbers. To this end, some argue that the state should not only play an important role in funding relevant R&D but also in the necessary stockpiling of these products for future use.

Bovine spongiform encephalopathy (BSE) diagnostics[190]

Modern biotechnology has enabled the provision of the only rapid tests (immunoassays) available for the detection of BSE. These are postmortem diagnostic kits that allow samples to be taken at the abattoir to give results which can be reported back the next day, allowing the carcass to enter the food chain in case of a BSE-negative result. Prior to the development of these kits, testing for BSE took three to five days. The new diagnostic kit allows many more samples to be tested, enabling the level of surveillance as required by Regulation (EC) 999/2001[191]. Thirteen tests produced by ten companies have been approved for use in the EU. Of these companies, six are based in the EU (in the UK, Germany, France, Ireland and the Netherlands), two in the US and one each in Japan and Switzerland. The EU market is dominated by two of the six EU companies, with a third being a major competitor in the field due to its production and use of small ruminant tests alongside its BSE tests. The other

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

[191] Regulation (EC) No 999/2001 of the European Parliament and of the Council of 22 May 2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies, OJ L 147, 31.5.2001, p. 1–40. http://ec.europa.eu/food/fs/afs/marktlab/marktlab14_en.pdf.

companies hold very little, and in some cases no share of the EU market at all. Globally, three of the companies producing kits used in the EU, are located outside of the EU – Prionics (Switzerland), Idexx (US) and Fujirebio (Japan). Of these, Prionics and Idexx have major shares of the global market in rapid diagnostic tests (the worldwide market is dominated by Prionics, Enfer Scientific (Ireland), Bio-Rad (US) and Idexx), with the Fujirebio product being more recently released and approved. The surveillance programme tests over 10 000 animals annually, a number which could not be achieved without the use of the rapid test kits. The rapid diagnostic kits are mainly used in the appointed veterinary laboratories in Member States, as part of required surveillance for BSE with the approved kits. Taking as a conservative cost of a BSE diagnostic at EUR 10 (cost of immunoassay) and of a laboratory analysis at EUR 45 (range reported is EUR 40 - 50), the annual turnover of test kit producers and laboratory analysis is estimated at EUR 100 000 and EUR 450 000, respectively (assuming that most of the testing is done through the use of the modern biotechnology-based test kits). The implementation of BSE surveillance has had a positive impact on employment. The impact on employment in the EU is estimated to be similar for diagnostics producers as well as for the agencies conducting the analyses, with at least a 200 - 300% expansion for coping with the demands of the passive surveillance programme. This has led to the creation of regional laboratories, as well as outsourcing contracts to other laboratories to handle the increased throughput.

However, the surveillance comes at a cost: about EUR 1.56 million were spent per identification of a BSE case in healthy animal stocks, and EUR 0.07 million per BSE case in (at risk) animal stocks. These costs are mainly borne by individual Member States, with some state aid from the EU. Moreover, additional costs, such as related to fallen stock and emergency slaughter of farm animals, are covered by the Member States with some support from the EU, but also indirectly, by the cattle industry and the consumers.

Besides the direct impacts of the production and use of the test kits, enabling the EU-wide surveillance programme has had an indirect economic impact through the reopening of market borders. For example, beef was recently re-approved for export from the UK to EU Member States. This was achieved through the continued surveillance for BSE, which proved that the incidence of the disease was below the agreed threshold, and that there was compliance with the introduced measures designed to eradicate the disease. Moreover, the modern biotechnology-based diagnostics may also be seen as aiding in the avoidance of a new outbreak, and thereby preventing the effects experienced after previous outbreaks: in the UK, sales of beef fell by 40%, the price of beef fell by more than 25%, export markets were lost (trade estimated at about GBP 520 million), and there were effects on employment, as abattoirs temporarily closed or reduced their working hours. Moreover, it was estimated that, in the year following the start of the BSE crisis, the total economic loss to the UK was between GBP 740 million and 980 million (0.1 - 0.2% of the UK GDP). This pattern (a fall in consumer confidence and its follow-on economic effect) was mirrored in some other EU countries where BSE was discovered. 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[192]. In the EU, BSE surveillance is likely to decline over time, as the number of cases detected decreases, and therefore the current surveillance programme may be less cost-effective in the long-term. Looking into the future, modern biotechnology companies are currently working on the development of live animal tests, as well as on prion-

[192] Cunningham, E.P. (ed.) (2003). After BSE: a future for the European livestock sector. EAAP Series no. 108, Wageningen Academic Publishers, Wageningen.

specific diagnostic tests for humans. In addition, some companies have started branching out to other areas of surveillance of animal diseases.

Salmonella diagnostics[193]

Salmonella causes food poisoning and is the second most prevalent food pathogen after *Campylobacter*[194]. The mere frequency of the occurrence of salmonellosis is a sufficient indication of the significant public health costs it incurs. For example, a cost assessment made in the US in 2005, provides an estimate of the annualised cost of salmonellosis at about USD 2.4 billion with an average cost of USD 1709 per case, of which 89% relates to premature deaths, 8% to direct medical costs and 3% to productivity loss[195]. A new generation of modern biotechnology diagnostic methods, both DNA- and immunoassay-based, enables a faster detection of the food pathogen *Salmonella* bacterium. Faster detection is considered crucial in avoiding salmonella outbreaks, and thereby preventing the associated costs. Conventional analysis for salmonella, dominantly used, requires 4-7 days for presumptive evidence of salmonella in foodstuffs. This is often too long a time from public health perspectives when an outbreak can get expensive and serious in this timeframe. Overall, it is expected that rapid tests reduce testing times by 1 - 5 days.

Over 75 companies are currently providing salmonella diagnostic products, kits or services in the EU. In a few cases, the parent firm is US based but has considerable EU presence; all the other firms are based in EU Member States. The costs related to the surveillance for salmonella is borne mainly by the food industry (farmers, retailers, processors) for ensuring salmonella control and safety, while the costs in the case of human salmonellosis outbreaks are borne by the patients and the public health budgets. Nevertheless, it is difficult to attribute changes in reported disease incidences to modern biotechnology for pathogen detection. In several cases better enforcement by an EU Member State and 'therapeutic' or 'preventative' techniques such as heat-treatment of eggs or vaccination of poultry are identified by the respective Member State's regulatory agencies as the key cause of the falling incidence of human zoonotic cases.

Many US firms have recently acquired smaller EU firms, as illustrated by Neogen's acquisition of a Scottish base for serving the European and worldwide market better and Neogen's plans to add more R&D staff in Ayr, Scotland. This shows an increased interest in the EU market for salmonella detection as well as in EU research, by non-EU firms. The latter, in combination with the high level of activity in the development of improved diagnostics, illustrate the promise of emerging biotechnologies in salmonella detection and wider food safety issues, indirectly indicating expectations for growth in revenue and employment by firms that develop or provide these new biotechnology applications.

[193] Non-referenced information is based on expert opinion and data from (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).
[194] The EFSA Journal (2006), 94, The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial Resistance and Foodborne Outbreaks in the European Union in 2005.
[195] Economic Research Service (2006). Foodborne illness cost calculator: salmonella. Economic Research Service, US Department of Agriculture, Washington, D.C. http://www.ers.usda.gov/Data/FoodborneIllness/salm_Intro.asp.

Diagnostics for GMO traceability[196]

Modern biotechnology provides the only means for the identification and quantification of GMOs in the food chain, through the availability of specific DNA-based and antibody-based assays. The availability of these diagnostics has several implications for the EU: firstly, it ensures freedom of choice for EU consumers and users of GM and non-GM products; secondly, it enables the implementation of the EU regulations dealing with the approval, labelling and traceability of GMOs[197]; and thirdly, it provides the tool towards long-term monitoring of GMOs for the control of potential risks (e.g. related to the environment or human health).

There are about 50 diagnostic laboratories in the EU which deal with GMO analyses, and most of them are located in France, Germany and Austria. Information was largely gathered based on interviews with company representatives. In Germany, 15% to 20% of all diagnostic laboratories carry out GMO testing. The largest share of the products is DNA-based due to their higher accuracy for quantitative analyses, which are particularly used for checking against the obligatory thresholds. GMO tests are usually an additional service offered by diagnostics providers, and the share of revenues specific to GMO testing ranged between 9% and 13% of the total annual revenues of the interviewed companies. Moreover, the interviewees suggested that GMO test-kit production and laboratory analysis is non-profitable per se, as it is a small part of their overall activities and is accompanied by higher costs compared to other tests. These costs result particularly from the need to update the test kits (due to new GMO varieties) and to adjust the test kits to adhere to certain standards. According to the interviewees, on the one hand, it is difficult for private suppliers of GMO test kits to compete with national laboratories, while on the other hand, firms which produce test kits for the identification of GMOs are not yet exposed to much competition.

The impact on employment seems to have been relatively small, as the companies producing test kits and providing the analyses were already well structured for the provision of similar services, and as the GMO related activities account for only a small part of their overall activities.

Nevertheless, the tests are necessary for the food and feed industries concerned: results of a survey conducted in Germany revealed that the majority of the oil mills (75%) carry out analytical tests for the identification of GMOs, compared to 28% of companies from the dairy industry, 37% for the bakery industry, 44% from the confectionary industry and 43% from the feed industry. The relative proportions are highly correlated to the existence of raw materials or products for which GMOs are used. Overall, only a limited number of the German food and feed industry companies carry out analytical GMO tests internally, 94 - 100% of the respondents indicated that they assign external diagnostic laboratories for this task.

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

[197] For example: Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed, OJ L 268, 18.10.2003, p. 1–23. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0001:0023:EN:PDF; Regulation (EC) No 1830/2003 (22 Sept. 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 L 268, 18.10.2003, p. 24-8. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0024:0028:EN:PDF.

As in all traceability programmes, ensuring GMO traceability comes at a cost, which is mainly borne by the food industry: approximately 40% of the German food and feed producers reported additional costs due to GMO analyses; nevertheless, current indications show that these costs are small in relation to the total revenues of the companies.

The market developments related to GMO detection in the coming five years will be mainly dependent on the commercialisation of new GM varieties in the EU and on the regulatory framework in the EU. This is likely to have an impact on costs and revenues as well as on the number and qualification of the employees. However, as the demand for test kits for the identification of GMOs will presumably increase, the higher costs may be overcompensated by the growth in revenues thus leading to decreasing costs per unit due to economies of scale. In addition, the interviewed companies expected that they will create a limited number of new jobs in the future, in particular for highly qualified staff, due to an increase in the production of test kits.

2.3.5.3 Food and feed additives, and veterinary products

Modern biotechnology is used in a number of processes for the production of various inputs to primary production and the food chain, such as animal and plant health related products (e.g. vaccines, therapeutics, pesticides), as well as food and feed additives and fertilisers. These products are provided by companies falling into several manufacturing subsectors (mainly under NACE DG 24), but statistics are not available at a level of disaggregation that would allow a complete analysis.

Within these input sectors, modern biotechnology has been mainly applied in the production of livestock pharmaceuticals, particularly vaccines, and in the industrial production process of some therapeutics (such as antibiotics), and of food and feed additives, particularly food/feed enzymes (e.g. phytases, amylases), amino acids (e.g. lysine, threonine, tryptophane) and vitamins (e.g. riboflavin). All these products are produced by the manufacturing sector (where the direct contributions to the economy will be reflected), and are used by the primary production and/or the food and feed processing sectors (reflecting the indirect contributions). Plant protection products and fertilisers are not included in this analysis as they do not involve modern biotechnology in their production process to a significant extent[198].

Modern biotechnology-based products can be categorised according to product groups in chemicals (including enzymes) and vaccines. Vaccines will be treated separately in the section on animal health products, as they form a rather different product category. Modern biotechnology-based chemicals, however, while comprising diverse products, share some common features. These products are relevant in their use as food and feed additives (including therapeutics such as antibiotics), and are produced mainly through fermentation and/or through enzymatic production processes. According to a market study[199], the major

[198] Biofertilisers and biopesticides are still emerging applications, and may, in some cases, involve biotechnology steps.

[199] Leuchtenberger, W., Huthmacher K. and Drauz, K. (2005). Biotechnological production of amino acids and derivatives: current status and prospects. Applied Microbiology and Biotechnology, 69:1-8. http://dx.doi.org/10.1007/s00253-005-0155-y. *And* Maertz, U. (2005). World markets for fermentation ingredients. http://www.bccresearch.com/RepTemplate.cfm?ReportID=221&cat=fod&RepDet=HLT&target=repdetail.cfm

product groups are enzymes, amino acids and derivatives, crude antibiotics, organic acids, vitamins and other products, such as xanthan. The global market for fermentation products (excluding ethanol) was estimated to be approximately EUR 11 billion in 2004, accounting for EUR 3.9 billion of crude antibiotics, EUR 2.7 billion of amino acids, EUR 1.8 billion of organic acids, EUR 1.5 billion of enzymes, EUR 800 million of vitamins, and EUR 300 million of xanthan.

The global market of amino acids has been estimated to be EUR 3.5 billion[200], which leaves EUR 800 million derived mainly through enzymatic catalysis (also modern biotechnology-based) and to a minor extent through chemical synthesis. It has been estimated that food and feed amino acids account for about 56% and 32% of the global amino acid market, respectively, which corresponds to approximately EUR 3.1 billion, nearly all produced through modern biotechnology. Assuming an EU share in production of 20%[201] provides an estimated turnover of EUR 620 million (of which EUR 400 million are for feed additives and EUR 220 million are for food additives).

Regarding vitamins, the 2002 global market had been estimated to be EUR 1.7 billion[202], all of which can be allocated to food and feed use[203], the latter having a larger share. The share of modern biotechnology-based products (the turnover estimated above to be about EUR 800 million) accounts for approximately 50% of the total. As EU companies reportedly have an important share in global vitamin production (50%[204]), the modern biotechnology-based, EU-related turnover is estimated to be EUR 400 million.

As far as biotechnology-based crude antibiotics are concerned, the agro-food relevance is relatively low: while the exact share of the veterinary or EU-related turnover is not known, a best estimate can be taken as 1.8%[205] and 30%, respectively, which accounts for approximately EUR 20 million. Organic acids (the main product being citric acid) are used in a variety of applications, with food and feed uses having a major share. For illustrative purposes, assuming that food and feed accounts for 50% of the total consumption and an EU share similar to that for the amino acid market (20%) yields an estimated turnover of EUR 180 million. Xanthan represents the smallest group of fermentation products globally, of which approximately 70% is used in food applications[206]. Using as a best estimate an EU share of 20%[207], yields an estimated turnover of EUR 40 million.

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[200] Leuchtenberger, W., Huthmacher K. and Drauz, K. (2005). Biotechnological production of amino acids and derivatives: current status and prospects. Applied Microbiology and Biotechnology, 69:1-8. http://dx.doi.org/10.1007/s00253-005-0155-y.

[201] IPTS conservative estimate based on data provided by ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications: Lysine (which represents approximately 26% of the feed additives market): EU companies produce 40% of total production, while 14% of the total production takes place in the EU.

[202] BCC Research (2003). The global market for vitamins in food, feed, pharma and cosmetics.

[203] A minor share also targets the pharmaceutical and cosmetics markets.

[204] From Prepared Foods (2003) Taking vitamins - in the know, accessed online at http://findarticles.com/p/articles/ mi_m3289/is_9_172/ai_108051736 (Original Source. BCC Inc): DSM/Roche and BASF/Takeda hold 27% and 21% of the global vitamin business, respectively.

[205] 1.8% is the estimated share of farm animal-related pharmaceuticals over the total (3% of veterinary pharmaceuticals of which 60% is farm animal-related; see ETEPS (2006). Bio4EU Task 2 Main report)

[206] J.L. Flores Candia and W.D. (1999). Xanthan Gum in Encyclopedia of Bioprocess Technology: Fermentation, Biocatalysis, and Bioseparation. John Wiley & Sons, Inc. Accessed online at: Deckwer http://www.mrw.interscience.wiley.com/ebt/articles/ebt222/abstract-fs.html.

[207] It is reported that the larger producer is the US company CP Kelco which is part of Huber, while the Chinese are also very strong. The main EU player is Danisco.

Enzyme production itself, presented in more detail in Section 2.4, has been estimated as having a global value of EUR 1.8 billion, the EU having a share of 75% (turnover of EUR 1.3 billion) of which up to 48% is food and feed related (EUR 650 million[208]).

In total, the modern biotechnology-based food and feed additive production (direct contribution to the economy) is calculated from the above estimates to be EUR 1.91 billion. In the following sections, the various product groups will be described in more detail from a sectorial viewpoint.

Feed additives

Feed additives are estimated to be EUR 4.8 billion globally[209] including amino acids, vitamins, minerals, antibiotics, enzymes and acidifiers. While the exact shares for the EU are not available, a conservative estimate of 20%[210] has been used, which corresponds to EUR 960 million. As the majority of feed additives (mainly amino acids and enzymes, but also organic acids, antibiotics, etc.) are produced through modern biotechnology a large share of the figure estimated above will correspond to the direct contribution of modern biotechnology for feed additives. Assuming, as a best estimate, that 90% of the feed additives are modern biotechnology derived, results in a turnover of EUR 864 million[211], which is approximately 50% of the turnover estimated for both food and feed additives of the respective categories[212].

Feed additives have been gaining importance globally as animal production is gaining importance to consumers. The European Feed Manufacturers Federation (FEFAC) estimates that approximately 3% of feed material consumption is related to feed additives (out of the approximately 143 million tonnes European feed production in 2005)[213]. It has been estimated that 65% of poultry and 10% of swine feed already contains enzymes such as carbohydrases or phytases[214], the feed enzyme market amounting to approximately EUR 120 million. Moreover, the EU and the US are currently the global leaders of compound feed production, at 143 millions tonnes (24% share) and 150 millions tonnes (25% share), respectively, while

[208] From DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.33; 46% of enzymes production was allocated to food, and 2% to silage and feed; In Section 2.4, a rounded-up range of 30-45% is provided corresponding to food-related enzymes (information from two different sources).

[209] ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

[210] IPTS conservative estimate based on shares from three different case studies provided by ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.: i) Lysine (which represents approximately 26% of the feed additives market): EU companies produce 40% of total production, while 14% of the total production takes place in the EU; ii) Riboflavin: EU companies hold 30% of total production; iii) Cephalosporin intermediates: about 35% of 7-ACA and 50% of 7-ADCA are produced in the EU.

[211] IPTS estimate based on 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.: Amino acids represent about 33% of all feed additives, while expert opinion indicates that nearly all amino acids used as feed additives are produced via modern biotechnology. Moreover, all enzymes used as feed additives may be considered modern biotechnology, while a number of important vitamins (e.g. vitamins C, B12, B2), antibiotics (e.g. cephalosporin intermediates) and organic acids (e.g. citric acid) are mainly modern biotechnology-based.

[212] As feed-related amino acids account for EUR 400 million, it is implied that feed has a 36% share of the remaining product categories.

[213] FEFAC (2006) From Farm to Table: key figures 2005. http://www.fefac.org/file.pdf?FileID=3669.

[214] J.B. van Beilen and Li Z. (2002). Current Opinion in Biotechnology **13**: 338-344. http://dx.doi.org/10.1016/S0958-1669(02)00334-8.

the annual turnover of the EU compound feed industry was estimated to be approximately EUR 36 billion in 2004.

The role of feed additives is mainly to complement the nutritional profile[215] of feeds in several ways. Feed enzymes mainly function as digestibility enhancers, whereas vitamins, amino acids and minerals mainly directly complement the lacking nutrients. Modern biotechnology has been applied in the production of a large number of feed additives, but mainly in feed enzymes (e.g. phytases, carbohydrases, enhancing the digestibility of phosphorus and carbohydrates), amino acids (e.g. lysine) and vitamins (e.g. riboflavin). The production of enzymes in general is described in greater detail in Section 2.4. The use of enzymes in feeds (at an estimated value of EUR 30 million[216]) may induce a variety of changes, mainly related to feed formulation and ingredient composition. Feed formulation has been traditionally driven by least-cost objectives, but now it increasingly accommodates environmental and food quality objectives. Therefore the indirect economic impacts of the use of modern biotechnology derived enzymes relate to the induced changes in ingredient selection. For example, the use of phytase may accommodate more plant ingredients (or more types of plant ingredients used) in the feeds for monogastric animals (such as pigs, poultry and some fish) and less use of inorganic mineral supplements. The indirect impacts may take place at the level of the feed ingredient producers (which may impact back to the raw material provider, farmer, etc.), the feed manufacturer, all the way to the animal producer.

Amino acids and vitamins are supplements that provide the essential nutrients lacking in the macro-ingredients used in the feeds. As with enzymes, the direct impacts relate to the turnover realised at the industrial production step (a more detailed analysis can be found in Section 2.4). The indirect impacts are similar to those of enzymes, as modern biotechnology has enabled the cost-effective use of such additives. Amino acids, almost all of which are produced using modern biotechnology, represent about 36% of the feed additives market. An illustrative example is the case of lysine: modern biotechnology enabled the cost-effective production of lysine which, in turn, facilitated its use in a large share of prepared animal feeds, mainly for monogastric animals (particularly pigs, but also poultry and farmed carnivorous fish). This change brings about several effects, such as the partial substitution of soya-derived ingredients by wheat- and corn-derived ingredients (which have a lower lysine content compared to soya) in pig feeds. This substitution may also have impacts on the EU crop-growing sector and trade dependence, as among the various protein-rich feed materials, soya bean meal has one of the lowest levels of self-sufficiency in the EU[217].

Another example is the biotechnological production of riboflavin, with direct impacts found in the turnover realised from its production by the manufacturing industry, and indirect impacts related to its various uses, such as in prepared animal feeds, in food supplements, and as a colouring agent. 70% of the global production of riboflavin is used for animal feed. The production of riboflavin using modern biotechnology seems to have resulted in cost

[215] Another role is to increase the physical performance of the feed, but as this is not relevant for biotechnology-based feed additives, it is not developed any further here.
[216] From DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.33; 46% of enzymes production was allocated to food, and 2% to silage and feed; In Section 2.4, a rounded-up range of 30-45% is provided corresponding to food-related enzymes (information from two different sources).
[217] FEFAC (2006). Feed and Food – Statistical Yearbook 2005. http://www.fefac.org/file.pdf?FileID=5071.

reductions of 40 - 50% compared to the conventional, chemical production process[218] 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 the livestock producers) more attractive. The most simplistic approach to providing some estimate to the indirect contribution of feed additives would include the estimate of the turnover share of prepared farm animal feeds that contain such products (approximately EUR 38 billion for 2004[219]). Similarly, the share of livestock produced from feeds containing these products could also be included. However, as explained earlier, these kinds of estimates include many shortcomings.

Food additives

Food processing using enzymes is described in detail in Section 2.4. The direct impacts of modern biotechnology concern the turnover realised by the enzyme producers relevant to food applications (approximately EUR 390 million) as well as the turnover specific to the biotechnology-based production of chemicals (e.g. related to some vitamins and amino acids), whereas the indirect impacts refer to the shares of food and beverage manufacturing turnover using enzymes (estimated to about EUR 304 billion; Section 2.4) and other food additives. While there are no comprehensive estimates on the total and modern biotechnology-based turnover related to chemicals used as food additives (of the chemical groups considered herein), a conservative estimate can be made as the difference between the total figure of EUR 1.9 billion calculated for food and feed additives together, the figure estimated for feed additives of EUR 860 million, and the figure estimated for food enzymes, which results in a turnover of approximately EUR 455 - 650 million. The indirect implications of the use of these products are related to their downstream use in the various food and beverage products and the food chain in general.

Animal health products

The emphasis in the livestock sector is put more and more on prevention rather than treatment, especially on environmental (microbial resistance) and human health grounds. Therefore, vaccines (along with diagnostics) are gaining importance in the farm animal health sector. Modern biotechnology has been applied to a greater extent in vaccine production in the animal health sector when compared with the human health sector. In the therapeutics area, we find mainly anti-parasitic, anti-inflammatory and analgesic products, the latter two being mainly used in companion animals. Modern biotechnology approaches in the anti-parasitic field are focusing on the development of vaccines for parasite species rather than on chemical treatments. In general, there is no major demand for products focusing on treatment, and therefore little developmental activity.

The global market for animal health products was estimated to be approximately EUR 13 billion[220] in 2004. Five out of the ten largest veterinary pharmaceutical companies (in terms of

[218] OECD (2001). The application of biotechnology to industrial biotechnology. OECD, Paris. *And* EuropaBio (2003). White biotechnology: gateway to a more sustainable future. EuropaBio, Brussels. http://www.europa-bio.be/documents/100403/press_release_en-1.pdf.
[219] Eurostat data, accessed online at http://epp.eurostat.ec.europa.eu.
[220] ETEPS (2006). Bio4EU Task 2 Main report.

turnover) are based in the EU[220], and therefore a reasonable estimate of the EU-share of the global market can be given as EUR 6.5 billion (including diagnostics, estimated above as being approximately EUR 700 million), which is similar to the veterinary product consumption by EU livestock producers of about EUR 5.2 billion[221]. The veterinary vaccines sector accounted for 20% of global animal health product revenues in 2004 with revenues of EUR 2.52 billion, and is expected to grow in excess of EUR 3.1 billion by 2009. In the absence of specific information, an estimate of the biotechnology-related turnover for vaccines can be given as follows: assuming that 50% of the global vaccine turnover is EU-derived (this share is based on the number of the largest veterinary pharmaceutical companies and their turnover) and considering that 24 out of the 33 vaccines approved by EMEA (73%) are based on modern biotechnology[222], the direct contribution of modern biotechnology-based vaccines in the EU is estimated to be approximately EUR 920 million (0.08% of the agro-food sector turnover).

The vaccine market for farm animals is highly dependent on official vaccination programmes and the respective disease status in the EU Member States. Additionally, as vaccines are used for prevention, and as their further use is prohibited in the EU when eradication is achieved (for disease monitoring purposes), it is reasonable to assume that the largest share of the turnover is provided by newly developed (and therefore mainly modern biotechnology-based) vaccines. The indirect impacts of vaccines are to be found in the turnover realised by animal producers, as their use ensures the avoidance of economic losses due to disease outbreaks, as well as the assurance of animal trade between different Member States.

An analysis of the modern biotechnology vaccine for Aujeszky's disease (pseudorabies), the first example of the so-called DIVA (Differentiating Infected from Vaccinated Animals) or marker vaccines provides some insights into the indirect impacts that may be expected[223]. Marker vaccines in the eradication process, although not essential, make it possible to differentiate between vaccinated and infected animals and this greatly shortens the time needed to complete the eradication. Furthermore, because of the DIVA characteristic of the modern biotechnology-based vaccine, it is the only authorised product in the EU for Aujeszky's disease. In addition, all authorised products are sourced from European companies, except for products from Fort Dodge (US), which is, however, partly located in the Netherlands (serving the EU market). Based on the information gathered, there are approximately six companies offering several products each, of which only one has received EU-wide authorisation. A large majority of the companies' revenues come from the EU, although at least one company reported some activity in South East Asia.

As there are no alternative non-modern biotechnology products available, a comparison of the significance of the vaccine can only be made to alternative eradication methodologies or to non-eradication. Compared to non-eradication, the benefits are clear as the disease was responsible for substantial economic losses to the pig sector. Before the development of the vaccine, animal culling was the only approach for containment. Information on the effectiveness of eradication programmes was available for seven countries, namely Belgium,

[221] EUROSTAT, European Agricultural Accounts, Agricultural Information System - Key indicators (2003)(accessed online at http://epp.eurostat.ec.europa.eu/portal/page?_pageid=0,1136206,0_45570467&_dad=portal&_schema=PORTAL).

[222] They use recombinant strains or antigens produced using recombinant technology; six are sub-unit vaccines as described above, while two others use other biotechnology-based approaches; from ETEPS (2006). Bio4EU Task 2 Main report.

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

the Netherlands, the Czech Republic, Denmark, France, the UK, and Germany. Figures show that in the long-term it has proved to be more cost-effective to attempt a full programme of eradication rather than to treat the disease or allow it to remain endemic in the pig population. Economic benefit is much greater when taking into account the full savings made through eradicating the disease, especially in light of the trade and livestock movement restrictions introduced by Decision 93/24/EEC[224]. Moreover, it may be argued that the EU followed a more successful path compared to the US, by taking a centralised decision and by pursuing and using specifically the Glycoprotein E (gE)-negative marker vaccine. Currently, from 13 EU Member States from which information was available, ten are disease-free with or without continuing vaccination and three are currently vaccinating the endemically affected pig population.

In the therapeutics area, the adoption of modern biotechnology is limited to its use in specific steps of the industrial production process, such as in the production of the antimicrobial cephalosporins (covered in more detail in Section 2.4.2.4). While the use of antimicrobials will have an impact on the turnover realised by livestock producers, specific information is not available. Furthermore, and as mentioned earlier, antimicrobials are used less and less in the farm animal sector.

2.3.5.4 Summary

A summary of the economic contribution of modern biotechnology to the agro-food sector is provided in Table 20. The total direct impacts from the application of modern biotechnology to the agro-food sector have been estimated in a range of approximately EUR 3 - 5.6 billion. This represents 13 - 23% of the total turnover realised by the input sectors using modern biotechnology, 0.26 - 0.47% of the agro-food sector, and 0.01 - 0.02% of the total EU GVA[225]. It is interesting to note that these estimates fall within the range of the aggregated estimate (0.3% and 0.01%, respectively; see Section 2.3.4). Overall, the largest share of the direct contribution relates to modern biotechnology applied in the agro-food related manufacturing sectors (e.g. food enzymes, chemicals and veterinary products) followed by the breeding sectors. The relatively large variation between the low and high estimates is mainly due to the large uncertainty of the use of MAS in plants (see Figure 18 and Figure 19).

The indirect contributions to the economy have been estimated to a value of about EUR 380-450 billion, which accounts to 32 - 38% of the agro-food sector, or 1.3 - 1.55% of the total EU GVA[225]. The indirect implications are therefore approximately two orders of magnitude larger than the direct ones, indicating the important diffusion of modern biotechnology-derived products to the user sectors. The largest share of the indirect impacts relates to the use of modern biotechnology by the food processing sector, followed by the livestock sector and the plant sector. The range in the estimate is also mainly due to the uncertainty in the use of MAS in the various sectors (see Figure 20 and Figure 21).

[224] Commission of the European Communities 93/24/EEC: Commission Decision of 11 December 1992 concerning additional guarantees relating to Aujeszky's disease for pigs destined to Member States or regions free of the disease OJ L 016 , 25/01/1993 p. 0018 – 0021.

[225] The turnover values were multiplied by 0.3 to estimate the GVA (0.3 is the average GVA:turnover ratio of the primary production and agro-food industry), see Annex 3 – Agro-Food).

Table 20: Summary of the economic contribution of modern biotechnology in the agro-food sector

	Biotechnology application		EU turnover, EUR million (input sectors)		Share (in %)[1]	EU turnover, EUR million (downstream users)		Share (in %)[1]
			Biotechnology	Total		Biotechnology	Total	
Plants	Molecular markers	Maize	133-405	405	33-100	2429-7360	7360	33-100
		All crops	2013	6100	33	55 583	168 432	33
	Micropropagation	All plants flowers	39-313	6400	0.6-5	50-389	8268	0.6-5
	Genetic modification	Maize	12	405	3	85	7360	1.2
		All crops	12	6100	0.2	85	168 432	0.05
Livestock	Molecular markers	All livestock	207-560	2000	10-30	12 737-35 664	127 374	10-30
	Embryo transfer	Cattle	190	600	32	55 170	73 560	75
		All livestock	190	2000	10	55 170	127 374	43
Fish	Molecular markers	Salmon	10	34	30	133	443	30
		Trout	11	38	30	149	498	30
		Oysters	2	21	10	28	277	10
		All fish	23	210	11	310	2769	11
	Ploidy/sex manipulation	Trout	18	38	50	249	498	50
		Oysters	4	21	20	55	277	20
		All fish	23	210	11	304	2769	11
	Both technologies	All fish	32-46[2]	210	15	437-614	2769	15
Agro-food chain	Veterinary products	Vaccines	920	1260	73	-	-	-
		All products	920	5200	18	-	-	-
	Diagnostics	All	300	700[3]	43	1500	3500[3]	43
	Other inputs (chemicals and biologicals)	Food and feed additives	1250[4]	2300[5]	75	304 030[6]	797 069	38
	Total		**3083-5604**	**22910**	**13-23**	**376 439-453 035**	**1 193 763**[7]	**32-38**

[1] Rounded figures

[2] The low estimate assumes that both technologies are applied simultaneously and therefore only the highest value per technology per species is counted in order to avoid double counting; the high is the sum of the two technologies assuming no overlap.

[3] The totals are not comprehensive, so the calculated share of the modern biotechnology-based diagnostics may be overestimated.

[4] Feed additives estimated at EUR 860 million and enzymes related to food processing estimated at EUR 390 million.

[5] The totals are not comprehensive as they only include specific product categories (food and feed related amino acids, vitamins, organic acids, antibiotics and xanthan, see Section 2.3.5.3), so the calculated share of the modern biotechnology-based food and feed additives may be overestimated.

[6] Only refers to the use of food enzymes in food manufacturing.

[7] The total refers to the total turnover of the agro-food sector (see Table 12).

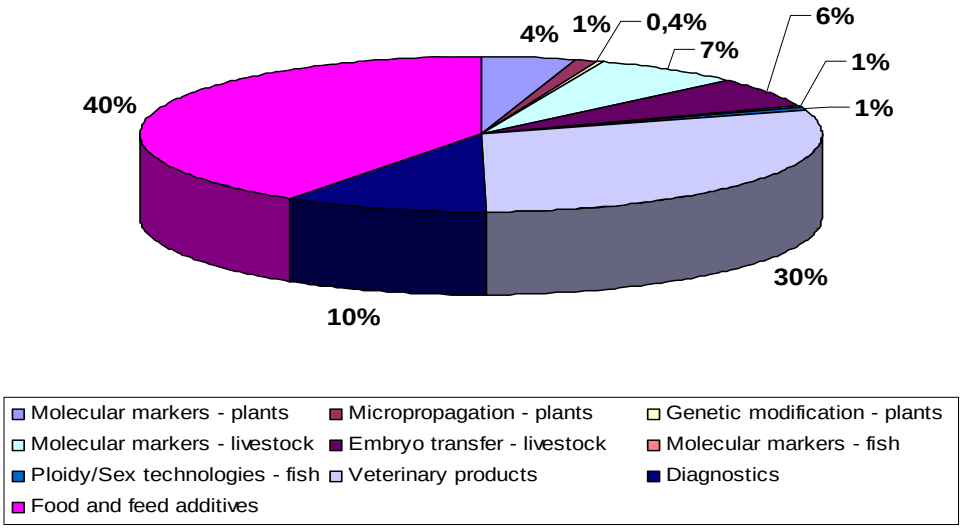

Figure 18: Shares of the different biotechnology applications to the direct contribution to the economy: Low estimate

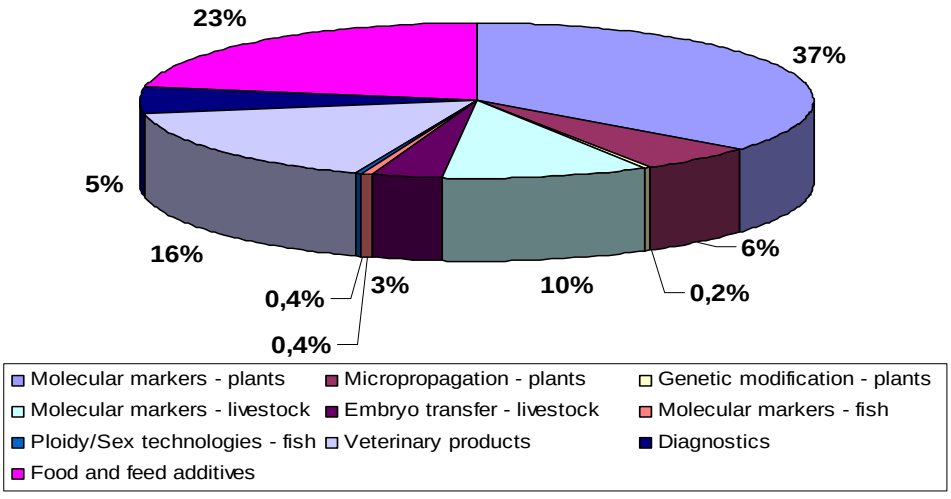

Figure 19: Shares of the different biotechnology applications to the direct contribution to the economy: High estimate

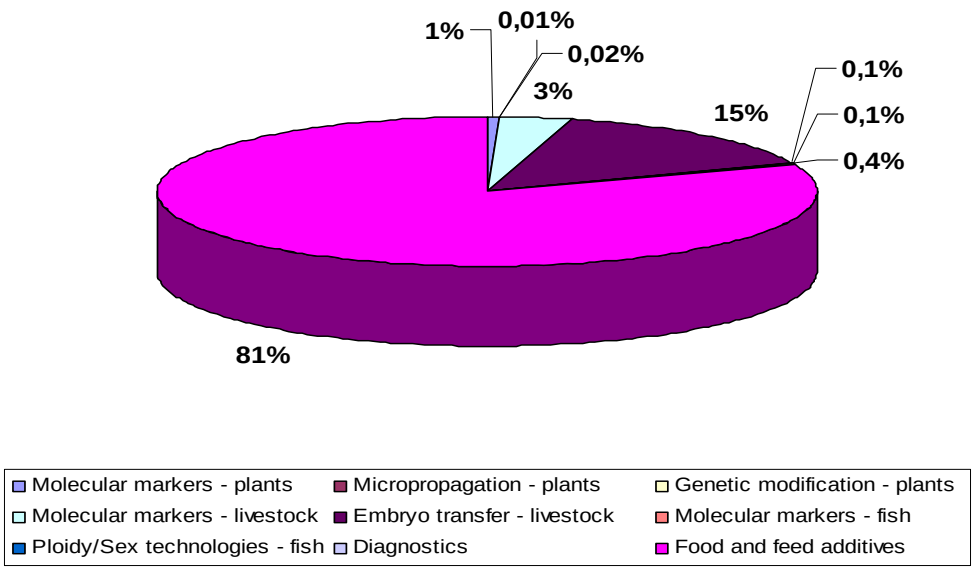

Figure 20: Shares of the different biotechnology applications to the indirect contribution to the economy: Low estimate

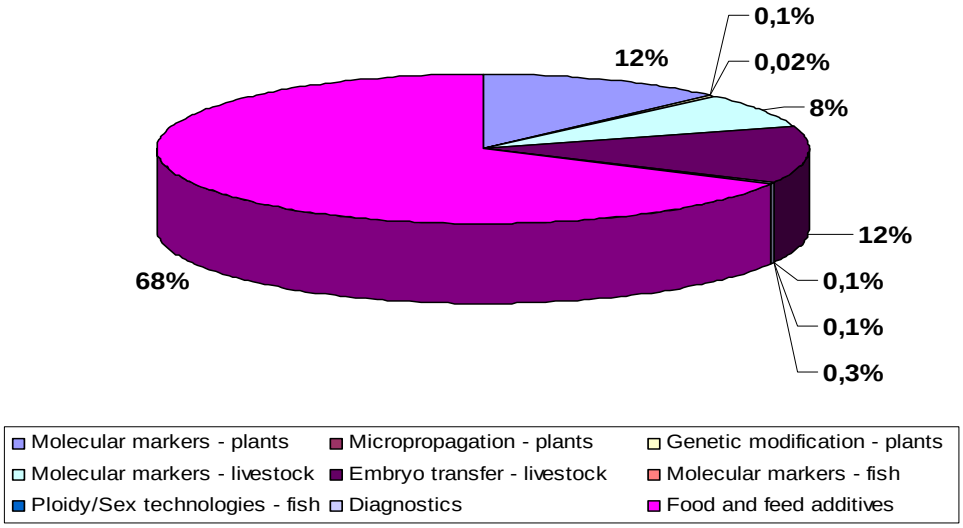

Figure 21: Shares of the different biotechnology applications to the indirect contribution to the economy: High estimate

2.4 Industrial biotechnology

Of growing importance within the broad area of biotechnology are industrial biotechnology applications. Apart from the actual producers of biotechnological goods and services (mainly enzyme producers), this includes a broad spectrum of applications from bioenergy (including biofuels) to biotechnological industrial processes and decontaminating environmental media. The full range of modern biotechnology is applied in industrial biotechnology, mainly for the identification, adaptation and large scale production of enzymes as catalysts and their adaptation to extreme production process conditions, which are then applied in the different application areas.

2.4.1 The contribution of the manufacturing sector to the EU economy

Modern biotechnology in industrial biotechnology applications is mainly used in the manufacturing sector. The manufacturing sector, although losing importance over the past decades in relation to the different services sectors, plays an important role in achieving the objectives of the Lisbon Strategy. Manufacturing is the second biggest employer and contributor to gross value-added (GVA) in the EU (after category NACE K 'Real estate, renting, business').

Overall GVA in the EU was EUR 9484 billion in 2004, generated by about 200 million employees[226]. In the same year, the manufacturing sector contributed a share of 17.4% or EUR 1528 billion to the overall GVA (see Figure 22), generated by 33 million employees, 16.5% of all employees.[227].

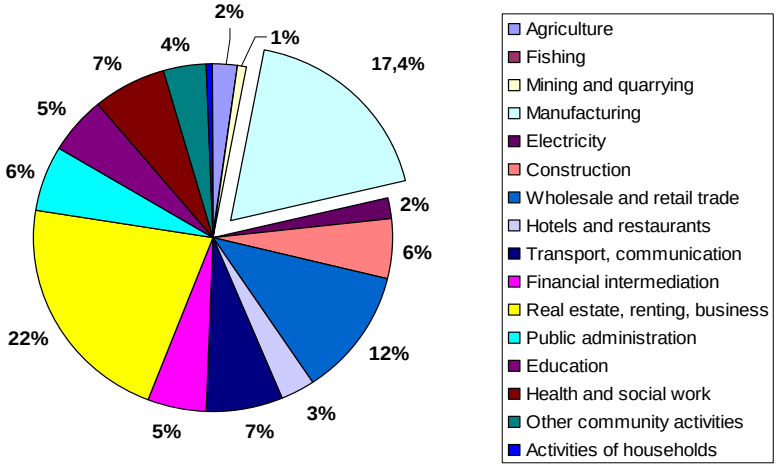

Figure 22: Share of manufacturing to the EU's gross value-added 2004
Source: Data from Eurostat[228]

[226] Eurostat (2006). European business - facts and figures, p.17-18. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-BW-05-001/EN/KS-BW-05-001-EN.PDF.
[227] Eurostat (2005). Europe in figures: Eurostat yearbook 2005. European Commission, Eurostat, Luxembourg, p. 234. http://bookshop.europa.eu/uri?target=EUB:NOTICE:KSCD05001:EN.
[228] Eurostat database. http://epp.eurostat.ec.europa.eu/.

The manufacturing sector in itself is heterogeneous. It consists of 14 subsectors, which are classified in the European NACE categories NACE DA-DN. In 2002[229], the largest manufacturing sectors regarding their contribution to the EU's GVA were metal, food, electrical/optical equipment, machinery, transport equipment and chemicals, all with a contribution of roughly 2% to the overall GVA of the EU, respectively 10 - 12% to EU manufacturing (see Table 21).

Table 21: Contribution of manufacturing sectors to the EU's GVA (2002)
Source: Data from Eurostat [230]

		Share of the EU's GVA (in %)	Share of manufacturing GVA (in %)
EU GVA (All economic activity)		100.00	
NACE D Manufacturing (total)		17.41	100.00
DA 15, 16	Manufacture of food products; beverages and tobacco products	2.19	12.56
DB 17, 18	Manufacture of textiles and textile products, and apparel, dressing and dying of fur	0.77	4.44
DC 19	Manufacture of leather and leather products	0.18	1.01
DD 20	Manufacture of wood and wood products	0.41	2.35
DE 21, 22	Manufacture of pulp, paper and paper products; publishing and printing	1.70	9.77
DF 23	Manufacture of coke, refined petroleum products and nuclear fuel	0.28	1.63
DG 24	Manufacture of chemicals, chemical products and man-made fibres	1.95	11.21
DH 25	Manufacture of rubber and plastic products	0.86	4.92
DI 26	Manufacture of other non-metallic mineral products	0.83	4.76
DJ 27, 28	Manufacture of basic metals and fabricated metal products	2.35	13.50
DK 29	Manufacture of machinery and equipment n.e.c.	1.96	11.24
DL 30-33	Manufacture of electrical and optical equipment	2.09	11.99
DM 34, 35	Manufacture of transport equipment	1.95	11.20
DN 36, 37	Manufacturing not classified, including recycling	0.74	4.22

n.e.c.: not elsewhere classified

The manufacturing sector and its subsectors are not static. As mentioned above, the share of manufacturing to the EU's GVA has been decreasing slightly over the last decades, whereas service related business is gaining importance. Also the internal structure of the sector is changing, the relative weight of textiles production, for example, has been decreasing for

[229] 2002 is taken as the reference year for the analysis, as it is the most recent year with rather complete data sets in Eurostat. The main conclusions are not affected when combining these data with more recent figures from IPTS research, as the relation between the sectors has been relatively stable over time.
[230] Eurostat database. http://epp.eurostat.ec.europa.eu/.

several years[231].

Biotechnology does not appear as a separate category amongst the NACE categories. However, industrial biotechnology as a horizontal enabling technology is applied in different manufacturing subsectors. Industrial biotechnology applications can be assigned to NACE categories as follows:

Enzyme producers which provide the manufacturing sector with modern biotechnology products (direct impacts of modern biotechnology):

- **NACE DG 24: Manufacture of chemicals, chemical products and man-made fibres**
  This sector includes the enzyme producers in the area of fine chemicals. Also chemical intermediate producers using biotechnological processes fall in this category.

Biotechnology users, i.e. sectors which use modern biotechnology products (indirect impacts of modern biotechnology) by application area:

- **NACE DA 15: Manufacture of food products, beverages**
  Modern biotechnology is used in practically the entire category 15. It represents an important and long established production factor.
- **NACE DB 17: Manufacture of textile and textile products**
  In this category, enzymes are applied in the finishing of several different textiles (cotton, wool, silk), as well as in processes such as polishing, desizing, etc.
- **NACE DB 18: Manufacture of apparel; dressing and dyeing of fur**
  This category includes the processing of leather clothes, which uses enzymes in several production steps (soaking, liming, bating, etc.).
- **NACE DC 19: Manufacture of leather and leather products**
  This category includes all other non-clothing leather products (saddlery, luggage, footwear, etc.), which apply similar enzymatic treatment in production as in NACE DB 18.
- **NACE DE 21: Manufacture of pulp, paper and paper products**
  Pulp and paper uses enzymatic processes at different stages of the value chain (raw material treatment, bleaching, de-inking, etc.).
- **NACE DF 23: Manufacture of coke, refined petroleum products and nuclear fuel**
  This category includes the petrol fuel sector, which is the reference when describing the economic impact of biofuels.
- **NACE DG 24: Manufacture of chemicals, chemical products and man-made fibres**
  This category not only contains the enzyme and chemical producers, but also some of the most important users of enzymes (detergents, polymers, pharmaceuticals, etc.).

This list is not exhaustive. Enzymes are used in other industrial sectors as well, such as mining (bioleaching), but these applications are applied to such a limited extent that they are not relevant when analysing the economic impact of industrial biotechnology in the EU.

The application of biotechnology in end-of-pipe technologies such as the treatment of contaminated air, soil, water and waste are not counted as manufacturing activities (except: recycling). Efforts are under way to collect information on environmental goods and services for statistical use, but currently the information is rather scattered and appears in different NACE categories:

[231] According to the Eurostat database the contribution of textile production to manufacturing decreased by 35% between 1995 and 2005. http://epp.eurostat.ec.europa.eu/.

- **NACE DN 37: Recycling**
  This category includes the recycling of non-metal waste and scrap (DN 37.2) as relevant category for biotechnology.
- **NACE E 41: Collection, purification and distribution of water**
  This category includes waste water treatment, a traditional application area for biotechnology.
- **NACE O 90: Sewage and refuse disposal, sanitation and similar activities**
  This category includes the treatment of contaminated soil, e.g. by micro-organisms (bioremediation).

An overview of the sectors of relevance for industrial biotechnology, including the respective GVA as well as their share to the EU's GVA and to the manufacturing sector's GVA, is presented in Table 22.

Table 22: Contribution to the EU's GVA by the industrial biotechnology relevant sectors
Source: Data from Eurostat[232]

Year 2002		GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)
EU GVA (all economic activity)		8 782 816	100.00	
NACE D Manufacturing (total)		1 528 982	17.41	100.00
DA 15	Manufacture of food products; beverages	181 220	2.06	11.85
DB 17, 18	Manufacture of textiles and textile products	67 894	0.77	4.44
DC 19	Manufacture of leather and leather products	15 418	0.18	1.01
DE 21, 22	Manufacture of pulp, paper and paper products; publishing and printing	149 367	1.70	9.77
DF 23	Manufacture of coke, refined petroleum products and nuclear fuel	24 866	0.28	1.63
DG 24	Manufacture of chemicals, chemical products and man-made fibres	171 361	1.95	11.21
DN 36, 37	Manufacturing not classified, including recycling	64 590	0.74	4.22
E 41	Collection, purification and distribution of water	19 705	0.22	*Not manufacturing*
O 90	Sewage and refuse disposal, sanitation and similar activities	*No data available*	*No data available*	*No data available*
Total		**705 278**	**7.91**	**44.13**

Table 22 summarises those sectors in which modern biotechnology applications are used. For NACE O 90 no data were available from the Eurostat database. Altogether, the sectors in question contributed around EUR 700 billion or 8% to EUs GVA in 2002, or 44% to the manufacturing GVA (water treatment is excluded as it is not including manufacturing).

[232] Eurostat database. http://epp.eurostat.ec.europa.eu/.

However, a further disaggregation of the NACE categories reveals a much smaller share: For example in E 41, biotechnology is applied only to water purification, not to collection and distribution. This means that the overall share of the sectors in which industrial biotechnology can be applied contributes most probably less than 5% to the EU's overall GVA. This further disaggregation will be carried out in the following sections dealing with individual industrial sectors.

2.4.2 The contribution of industrial biotechnology

2.4.2.1 Enzyme production

The substitution of chemical catalysts in production processes through biological systems achieving the same effect in a more efficient manner, i.e. biocatalysts, represents the classical application area for industrial biotechnology. Biocatalysts are, in some applications, entire organisms, which are referred to as whole cell conversions. In most cases enzymes are used as catalysts. The advantages as compared to chemical catalysts are the increased efficiency, improving often up to several orders of magnitude, and the reduced energy consumption, as enzymes often work at room temperature. Enzymes are derived from micro-organisms, in some cases from extremophiles – organisms which live under 'extreme' conditions. These enzymes can also be applied under high pressure and temperature conditions. Table 23 shows the main enzyme groups together with the reaction catalysed by them, as well as the applying industries.

Table 23: Different groups of enzymes and reactions
Source: Lievonen 1999[233]

Type of enzyme	Substrate	Reaction catalysed by the enzyme	Industry
Proteases (proteolytic enzymes)	Proteins	Proteins are broken into shorter fragments, peptides and eventually into 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
Pectinases	Pectins	Clarification of fruit juices	Food, beverage
Cellulases	Cellulose	Hydrolysis of cellulose	Pulp, textile, feed, detergents
Amylases	Polysaccharides	Hydrolysis of starch into smaller carbohydrate molecules such as glucose and maltose	Food

[233] Lievonen, J. (1999). Technological opportunities in biotechnology. Working Paper 43. VTT Group of Technological studies, Espoo, p. 24. http://www.vtt.fi/inf/julkaisut/muut/1990s/wp43.pdf.

Table 23 illustrates the multipurpose character of different enzyme classes, which makes it particularly difficult to assign capital and labour costs at the level of enzyme producer to enzyme induced costs and benefits down the value chain.

Currently, 117 enzyme producers can be identified globally[234]. The majority of them are located in Europe, where 80 enzyme producing companies are active (including five companies in Switzerland). Almost 20% of them are located in France. The leading world market companies are located in Denmark. 21 companies can be found in the US, the rest is distributed in other regions (see Figure 23).

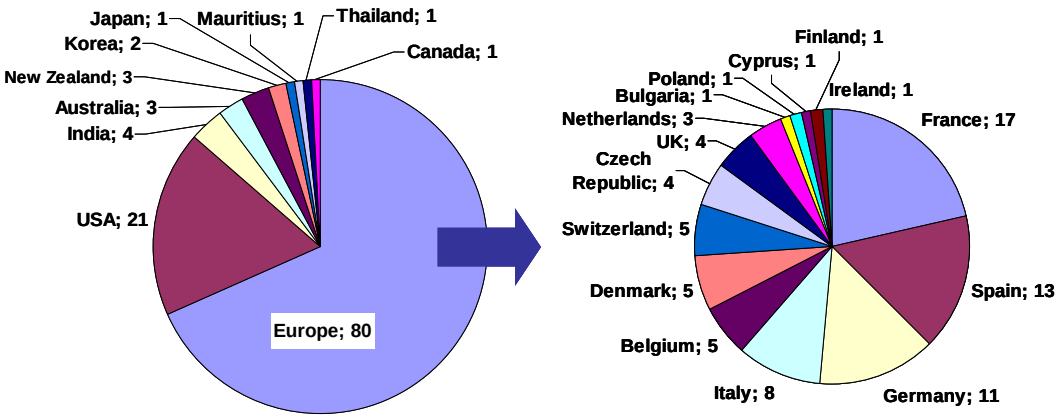

Figure 23: Global and European distribution of companies producing enzymes

The most important companies in terms of production volumes are Novozymes (Denmark), Danisco/Genencor (Denmark), DSM (the Netherlands), AB Enzymes (Finland), Chr. Hansen (Denmark) and DIREVO Biotech AG (Germany). The world production volume for enzymes was estimated to be 53 000 tonnes in 2001, with Europe (including Switzerland) having a share of 79%. With an estimated 5% growth of the enzyme market, a production volume of around 65 000 tonnes for 2005 can be assumed[235].

The value of the global enzyme market is currently estimated to be around EUR 1.6 - 1.8 billion[236]. Under the assumption of an EU share of 75% in enzyme production and an even distribution of enzyme price levels, it can be concluded that in 2005, EUR 1.2 billion worth of enzymes were sold. A comparison with the 2005 business report of Novozymes shows that their sales of technical, food and feed enzymes amount to EUR 770 million in 2004. That would result in a share of around EUR 540 million for the other EU producers, which falls into a plausible range.

[234] ETEPS (2006). Bio4EU Task 2 Main report.
[235] DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.29. http://biotech.dechema.de/img/biotech_/brennpunkt/041110.htm. *And:* Gavrilescu, M. and Y. Chisti (2005). Biotechnology Advances **23**: 471-499. http://dx.doi.org/10.1016/j.biotechadv.2005.03.004.
[236] DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.43. http://biotech.dechema.de/img/biotech_/brennpunkt/041110.htm. *And:* Novozymes (2005). The Novozymes report 2005. Novozymes, Bagsværd, p. 11. http://www.report2005.novozymes.com/Services/Download+report (conversion: 1 DKK = EUR 0.135).

What is the contribution of enzyme production to the EU economy? Enzymes can be classified as fine chemicals or specialities. For a first approximation, the production volume and sales are compared against the relevant subsector in the NACE classification, which is DG 24.66 – manufacture of other chemical products (see Table 24)[237].

Table 24: Enzyme production compared to NACE sector DG 24
Source: Data from Eurostat[238], IPTS calculations

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)
EU GVA (All economic activity)	**8 782 816**	**100.00**	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DG 24 Manufacture of chemicals and chemical products	170 555	1.94	10.64
DG 24.6 Manufacture of other chemical products	14 857	0.17	0.93
DG 24.66 Manufacture of other chemical products (2003)	7906	0.09	0.49
Enzyme production*	**741**	**0.0084**	**0.05**

**Estimate*

In 2003 the total sales of subsector DG 24.66 amounted to EUR 30.5 billion, with a value-added of EUR 7906 million, corresponding to a relation in sales and value added of around 25% (see Table 24). Compared to that, the biggest enzyme producer, Novozymes, declares their GVA to be 57% of the turnover[239]. This indicates that within the area of fine chemicals, which can be characterised as low volume/high value products, enzyme production is in the area of very high value products.

If the turnover and value-added relation of 57% is applied to the total enzyme sales of EUR 1.3 billion of all EU producers, a value-added of around EUR 741 million can be estimated (see Table 24). These figures reflect a small contribution of enzyme production to the EU economy (0.0084% to the EU's overall GVA, or 0.05% to EU manufacturing). Based on these figures, enzyme producers can be characterised as profitable enterprises producing high technology intermediate products, which unfold their impact on the EU economy in the application areas down the supply chain, as will be seen in the analysis of industrial applications (see Section 2.4.2.2).

Employment effects

Although no precise data are available, employment effects in terms of jobs being created in the industry producing enzymes can be roughly calculated. An expert estimate for the fruit

[237] NACE DG 24.66 includes amongst other items: protein substances, materials used in the finishing of textiles and leather, catalysts and other chemical products for industrial use.
[238] Eurostat data from on-line database. http://epp.eurostat.ec.europa.eu/.
[239] Novozymes (2005). The Novozymes report 2005. Novozymes, Bagsværd, p. 22. http://www.report2005.novozymes.com/Services/Download+report (turnover DKK 6024 million, GVA DKK 3424 million).

juice enzyme business counts a total of 200 employees for this area from R&D down to marketing and sales operations[240]. As this segment represents half of 'fruit utilisation and wine', i.e. 3.5% of all enzyme production[241], the extrapolation to all enzyme production results in approximately 6000 employees in EU enzyme production, assuming that the production of enzymes for different application areas requires a similar input of capital and labour. This corresponds to about 0.003% of EU employees, or 0.02% of the employees in EU manufacturing. Again Novozymes serves as the benchmark. It states its employees number at 4000, which corresponds to Novozymes' 66% of EU enzymes production. Half of these work outside the EU. In total, it can therefore be assumed that in EU enzyme production between 4000 and 6000 people are employed, representing 0.015 – 0.02% of the manufacturing employment (see Table 25).

Table 25: Employment in enzyme production

Year: 2002	Employment	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU employment (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DG 24 Manufacture of chemicals and chemical products (2001)	1 928 800	0.96	5.84
DG 24.6 Manufacture of other chemical products	208 400	0.10	0.63
DG 24.66 Manufacture of other chemical products (2003)	117 200	0.06	0.36
Enzyme production*	**4000 - 6000**	**0.002 - 0.003**	**0.015 - 0.02**

**Estimate*

As can be seen from Table 26, the relation between employment and value-added – the labour productivity – reveals that the chemical sector with a value of 2.0 is generating double the GVA per employment unit than the EU average. Subsectors DG 24.6 and DG 24.66 also show high values with 1.6 and 1.5, respectively. Enzyme production with 2.8 - 4.2 has a very high labour productivity, indicating a mature large scale industry with a high degree of automatisation.

[240] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications

[241] DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.30. http://biotech.dechema.de/img/biotech_/brennpunkt/041110.htm.

Table 26: Labour productivity in enzyme production

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU (All economic activity)	100.00	100.00	1.0
NACE D Manufacturing (total)	17.41	16.50	1.1
DG 24 Manufacture of chemicals and chemical products (2001)	1.94	0.96	2.0
DG 24.6 Manufacture of other chemical products	0.17	0.10	1.6
DG 24.66 Manufacture of other chemical products (2003)	0.09	0.06	1.5
Enzyme production*	**0.0084**	**0.002 - 0.003**	**2.8 - 4.2**

**Estimate*

Outlook

The future development of enzyme production depends on the future demand in user markets. These are mainly detergents and food/feed, whereas pulp and paper, textiles and leather processing only account for a smaller share in enzyme production. Some general factors will influence the market penetration of enzymes in all of these segments, such as the increasing need to reduce energy consumption and greenhouse gas emissions. These targets are supported by the energy efficiency of enzymatic processes in general. Besides that, the outlook differs when looking at the characteristics of the specific markets.

2.4.2.2 Downstream users in industry: detergents, pulp and paper, textiles, and food

In addition to the direct impacts of modern biotechnology generated by enzyme producers, indirect impacts are generated by the use of enzymes in the main application areas in industry – production of detergents, pulp and paper processing, textile finishing, and food processing. These sectors are analysed in the following sections.

2.4.2.2.1 Detergents containing enzymes

The world's leading detergent enzyme producing companies are European, with Novozymes holding 50% of the world market and Danisco/Genencor 20%. Total sales in 2005 amounted to EUR 592 million (see Table 27), which corresponds to 33% of the overall enzyme market volume (EUR 1.8 billion in 2005[242]). As can be derived from Table 27, the market for detergent enzymes grew in the EU and Japan by approximately 4.5% per year, and in the US

[242] DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.43. http://biotech.dechema.de/img/biotech_/brennpunkt/041110.htm. *And:* Novozymes (2005). The Novozymes report 2005. Novozymes, Bagsværd, p. 11. http://www.report2005.novozymes.com/Services/Download+report (conversion: 1 DKK = EUR 0.135).

by 5.5% per year. Two thirds of all enzymes for detergents are sold in the EU, US and Japan. Global market growth therefore exceeds the growth of the EU economy, which was between 1% and 2% in recent years. The main reasons for this are the growing demand to lower energy consumption, the increasing dishwasher market and the uptake of enzymatic processes in the production of liquid detergents.

Table 27: Annual sales for detergent enzymes by region (EUR million)
Source: ETEPS 2006[243]

Region/year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
EU	160	168	175	181	192	200	206	214	224	232
US	110	117	123	130	138	147	153	162	171	180
Japan	50	53	54	57	59	61	64	67	70	73
World total	491	517	537	557	592	619	641	669	700	731

The high share of enzymes for detergents out of the total enzymes market as well as the continuous market growth indicate a well established market. In fact, this segment is the most important one for most of the enzyme companies. For Novozymes, one third of sales stem from detergent enzymes, for Genencor this is 50%[244].

The development of the enzyme market for detergents depends on the market for cleaning products. The corresponding EU industry sector is NACE DG 24.51 – manufacture of soap, detergents, cleaning and polishing. The growth rate of this sector was 1.5% in 2001, 0% in 2002 and 2% in 2003. The growth rate of detergent enzymes of 4.5% per year in the same period indicates a growing share of detergents containing enzymes. In terms of turnover, the share of detergents containing enzymes out of total detergents was between 30% and 50% in 2005.

Table 28: Contribution of detergents containing enzymes to the EU's GVA

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing (in %)
EU GVA (all economic activity)	8 782 816	100.00	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DG 24 Manufacture of chemicals and chemical products	170 555	1.94	11.15
DG 24.51 Manufacture of soap, detergents, cleaning and polishing (2003)	7807	0.09	0.51
Detergents containing enzymes *	**2500 – 4000**	**0.03 – 0.05**	**0.16 – 0.25**

**Estimate*

[243] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications; original figures in US Dollar (conversion: 1 USD = EUR 0.7765; 22 November 2006). http://www.profound.com/research/.
[244] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

The overall sales of soap, detergents and maintenance products totalled around EUR 30 billion in 2005, according to AISE[245]. According to Eurostat, the equivalent NACE sub-category DG 24.51 (Manufacture of soap, detergents, cleaning and polishing) showed a turnover of EUR 32 billion in 2003, which confirms the order of magnitude. In order to calculate the contribution of detergents containing enzymes to the EU's GVA, their share of turnover in all detergents (30 - 50%) is applied to the value-added of the category NACE DG 24.51, which results in a contribution of EUR 2.5 - 4 billion, or 0.03% - 0.05% of the EU's GVA (see Table 28).

The use of enzymes in the production of detergents does not lower the production cost[246]. The incentive to use enzymes seems to be therefore in the savings on the end-user side through lower washing temperatures, which gives detergents containing enzymes a competitive advantage.

Employment effects and labour productivity in detergent production

Indirect employment effects through the application of modern biotechnology, i.e. enzymatic processes, in detergent production can be roughly estimated. According to Eurostat, in category NACE DG 24.51 the number of employees amounted to 120 000 in 2003. Applying the share in turnover of enzymatic detergents from all detergents (30 - 50%), it can be assumed that between 36 000 and 60 000 jobs can be assigned to detergent production processes which include the application of modern biotechnology (see Table 29).

Table 29: Employment in detergents production using enzymes

Year: 2002	Number of employees	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU employment (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DG 24 Manufacture of chemicals and chemical products (2001)	1 928 800	0.96	5.84
DG 24.51 Manufacture of soap, detergents, cleaning and polishing (2003)	119 100	0.06	0.36
Detergents containing enzymes *	36 000 – 60 000	0.02 – 0.03	0.11 – 0.18

**Estimate*

As can be seen from Table 29, the absolute contribution to overall EU employment as well as to the manufacturing sector is marginal with a share of 0.02 - 0.03% or 0.11 - 0.18%, respectively. The look at labour productivity reveals that the value-added of enzymatic detergent production is almost the same as in conventional production. With a relation of 1.5 both are relatively efficient when compared to overall manufacturing labour productivity 1.1 (see Table 30).

[245] International Association for Soaps, Detergents and Maintenance Products. http://www.aise-net.org/.
[246] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

Table 30: Labour productivity in detergent production using enzymes

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU (all economic activity)	100.00	100.00	1.0
NACE D Manufacturing (total)	17.41	16.50	1.1
DG 24 Manufacture of chemicals and chemical products (2001)	1.94	0.96	2.0
DG 24.51 Manufacture of soap, detergents, cleaning and polishing (2003)	0.09	0.06	1.5
Detergents containing enzymes *	0.03 – 0.05	0.02 – 0.03	1.5 – 1.6

**Estimate*

Outlook

The large enzyme market for detergents is expected to grow in the range of around 5% after a phase of stagnation[247]. The main reasons for this are the already mentioned need to lower the washing temperature as an energy saving measure, the growing sales of automatic dishwashers and the growing liquid detergent market. Due to technological progress it can also be expected that enzymes are developed for specialised detergent applications, such as the removal of specific stains, or the cleaning of utensils in hospitals or of delicate surfaces[247].

2.4.2.2.2 Enzymes in pulp and paper processing

Enzymes are applied at different stages during the production of pulp and paper. The most important processes in terms of sold enzymes is the bleaching of chemical pulp (see Table 31).

Table 31: Share of enzymes for different pulp and paper process steps
Source: ETEPS 2006[247]

Process	Enzyme applied	Share in total pulp and paper enzyme sales (in %)
Bleaching of chemical pulp	Xylanase	67
Stickies control	Lipase	8
Deinking, fibre modification	Cellulase	8
Others (e.g. slime control)	Others (e.g. pectinase, polysaccharidase)	17

The most important enzyme producers for the pulp and paper industry are AB Enzymes (Finland), Novozymes (Denmark), Iogen (Canada), Buckman (US) and Danisco/Genencor

[247] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

(Denmark). Market shares amongst these companies are not known, as they have strengths in different types of enzymes, which compete on different markets. However, it seems that AB Enzymes and Iogen have the highest share in xylanase production. Xylanase for bleaching is used in around 20 mills in North America, Scandinavia, and Russia, and to a lesser extent in Asia. Overall it is estimated that 10% of all pulping is done with enzymatic processes[248].

Table 32: World market for enzymes used in pulp and paper processing (in EUR million)
Source: ETEPS 2006[248]

Enzyme	2002	2003	2004	2009
Xylanase	29.6	30.5	31	38.3
Lipase	3.7	3.8	3.9	4.5
Cellulase	3.7	3.8	3.9	4.5
Others*	7.5	7.7	7.8	8.9
Total	44.5	45.8	46.6	56.2

* Others include pectinases and other polysaccharidases

Table 32 shows that the share between the different enzyme groups used in the processing of pulp and paper, as shown in Table 31, has been stable over the past years. Growth of the world market slowed down from 3% in 2003 to 1.7% in 2004. Nevertheless, it is expected that the growth rate will accelerate to a 3.5% yearly average until 2009[248]. When looking at the sales of enzymes for the pulp and paper industry in different global regions, a similar picture emerges. Sales in North America, Western Europe and the rest of the world show limited but constant growth rates (about 2.5% globally) (see Table 33).

Table 33: Regional sales of enzymes for the pulp and paper industry (EUR million)
Source: ETEPS 2006[248]

Region	2002	2003	2004	2009
North America	16	16.4	16.9	20.2
Western Europe	14.7	15.2	15.5	18
Rest of the world	14	14.2	14.5	18
Total	44.7	45.8	46.9	56.2

The GVA of overall pulp manufacturing, with and without enzymes can be estimated to be around EUR 2 billion in 2002 (see Table 34)[249]. On the basis of the 10% share estimated for enzymatic pulping, a rough approximation results in a GVA of EUR 200 million for this process in the EU. However, in reality the value will be higher, as the share of enzymatic pulping is higher in the EU, North America and Russia, than in other global regions, in particular in Asia[248]. Furthermore, xylanase in pulp bleaching represents two thirds of enzymatic processes in pulp and paper production, so that the overall GVA with some plausibility is in the range of EUR 300 million.

[248] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[249] For DE 21.11 (manufacture of pulp) only the turnover of around EUR 6.8 billion (2003) is known. It was assumed that the relation between turnover and value-added is like in the next higher NACE category DE 21.1 (29% for manufacture of pulp, paper and paperboard), and was calculated accordingly.

Table 34: Contribution of pulp produced with enzymes to the EU's GVA

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in%)
EU GVA (All economic activity)	8 782 816	100.00	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DE 21 Manufacture of pulp, paper and paper products (2003)	46 160	0.53	3.02
DE 21.1 Manufacture of pulp, paper and paperboard	22 173	0.25	1.45
DE 21.11 Manufacture of pulp*	2000	0.02	0.13
Manufacture of pulp using enzymes*	**300**	**0.0034**	**0.02**

**Estimate*

On average, the production cost in pulp bleaching is lowered by 5 - 6% because of the use of xylanase[250]. As this cost-saving emerges on the capital input side and not on the labour input side, savings will probably be higher in global regions where labour is cheaper, i.e. in Russia and Asia (except Japan).

Employment effects and labour productivity in pulp and paper processing

When only looking at the most important application of modern biotechnology in pulp and paper processing, the bleaching of pulp with xylanases, it is reasonable to apply the 10% diffusion rate of this process to industry also to employment. No data are available on employment in pulp processing, but an approximation can be made based on Eurostat data. In the NACE category DE 21.1 (Manufacture of pulp, paper and paperboard), a turnover of EUR 75 billion was generated by 246 500 employees in 2002. Applying this relation to subcategory DE 21.11 (Manufacture of pulp), a turnover of EUR 6.8 billion (2003) results which was generated by roughly 22 000 employees.

As 10% of pulp is manufactured with enzymatic bleaching, it can be assumed that the indirect impact on employment, i.e. jobs created though manufacturing processes which rely, at least partly, on modern biotechnology, can be assigned to around 2200 employees. Taking into account that, on the one hand, the share of enzymatic pulp bleaching in the EU is probably a bit higher than in other global regions, and on the other hand, that the application of xylanase accounts for only around two thirds of all enzymatic processes in the pulp and paper sector, employment figures in modern biotechnology-related production can be estimated to be around 3000 (see Table 35).

[250] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

Table 35: Employment in pulp and paper processing using enzymes

Year: 2002	Number of employees	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU Employment (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DE 21 Manufacture of pulp, paper and paper products (2003)	738 600	0.37	2.24
DE 21.1 Manufacture of pulp, paper and paperboard	243 500	0.12	0.74
DE 21.11 Manufacture of pulp*	22 000	0.011	0.07
Manufacture of pulp using enzymes*	3000	0.0015	0.01

**Estimate*

Similar to the case of detergents containing enzymes, the contribution of enzymatic pulp and paper processing to EU employment of 0.0015% is marginal. In terms of labour productivity, the enzymatic process is with a labour productivity of 2.3 more efficient than the conventional one with 2.1 (see Table 36). Both processes are far above the EU manufacturing average, which indicates well established technology in this sector.

Table 36: Labour productivity in pulp and paper processing using enzymes

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU (All economic activity)	100.00	100.00	1.0
NACE D Manufacturing (total)	17.41	16.50	1.1
DE 21 Manufacture of pulp, paper and paper products (2003)	0.53	0.37	1.4
DE 21.1 Manufacture of pulp, paper and paperboard	0.25	0.12	2.1
DE 21.11 Manufacture of pulp*	0.0227	0.011	2.1
Manufacture of pulp using enzymes*	0.0034	0.0015	2.3

**Estimate; **2003 data*

Outlook

In the pulp and paper sector, enzymatic processes have not diffused into industrial use as was expected some 20 years ago. However, some processes are now established, and the maturity of the enzyme markets for pulp and paper processing is very well reflected in the slow but steady growth, which has been predicted to continue by around 3.5% per year until 2009[251].

[251] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

2.4.2.2.3 Enzymes in textile processing

Enzymes are applied at several stages in the production and processing of textiles. The use of cellulase for denim finishing and biopolishing is the largest application, with around two thirds of global enzyme sales for textile processing. Other processes include desizing of starch from textile fibres with amylases, scouring of textiles with pectinases (bioscouring), the degradation of residual hydrogen peroxide with catalases (post bleaching) and proteases for the treatment of silk (removal of natural fibrin).

The uptake of enzymatic processes into EU textile finishing applications is as follows:

- desizing with amylases: 100%
- post bleaching with catalases: 40 - 50%
- denim finishing with cellulases: 80 - 90%.

For bioscouring and biofinishing the degree of diffusion into the industry is not known, although 25% of sold textile enzymes are used for biofinishing processes.

The world market volume of enzymes for textiles is estimated to be around EUR 140 million, which corresponds to 8% of all enzyme sales (EUR 1.8 billion). 32% of textile enzymes are sold to China, 15% to India and 25% to South and Central America, which indicates the concentration of parts of textile manufacturing in these countries[252]. The remaining 28% are sold to Europe, Africa and Far East. According to Novozymes, the growth in textile enzyme sales was mainly based in the development of the Chinese and Far East markets.

Figure 24 shows a model of a textile finishing process for cotton. According to this simplified structure, the finishing process consists of six steps. In four of those, enzymes can be applied. For Step 1 'desizing', 100% diffusion is estimated, for Step 4 'bleach clean-up', 40 - 50%[252] (45% will be used hereafter). For the two steps in which the degree of diffusion is not known (Step 2 scouring, Step 6 rinsing), a 50% application is assumed. In total, this sums up to two production steps with no enzymatic processes, one step with 45%, two steps with 50%, and one step with 100% application. If all production steps are given the same weight in terms of cost, resource use etc., an average diffusion of enzymatic processes into textile finishing of around 40% results.

The textile sector in the EU has been shrinking continuously throughout the last years and contributed 0.41% to the EU's GVA in 2002. According to Eurostat, the contribution of the textile sector to the EU's GVA decreased by 35% between 1995 and 2005[253]. Within the sector, the initial production process steps, like weaving, decreased more than textile finishing, which contributed 0.05% to the EU's GVA in 2002, or 0.28% to EU manufacturing (see Table 37).

[252] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[253] Eurostat http://epp.eurostat.ec.europa.eu/.

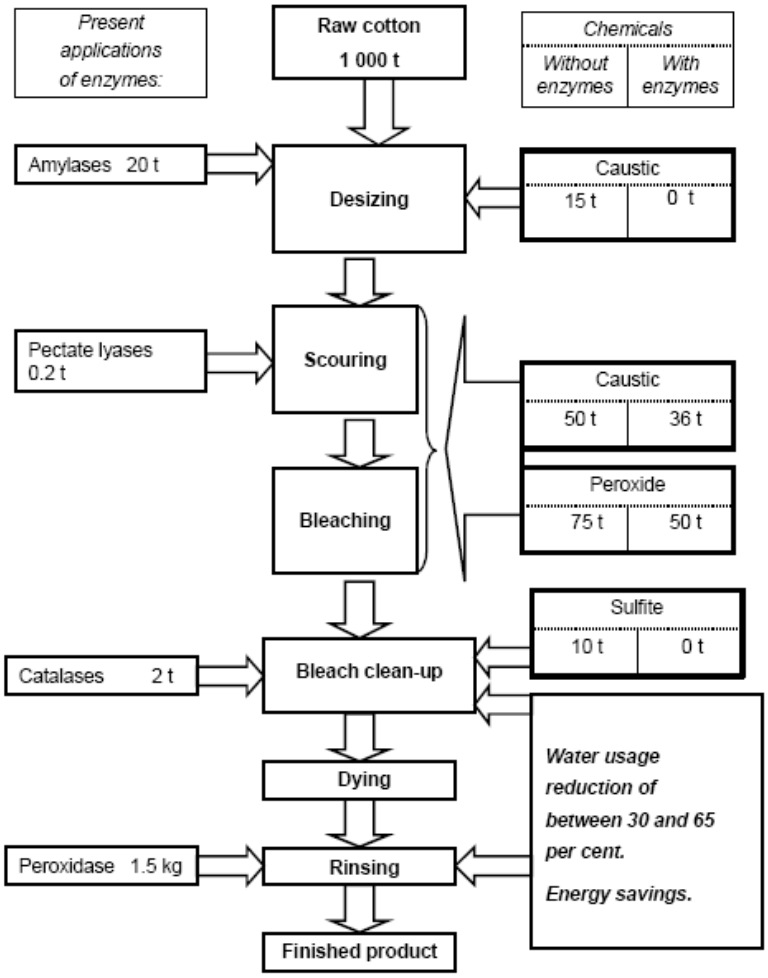

Figure 24: Model process for cotton manufacturing
Source: Kvistgaard and Wolf 2002[254]

A model calculation results in a cost reduction of approximately 80% for both the scouring and the bleach clean-up process steps[254]. For desizing, a price increase in direct material cost was calculated for the enzymatic process, in other words, the input enzymes per unit are more expensive than the input chemicals. However, as the enzymatic process is applied 100%, it can be assumed that the additional cost is more than offset through savings in energy and water cost. Under the assumption that the application of peroxidases as well as the desizing step with amylases are cost neutral, and the two non-enzymatic production steps in the model application remain unchanged, an overall average cost reduction of around 25% can be estimated through the application of enzymes in textile finishing. This results in a higher value-added figure per unit, as less capital costs occur.

[254] Kvistgaard, M. and Wolf O. (eds.) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, IPTS, EUR 20407, p.44. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1022.

Table 37: Contribution of textile finishing using enzymes to the EU's GVA
Source: Data from Eurostat[255], IPTS calculations

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing (in %)
EU GVA (all economic activity)	8 782 816	100.00	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DB 17 Manufacture of textiles	35 795	0.41	2.34
DB 17.3 Finishing of textiles	4307	0.05	0.28
Textile finishing with enzymes*	2000	0.02	0.13

**Estimate*

Under the assumption that 40% of textile finishing uses enzymatic processes, it is plausible to say that of the EUR 4.3 billion GVA contributed by textile finishing, EUR 2 billion are generated through enzymatic processes (see Table 37). This corresponds to a 0.02% contribution of enzymatic textile finishing to the EU's GVA (0.11% to EU manufacturing).

Employment effects and labour productivity in textile production

No data are available with respect to employment shares for enzymatic processes in textile finishing. According to Eurostat, 121 200 people were employed in textile finishing in 2002 (see Table 38). The simple application of the estimated 40% share of enzymatic processes to this figure results in 48 480 employees in textile finishing with enzymatic processes. This is a very rough approximation, as in reality no clear-cut distinction between staff working in enzymatic processing and non-enzymatic processing can be made.

Table 38: Employment in textile finishing using enzymes
Source: Data from Eurostat[255], IPTS calculations

Year: 2002	Number of employees	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU employment (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DB 17 Manufacture of textiles	1 157 700	0.58	3.51
DB 17.3 Finishing of textiles	121 200	0.06	0.37
Textile finishing with enzymes*	48 480	0.02	0.15

**Estimate*

If the contribution of textile manufacturing and textile finishing – with and without enzymes – is compared to the respective contributions to EU GVA, a mixed picture emerges. Overall labour productivity in textile manufacturing is 0.7, i.e. 30% below the EU average or almost

[255] Eurostat database. http://epp.eurostat.ec.europa.eu.

40% below the manufacturing overage. This indicates that more staff are needed to generate value-added than in other manufacturing sectors. Labour productivity in textile finishing is 0.8, which is still less than the overall EU economy and manufacturing values, but 15% higher than textile manufacturing. This confirms that textile finishing is a more capital intensive kind of manufacturing. The use of enzymes in textile finishing, based on rough estimates, leads to a labour productivity of 0.9 (see Table 39). This is still below the EU economy and manufacturing values, but points to technological optimisation of the capital input through the application of enzymes.

Table 39: Labour productivity in textile finishing using enzymes

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU (all economic activity)	100.00	100.00	1.0
NACE D Manufacturing (total)	17.41	16.50	1.1
DB17 Manufacture of textiles	0.41	0.58	0.7
DB17.3 Finishing of textiles	0.05	0.06	0.8
Textile finishing with enzymes*	0.0227	0.024	0.9

**Estimate*

Outlook

In the case of enzymes for textile finishing, the situation is different to other enzyme markets due to the development of the textile sector itself. On the one hand, the sector has been shrinking over the years. On the other hand, the internal structure of the sector moves away from textile producing activities, such as weaving, towards textile finishing processes, which are more enzyme intensive. These, which are usually combined with enzymes when using washing processes, allowed a slow growth of 2.7% for the enzyme market for textiles in the EU. The non-EU markets for textile enzymes, which are also dominated by EU producers, are growing at a faster pace: 3.3% in the US and 3.9% in Asia[256].

2.4.2.2.4 Enzymes in food processing

Biotechnology has been used in food production for several thousand years. Classical techniques like fermentation have been applied to beverages, food and feed. Today, modern biotechnology is established in almost all areas of food production. This is reflected in the importance of food and feed enzymes in the overall enzyme market. The overall share of food and feed enzymes in global enzyme sales ranges between 30% and 45%[257]. A few examples illustrate the diversity of enzymatic reactions and the targeted processes and products. Since the early 1960s, all glucose production is done by enzymatic hydrolysis instead of acid hydrolysis. This process cuts steam costs by 30%, ash by 50% and by-products by 90%[258].

[256] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[257] DECHEMA (2004). Weiße Biotechnologie: Chancen für Deutschland. Gesellschaft für Chemische Technik und Biotechnologie, Frankfurt a.M., p.30. http://biotech.dechema.de/img/biotech_/brennpunkt/041110.htm. *And:* ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[258] Olsen, H.S. (2004). Enzymes at work. Novozymes, Bagsværd, p. 27. http://www.novozymes.com/en/MainStructure/PressAndPublications/Brochures/Brochures+about+enzymes/.

Laccases, as another example, are used in the clarification of juice as well as in baking in the treatment of dough[259]. Also amylases, proteases and xylanases play important roles in baking, cheese production, sweetener production and other food production processes.

The examples show the 'multi-target' character of many enzymes, which are applied in a variety of completely different processes and products[260]. This makes it difficult to assign the economic impact of modern biotechnology to individual enzymes and to avoid double counting at the same time. An economic analysis is furthermore hampered by the fact that most of the enzymatic food production processes have been adopted by the whole industry, i.e. the alternative non-enzymatic process as an efficiency benchmark is not available. This challenge is very well illustrated by the case of fruit juice production, which will be discussed below.

Table 40: Share of enzyme sales per application area in the food sector
Source: ETEPS 2006[261]

Food application area	Enzyme sales in 2006 (in %)
Dairy	26
Starch and sugar	25
Bakery processing	24
Fruit juice	7
Wine making	7
Brewing	6
Nutrition and dietary supplements	5
Total	**100**

Nevertheless, different food production subsectors use enzymes to a different extent. Table 40 shows the EU food enzymes market disaggregated to application areas. Only the food subsectors mentioned in Table 40 are dealt with in the analysis as users of modern biotechnology, i.e. enzyme users. It has to be kept in mind that enzymes are used in practically all food manufacturing, however, applications other than the ones mentioned in Table 40 play such a minor role that their impact on the EU economy and employment is negligible. From this perspective, the food production subsectors analysed for the indirect impact of modern biotechnology are as shown in Table 41. Around 50% of the food manufacturing sector uses larger quantities of enzymes in production. The contribution to EU GVA is 1%. The contribution of these food production processes to the overall manufacturing sector's GVA is 5.76%.

[259] Rodríguez Couto, S. and Toca Herrera J.L. (2006). Biotechnology Advances **24**: 500-513. http://dx.doi.org/10.1016/j.biotechadv.2006.04.003.
[260] The company websites of enzyme producers provide a good overview: information of AB Enzymes on speciality products (http://www.abenzymes.com/?page=page&view=27), Direvo's information on industrial enzymes (http://www.direvo.com/industrial-enzymes/), and Novozymes' report "Enzymes at work" (see footnote 258).
[261] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

Table 41: Share of food production using enzymes in overall food production, manufacturing and the EU's GVA
Source: Data from Eurostat, IPTS calculations[262]

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufactu-ring GVA (in %)	Share of food products GVA (in %)
EU GVA (all economic activity)	8 782 816	100.00		
NACE D Manufacturing (total)	1 528 982	17.41	100.00	
DA 15 Manufacture of food products (2003)	181 220	2.06	11.85	100.00
DA 15.3 Fruit and vegetables	10 758	0.12	0.70	5.94
DA 15.4 Vegetable and animal oils and fats (2003)	5011	0.06	0.33	2.77
DA 15.5 Dairy products (2001)	17 505	0.20	1.14	9.66
DA 15.62 Starch and starch products (2003)	797	0.01	0.05	0.44
DA 15.7 Prepared animal feed	6916	0.08	0.45	3.82
DA 15.81 Bread, pastry, cakes (2003)	26645	0.30	1.74	14.70
DA 15.83 Manufacture of sugar*	1946	0.02	0.13	1.07
DA 15.93 Wine making (2003)	4413	0.05	0.29	2.44
DA 15.94 Cider and fruit wines	590	0.01	0.04	0.33
DA 15.96 Manufacture of beer	13 464	0.15	0.88	7.43
Food production subsectors using enzymes	**88 046**	**1.00**	**5.76**	**48.59**

**Estimate*

Example: Juice production

Enzymatic preparations have been used for 60 years in fruit juice processing[263]. The enzymes used are pectinases, hemicellulases, amylases and proteases. They are used for clarification of the juice, degrading of carbohydrates, and breaking down cell walls. As in other food production areas, the share of enzymatic processes in the particular production steps is 100%, i.e. no non-enzymatic fruit juice production exists which could be used as a comparison to benchmark efficiency gains. For process comparisons, the production of naturally cloudy apple juice, which does not need enzymatic treatment for clarification could be taken into account[264]. However, enzymes may be used even in this case for peeling the fruit and conserving the final product. Furthermore, naturally cloudy apple juice is to be treated as a different product with different end consumer markets. Production price comparisons would not be meaningful. This illustrates the basic challenge in assessing the impact of modern biotechnology in food production. Enzymes are the state-of-the-art technology and cannot be compared to a non-biotechnology production technology. Therefore it is reasonable to account the entire output of fruit and vegetable juice as an indirect impact of modern

[262] Eurostat database. http://epp.eurostat.ec.europa.eu.
[263] Olsen, H.S. (2004). Enzymes at work. Novozymes, Bagsværd, p. 42. http://www.novozymes.com/en/MainStructure/PressAndPublications/Brochures/Brochures+about+enzymes/.
[264] Bates, R.P et al. (2001). Principles and practices of small and medium scale fruit juices processing. FAO Agricultural Service Bulletin **146**, p.162. ftp://ftp.fao.org/docrep/fao/004/y2515e/Y2515E05.pdf.

biotechnology. The same assumption is made for the other food production processes listed above in Table 41.

Table 42 shows the contribution of NACE category DA 15.32 (fruit and vegetable juice) to the food sector's GVA, to manufacturing sector's and to the EU's GVA in total. It can be seen that the food sector is one of the largest subsectors in manufacturing, with a contribution of around 12% (2% to the EU's GVA). Within that, NACE DA 15.3 is amongst the smaller segments, and juice production contributes 0.12% to EU manufacturing GVA (0.02% to the EU's GVA).

Table 42: Share of juice production in food production, manufacturing and the EU's GVA
Source: Eurostat[265]

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)	Share of food production GVA (in %)
EU GVA (all economic activity)	8 782 816	100.00		
NACE D Manufacturing (total)	1 528 982	17.41	100.00	
DA 15 Manufacture of food products	181 220	2.06	11.85	100.00
DA 15.32 Fruit and vegetable juice	**1894**	**0.02**	**0.12**	**1.05**

As Table 42 also shows, fruit and vegetable juice have a share of around 1% in overall EU food processing. At the same time, the share of enzymes for fruit and vegetable juice out of total food enzymes sales in the EU is 7%[266]. This shows that within food processing, this is a rather enzyme-intensive production process. These 7% correspond to a value of EUR 12.8 million, out of the total EU food enzymes market with a value of EUR 184.9 million[266]. In the US, the market for food enzymes in total is around EUR 110.5 million, out of which fruit juice enzymes with EUR 3.9 million have a share of around 3.5%[266]. On a global scale, fruit juice enzymes have a share of around 5.75% (ca. EUR 23 million) out of the entire food enzymes market (ca. EUR 400 million)[267].

Development of fruit juice consumption since 2000 in Europe shows a growing market (see Figure 25). In four years, consumption grew in Eastern Europe by around 90%, in Western Europe by 10%, and in total by 25% (which corresponds to a yearly growth of approximately 6%). As enzymatic production processes are the rule in this industry, it shows that this application area of modern biotechnology is growing several times faster than the EU economy in general.

[265] Eurostat database. http://epp.eurostat.ec.europa.eu/
[266] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[267] ETEPS (2006). Bio4EU Task 2, main report (conversion: 1 USD = EUR 0.7765).

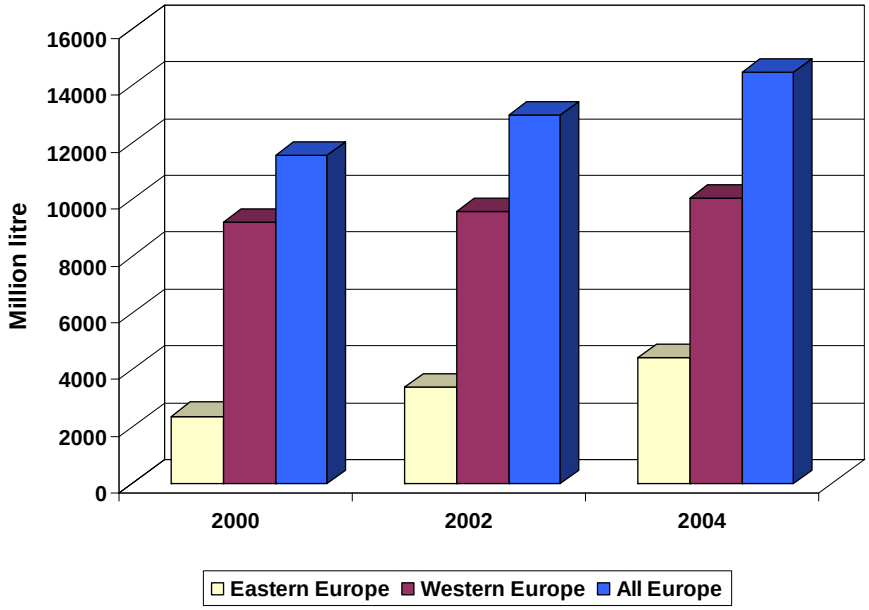

Figure 25: Consumption of fruit juice and nectar in Europe
Source: Doehler Group[268]

This growth is similar to that of the direct competitors in the market for non-alcoholic beverages (water, carbonated drinks, still drinks)[268]. Price competitiveness through optimised production processes plays a crucial role in maintaining a strong position in this market. Enzymatic processes are one important element in process optimisation for fruit juice production, as this is a rather enzyme-intensive manufacturing subsector, as discussed above.

Employment effects in juice production

The strong reliance on enzymatic processes in fruit juice production is also underlined by the fact that fruit juice producers maintain staff with enzyme expertise in laboratories[269]. However, the direct impact on labour markets is rather small in absolute terms: Around 200 persons in the EU are employed in fruit juice enzyme production. Of more interest is the indirect effect. Following the line of argumentation that the entire fruit juice production represents an indirect impact of modern biotechnology, as all fruit juice is produced with enzymatic processes, the entire workforce can also be counted in the same manner. No data are available in the Eurostat database on that issue, but an approximation can be made. In the NACE category DA 15.3 **(**Processing and preserving of fruit and vegetables), 265 600 employees generated a value-added of EUR 10.75 billion in 2002. The value-added generated in the NACE sub-category DA 15.32 (fruit and vegetable juice), was EUR 1.89 billion in 2003. Assuming the same relation between value-added and employment, a workforce estimate of roughly 47 000 employees in the EU can be calculated (see Table 43). This figure, corresponding to 0.02% of overall EU employment (0.12% of EU manufacturing employment) is most likely to increase, as the above shown market development of fruit juice in Europe indicates.

[268] Doehler Group, http://www.doehler.de/en/markets_and_trends/.
[269] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

Table 43: Employment in fruit and vegetable juice production

Year: 2002	Number of employees	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU employees (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DA 15 Manufacture of food products	4 434 100	2.22	13.44
DA 15.32 Fruit and vegetable juice*	**47 000**	**0.02**	**0.12**

**Estimate*

In terms of labour productivity, the production of fruit and vegetable juice shows an employment:value-added ratio of 0.9, which corresponds precisely to the average of food production (see Table 44). The average of 0.9, which is below the EU average, implies that food processing (excluding agriculture) is a labour-intensive manufacturing sector.

Table 44: Labour productivity in fruit and vegetable juice production

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU (all economic activity)	100.00	100.00	1.0
NACE D Manufacturing (total)	17.41	16.50	1.1
DA15 Manufacture of food products	2.06	2.22	0.9
DA15.32 Fruit and vegetable juice*	**0.02**	**0.02**	**0.9**

**Estimate*

The food sector in the EU

As discussed above, the assessment of the impact of modern biotechnology on the EU food sector is shaped by some special characteristics of both the enzymes in use and the food sector itself. Most importantly, it is the long tradition of enzymatic processes in the food industry, which led to a wide diffusion of this technology in basically all subsectors of food processing. Additionally, most of the enzymes are used for several different purposes, which makes it very difficult to assign economic impacts to individual enzymes. Furthermore, enzymatic processes, where applied, have in most cases become the state-of-the-art process which can hardly be benchmarked against a conventional process.

Table 45: Employment in food manufacturing sectors using large quantities of enzymes

Year: 2002	Number of employees	Share of EU employment (in %)	Share of manufacturing employment (in %)
EU employment (all economic activity)	200 000 000	100.00	
NACE D Manufacturing (total)	33 000 000	16.50	100.00
DA 15 Manufacture of food products (2003)	4 434 100	2.22	13.44
DA 15.3 Fruit and vegetables	265 600	0.13	0.80
DA 15.4 Vegetable and animal oils and fats (2003)	59 100	0.03	0.18
DA 15.5 Dairy products	396 200	0.20	1.20
DA 15.62 Starch and starch products (2003)	17 300	0.01	0.05
DA 15.7 Prepared animal feed	130 900	0.07	0.40
DA 15.81 Bread, pastry, cakes (2003)	1 226 000	0.61	3.72
DA 15.81 Bread, pastry, cakes (2003) (adjusted to industrial bread production)	*224 682*	*0.11*	*0.68*
DA 15.83 Manufacture of sugar*	55 800	0.03	0.17
DA 15.93 Wine making (2003)	77 200	0.04	0.23
DA 15.94 Cider and fruit wines	7900	0.00	0.02
DA 15.96 Manufacture of beer	140 400	0.07	0.43
Share of food production subsectors using enzymes	2 376 400	1.19	7.20
Share of food production subsectors using enzymes *(adjusted to industrial bread production)*	**1 375 082**	**0.69**	**4.17**

**Estimate*

However, the share of enzyme sales in the food sector (see Table 40) makes it possible to concentrate on a number of selected food production processes, which use enzymes in large quantities. Table 41 shows the different manufacturing sub-categories, which apply modern biotechnology at different stages of the production process. Their GVA amounts to EUR 88 billion, generated by 2.376 million employees in 2003 in the EU, which is regarded as an indirect impact of modern biotechnology in the EU (see Table 45). The contribution to the EU's GVA is 1% and to EU employment it is 1.2% (agriculture is not included in this calculation).

However, for the assessment of the labour productivity of the food manufacturing sector using enzymes one important adjustment has to be made with regards to NACE category DA 15.81 (bread, pastry and cakes). This category represents a statistical outlier in two respects. On the one hand, with around 1.2 million employees it has the highest number of employees amongst all industrial biotechnology sectors discussed in this study; on the other hand, it has the lowest labour productivity (0.5). These two facts are directly linked to each other: this subcategory is particularly labour intensive, because in EU countries with the highest bread

consumption, the structure of the bakeries market is dominated by small family owned shops. This leads to a rather strong distortion in the overall results of this study. The aim is, therefore, to separate the share of bread which is industrially produced on a large scale from bread that is crafted in micro-enterprises. Based on this for industrially produced bread the following figures can be estimated: 224 000 employees in NACE category DA 15.81 generated a value-added of EUR 8.5 billion[270]. These adjusted figures are taken for the calculation of the overall EU employment in food manufacturing and the corresponding labour productivity (see Table 46). As a result it appears that the food manufacturing subsectors using large quantities of enzymes, have a weighted average labour productivity of 1.2, which is 30% higher than the average value of 0.9 for the entire food manufacturing sector.

Table 46: Labour productivity in overall food manufacturing

Year: 2002	Share of EU GVA (in %)	Share of EU employment (in %)	Labour productivity
EU employment (all economic activity)	100.00	100.00	
NACE D Manufacturing (total)	17.41	16.50	1.1
DA 15 Manufacture of food products (2003)	2.06	2.22	0.9
DA 15.3 Fruit and vegetables	0.12	0.13	0.9
DA 15.4 Vegetable and animal oils and fats (2003)	0.06	0.03	1.9
DA 15.5 Dairy products	0.20	0.20	1.0
DA 15.62 Starch and starch products (2003)	0.01	0.01	1.0
DA 15.7 Prepared animal feed	0.08	0.07	1.2
DA 15.81 Bread, pastry, cakes (2003) *(adjusted to industrial bread production)*	0.10	0.11	0.9
DA 15.83 Manufacture of sugar*	0.02	0.03	0.8
DA 15.93 Wine making (2003)	0.05	0.04	1.3
DA 15.94 Cider and fruit wines	0.01	0.00	1.7
DA 15.96 Manufacture of beer	0.15	0.07	2.2
Share of food production subsectors using enzymes	**0.80**	**0.69**	**1.2**

**Estimate*

Outlook

As discussed above, enzyme applications used in food manufacturing are manifold, and it may well be that different subsectors develop at different paces. On average, this market has

[270] This calculation is based on the information that out of 25 million tonnes of bread sold in the EU in 2005, 8 million were produced industrially. A large bread producer generates a turnover of EUR 89 544.33 per employee (http://www.bimbo.com). These figures, combined with EUR 60 billion turnover/EUR 27 billion value-added for all bread in the EU, resulted in the adjusted figures.

shown continuing growth in the past, and for the coming five years a growth rate of 2 - 3% in the EU has been estimated[271]. Since EU food enzyme producers are world market leaders, market developments in other regions are relevant as well. Growth in the US, with enzymes for starch and sugar processing as the largest segment, grew by 3.4% in recent years. The modest but linear growth (past and predicted) shows that food enzymes represent a mature market with limited volatility. High technical entry barriers for future competitors, and regulations in the EU which restrict the use of new types of enzymes in food manufacturing are further stabilising factors for the market[272].

2.4.2.3 Modern biotechnology in bioethanol production

The production of bioethanol is the only application area of modern biotechnology in the field of biomass energy supply which has been taken into account in the context of this study. The majority of ethanol production processes are dedicated to its use as a transport fuel. Therefore it makes sense to describe the economic dimensions in relation to the fossil fuel production sector. A look at NACE DF 23.2 (manufacture of refined petroleum products) shows the size of the sector. The sector includes more than just transport fuel, as refineries also provide intermediate chemical products. In 2003, refinery products included the following[273]:

- **gas/diesel oil** **36.0%**
- **gasoline** **20.9%**
- **residual fuel oils** **15.6%**
- naphtha 5.9%
- **kerosene/jet fuels** **6.1%**
- refinery gas 3.3%
- liquefied petroleum gases (LPG) 2.9%
- various other petroleum products 9.4%

This list shows that 78.6% of refinery products go into fuel production (see list items in bold). Therefore it is estimated that 80% of the GVA of NACE sector DF 23.2 accounts for petrol fuel products (see Table 47).

NACE category DF 23 employs around 175 000 people in the EU and contributes 0.28% to the EU's GVA (respectively 1.63% to EU manufacturing GVA). NACE category DF 23.2 (manufacture of refined petroleum products) is the largest subsector, employing 135 000 people and contributing 0.25% to the EU's GVA (or 1.44% to EU manufacturing GVA). As discussed above, it is assumed that 80% of NACE DF 23.2's output (at the refinery gate) are transport fuels, whereas the remaining 20% are chemicals and other products. Consequently it is assumed that transport fuel contributes with 0.2% to the EU's GVA, (or 1.15% to EU manufacturing GVA) and employs around 100 000 staff, as shown in Table 48. These relations have been more or less stable over the past years, and it can be assumed that the share remains roughly similar, although the workforce is decreasing by about 0.5% per year.

[271] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[272] For example, in the fruit enzyme market, EU regulations only permit pectases, amylases and proteases (ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications).
[273] Eurostat (2006). European business - facts and figures, p.56. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-BW-05-001/EN/KS-BW-05-001-EN.PDF.

The transport fuel production is a mature sector with large scale production facilities. The production volume per average oil refinery amounted to roughly 6 million tonnes fuel in 2005. The resulting turnover per employee sums up to EUR 5.3 million (see Table 48).

Table 47: Share of fuel production in manufacturing of refined petroleum products, manufacturing and the EU's GVA
Source: Eurostat[274]

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)
EU GVA (all economic activity)	8 782 816	100.00	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DF 23 Manufacture of coke, refined petroleum products and nuclear fuel	24 866	0.28	1.63
DF 23.2 Manufacture of refined petroleum products*	21 974	0.25	1.44
Fuel share in DF 23.2*	17 579	0.20	1.15

**Estimate*

In contrast to the production of fossil fuel, bioethanol production is a young industry, which still undergoes rapid economic and, in particular, technological development. Table 48 shows basic figures of the economic impact of bioethanol production in comparison to fossil fuel production. For 2005 there is a share of 0.21% of bioethanol in the GDP fraction of total liquid fuels. This results in a share of 0.0005% of bioethanol production in overall GDP (2005)[275]. In 2005, 525 people were employed directly, and around 5000 indirectly in bioethanol production, which corresponds to 0.3% of NACE DF 23.2 employment, or around 0.015% of overall EU employment in manufacturing.

Table 48 also shows that the average production cost of bioethanol still exceeds the cost of fossil fuel production by far. Whereas in 2005 one litre fossil fuel production cost EUR 0.33, a litre of bioethanol cost EUR 0.53 (i.e. it was 60% more expensive)[276]. If the energy contents are to be compared, it cost EUR 0.76 in 2005 to produce the energy equivalent of fossil fuel with bioethanol (130% more expensive). In 2004, production costs were still twice as high: the production of one litre bioethanol was 150% more expensive, and the production of the fossil fuel energy equivalent was 270% more expensive. The comparison of the average yearly production volumes per production plant (fossil fuel: 6 000 000 tonnes, bioethanol: 100 000 tonnes) shows that oil refineries produce on a larger scale, and that there is still room for development in the bioethanol production figures to lower the production cost per unit. Nevertheless, a prediction of future cost development for biofuels on the basis of past experience can only be done within certain limitations. The growth of production volume of individual plants is limited due to geographic dependence on raw material supply (biomass).

[274] For DF 23, the GVA at basic and at factor prices was available on the Eurostat database, for DF 23.2 the GVA was available at factory prices only. The estimation made in Table 49 is based on extrapolating the known relation DF23/DF23.2 at factory prices to the unknown relation DF23/DF23.2 at basic prices.
[275] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[276] The price/unit relation for biofuel is indicative and is slightly different depending on the raw material used and the different production pathways. The cost comparison to fossil fuel, however, should reflect the approximate range.

And, related to that, the large scale production of biofuels has repercussions for the raw material price itself, which might compensate cost reductions through efficiency gains.

Table 48: Comparison of fossil fuel and bioethanol contributions to the EU economy

	Fossil fuel in the EU	Bioethanol in the EU
Contribution to EU economy	0.25% GVA share (2002)	0.0005% GDP share (2005)
Contribution to EU manufacturing	1.15% (Share NACE D in 2002)	0.0023% (Share NACE D in 2005)
Employment (2005)	Direct: 40 000	Direct: 525
	Total: ca. 100 000 *	Total: ca. 5500
Contribution to employment in the EU	0.05% (2002)	0.0003% (2005)
Turnover per employee (2005)	EUR 5 300 000	EUR 800 000
Production cost (2005)	EUR 0.33/litre	EUR 0.53/litre
Production cost (petrol energy eq.)	EUR 0.33/litre	EUR 0.76/equivalent petrol litre
Overall production (2005)	600 000 000 tonnes *	750 000 tonnes
Output average production plant (2005)	6 000 000 tonnes/year	100 000 tonnes/year **
Number of factories	104 refineries (2005)	16 (2005), 23 (2006)
Sales (2004)	EUR 139 billion	EUR 192 million
Trade (2004)	Not available	13% imports

* 0.8 x DF 23.2 employment; ** *Estimate*

Altogether, empirical evidence reflected in Table 48 shows a modest contribution of bioethanol to EU economic performance. A look at bioethanol development over time reveals a picture of an industry with high growth rates (see Table 49). Bioethanol production in the EU shows large differences in output from year to year, but overall a strong growth of more than 100% between 2002 and 2005. The development from 2004 to 2005 reflects strong growth rates for all bioethanol economic indicators (see Table 49). This has several reasons, such as technological progress, recent changes in the crude oil market price and, as a knock on effect from this, a changing legal framework at national and EU level. The EU set a target of 5.75% for biofuel's share in overall EU road transport fuel, which was recently increased to 10% by 2020[277]. Some Member States already design their national policies accordingly, such as The Netherlands and Germany, which recently announced a 10% obligatory biofuel share until 2014[278].

[277] Brussels European Council, 8 and 9 March 2007, Presidency conclusions (7224/1/07). http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/ec/93135.pdf.

[278] FTD (2006). Koalition zwingt Ölkonzernen zehn Prozent Biosprit auf. Financial Times Deutschland (Hamburg), online version 24 October 2006. http://ftd.de/unternehmen/industrie/124573.html.

Table 49: Bioethanol's key parameter development over the past years in the EU

Bioethanol	2002	2003	2004	2005	2006
Total production volume (1000 tonnes)	346	446	419	750	---
Change to previous year	---	*+29%*	*-6.1%*	*+79%*	---
Bioethanol share out of total liquid fuel	---	0.077%	0.071%	0.12%	---
Change to previous year	---	---	*-7.8%*	*+70%*	---
Share of European bioethanol production out of world production	---	1.7%	2.1%	2.6%	---
Change to previous year	---	---	*+23.5%*	*+23.8%*	---
Sales (EUR million)	---	204	192	427	---
Change to previous year	---	---	*-5.9%*	*+122%*	---
Employment	---	312	413	525	---
Change to previous year	---	---	*+32.4%*	*+27.1%*	---
Number of factories	---	---	---	16	23*
Change to previous year	---	---	---	---	*+43.7%*

*Additionally the construction of 8 more bioethanol factories has been approved, which therefore could be counted as 31 new factories or an increase of 94%

International comparison

As Table 49 shows, bioethanol as a transport fuel only plays a minor role for EU transport and the overall economy at the moment. Outside the EU, bioethanol as a fuel plays a similar role although at different scales. Of particular interest is the EU comparison with the US, Brazil and Japan.

As Figure 26 shows, the world fuel bioethanol production has been increasing since the mid 1970s at high growth rates, with an accelerating trend in the last five years. The distribution of the 29 million tonnes of bioethanol fuel production shows the dominating position of the US and Brazil (see Table 50).

Historically this development is related to a series of events on the oil market. So it is no coincidence that the start of this development took place shortly after the first oil price crisis in the early 1970s. At that time, Brazil was the only country which decided to cover its national fuel demand with bioethanol, favoured by the national large scale sugar cane production. The US only showed interest in bioethanol as a large scale product more recently, because the price of oil rose rapidly in the early 2000s. Since then, bioethanol production is a policy priority in the US.

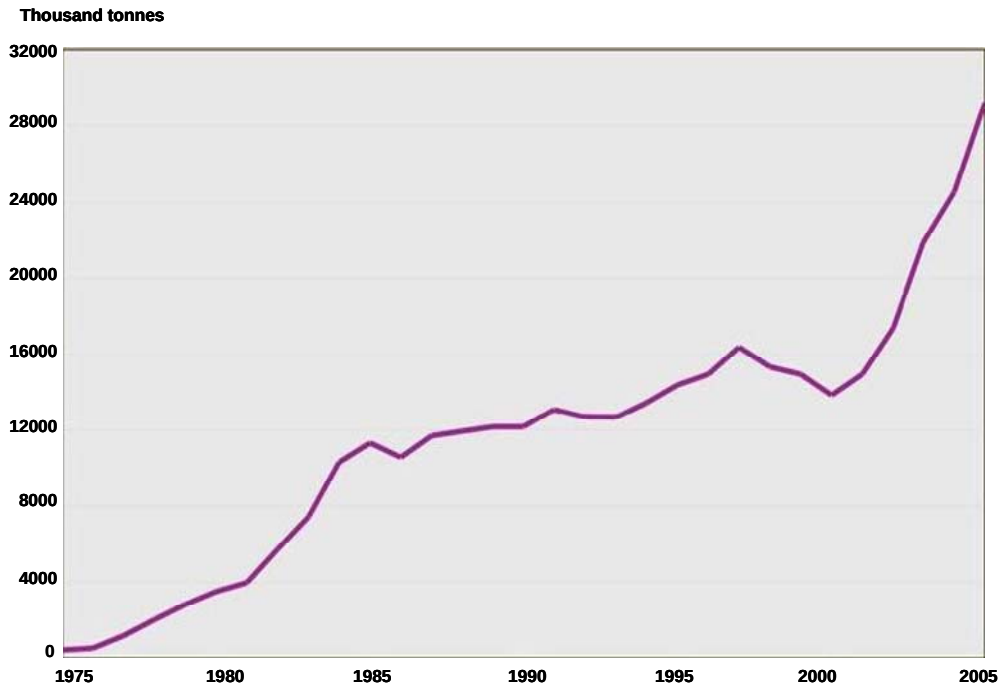

Figure 26: Global production of bioethanol for fuel in thousand tonnes
Source: Worldwatch Institute[279]

Growth rates in fuel bioethanol production have been very high in all the major bioethanol producing countries and regions. In the EU and the US bioethanol production doubled between 2002 and 2005, in Brazil the increase seemed to be less with 30% because production had already been at a high level before, and in contrast, Chinese production increase was very high, because production levels were very low in 2002. India just entered the picture in 2005. A production volume of 240 000 tonnes indicates that production there had also passed the pilot phase. In 2004 and 2005 Japan did not produce bioethanol as a transport fuel, but imported around 400 000 tonnes.

Table 50: Global bioethanol production volumes
Source: Worldwatch Institute[280]

	Production (1000 tonnes) in 2002	Production (1000 tonnes) in 2005	**Growth between 2002 and 2005 (in %)**
Brazil	10 000	13 000	30
US and Canada	6700	13 000	91
China	230	1600	592
EU	346	750	117
India	---	240	---
Japan	---	---	---

[279] Worldwatch Institute (2006). Biofuels for Transportation, p.5. http://www.worldwatch.org/system/files/EBF038.pdf.
[280] Worldwatch Institute (2006). Biofuels for Transportation. http://www.worldwatch.org/system/files/EBF038.pdf; *And:* IEA (2004). Biofuels for transport. International Energy Agency, Paris. http://www.iea.org/Textbase/publications/free_new_Desc.asp?PUBS_ID=1262.

Bioethanol is not competitive as is fossil fuel (except in Brazil). Therefore it is pushed into the market through legal measures. Table 51 shows the bioethanol share of all liquid fuels for different countries, thereby revealing its political importance in different global areas.

Table 51: Bioethanol volume development in different global areas
Source: ETEPS, Worldwatch Institute, IEA[281]

Bioethanol	1999	2000	2001	2002	2003	2004	2005
Global production volume (1000 tonnes)	14 600	13 800	15 000	18 200	22 100	23 000	29 000
US - Bioethanol share in national liquid transport fuel					1.20%	1.50%	1.90%
Brazil - Bioethanol share in national liquid transport fuel					14%	14%	14%
EU - Bioethanol share in national liquid transport fuel					0.15%	0.14%	0.21%
US - Share in world production	~30%	35%	35%	35%	38%	44%	45%
Brazil - Share in world production	~70%	63%	58%	52%	48%	48%	45%
EU - Share in world production	0.80%	1.40%	1.40%	1.80%	1.70%	2.10%	2.60%
Others - Share in world production	0%	0.60%	6.60%	10.20%	12.30%	5.90%	6.30%

The global production volume has more than doubled since 1999 (see Table 51). The main contributor to this growth has been the US, which increased their world market share from about one third in 1999 to approximately 45% in 2005. At the same time, the Brazilian share in global bioethanol production decreased from 70% in 1999 to around 45% in 2005, due to production increases in other global regions. The EU showed an increasing share in world bioethanol production, which has more than tripled since 1999, although starting from a low level.

Table 51 also shows that the share of bioethanol in the national transport fuel supply has remained stable in Brazil over the years, which indicates that a desired level has been reached and no additional incentives have been set. The numbers indicate a different background for the US and the EU. The share of bioethanol in the national transport fuel supply is increasing, which indicates regulatory measures such as tax exemptions in order to push non-competitive bioethanol into the market.

Outlook

A prediction of bioethanol production volumes over the coming five years is very difficult to make. The short-term trend indicates an increase: several new large bioethanol plants in Germany, Spain and France have been built since 2004. Whereas 16 plants producing bioethanol existed in 2005, there were 23 in 2006, which corresponds to an increase of 50%. Plans have been made in several other EU Member States to construct bioethanol plants (e.g.

[281] ETEPS (2006). Bio4EU Task 2, main report *And:* Worldwatch Institute (2006). Biofuels for Transportation. http://www.worldwatch.org/system/files/EBF038.pdf; *And:* IEA (2004). Biofuels for transport. International Energy Agency, Paris. http://www.iea.org/Textbase/publications/free_new_Desc.asp?PUBS_ID=1262.

Belgium and The Netherlands). According to experts, the amount of bioethanol produced in the EU may triple or even quadruple in the coming five years. The EU production of fossil fuels is growing by 2% each year, but may level off because of a lower demand caused by price increases. Therefore, the share of bioethanol in liquid fuel may grow beyond 1% in the near future.

As mentioned before, regulatory initiatives and fixed targets for the share of bioethanol in transport fuel at EU level (5.75% and recently 10%) as well as at Member State level (e.g. 10% in Germany) are likely to support the increase in production volumes. The US have announced that they will cover national fuel supply with 30% biofuels by 2030[282].

This growth could be accelerated through current attempts to lower the production cost for second generation bioethanol. Modern biotechnological processes already exist to make organic raw material, such as wood, waste and other organic material (cellulosic biomass), available for bioethanol production, which would lead to a lowering of raw material price and therefore an increase in the competitiveness of bioethanol. Pilot plants are running, for example, in Sweden, but information on production cost is not available. The availability of this second generation cellulosic ethanol is the pre-condition for reaching the US 30% target, accordingly research funds and other subsidies are being made available particularly for this. Overall subsidies for bioethanol in the US reached the level of USD 5.1 - 6.8 billion/year, and are expected to reach USD 6.3 - 8.7 billion/year during the coming five years[283]. As a result, companies such as Novozymes (enzyme development) and Broin (the largest dry mill ethanol producer in the US) announced their collaboration for the accelerated development of cellulosic ethanol[284].

2.4.2.4 Biotechnology-based polymers and other biotechnology-based chemicals

2.4.2.4.1 Biotechnology-based polymers

A number of different technologies for the production of biotechnology-based polymers are already established. The most prominent amongst these is the starch-based poly-lactic acid (PLA). However, the large scale production of PLA is concentrated in the US and Japan, although a number of PLA plants have now been established in the EU as well. Currently, their contribution to EU economic growth and employment is rather modest. There are also other biotechnology-based polymers produced in the EU. In total, eight companies could be identified (see Table 52).

[282] DOE (2006). DOE published roadmap for developing cleaner fuels. Press release, 7 July. US Department of Energy, Washington, D.C. http://www.doe.gov/news/3804.htm.

[283] 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. http://www.globalsubsidies.org/article.php3?id_article=6.

[284] Novozymes (2006). Broin and Novozymes to collaborate on the development of ethanol from cellulosic biomass. Press release, 26 October. Novozymes, Bagsværd. http://www.novozymes.com/en/MainStructure/PressAndPublications/PressRelease/2006/NzBroinBiomass.htm.

Table 52: Companies producing biotechnology-based polymers in the EU

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 450 000 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®)	

Production volumes of biotechnology-based polymers has 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 0.4%[285].

Table 53: Contribution of production of biotechnology-based polymers to the EU's GVA
Source: Data from Eurostat[286], IPTS calculation

Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)
EU GVA (all economic activity)	8 782 816	100.00	
NACE D Manufacturing (total)	1 528 982	17.41	100.00
DG 24 Manufacture of chemicals and chemical products	170 555	1.94	11.15
DG 24.16 Manufacture of plastic in primary form (2003)	16 153	0.18	1.06
Biotechnology-based polymers*	33.7	0.0003	0.0021

**Estimate*

Cost-efficiency is currently not the overriding motivation for the production of biotechnology-based polymers. This manufacturing subsector is in the technological start-up phase, with a steep learning curve. The situation is comparable to that of bioethanol producers, being at an even earlier stage. The most competitive biotechnology-based polymer is currently solanyl, with a production price of around EUR 1.13/kg. The price per kilo is currently estimated to be EUR 2.2 - 3.4 for PLA and EUR 20 for polyhydroxyalkanoates

[285] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[286] Eurostat database. http://epp.eurostat.ec.europa.eu.

(PHA)[287]. In summary, biotechnology-based polymers are between 4 and 26 times more expensive than the oil-based competing products. The meaningfulness of these figures is limited. Different conventional polymers have different technical characteristics and therefore different end-user markets. Accordingly, biotechnology-based polymers are developed to meet different technical criteria. Some of them might be applied in specialised medical uses, others in bulk applications like plastic bags. This has, in turn, a direct impact on the competitiveness threshold in each individual case.

As no evidence is available on employment created through the production of biotechnology-based polymers, and cost-efficiency assessments do not lead to meaningful results, the impact of biotechnology-based polymers in the EU currently can be regarded as negligible. In the US and Japan, the situation is somewhat different. In 2002, the then largest PLA production site (140 000 tonnes/year) was up and running in the US. Cost figures are not available for this plant. However, it is obvious that in comparison to oil-based polymers, the threshold for competitiveness has still not been reached. Global production capacities for PLA are growing, in the US as well as in Japan and the EU. This indicates that the product is expected to become competitive in the near future.

In Japan, Mitsubishi Rayon is the world's largest producer of acrylamide, another biotechnology-based polymer, producing 20 000 tonnes per year of the 100 000 tonnes yearly global production. This process has a long tradition and has developed into a competitive production process over time.

Outlook

Price reductions are expected for all biotechnology-based polymers in the near and mid-term future. The average cost for PLA production is expected to decrease to EUR 1.35/kg, the price for PHA might even decrease to EUR 3-5/kg by 2010[288]. The average price of different oil-based polymers today is around EUR 0.75/kg. It can be concluded that the competitiveness gap is shrinking, but that in the coming five years biotechnology-based polymers will not break substantially into the market for primary plastics, apart from highly specialised application areas.

2.4.2.4.2 Other biotechnology-based chemicals

One of the key strengths of enzymes is their ability to replace chemical catalysts. Enzymatic reactions therefore have been taken up in the chemicals industry. The variety of processes in use is large, and well-known examples include the large scale production of acrylamide, the production of lactic acid as an intermediate chemical product (see above section on biotechnology-based polymers), or the production of the cephalosporins (a group of antibiotics, see below). Other prominent examples are the applications of enzymatic processes in the production of (bio)pharmaceuticals, vitamin B2 and bioethanol. Nevertheless, aggregated data for this group of biotechnology-based chemicals are practically not available. The contribution of this sector to the EU economy will therefore have to be carried out qualitatively.

[287] Crank, M. et al. (2005). Techno-economic feasibility of large-scale production of bio-based polymers in Europe. European Commission, IPTS, EUR 22103. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1343.
[288] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

About 305 companies in the EU could be identified as developers and producers of biotechnology-based chemicals. This includes a very heterogeneous group of processes and products (including service providers), as well as large companies and SMEs. If only the known producers of chemical substances (33) as well as bioethanol (16) and biotechnology-based polymers (7) producing companies are taken into account, this figure narrows down to 56[289]. Compared to the 60 000 chemical companies in the EU this is a small fraction (0.1%). In the US, this relation is significantly higher: 1.7% of all chemical companies (16 000) are developers or producers of biotechnology-based chemicals (266). In Japan, 2.5% of all chemical companies are producers of biotechnology-based chemicals (127 out of 5000).

The contribution of chemicals, which are produced through the application of modern biotechnology, represents only an insignificant share to the EU economy. Due to this, and because of the absence of reasonable data on employment, cost-efficiency and future market developments, this application area is not included in the overall assessment of industrial biotechnology impacts on the EU economy.

Example: Cephalosporins

For individual products, data coverage is better, as for example for the manufacturing of 7-ACA/7-ACDA[290] (building blocks for cephalosporins), but the range of biotechnology-based chemicals is too heterogeneous to extrapolate figures from this case to the entire sector.

The antibiotic cephalosporin falls in the category of pharmaceuticals which are produced through the application of modern biotechnology. Some cephalosporins are produced on the basis of 7-ACA, which is derived from cephalosporin C. Other cephalosporins are produced on the basis of 7-ADCA, which is derived from penicillin G[291]. The production route for both 7-ACA and 7-ADCA includes several steps, starting with fermentation. The following steps, initially chemical, have recently been carried out partially by biotechnological processes.

The market volume for 7-ACA was 5000 tonnes in 2006, 35% of which was produced in the EU. World production is manufactured to 85% by 10 companies[291]. In the EU the largest producers are Antibioticos (Italy) with a capacity of 600 tonnes/year and Sandoz (Switzerland, but with its production facilities in Frankfurt, Germany) with 400 tonnes/year.

20% of 7-ACA's production is manufactured biotechnologically. As all Sandoz's production is biotechnological, and Antibioticos is known to produce 50% of its output biotechnologically, it can be estimated that with 900 tonnes the EU contributes 75% of all biotechnologically produced 7-ACA[291]. The world market value for 7-ACA was EUR 300 million in 2006. Cost-efficiency gains cannot be calculated. However, due to legal requirements Sandoz changed the production in Frankfurt from chemical to biotechnological manufacture. Due to this change Sandoz managed to produce 99.3% less undesired by-products that need to be incinerated[291]. This indicates that the biotechnological route is at least as cost-efficient as the chemical synthesis. Employment in the EU production of 7-ACA is estimated to be 1200 staff.

[289] ETEPS (2006). Bio4EU Task 2, annex report data tables.
[290] 7-ACA: 7-aminocephalosporanic acid; 7-ADCA: 7-aminodeacetoxycephalosporanic acid
[291] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

The case is similar for the production of 7-ADCA. The Dutch company DSM is the world's largest producer with several hundred tonnes production capacity. The value of the world market lies currently at EUR 200 million. The EU share in production and sales is around 50%. The change from chemical to biotechnological synthesis led to savings in energy use of 40% and in input materials of 35%. The use of solvents in the process was reduced by 91%[292].

In international comparison, the EU has a competitive position in the production of 7-ACA and 7-ADCA. This is indicated through the high world market shares in production volumes. Worldwide only a few producers are active and actually form a global oligopoly. The uncertain factor in this situation is, like in other areas of industrial biotechnology, the rapid development of production capacity in China. The North China Pharmaceutical Corporation NCPC and the Harbin Pharmaceutical Group, which alone employs more than 8000 staff, produce several thousand tonnes of antibiotics, including 7-ACA and 7-ADCA. It is known that NCPC is developing biotechnological production routes for future production processes. It cannot be predicted how this will influence the current world market structure.

2.4.2.5 Modern biotechnology in bioremediation

Bioremediation is the collective term for the 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.

Among 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 micro-organisms adapted to degrade 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 micro-organisms are found in the direct environment of the contaminated material.

Bioremediation has been thoroughly reviewed by the OECD, which collected a number of examples[293]. For air and off-gases, micro-organisms 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 – the introduction of specific strains or consortia of micro-organisms on the contaminated site to improve the capacity for pollutant degradation – is at a comparatively early stage of development[294]. 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 and during composting. Degradation in

[292] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[293] OECD (1994). Biotechnology for a clean environment. OECD, Paris. http://www.oecd.org/dataoecd/47/50/2370637.pdf.
[294] El Fantroussi, S. and Agathos S.N. (2005). Current Opinion in Microbiology **8**: 268-275. http://dx.doi.org/10.1016/j.mib.2005.04.011.

an oxygen-depleted environment produces usable methane. Waste water treatment has the longest record of applying micro-organisms for clean-up purposes with several different technologies[295].

Currently, limited use is made of modern biotechnology in bioremediation. It is used, for example, to support the efficient production of enzymes[296], 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 during decontamination[297].

The fact that micro-organisms are able to adapt to the degradation of a wide range of problematic pollutants, such as chlorinated solvents, sparked expectations in the 1980s that modern biotechnology would enhance possibilities of bioremediation through the modification of micro-organisms. Modification aimed at increasing the degradation capacity, both by improving the degradation rate, i.e. enabling the micro-organisms to clean material faster, and also by enlarging the applicability to a greater 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[298].

The use of modified micro-organisms in bioremediation, however, faced several challenges. With the exception of a few cases, modified micro-organisms have performed poorly in degrading pollutants compared with their naturally occurring counterparts. One exception is the use of transgenic plants for the decontamination of soil, for example modified tobacco plants for phytodetoxification of explosives (TNT) in soil[299]. However, this application is not actually being used to remove explosive residues from soil. In addition, the interaction of modified micro-organisms with the natural environment is difficult to predict, and newly introduced micro-organisms have often turned out not to be as fit than their competitors and have been eliminated[298]. The potential risks associated with uncontrolled growth and proliferation of the genetically modified organisms (GMOs) in the environment, and with the possibility of gene transfer to other organisms have limited the applications of GMOs in bioremediation up to now.

Another example of the use of modern biotechnology in environmental applications is the development of biosensors. Biosensors are analytical devices incorporating biological material, such as micro-organisms, enzymes, antibodies, etc., which are associated with, or integrated into, a physicochemical transducer system, which may be e.g. optical or electrochemical[300]. 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 true biosensor systems (which do not need additional, external physical translation of signals) are currently on the market.

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[295] Gaugitsch H. and Schneider M. (1997). Einleitung, Zusammenfassung und Bewertung. In: Umweltbiotechnologie in Österreich, Schwerpunkt: Nachsorge, Monographien Band 85B, Bundesministerium für Umwelt, Jugend und Familie, Vienna, p. 501-510.

[296] Alcalde, M. et al. (2006). Trends in Biotechnology **24**(6): 281-287. http://dx.doi.org/10.1016/j.tibtech.2006.04.002.

[297] Sutherland, T. et al. (2002). Pesticide Outlook **13**: 149-151. http://dx.doi.org/10.1039/b206783h.

[298] Cases I. and de Lorenzo V. (2005). International Microbiology **8**: 213-222. http://www.im.microbios.org/0803/0803213.pdf.

[299] Hannink, N. et al. (2001). Nature Biotechnology **19**: 1168-1172. http://dx.doi.org/10.1038/nbt1201-1168.

[300] ETEPS (2006). Bio4EU Task 2 Case studies report – Industrial Biotechnology Applications.

2.4.3 Summary

Indirect effects of modern biotechnology are several magnitudes higher than direct effects (if looking at enzyme producers and users). In this study only the sectorial analysis has been carried out, looking at immediate users of enzymes. A macroeconomic perspective has not been taken.

Enzyme producers can be characterised as profitable enterprises, producing highly technological intermediate products, which unfold their impact on the EU economy in the application areas down the supply chain. In comparison with other manufacturing sectors such as detergents production or pulp and paper processing, contributions of food production seem to be quite large. This picture reflects the actual situation rather well. Food production is the manufacturing sector with the longest tradition in the use of enzymes, and it is the one which currently exploits the potential of modern biotechnology to optimize production processes with the largest degree of uptake into production processes.

The large scale production of biotechnology-based polymers is dominated by the US and by Japan, although EU producers have increased the production volume, currently to the level the US production achieved 5 years ago. The US embarked later on working on technology for the production of bioethanol, but through policy support gained a large share of world production a few years later. Both, the markets for bioethanol and biotechnology-based polymers indicate a general willingness in the US to embark on large-scale production of products which are expected to become competitive only in the future.

Due to the lack of quantifiable information, the development of industrial biotechnology in India, and in particular in China, has not been incorporated into this analysis. One of the few evident facts is the build-up of very large bioethanol production capacities in China during the past three years, representing today more than twice the capacity of the EU's production. For the near future one single production site with a capacity of 600 000 tonnes is planned (as a comparison: the EU's production in 2005 was 750 000 tonnes), indicating that China will outpace the EU both in growth rates and market volumes very soon. Information from other industrial biotechnology applications (e.g. cephalosporin production) has indicated a similar behaviour when entering into the market: Once a decision to embark on this technology has been taken, very large production capacities are developed.

Labour productivity is the relation between 'share of the EU's GVA (in %)' and 'share of the EU's employment', which is used in this study as a very basic parameter to compare manufacturing using enzymes with manufacturing not using enzymes. If the total GVA is considered, it can be seen that 2.4% of EU employees generate 2.47% of the EU's GVA. This indicates that, in summary, over all the manufacturing sectors, labour productivity is close to 1, i.e. one per cent of the labour input factor generates one per cent of value-added.

The look at modern biotechnology applications shows a surprising difference: 1.06% of EU GVA is generated by 1.23% of EU employees. This indicates a labour productivity of 0.86, i.e. those manufacturing sectors work less efficiently when modern biotechnology is applied.

Disaggregation makes things clearer. Enzyme production is a high tech sector: 0.0078% of the EU's GVA is generated by 0.003% of EU employees, i.e. labour productivity is very high (2.6). In the comparative sector of fine chemicals, labour productivity is around 1.5, i.e. substantially lower.

The results are similar for industrial applications: In pulp and paper as well as in detergents manufacturing using enzymes the labour productivity of the production processes using enzymes can be 2 or even more. This is much above the EU average, and in all cases equal or more to conventional production. Even in the traditional and labour intensive food sector, which has an average labour productivity of 0.9, those subsectors which use large quantities of enzymes have a labour productivity of 1.2, i.e. they are more efficient.

The important outlier is the production of bioethanol, and with a labour productivity of 0.7, shows only 70% of the EU average. This value, however, indicates that this technology is at a very early stage in its life cycle, and still has a steep learning curve. The lowering of production costs from year to year shows that efficiency gains can be achieved.

As a general conclusion it can be said that the contribution of modern biotechnology to EU economic growth and employment is modest in absolute terms, but a new technology, which is superior to conventional processes in economic terms, can find its way into the EU economy. With the exception of bioethanol, which has attracted a lot of attention as a potential substitute for fossil fuels, data availability for industrial biotechnology is poor.

Table 54 summarises the key figures.

Table 54: Economic and employment figures for modern industrial biotechnology in the EU

	Year: 2002	GVA (EUR million)	Share of EU GVA (in %)	Share of manufacturing GVA (in %)	Employment	Share of EU employment	Share of manufacturing employment	Labour productivity
EU GVA (all economic activity)		8 782 816	100.00		200 000 000	100.00		1.0
NACE D Manufacturing (total)		1 528 982	17.41	100.00	33 000 000	16.50	100.00	1.1
Direct impacts								
Enzymes	DG 24.66 Manufacture of other chemical products**	7906	0.09	0.49	117 200	0.06	0.36	1.5
	Enzyme production*	**741**	**0.0084**	**0.05**	**4000 - 6000**	**0.002 – 0.003**	**0.015 – 0.02**	**2.8 – 4.2**
Indirect impacts								
Detergents	DG 24.51 Manufacture of soap, detergents, cleaning and polishing**	7807	0.09	0.51	119 100	0.06	0.36	1.5
	Detergents containing enzyme * **	**4000**	**0.045**	**0.26**	**60 000**	**0.03**	**0.18**	**1.5**
Textiles	DB 17.3 Textile finishing	4307	0.05	0.28	121 200	0.06	0.37	0.8
	Textile finishing using enzymes	**2000**	**0.0227**	**0.13**	**48 480**	**0.024**	**0.15**	**0.9**
Pulp and Paper	DE 21.11 Manufacture of pulp*	2000	0.0227	0.13	22 000	0.011	0.07	2.1
	Manufacture of pulp using enzymes	**300**	**0.0034**	**0.02**	**3000**	**0.0015**	**0.01**	**2.3**
Fuel	DF 23.2 Refined petroleum products (calculated with 0.8 ratio to focus on fuel)	17 579	0.20	1.15	108 000	0.05	0.33	3.7
	Bioethanol**	**16**	**0.0002**	**0.0011**	**525**	**0.0003**	**0.0016**	**0.7**
Food/Feed	DA 15 Manufacture of food products**	181 220	2.06	11.85	4 434 100	2.22	13.44	0.9
	Food manufactured using large enzyme quantities	**69 927**	**0.8**	**4.57**	**1 375 400**	**0.69**	**4.17**	**1.2**
	Total sectors	212 914	2.42	13.93	4 804 400	2.40	14.56	1.0
	Total indirect impacts	76 243	0.87	4.98	1 487 405	0.74	4.51	1.2
Total sectors		**220 819**	**2.51**	**14.42**	**4 921 600**	**2.46**	**14.91**	**1.0**
Total modern biotechnology contribution		**76 984**	**0.88**	**5.03**	**1 493 405**	**0.75**	**4.53**	**1.2**

*Estimate; **2003 data; ***Detergents calculated with enzymes share = 50%; ****2005 data, only direct employment counted

3 Contribution of modern biotechnology to environment and energy

3.1 General outline and overall contribution of modern biotechnology

Regarding 'environment and energy', relevant EU policies are described in the following documents: the Sustainable Development Strategy[301], the 6th Environmental Action Programme[302], the Environmental Technology Action Plan[303], the Green Paper on energy supply[304], and are considered in the Common Agricultural Policy as well as the Common Fisheries Policy[305].

The policy objectives that were derived from these sources are: i) improved resource productivity, ii) better waste prevention, iii) improved air, soil and water quality, iv) better preservation of biodiversity, v) reduction of greenhouse gas emissions and vi) improved energy supply security (see Annex 1 – Methodology).

The contributions of modern biotechnology to these policy objectives differ widely between the individual application areas. The more obvious contributions of modern biotechnology relate to improvements in *resource productivity* and reductions of *greenhouse gas emissions*: increasing production efficiency and reducing input use has been a main objective of technical innovations both in primary and in industrial production, and replacing fossil fuels by bio-ethanol can also reduce the emission of greenhouse gas in the EU. At the same time, diversifying the energy portfolio with the help of renewable energy sources such as bioethanol could also improve *energy supply security*. In primary production, improvements in resource productivity assisted by modern biotechnology are also linked to improvements in nutrient or other harmful substance emissions, mainly by lowering the relevant emissions per unit output. Moreover, direct impacts have been realised, such as the replacement of drug and antibiotic treatments, with the use of vaccines in animal production, many of which are produced using modern biotechnology. Furthermore, modern biotechnology supported the reduction of harmful emissions due to the use of improved crop varieties or biotechnology-based feed additives. In industrial production, modern biotechnology also leads to reduced waste generation and less water usage. Together with reduced emissions, this can be expected to improve *air, soil and water quality*. Regarding the *preservation of biodiversity*, concerns have been raised about potential risks from the cultivation of genetically modified organisms (GMO), which requires a case-by-case evaluation. To this end, the EU has put in place

[301] European Commission COM (2001) 264 final: Communication from the Commission A Sustainable Europe for a Better World: A European Union Strategy for Sustainable Development. http://europa.eu/eur-lex/en/com/cnc/2001/com2001_0264en01.pdf; *AND*: Council of the European Union (2006) DOC 10917/06: Renewed EU Sustainable Development Strategy. http://register.consilium.europa.eu/pdf/en/06/st10/st10917.en06.pdf.

[302] 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. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2001:0031:FIN:EN:PDF

[303] 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. http://ec.europa.eu/environment/etap/pdfs/com_2004_etap_en.pdf

[304] European Commission COM (2006) 105: Green Paper A European Strategy for Sustainable, Competitive and Secure Energy. http://ec.europa.eu/energy/green-paper-energy/doc/2006_03_08_gp_document_en.pdf.

[305] European Commission (2007). Common Agricultural Policy: http://ec.europa.eu/agriculture/index_en.htm; About the Common Fisheries Policy. http://ec.europa.eu/fisheries/.

specific legislation making obligatory the carrying out of comprehensive risk assessments before placing such products on the EU market.

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, strengthen its role in assisting in the decoupling between economic growth and environmental pressures.

3.2 Human and animal health biotechnology

Biotechnology-based products used for the treatment (or diagnosis) of humans or animals may have a potential impact on the environment as a result of their use and/or manufacturing. Although direct evidence for this has been scarce, it is often thought that the production of medicinal products using biotechnological approaches (e.g. recombinant DNA technology) might have fewer negative consequences on the environment than previous methods. One example to this end could be the production of recombinant human insulin, which replaced the extraction of insulin from animal pancreases. Although there are no specific data on the environmental consequences of the animal pancreas extraction process, it is likely to have had significant environmental impacts as it involved extraction of insulin from large quantities of imported animal pancreases and required the disposal of a large residue of biological matter.

The potential environmental impact of biotechnology-based products has been recognised by regulatory authorities. In the EU, Directive 2001/83/EC[306] 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 being given marketing authorisation. The Directive also requires that specific arrangements to limit impacts are considered. In this context, the European Medicines Agency (EMEA) has recently published guidelines on the environmental risk assessment of medicinal products for human use[307] which focus on the potential risks arising from the use of the products and not from their manufacturing. Another EMEA guideline also addresses the environmental risk assessment of products containing or consisting of genetically modified organisms[308], based on the requirement of pharmaceutical legislation (Regulation EC/726/2004[309]) that human medicinal products respect the environmental safety requirements foreseen in Directive 2001/18/EC[310] on the deliberate release into the environment of genetically modified organisms. At the same time ERAPharm, a programme funded by the EU Research Framework Programme 6 and aiming at improving the scientific basis and the methods for evaluating potential risks that pharmaceuticals pose to the environment, is expected to finalise its results and provide relevant recommendations in 2007[311].

In addition to biopharmaceuticals, biotechnology is applied to the development of non-biotechnology drugs, e.g. small molecules or fine chemicals. The share of biotechnology processes related to chemical processes is estimated to be between 10% and 15%. Their

[306] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. OJ L 311, 28/11/2004, p. 67-128. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/consol_2004/human_code.pdf.

[307] Committee for Medicinal Products for Human Use (2006). Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00. European Medicines Agency, London. http://emea.europa.eu/pdfs/human/swp/444700en.pdf.

[308] Committee for Medicinal Products for Human Use (2005). Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs). European Medicines Agency, London. http://emea.europa.eu/pdfs/human/bwp/13514804en.pdf.

[309] Regulation (EC) No 726/2004 of the European Parliament and of 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. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf.

[310] Directive 2001/18/EC of the European Parliament and of 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, 17.4.2001, p. 1. http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_106/l_10620010417en00010038.pdf.

[311] Internet: http://www.erapharm.org/.

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, reducing emissions of other pollutants to water, air and soil, and reducing waste generation. One example illustrating this point is the production of cephalosporin, discussed in Section 3.4.3.5.

3.3 Agro-food biotechnology

3.3.1 The relevance of primary production and agro-food to environment and energy

The agro-food sector interacts in a variety of ways with the environment. Section 2.3.3 provides a detailed description of the sector as well as of the use of modern biotechnology within the sector. Therefore, this section will only address the energy and environment relevant issues.

The agro-food sector, in life cycle terms, has been identified as being one of the major contributors to environmental pressures in the EU, of which animal products account for a significant share[312,313]. For a comprehensive evaluation of the environmental implications of the agro-food sector, the complete life cycle of the supply chain needs to be taken into account (see Figure 27). Previously conducted life cycle assessments in agro-food have indicated that the largest share of environmental pressure is associated with the primary production phase. Moreover, as indicated in Section 2.3, modern biotechnology is mainly relevant in two phases of the agro-food supply chain:

- the primary production stage, which includes agriculture and fisheries activities
- the industrial manufacturing stage, which includes the production of inputs as well as the downstream processing of products from the primary production sector.

The environmental issues of the agro-food related manufacturing activities (i.e. enzyme production and use, e.g. for feed additive production and food processing) are common to those covered in Section 3.4 on industrial biotechnology and will be presented there.

At the primary production phase, the agricultural sector (including animal production) is a major source of environmental pressure as farmers manage more than half of the EU land area[314]. Agricultural activities are relevant for a range of environmental concerns[315], the main ones being the pollution of surface waters and seas by nutrients and pathogens, the pollution of groundwater by nitrate and pesticides, the loss of biodiversity through habitat degradation and ultimately the loss of species, the pollution of air through greenhouse gases and other air pollutants that contribute to climate change and acidification, and the over-abstraction of water for irrigation. Agriculture (at the farm stage) is a major contributor to all of the above environmental pressures, but to a lesser extent for the emission of greenhouse gases and the use of energy and the emission of tropospheric ozone precursors: it is responsible for about 10% of greenhouse gas emissions and less than 5% for use of energy and ozone precursors.

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[312] A. Tukker, G. Huppes, J. Guinée, R. Heijungs, A. de Koning, L. van Oers, S. Suh, T. Geerken, M. Van Holderbeke, B. Jansen, P. Nielsen. Editors: P. Eder and Delgado L. (2006). Environmental Impact of Products (EIPRO) - Analysis of the life cycle environmental impacts related to the final consumption of the EU-25. European Commission, IPTS, EUR 22284. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1429.

[313] Steinfeld, H. et al. (2006). Livestock's long shadow: environmental issues and options. Food and Agriculture Organisation, Rome. http://www.virtualcentre.org/en/library/key_pub/longshad/A0701E00.pdf.

[314] EEA (2006), Land accounts for Europe 1990 – 2000: Towards integrated land and ecosystem accounting, EEA Report No 11/2006. http://reports.eea.europa.eu/eea_report_2006_11/en/eea_report_11_2006.pdf.

[315] EEA (2006), Integration of environment into EU agriculture policy — the IRENA indicator-based assessment report. EEA Report No 2/2006. http://reports.eea.europa.eu/eea_report_2006_2/en/IRENA-assess-final-web-060306.pdf.

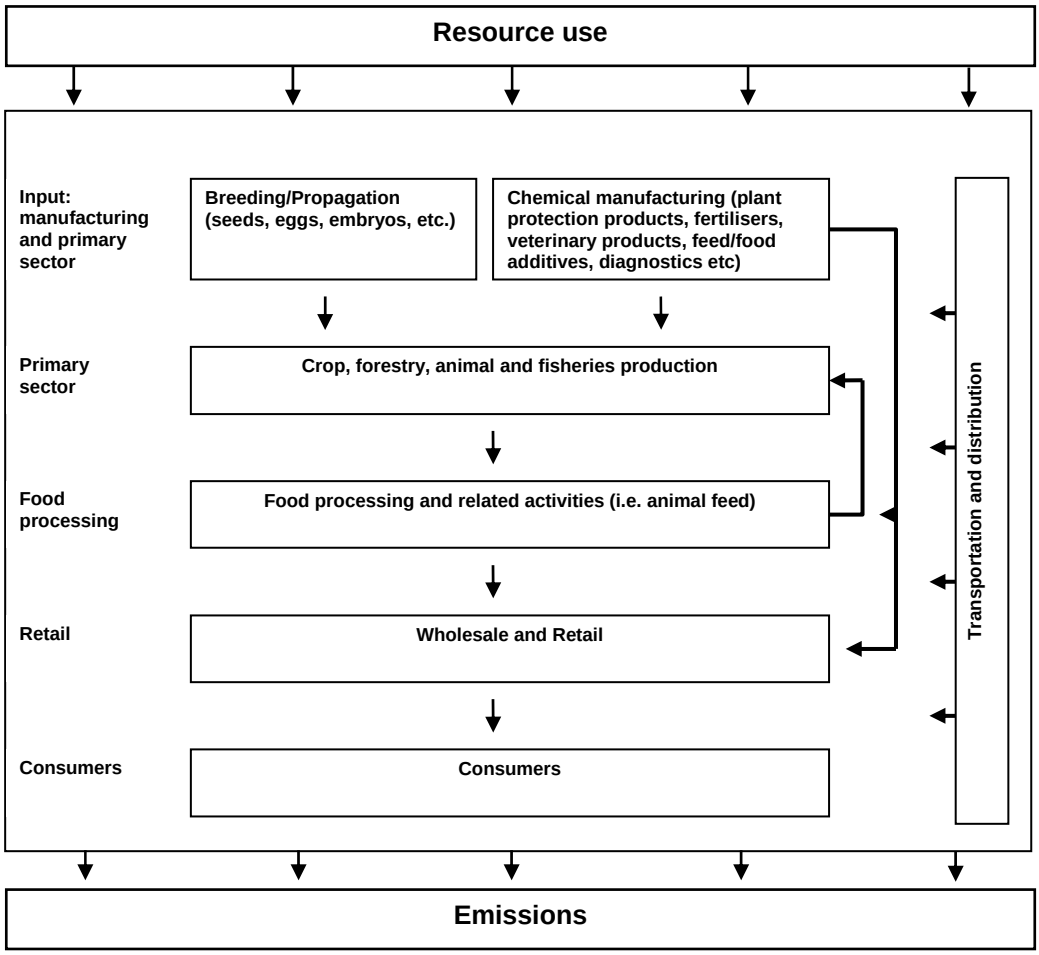


Figure 27: The life cycle of the agro-food supply chain

As far as the fishery sector is concerned for harvest fisheries, the main environmental issue is related to biodiversity loss through overfishing, while for aquaculture, the concerns are similar to those encountered in agriculture, but to a lesser extent in absolute terms, as the sector itself is considerably smaller. Fish farming may, however, be an important contributor to environmental pressure at a local scale, such as regarding nutrient emissions to the aquatic environment. Moreover, fish farming has some additional environmental concerns that are specific to the sector, such as the transfer of pathogens and potential genetic impacts to wild fish populations.

The likely developments of environmental pressure from economic activities of the primary sector depend on two main factors: 1) the level of activity and 2) its eco-efficiency (i.e. the environmental impact per unit output). It is, therefore, the interaction between these two factors that will determine the final outcome. For the agricultural sector, data from the European Environment Agency (EEA) for the period 1990 - 1998 indicate that while the GVA increased by 5%, so did the eco-efficiency of agriculture, resulting in absolute decoupling between acidifying substances and ozone precursors[316]. While there was also an improvement in the eco-efficiency for energy use and related greenhouse gas emissions, the use of energy, water and irrigated land, as well as of fertilisers and pesticides was comparatively stable in absolute terms (see Figure 28). Overall, in the 1990s there was a

[316]EEA (2005). The European environment - state and outlook 2005. EEA Report No 1/2005. http://reports.eea.europa.eu/ state_of_environment_report_2005_1/en/SOER2005_all.pdf.

limited improvement in the eco-efficiency of the agricultural sector, when compared with the energy and industry sectors.

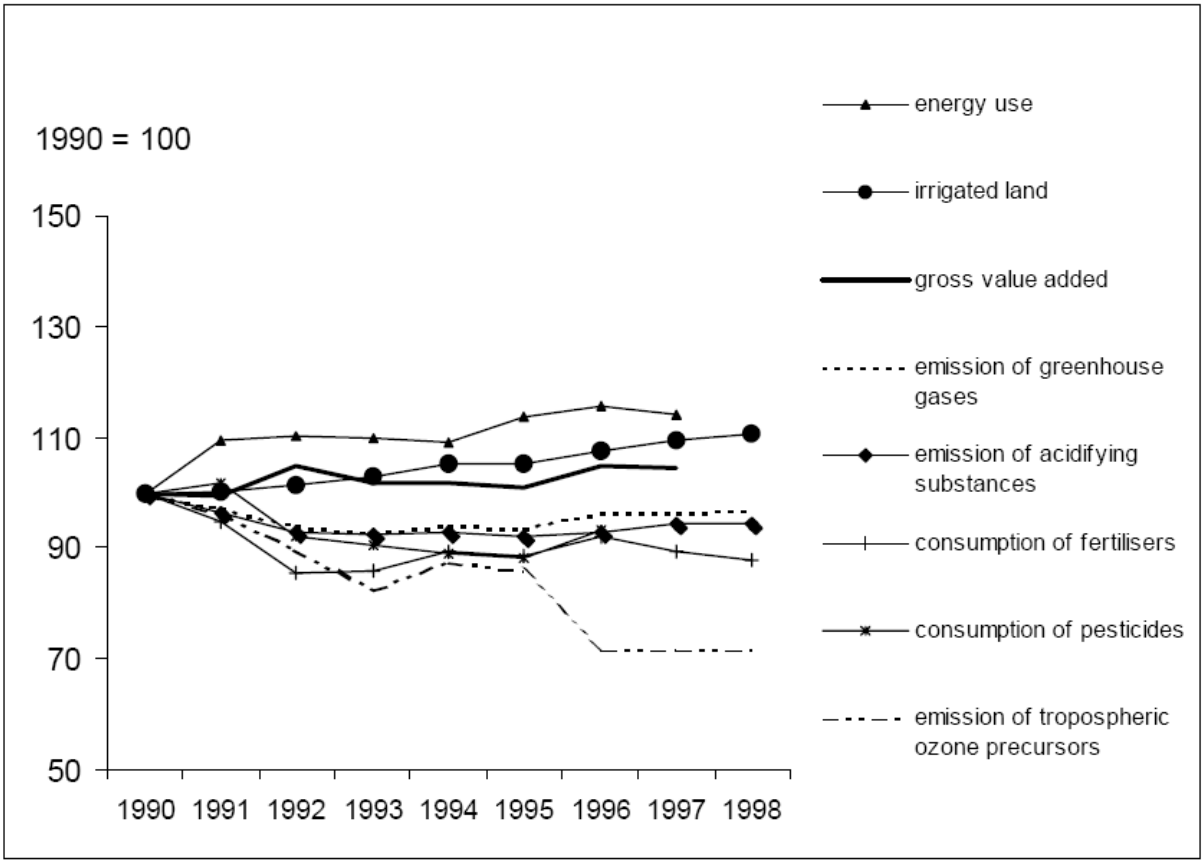
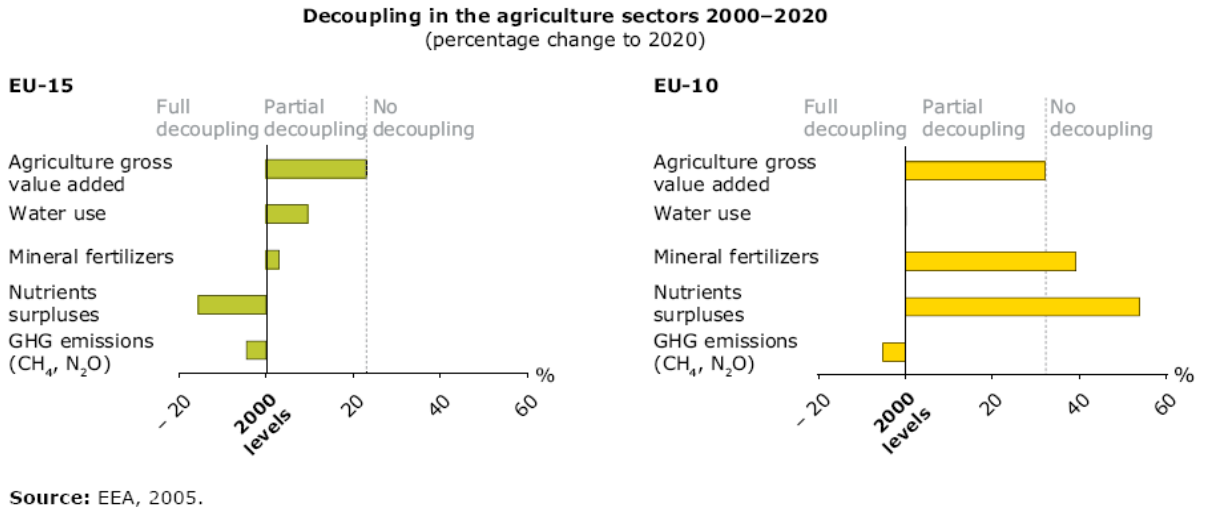


Figure 28: Eco-efficiency of agriculture in the EU
Source EEA[316]

Recent trends and forecasts show some decoupling of the agricultural economic activity from some environmental pressures (see Figure 29).

Of interest in primary production is the discussion surrounding the levels of intensity of different production systems. Nevertheless, improvements in eco-efficiency may take place in both intensive and extensive (such as the so-called High Nature Value farmland, HNV) systems, and may involve improvements in all environmental issues, such as in resource use as well as in emissions of harmful substances. While biodiversity of wild fauna and flora is, in general, higher in HNV farmland when compared with the intensive system type, and several national livestock breeds are better fit to specific HNV farmlands, they are in general not competitive in the global market, and therefore, specific targets have been set towards the conservation of HNV farmland through agri-environmental measures under the EU's Common Agricultural Policy.

In general, R&D has been important for the introduction of technological innovations that have improved resource productivity, and environmental pressure. Other factors, such as sector structural changes, have however also been important.



Source: EEA, 2005.

Figure 29: Decoupling in the agriculture sectors 2000 and 2010 - outlook for key environmental resources and pressures
Source EEA[317]

Besides the core generic environmental indicators that are used in global comparisons, there are other issues of a more specific nature, which may have important environmental implications because e.g. being related to higher and/or more immediate potential risks, of high uncertainties regarding potential risks, of a high local relevance. These issues may be relevant only in specific sectors/applications/environments which renders their full coverage and analysis in this study difficult. Such issues will be mentioned, however, wherever they are of relevance to modern biotechnology in the following sections.

3.3.2 The contribution of agro-food biotechnology

The application of modern biotechnology may have diverse effects on the environmental performance of the agro-food sector. This analysis follows the same structure as in Section 2.3, in the sense that it looks at both direct and indirect impacts. Direct impacts relate to the activities using modern biotechnology whereas indirect impacts relate to the activities using biotechnology-derived products. As described in Section 2.3, the first are to be found almost exclusively with the providers of inputs to primary production and food processing, which mainly comprise manufacturing and breeding activities. Therefore, the direct environmental impacts are relevant for the activities of these subsectors, while the indirect environmental impacts are related to the activities of biotechnology product users, mainly in the farming and food processing sectors.

3.3.2.1 Breeding and propagation

The environmental effects of modern biotechnology applications in breeding and propagation are relevant almost entirely at the level of farming (i.e. indirect impacts). Firstly, the

[317] EEA (2005). The European environment - state and outlook 2005. EEA Report No 1/2005. http://reports.eea.europa.eu/state_of_environment_report_2005_1/en/SOER2005_all.pdf.

production of biotechnology products, e.g. seeds and other propagating material, embryos, eggs and fry, breeders, does not really involve major qualitative differences in environmental terms compared to the grow-out phases; and secondly, the environmental exchanges during the production of biotechnology products, take place on a much smaller scale compared to the grow-out phases (i.e. in number of inputs used, output produced, etc.).

This analysis will, therefore, concentrate on environmental implications at the farm-level. As potential changes in the environmental effects depend more and more on the specific technology rather than the sector to which it is applied, the analysis is structured by technology. Where additional issues specific to different users arise, these are discussed accordingly.

The major breeding and propagation goals is to drive genetic selection, which has been traditionally aimed at improving agronomic traits, such as yield, efficiency, and resistance to various stress factors, and is now more and more aimed at more complex traits, such as product quality traits and disease resistance. While it is not possible to provide an exhaustive analysis of the change in the environmental performance of all production systems for all selection schemes, in general, genetic improvements have led, directly or indirectly, to improvements in productivity and/or efficiency over the years for all species of agricultural relevance (plants, animals and fish).

As a general rule, and as discussed above, technical change and innovation has had either a neutral or a positive effect on eco-efficiency while the level of economic activity in the various subsectors has been stable or increasing. Genetic selection has been considered an important driver of productivity improvements, but it is not the sole factor. Nevertheless, an important share of the improvements in resource productivity is also ascribed to genetic selection.

3.3.2.1.1 Marker assisted selection (MAS)

MAS is applied in a similar way to plants, livestock and fish, i.e. with the aim to aid in the selection of desirable traits, either directly or indirectly. When MAS is applied successfully, it results in improving the selection and introgression of desirable traits to the commercial populations, facilitating therefore conventional breeding schemes. Qualitatively, the impacts to be expected are similar to the ones taking place through conventional selection; an exception to this rule concerns the selection for traits that, until now, were not amenable to conventional techniques, such as disease resistance and product quality related traits (mainly multigene determined traits). The environmental implications of MAS will vary qualitatively, depending on the trait that is being targeted, and quantitatively, depending on the obtained difference in the targeted trait and the level of adoption of the technology. Currently, there is no comprehensive information on the specific traits that have been targeted through the use of MAS, but it is reasonable to assume that MAS has been used for a few important single nucleotide polymorphism (SNP) determined traits and, to a lesser extent, for the more complex approach through quantitative trait loci. In addition, molecular markers have been used more extensively in all types of breeding schemes for the determination of kinship, indirectly supporting breeding schemes, etc. (see Section 2.3.5.1)

For example, the case study on MAS in pigs[318] provided an overview of the major known traits targeted through MAS, none of which were of a direct environmental relevance. In general, there are no examples of the use of MAS providing direct benefits or harms to the environment, but the indirect impact may be considerable. An example is the improvement of the growth rate and food conversion ratio (using both traditional genetics or those supported through MAS), which reduces the amount of feed required to produce one kg of meat as well as the amount of emissions per unit output. In another example[318], the use of MAS to support genetic selection for improving the reproductive rate may reduce the amount of pollution arising from maintaining the breeding animals, through reducing the number of breeding animals that are required to be maintained in order to produce a slaughter generation animal.

As with plants and livestock, the environmental implications of using MAS 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. In absolute terms, however, the impacts are likely to be smaller, as the technology has, until now, been used to a lesser extent in fish farming compared to the other sectors. As far as ploidy and sex manipulation are concerned, expert opinion suggested positive implications due to the adoption of the technology, related to improved production efficiencies, and the reduced need for chemical treatment following a decrease of secondary infections caused by aggressiveness and stress[318].

The use of modern biotechnology in genetic selection schemes has been criticised to negatively affect the genetic diversity of the farmed populations (mainly through reducing the available gene pool); however, this is rather a general feature of mainstream agricultural practices, whose main goal has been the optimisation of the gene pool in terms of production objectives. Modern biotechnology also provides the tools for optimising the impacts on genetic diversity, e.g. through supporting the proper design of breeding schemes, as well as for mapping genetic diversity and aiding plans for breed/variety conservation and monitoring. In this context, the use of molecular information is also fundamental for improving the germplasm resources and therefore for the maintenance of the EU's biodiversity. Modern biotechnology provides several tools, while it is the proper use and management of the tool, in combination with other factors that determine what the impacts will be.

From the above, a qualitative estimate can be made that MAS, where applied, has mainly either a neutral or a beneficial impact on the eco-efficiency of the primary sector. While a negative effect cannot be ruled out, such as in situations where the selection of an important trait indirectly affects the resource efficiency, it is highly unlikely as resource efficiency also has important economic considerations.

3.3.2.1.2 Genetically modified crops

Any innovation that results in changing crop management may have an impact on the environment. There is scientific consensus that the impact of the introduction of genetically modified (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 (herbicide tolerance, insect resistance, etc.)[319].

[318] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.
[319] FAO (2004). The State of Food and Agriculture, 2003 - 2004. Food and Agriculture Organisation, Rome. http://www.fao.org/docrep/006/Y5160E/Y5160E00.HTM.

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 from Spain on changes in the use of insecticides due to Bt maize cultivation[320] show that 42% of conventional maize growers versus 70% of Bt maize growers do not use insecticides at all for controlling corn borers. Moreover, 21% of conventional maize farmers versus 2% of Bt maize growers give two or more treatments per year. On average, conventional maize growers applied 0.86 insecticide treatments/year compared with 0.32 treatments/year of Bt maize growers. This reduction is modest in absolute terms, because the conventional way of maize borer control (replaced through Bt maize) is not based on heavy insecticide use due to its limited efficacy.

Regarding the impacts on non-target organisms and the development of resistant pest populations, no detrimental effect of farm scale Bt maize cultivation in Spain has been observed on the activity and abundance of non-target arthropods, according to research commissioned by the Spanish Ministry for the Environment and performed by public institutions[321]. Data released after five years of commercial Bt maize plantings (1998 - 2003 period) did not show an increase in Bt-toxin resistance for corn borer populations sampled in Spain. However, the researchers argue for the need to maintain the systematic monitoring activity for longer periods. It should also be mentioned that any GM product currently available for growing in the EU needs to go through an obligatory risk assessment, including an environmental risk assessment.

3.3.2.1.3 Micropropagation

Micropropagation has rather marginal environmental implications compared to MAS 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[322]: 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 water, fertiliser and pesticides used; iii) micropropagation techniques can ensure that propagating material is disease-free, reducing pathogen transfer.

3.3.2.1.4 Embryo transfer (ET)

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 based on assisting the rapid and cost-effective dissemination of improved resource productivity based on genetic improvements. For example, the number of cattle in the EU is declining whilst output is steady or increasing. This is particularly obvious for milk production, which

[320] Gómez-Barbero, M., J. Berbel and Rodríguez-Cerezo E. (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.)
[321] De la Poza, M., et al. (2005). Crop Protection, 24: 677-684. http://dx.doi.org/10.1016/j.cropro.2004.12.003.
[322] ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications.

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%[323]. Embryo transfer combined with embryo freezing provides a very effective means of conserving biodiversity where breeds are under threat (it is more efficient for the recovery of a breed than frozen semen as semen only provides a hybrid in the first instance and it is then necessary to go through rounds of backcrossing to recover the lost breed) or for salvaging a population, for example, when eradication is required for disease control purposes (e.g. to control foot and mouth disease outbreaks)[324].

3.3.2.2 Feed additives and veterinary products[325]

Feed additives (whether biotechnology-based or not) in general optimise nutrient utilisation, thereby resulting in improvements of the environmental performance of animal production. Some feed additives have a direct environmental objective, such as some of the feed enzymes. Phytase addition, for example, is aimed towards the reduction of phosphorus emissions in pig and poultry production. On the other hand, many feed additives induce indirect environmental benefits by optimising nutrient metabolism and utilisation, such as the case of the amino acid lysine, which by optimising nitrogen metabolism, results in the reduction of nitrogen excretion in pig production[326]. Moreover, as the addition of lysine to pig feeds is associated with a concomitant replacement of soya beans by wheat or maize, and as the area needed to grow soya beans is larger than the respective area for maize or wheat, the use of lysine may also result in a considerable reduction of the agricultural area needed per unit output[327]. In general, as low protein and low phosphorus diets are increasingly used in animal production, partly due to stricter restrictions in environmental regulations, the use of such feed additives is gaining in importance.

The environmental implications of modern biotechnology applied in the production of animal health products are in general positive: firstly, there is a general trend towards prevention (vaccination and other immuno-stimulation methods, most of which are increasingly biotechnology-based) which leads to a decrease in the use of chemical treatments (e.g. antibiotics). A decrease in the use of antibiotics will reduce the occurrence of microbial resistance to antibiotics, while marker-vaccines are more effective in eradication programmes therefore reducing the number of animals that need to be culled. Moreover, the prevention of disease and the subsequent disease eradication inherently implies improvements in production efficiency associated with a healthy stock.

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[323] Table 4.1 in: Liinamo, A.-E. and Neeteson-van Nieuwenhoven A. (2003). Economic value of livestock production in the EU – 2003. Farm Animal Industrial Platform, Oosterbeek. http://www.effab.org/publications/effab-publications/doc_details/55-economic-value-of-livestock-production-in-the-eu-2003.

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

[325] The environmental implications at the manufacturing stage can be found in Section 3.4.

[326] Gâtel, F. and Porcheron E. (2003). The role of cereals in the European protein supply. In: Protein requirements and supply for a competitive European pig production in 2010: protein supply for European pigs 2010. Proceedings of a European Workshop, March 18, Brussels. Fefana, Brussels, p. 23-27. http://www.fefana.org/Publications.aspx.

[327] Toride, Y. (2002). Lysine and other amino acids for feed: production and contribution to protein utilisation in animal feeding. In: Protein sources for the animal feed industry: FAO Expert Consultation and Workshop, 29 April - 3 May, Bangkok. Food and Agriculture Organisation, Rome, p. 161-166. http://www.fao.org/docrep/007/y5019e/y5019e00.htm.

3.3.2.3 Modern biotechnology-based 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. S*almonella*) 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.

3.3.3 Summary

Food consumption is an important driver of major environmental pressures. Agro-food related modern biotechnology has environmental implications mainly for two stages of the agro-food chain, namely the primary production and manufacturing of input and food processing. The use of modern biotechnology in the manufacturing stage is, in general, beneficial for the environment as it is characterised by improvements in resource efficiency and related emissions (for more details see Section 3.4). However, it is the primary production stage that is considered to be the most important contributor for most of the relevant environmental pressures. Generally speaking, the adoption of modern biotechnology indirectly has positive environmental implications in primary production, as increased production efficiency has been a main target of technical innovations, and as a decoupling between economic growth and environmental pressures has been, at least partially, demonstrated. More direct impacts have also been realised, such as the reduction of drug and antibiotic treatments in animal production, partially enabled through the use of (recombinant) vaccines, or the reduction of harmful emissions through the use of modern biotechnology derived feed additives.

It should be stressed, however, that some modern biotechnology applications may also raise new challenges, requiring a case-by-case evaluation of specific aspects or potential risks. To this end, the EU has put in place specific legislation making obligatory the carrying out of comprehensive risk assessments before placing such products on the EU market.

In terms of overall environmental pressure, the EU primary production sector has been witnessing a relative stabilisation and/or decrease of farm-level economic activities in recent years, while technical efficiency has been improving[328]. Moreover, for some specific sectors, growth rates are still positive or are expected to increase even further in the near future (e.g. for the production of energy crops). The challenge for modern biotechnology will therefore be to provide the tools towards further improving resource productivity and aiding in the decoupling of economic growth from environmental pressures.

[328] 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.

3.4 Industrial biotechnology

Industrial biotechnology has impacts on resource and energy use, greenhouse gas (GHG) emissions, emissions of other pollutants to water, air and soil, and on the generation of waste. In the analysis of environmental impacts of industrial biotechnology, those sectors in the manufacturing sector (according to NACE) are looked at in which industrial biotechnology is applied. The key parameter in the analysis is the contribution to GHG emissions, and, related to that, the impact on energy use. In the majority of cases analysed here, the main part of carbon dioxide (CO_2) emissions stems from the energy used for industrial processes. Therefore a replacement of chemical processes with biotechnological ones usually reduces emissions directly in the process and through the reduced energy demand. Furthermore, the impact on water use and emission of pollutants to different environmental media is analysed. Where possible, the environmental impact of manufacturing using enzymes will be compared with the respective benchmark sector which does not use enzymes.

3.4.1 Overview of anthropogenic greenhouse gas emissions

When looking at the environmental impact of modern biotechnology in industrial manufacturing processes, the effect on GHG emissions is one of the key elements in the analysis for various reasons: climate change is amongst the environmental challenges with a high priority, GHG emissions are a EU-wide problem (with global repercussions), and the emissions are produced directly through industrial processes and indirectly through industrial fuel combustion, i.e. the energy generated for these industrial processes. From the opposite perspective this means that an alternative (biotechnological) production process can potentially affect GHG emissions at the source in industrial processes and through a changed industrial energy demand.

Figure 30 shows the distribution of anthropogenic GHG emissions in the EU for 2004. CO_2, methane (CH_4) and nitrous oxide (N_2O) are the three most important GHGs. CO_2 with 83% is by far the largest contributor; CH_4 and N_2O contribute with 7.5% and 8% respectively. The remaining 1.5% is generated by hydrofluorocarbons (HFCs), perfluorocarbons (PFCs) and sulphur hexafluoride (SF_6). Overall, industrial processes generate directly 8% of GHG emissions, and another 13% through industrial combustion. Transport contributes with 21% to overall GHG emissions in the EU. More than 90% of transport related emissions are generated by the combustion of road transport fuels (two thirds diesel and one third petrol combustion).

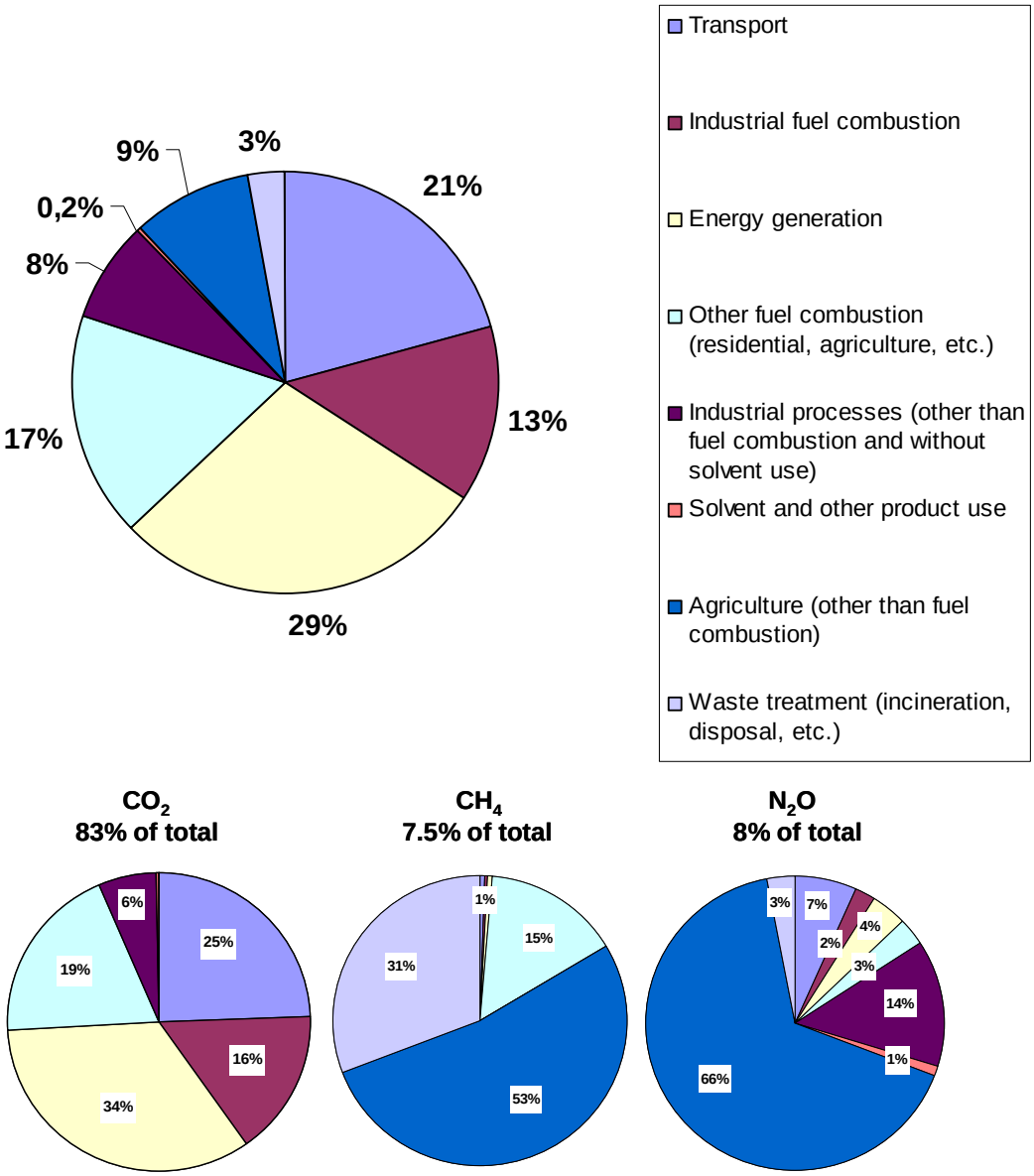

Figure 30: Anthropogenic greenhouse gas emissions by sectors in the EU (2004)[329]
CO_2, CH_4, N_2O, HFC, PFC, SF_6; all measured in CO_2 equivalent; HFC, PFC, SF_6 together contribute around 1.5% to overall GHG emissions, not shown.

A look at the individual GHG emissions shows that the major contributors to CO_2 emissions are transport, energy generation and industry (see Figure 30). CH_4 is generated mainly by agriculture, waste treatment and energy generation. The main N_2O emission contributors are agriculture and industrial processes. The remaining 1.5%, composed of HFCs, PFCs and SF_6 are generated mainly by industry.

[329] Calculated on the basis of the progress report of the EU to the IPCC, submission 2006, in: EEA (2006). The European Community's initial report under the Climate Change Protocol, Annex 2. European Environment Agency, Copenhagen. http://reports.eea.europa.eu/technical_report_2006_10/en/index_html.

3.4.2 Greenhouse gas emissions of the manufacturing sector

In Section 2.4 on economic impacts of industrial biotechnology, NACE categories have been identified, in which industrial biotechnology is applied. NACE categories are used for consistency and comparability, but the actual Eurostat information, which served as a framework for the economic analysis, provides no information on environmental impacts. The main industrial biotechnology applications can be found in the following sectors (for details see Section 2.4.1):

- NACE DA 15: Manufacture of food products, beverages
- NACE DB 17 Manufacture of textile and textile products
- NACE DB 18: Manufacture of apparel; dressing and dyeing of fur
- NACE DC 19: Manufacture of leather and leather products
- NACE DE 21: Manufacture of pulp, paper and paper products
- NACE DG 24: Manufacture of chemicals, chemical products and man-made fibres

This list is not exhaustive. Enzymes are used in other industrial sectors as well, such as mining (bioleaching), but these applications are applied to such a limited extent that they are not relevant when analysing the environmental impact of industrial biotechnology in the EU.

In the context of this analysis it is of interest to know which of the above listed manufacturing sectors are the strongest contributors to CO_2, CH_4 and N_2O emissions. Eurostat provides very scattered data on GHG emissions by industrial sector. The GHG emission contributions of the individual NACE categories can only be derived on the basis of 2001 data for four countries (Denmark, Germany, Italy and the UK)[330] (see below).

Carbon dioxide

As can be seen in Figure 30, industrial processes directly contribute 6% to CO_2 emissions, and indirectly an additional 16% through industrial fuel combustion, i.e. the generation of energy used for these processes. Together this represents a share of 22%. The contribution of the individual industrial sectors to these emissions is shown in Figure 31.

The following sectors are the manufacturing sectors which emit the most CO_2 and apply industrial biotechnology:

- chemicals:12%
- food, beverages, tobacco: 7%
- pulp and paper: 6%
- textiles: 2%
- leather: < 1%

Together these sectors emit about 27% of the CO_2 emissions of the manufacturing sector, i.e. emissions on which industrial biotechnology might impact. These figures only relate to immobile emission sources. The mobile sources have to be included, i.e. transport fuels, which make 25% of all CO_2 emissions and thereby represent one of the largest contributors.

[330] Data from Eurostat (http://epp.eurostat.ec.europa.eu/). For detailed values, see Annex 4. It is assumed that the GHG emission distribution of these four countries can be extrapolated to the EU as a whole.

The transport sector's impact on CO_2 emissions is affected by industrial biotechnology because of the application of bioethanol.

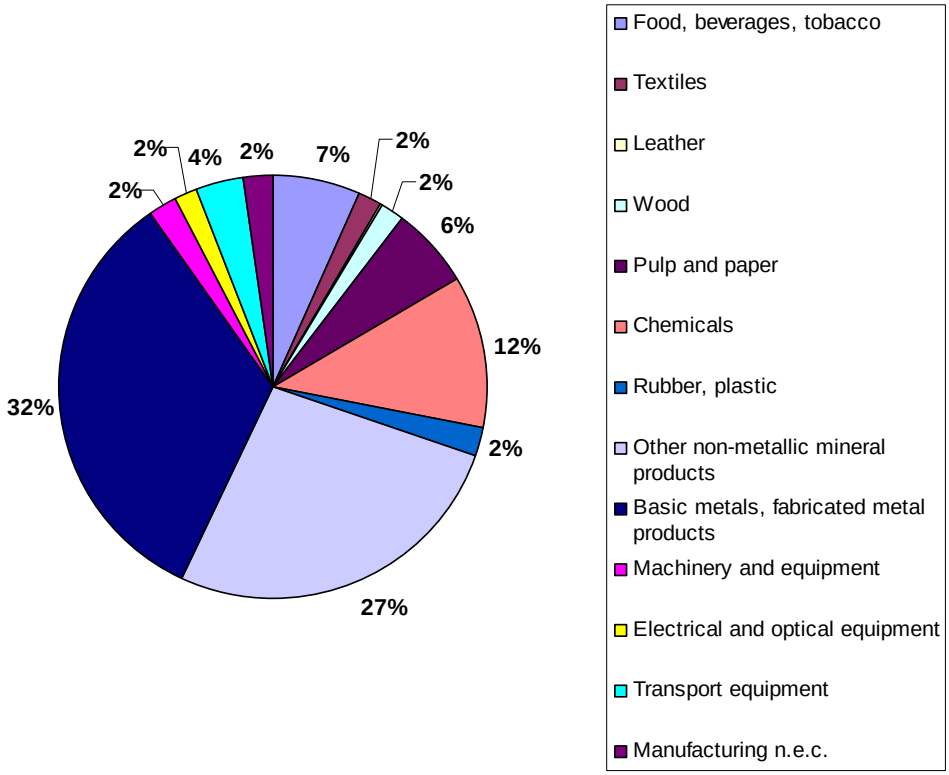

Figure 31: Contribution of NACE manufacturing sectors to CO_2 emissions
Source: data from Eurostat[331], IPTS calculations; n.e.c.: not elsewhere classified

As can be seen in Figure 30, industrial processes directly account for 6% of CO_2 emissions. Under the assumption that modern biotechnology is applied in sectors responsible for 27% of CO_2 emissions of the manufacturing sector, it shows that modern biotechnology could influence about 1.6% of CO_2 emissions[332]. As one central characteristic of enzymatic processes in industry is the reduction of energy use, the CO_2 emissions from industrial fuel combustion could be reduced as well, although this effect is difficult to quantify, as the main industrial sectors demanding energy (metal and steel, non-metallic mineral products) do not apply industrial biotechnology.

Methane

In the case of CH_4 emissions, the contributions of those manufacturing sectors in which industrial biotechnology is applied are:

- food, beverages, tobacco: 34%
- chemicals: 30%
- textiles: 4%
- pulp and paper: 2%

[331] Eurostat data from the online database. http://epp.eurostat.ec.europa.eu/.
[332] Considering the share of CO_2 emissions of the manufacturing sector out of the overall GHG emissions (5%) and based on the 27% share that modern biotechnology applying sectors have in these CO_2 emissions, modern biotechnology could influence about 1.3% of the overall GHG emissions.

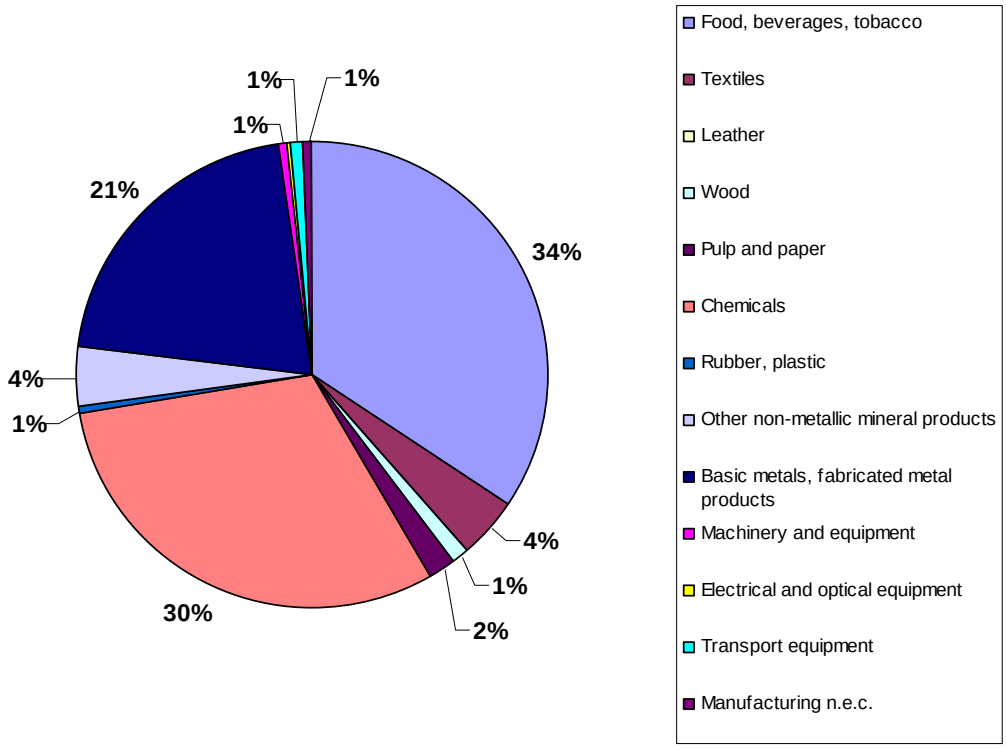

Figure 32: Contribution of NACE manufacturing sectors to methane emissions
Source: Data from Eurostat[333], IPTS calculations; n.e.c.: not elsewhere classified

This totals 70% of the CH_4 emissions of the manufacturing sector. However, as can be seen in Figure 30, industrial processes have a negligible contribution to methane emissions. Most of the emissions are caused by agriculture and waste disposal. Therefore CH_4 emissions will not be taken into further account in this analysis.

Nitrous oxide

Figure 30 shows that N_2O emissions account for 8% of total GHG emissions. Most of this is generated by agriculture, industrial processes contribute 14%. This share is mainly generated by chemicals, representing a share of 87% of manufacturing N_2O emissions (Figure 33).

[333] Eurostat data from the online database. http://epp.eurostat.ec.europa.eu/.

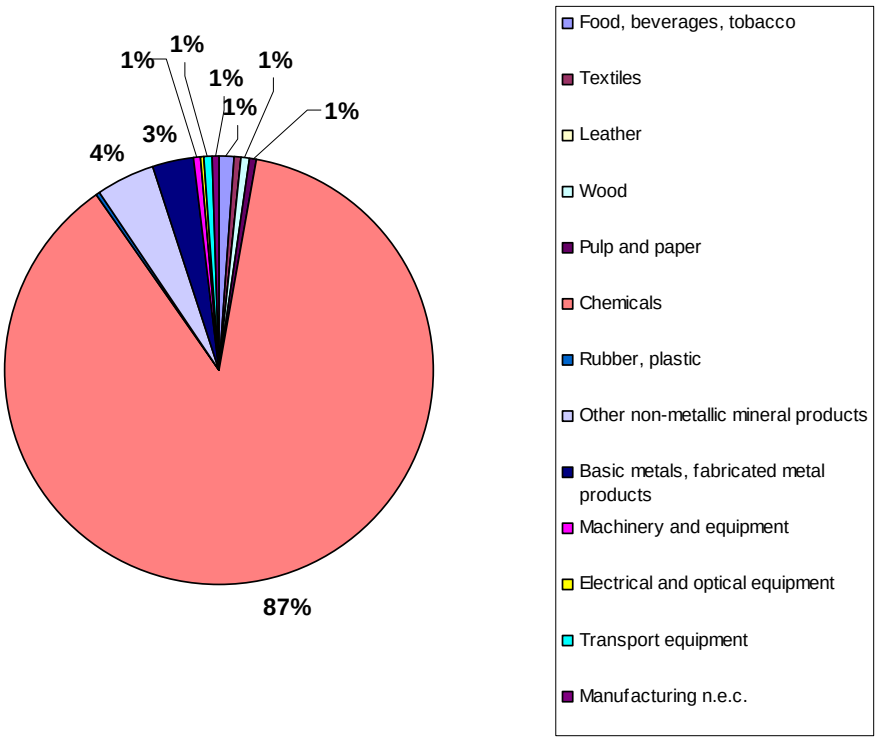

Figure 33: Contribution of NACE Manufacturing sectors to nitrous oxide emissions
Source: Data from Eurostat[334], IPTS calculation; n.e.c.: not elsewhere classified

Summarising the above information, it can be concluded that industrial processes in general (with and without enzymatic processes) only contribute to a limited extent to overall GHG emissions (8%, see Figure 30). These emissions consist of CO_2 emissions (5%), N_2O emissions (1.1%), and HFCs, PFCs and SF_6 (together 1.5%). The industrial fuel combustion to generate the energy for all industrial processes contributes with 13.3% to GHG emissions, which is more than the industrial processes themselves (see Figure 34).

The manufacturing sectors in which industrial biotechnology can be applied generate around 2.1% of overall GHG emissions (1.1% CO_2 and 1% N_2O, other GHG not taken into account). As the industrial N_2O emissions are almost exclusively generated by the production of two chemical substances (nitric acid and apidic acid), and these are not produced biotechnologically, the following analysis of industrial emissions concentrates exclusively on CO_2 emissions.

[334] Eurostat data from the online database. http://epp.eurostat.ec.europa.eu/.

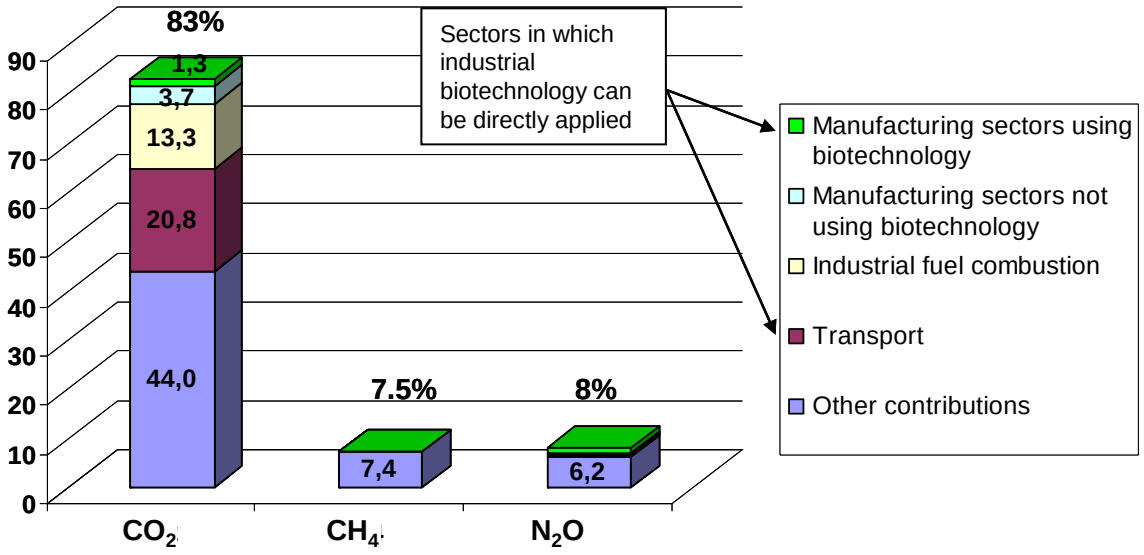

Figure 34: Contribution of manufacturing with and without biotechnological processes to GHG emissions in the EU (all values in %)

The transport sector contributes 21.4% to overall GHG emissions (20.8% CO_2, 0.1% CH_4 and 0.5% N_2O). 37% of GHG emissions from transport are generated through petrol combustion, which corresponds to a share of 7.9% to overall GHG emissions. As the application of modern biotechnology in the transport fuel sector is limited to bioethanol, these 7.9% represent the emissions which can be addressed through the substitution of petrol. As in the case of industrial GHG emissions, the analysis of environmental impacts of biofuel will concentrate exclusively on CO_2 emissions.

3.4.3 The contribution of industrial biotechnology

3.4.3.1 Enzyme production

The production of enzymes as an intermediate chemical product has environmental impacts itself in terms of energy use, process related GHG emissions and pollution to different environmental media. However, the actual impact is difficult to measure. The production of enzymes is targeted at a heterogeneous variety of applications in industry, partly replacing existing processes, and partly being used for new products. It is not possible to collect information on all the different 'conventional' chemical production processes and to benchmark enzyme production against them; however, fragmented information exists. Two issues are of interest in the context of this analysis: the replacement of chemical catalysts with enzymes, and the replacement of conventionally produced enzymes with enzymes produced with genetically modified organisms.

Example animal feed additive

Most environmental impact studies in the area of industrial biotechnology focus on environmental effects in the production process, in which an enzyme is applied, e.g. enzymatic processes in the textile industry (see below Section 3.4.3.2). Little information is

available analysing the environmental impacts of enzyme production itself. One example of comparing the actual production process of enzymes with the chemical it replaces has been provided by industry.

The enzyme Ronozyme, a phytase, serves to replace the animal feed additive monocalcium phosphate (MCP). Novozymes carried out a comparative life cycle assessment (LCA) which did not only look at the environmental savings from the application of the end product in pig feed, but also considered the production process itself[335]. The production of the enzyme is superior in all analysed environmental categories. Most notably, it takes 26 MJ to produce one kg of Ronozyme, while it takes 400 MJ to produce 29 kg of MCP (1 kg Ronozyme replaces 29 kg MCP). The difference in the impact on global warming is similar, as most of the CO_2 emissions are produced by the energy generation for the production processes. The overall environmental savings, including the production process and application, are shown in Table 55.

Table 55: Comparative LCA for ronozyme phytase (1 kg) and monocalcium phosphate (MCP, 29 kg)
Source: Nielsen and Wenzel 2006[335]

Impact category	Ronozyme phytase	MCP	Relation MCP/Ronozyme
Global warming, g CO_2 eq	1900	32000	17
Acidification, g SO_2 eq	4.8	530	110
Nutrient enrichment, g PO_4 eq	2.2	1500	700
Photochemical ozone formation, g C_2H_4 eq	1.5	12	8
Phosphate rock, g	<0.1	24000	>240000
Primary energy, MJ	26	400	15
Agricultural land, m^2/year	0.15	0	0

This is one isolated example, which does not allow drawing general conclusions with regard to environmental superiority of enzyme production. However, the replacement of large quantities of chemical catalysts (or other chemical intermediates) with comparably low quantities of enzymes seems to be the rule (see below in Section 3.4.3.2 examples for the pulp and paper and the textiles sector). Against this background it can be concluded that generally less energy is used in the production of enzymes than in the production of those substances they replace, and that accordingly CO_2 emissions are reduced, and thus the climate change impact (although this cannot be quantified).

Example enzyme production by genetically modified organisms

The environmental impact from the production of enzymes seems to be generally favourable when compared with the production of chemical substances they replace. However there are also different ways to produce enzymes. A study analysed the production of five different enzymes in a cradle to gate environmental assessment, i.e. focusing on the company's internal

[335] Nielsen, P.H. and Wenzel H. (2006). International Journal of Life Cycle Assessment, (Online-First), 7, http://www.novozymes.com/NR/rdonlyres/B79EB435-1C16-47EE-9BF4-1A9C749E40A5/0/lca2006082652.pdf

production process (here: Novozymes)[336]. The following environmental impact categories were analysed: global warming, acidification, nutrient enrichment, photochemical ozone enrichment, primary energy consumption, and use of agricultural land. Differences in the various environmental impact categories could be identified for all analysed enzymes, indicating that not all processes producing enzymes have the same environmental impact. Results show that the fermentation process stage was the main process responsible for global warming impacts. The environmental impact of enzyme production can differ when shifting from conventional production strains to genetically modified production strains (see Figure 35).

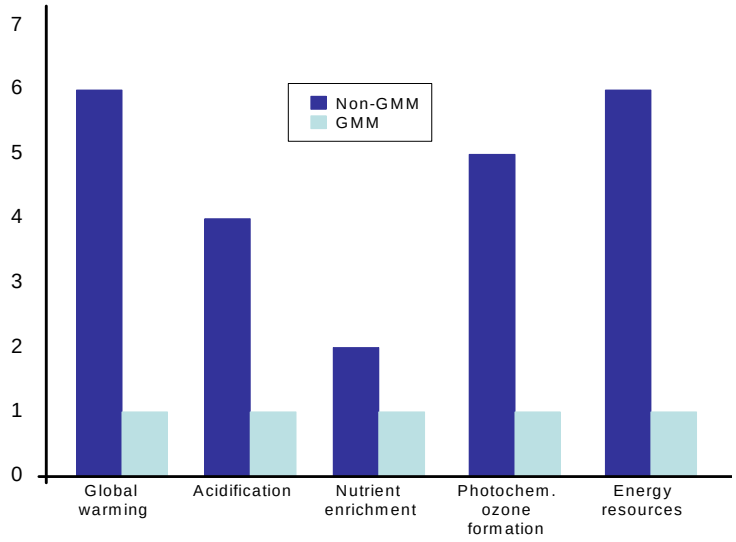

Figure 35: Comparative LCA for enzymes produced with and without GM product strains
Source: Nielsen et al. 2006[336]; Figures are normalised to the GMM produced enzyme; GMM: Genetically modified micro-organism

As can be seen in Figure 35, the environmental impacts from the production of enzymes with genetically modified organisms are lower in all impact categories. However, this has been demonstrated on the basis of an individual production process, so it is not possible to derive general conclusions from this.

3.4.3.2 Downstream use of enzymes

Enzymatic processes in pulp and paper production

The pulp and paper industry produces emissions to air and water, as well as solid waste as a by-product. Different processes with different environmental impacts are applied in pulp and paper production. Some of them, for example mechanical pulping, are resource intensive in terms of energy and water usage. The main pollutants are NO_x, SO_2, CO[337], CO_2 and particulate matters. Waste water contains adsorbable organic halogen compounds (AOX) and

[336] Nielsen, P.H. et al. (2006). International Journal of Life Cycle Assessment, (Online-First), 7, http://dx.doi.org/10.1065/lca2006.08.265.1
[337] NO_x: nirous gases; SO_2: sulphur dioxide; CO: carbon monoxide

is characterised by high biological and chemical oxygen demand (BOD and COD)[338]. Chlorine emissions 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 model production process has been developed in order to analyse the environmental and economic effects of the application of enzymes in the pulp and paper industry. It shows the different application areas in mechanical as well as in chemical pulping (see Figure 36 and Figure 37). The application of xylanase in the chemical pulping process reduces chlorine (Cl_2) use by 90%. This, in turn, leads to AOX reductions in waste water of between 15% and 20%[339].

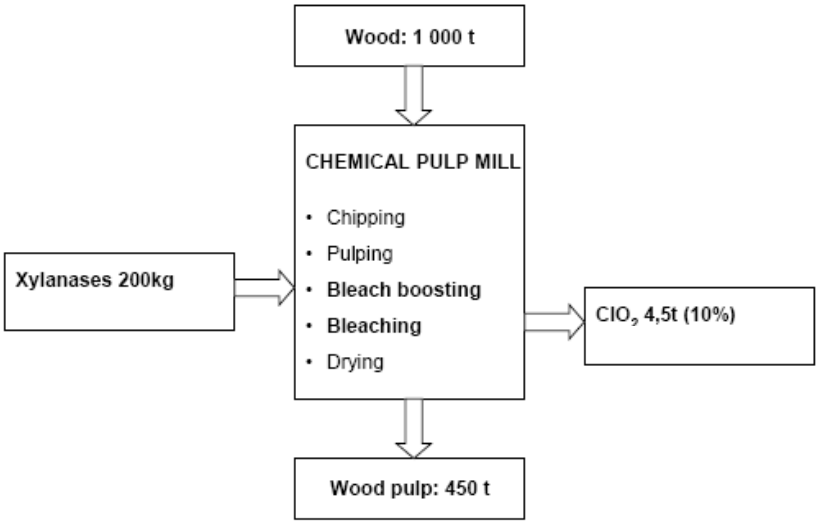

Figure 36: Model of chemical pulping
Source: Kvistgaard and Wolf 2002[338]

The application of cellulases in mechanical pulping, together with the application of the fungus *Ceriporiopsis subvermispora* leads to reductions in energy use of around 32%. However, the investment costs for the application of the fungal process step are high, and the actual acceptance by industry is not known. Energy reduction through enzymatic processes, in particular in mechanical pulping, leads to additional GHG emission savings. The direct average GHG emission savings through enzymatic processes in mechanical pulping are around 5%[340].

Laboratory scale tests have shown that enzymatic treatment of raw material before entering into the pulping process leads to energy savings of between 15% and 20%[340]. This is particularly interesting in the case of mechanical pulping, which uses energy up to 2.5 - 3.5 MWh/t. However, these processes are not yet applied in industry.

[338] Kvistgaard, M. and Wolf O. (eds) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, IPTS, EUR 20407, p. 24. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1022.
[339] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications. *And:* Kvistgaard, M. and Wolf O. (eds.) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, IPTS, EUR 20407, p. 30. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1022.
[340] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

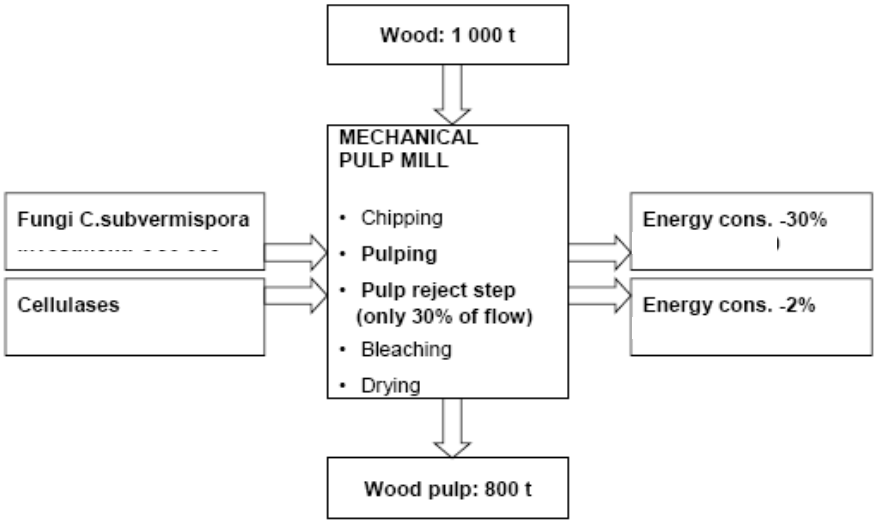

Figure 37: Model of mechanical pulping
Source: Kvistgaard and Wolf 2002[341]

Apart from the application of xylanases in chemical pulping, and cellulases in mechanical pulping, enzymatic processes are also applied in other production steps. In deposit control, proteases are used for controlling microbial activity in paper machines, leading to a reduction of chemical input.

In case of stickies control, esterases (lipases) are used to hydrolyse triglycerides to glycerol and free fatty acids in mechanical pulp. This leads to savings in the consumption of additives and surface active chemicals. Additionally, the fibre properties are improved. Cellulases are used for the deinking of recycled paper as raw material. This leads to reduced use of hydrogen peroxide and sodium hydroxide. For the reduced input of chemicals in deposit control, stickies control and deinking, no quantitative data are available.

In summary, it can be concluded that enzyme applications in pulp and paper manufacturing lead to reductions in CO_2 emissions directly and indirectly through reduced energy use. The main environmental impact is, however, the reduction of chemical input in several process steps, leading to a reduced load of pollutants in waste water streams.

Enzymatic processes in textile finishing

The textile industry shows a high usage of energy and water. In textile wetting, 100 litres of water are used for one kilogram of textiles. For further textile finishing (washing, dyeing, bleaching and other treatment), 15 - 20 kWh/kg are consumed[342]. In addition, textile processing steps such as the removal of contaminants, bleaching, application of dyes and other finishing processes generate a variety of pollutants. As most of these steps are carried out in wet processes, the main environmental impact occurs in the form of aqueous effluents.

[341] Kvistgaard, M. and Wolf O. (eds.) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, IPTS, EUR 20407, p. 30. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1022.
[342] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

The following list provides an overview of effluents generated on an average textile production site[343]:

- Salts
- Natural fibre contaminants
- Sizes (mainly starch derivatives, but also polyacrylates and polyvinyl alcohol)
- Preparation agents (mainly mineral oils, but also ester oils)
- Surfactants (dispersing agents, emulsifiers, detergents)
- Carboxylic acids (mainly acetic acid)
- Thickeners (starch derivatives)
- Urea
- Complexing agents
- Organic solvents
- Special auxiliaries with more or less ecotoxicological properties

Enzymatic processes are applied at several stages in textile finishing. Amylases are applied in desizing, i.e. the removal of starch size. As this process has been widely taken up by industry, the use of chemicals is, in this specific case, reduced to zero.

The application of lyases in the scouring of textiles (bioscouring) reduces the input of alkaline chemicals as well as overall water usage. BOD and COD as well as the salt load of waste water are diminished. Energy use is reduced through lowering the process temperature from 100°C to around 60°C. Additionally, the process time is decreased[344].

The application of catalases in the post bleaching process to remove bleaching residues such as hydrogen peroxide (H_2O_2), reduces the chemical load by 80%. Additionally, water usage is reduced by 50% and energy usage by 20%. The process time is shortened by 33%[344].

The use of laccases in denim bleaching leads to reductions in energy use by 9 - 14%, together with 17 - 18% less water usage. The process time is shortened by 9 - 10%.

In summary, it can be concluded that the environmental impacts of enzymatic processes in the textile industry are, as a rule, positive in the sense of reduced water and energy usage and reduced pollutants emitted mainly to water, as a consequence of reduced chemicals input. The secondary impact of the energy reduction is a reduced emission of GHG.

Detergents containing enzymes

The analysis of the environmental impacts of enzyme-based detergents is different from the discussion of other industrial applications such as pulp and paper processing. The main environmental impact occurs at the level of the detergent end-user and not in the actual detergent production process. The reason for this is that enzymes are not used to produce detergents, but are incorporated as part of the end product. Consequently, the desired effect emerges in the washing process at industrial or household level.

[343] Kvistgaard, M. and Wolf O. (eds.) (2002). The assessment of future environmental and economic impacts of process integrated biocatalysts. European Commission, IPTS, EUR 20407, p. 41. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1022.
[344] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

Washing needs water and energy to process the washing at the desired temperature. The main effect of enzymes in detergents is to remove stains at lower washing temperatures with the same efficiency. The washing temperature can be lowered in a lot of washing processes from 60°C to 40°C, leading to a reduction of CO_2 emissions which is around 75 g per kg of laundry[345]. When reducing the washing temperature from 95°C to 40°C, energy consumption is reduced by 70%[346]. Quantitatively, this effect cannot be measured, as the overall energy use for washing processes is not known.

Other environmental impacts of the application of enzymes in detergents are reduced water consumption and a shorter duration of the washing process, which in turn leads to a longer life of washing machines. Despite these advantages, large scale laundries are not applying detergents containing enzymes, while most household detergents are enzyme-based[346].

In addition to this, a number of toxic substances in detergents has been reduced by between 5% and 60%, such as benzoapyrene, lead, cadmium, sulphur oxide, etc. At the same time, exposure to enzymes can lead to allergic reactions. For this reason, enzyme-based detergents have so far not been used for open surface cleaning either in households or in industry[346].

Enzymatic processes in food processing

The analysis of environmental impacts of modern industrial biotechnological processes in food manufacturing meets similar challenges as the measurement of economic impacts. As most enzymatic processes in the food industry have been totally accepted, no benchmark sector is available for comparison. Therefore these processes cannot be analysed with regards to their environmental performance compared to traditional processes.

The case of fruit juice illustrates this well. Cell walls of fruits are broken down enzymatically, which subsequently leads to reduced energy use in pressing the fruit pulp compared to the hypothetical case of a non-enzymatic process. One reported example is the introduction of enzymes for clarification of lemon juice. This reduced the process time from several weeks to 6 hours compared to the conventional process using the fruits natural enzymes and calcium. A reduced use of chemicals is reported since no preservative needs to be added to avoid microbial spoilage and no calcium[346]. Enzymatic peeling of fruit as a relatively new technology replaces steam-based peeling, leading again to savings in energy.

In the heterogeneous area of food manufacturing, these examples do not allow for any generalisation. As for the environmental impacts of enzymatic processes in the food manufacturing sector, it can only be concluded that around 50% of food manufacturing subsectors use enzymes in large quantities (see Section 2.4.2.2), and that the contribution of food and feed manufacturing to CO_2 emissions is around 7% (excluding agriculture), respectively 0.89% of overall GHG emissions. The further introduction of enzymatic processes and the optimisation of existing ones will reduce negative environmental impacts in a similar way to other industrial applications (less usage of water and energy, reduction of input chemicals). These developments will, however, have a limited effect as enzymatic processes are already widely accepted in this manufacturing sector.

[345] Nielsen, P.H. and Nielsen J.D. (2005). Environmental assessment of low temperature washing. Submission by Novozymes in the context of this study's stakeholders dialogue (http://bio4eu.jrc.ec.europa.eu/stakeholders.html).
[346] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

3.4.3.3 Modern biotechnology in bioethanol production

The production of bioethanol has impacts on several environmental dimensions. These are mainly a reduced depletion of non-renewable fossil fuel resources and a reduction of GHG emissions. The environmental impacts differ, depending on the chosen production path. Further factors influencing environmental impacts are the share of imports from non-EU regions, the mix between diesel and petrol, the share of blending, and the (future) shift from first-generation to second-generation fuel, i.e. the shift to cellulosic biomass as a feedstock for bioethanol production. Impacts on GHG emissions have been estimated as presented in Table 56.

Table 56 shows for diesel as well as for petrol that the substitution through biofuels could lead to reduced GHG emissions. In the case of bioethanol produced from wheat, these could be reduced from 3.62 tCO_2eq/toe to 1.85 tCO_2eq/toe, which corresponds to around 50% reduction. Wheat is the main raw material used for bioethanol production in the EU. Table 56 also shows that the biofuel production from cellulosic biomass (straw or wood) could lead to a reduction of up to 90% GHG emissions.

Table 56: Estimated GHG emissions from different biofuels
Source: European Commission 2006[347]

	Greenhouse gas emissions (tCO_2eq/toe)	Savings (%)
Diesel	(3.65)	
Biodiesel from rape*	1.79	51
Biodiesel from soya*	2.60	29
Biodiesel from palm*	1.73	53
BTL from straw	n.a.	n.a.
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

*chemical transformation; BTL: biomass to liquid; toe: tonne of oil equivalent; n.a.: not available.

Against the background of a 7.9% share of petrol in GHG emissions, a hypothetical petrol substitution with bioethanol from wheat of 100% would lead to a 4% reduction of all GHG emissions (under the assumption of unchanged transport fuel demand). Achieving the 5.75% target of the EU[348] in 2010 would lead to a GHG reduction of around 0.23%. This calculation

[347] European Commission (2006). Accompanying document to the EC Biofuels Progress Report. SEC (2006) 1721/2, p. 20. http://ec.europa.eu/energy/energy_policy/doc/08_annexe_to_biofuels_progress_report_en.pdf.
[348] Directive 2003/30/EC of the European Parliament and of the Council of 8 May 2003 on the promotion of the use of biofuels or other renewable fuels for transport. OJ L 123/42, 17.5.2003. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:123:0042:0046:EN:PDF.

takes into account the whole lifecyle. In absolute terms, real CO_2 savings in the EU through bioethanol was 0.7 $MtCO_2eq$ in 2005[349].

In the biofuels progress report published by the European Commission at the beginning of 2007, different shares of biofuels in transport fuels are estimated up to the year 2020[350]. In the case of a 7% biofuels blend in road transport fuel in 2020, a saving of 48 $MtCO_2eq$ is estimated when compared with the situation without biofuels. In the case of a 14% blend, savings of 101 or 103 $MtCO_2eq$ are estimated[351]. The difference stems from assumptions on how much of the biofuel is imported and how much is produced domestically.

In a report published by the European Commission in 2006, the overall potential for a reduction in CO_2 emissions in the EU has been simulated for different scenarios. The most favourable scenario would be a combination of a high share of renewables in energy generation together with progress made in energy efficiency, leading to CO_2 emissions remaining well below the 1990 level over the whole projection period (-6.7% in 2010, -21.4% in 2020 and -29.3% in 2030), whereas the Kyoto protocol requests a reduction of 5% below 1990 levels. In absolute terms this means that in 2020 around 960 MtCO2eq would be saved when compared with a baseline scenario, and also that biofuels could contribute between 5% and 10% to this development[352]. The baseline scenario predicts an increase of CO_2 emissions from 3674 $MtCO_2eq$ in 2000 to 3928 $MtCO_2eq$ in 2020[353].

When discussing the environmental impacts of increased biofuel shares in EU transport fuel, the focus on GHG emissions has to be widened. Savings of CO_2 emissions as discussed above can be compensated if inappropriate land, for example wetland, is chosen to grow raw material for biofuels. The CO_2 balance could be neutralised or even reversed to negative. Large scale growth of raw material for biofuels might also impact on biodiversity. However, according to the European Environment Agency (EEA) enough biomass can be produced in the EU to cover even high demands for biofuels production[354]. So the challenge is not a bottleneck in land availability, but to identify appropriate land for growing raw material for biofuels.

An experiment has been carried out by Nielsen & Wenzel in order to compare environmental impacts of bioethanol as a substitute for petrol: The effect from driving one mile with a petrol car was compared to a flexifuel car running on E85 (the 15% share of bioethanol was produced from corn)[355]. A reduction of emissions of slightly more than 30% could be

[349] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[350] European Commission COM (2006) 845 final: Communication from the Commission to the Council and the European Parliament - Biofuels Progress Report. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2006:0845:FIN:EN:PDF.
[351] These estimates refer to accumulated saving through bioethanol and biodiesel.
[352] Mantzos, L. and Capros P. (2006). European energy and transport: scenarios on energy efficiency and renewables. European Communities, Luxembourg, p. 46. http://ec.europa.eu/dgs/energy_transport/figures/scenarios/energy_efficiency_en.htm.
[353] Mantzos, L. and Capros P. (2006). European energy and transport: trends to 2030 – update 2005. European Communities, Luxembourg, p. 37. http://ec.europa.eu/dgs/energy_transport/figures/trends_2030_update_2005/energy_transport_trends_2030_update_2005_en.pdf.
[354] EEA (2005). How much biomass can Europe use without harming the environment? Briefing, European Environment Agency, Copenhagen. http://reports.eea.europa.eu/briefing_2005_2.
[355] Nielsen, P.H. and Wenzel H. (2005). Environmental assessment of ethanol produced from corn starch and used as an alternative to conventional petrol for car driving. The Institute for Product Development, Technical University of Denmark, Lyngby. http://www.ipu.dk/upload/publikationer/bio-ethanol-report.pdf.

measured. Emissions of sulphur dioxide and phosphate increased, whereas emissions causing photochemical ozone formation were reduced. In other words, a changing from petrol to E85 reduces global warming and photochemical ozone formation, while acidification and soil nutrient enrichment will increase.

3.4.3.4 Production of biotechnology-based polymers

The production of oil-based polymers has environmental impacts in terms of energy use, GHG emissions and waste streams. Polymer production processes are large scale processes, which have been improved over the last decades in terms of reducing negative environmental impacts. The production of biotechnology-based polymers, however, has the potential to further reduce negative environmental impacts from the production and consumption of polymers. As there are a variety of different biotechnology-based polymers with different characteristics (see Section 2.4.2.4), the difference in environmental impact depends on the comparison with the oil-based polymer to be replaced. In Table 57 the impacts in terms of energy usage and GHG emissions are shown.

Table 57: Energy consumption and CO_2 emissions of biotechnology-based polymers production
Source: ETEPS 2006[356]

Polymer	Energy consumption	Direct CO_2 emissions
Production of Solanyl® compared to conventional oil-based plastics	40 % less than bulk plastics such as polyethylene (PE)	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 Bio-PDO-based polytrimethylene terephthalate compared to conventional oil-based plastics	16 % less than polyethylene terephthalate (PET)	No difference (indirect effects not included)

The production of Solanyl® needs 40% less energy than polyethylene (PE) production[356]. These energy savings lead to indirect savings of GHG emissions. Data on GHG emissions reduction in direct process comparison between polyethylene and Solanyl® are not available.

Poly-lactic acid (PLA) can be used as a substitute for different oil-based polymers. According to the polymer replaced the comparative savings in energy use as well as in GHG emission vary. The range of saved energy for the production of PLA is between 20% and 50%. The range of GHG emission reductions is between 50% and 67%.

Bio-PDO-based polytrimethylene terephthalate (PTT) is suitable to substitute polyethylene terephthalate (PET). A comparison between the production of these polymers shows energy savings of 16% for the production of the biotechnology-based polymers, also leading to indirect GHG emission reductions. Information for direct GHG emission savings from the production processes is not available.

[356] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

In the case of polyhydroxyalkanoates (PHA), LCAs show no clear results, probably due to different system boundaries. Different LCAs show GHG emission changes varying between savings in one case (27 - 48%) and increased emissions in another case (200%).

Polymers produced with modern biotechnology are at an early stage of development. This is illustrated by the fact that the first commercial PLA plant consumed much higher amounts of energy per polymer output unit than the conventional equivalent[357].

Ongoing process developments indicate changing environmental impacts in future (large scale) production processes. The US company Metabolix is investigating the modification of switchgrass for the direct production of PHA, which would eliminate the fermentation step and consequently reduce energy use and GHG emissions. The US producer Cargill started research on making lignocellulose biomass accessible for the production of PLA. This would lower the fossil energy used for the production of PLA by 80%[358].

A further aspect with regard to the environmental impacts of biotechnology-based polymers is that they differ from oil-based polymer waste streams. PLA can be composted, incinerated, or it can go to pre-consumer recycling and to 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[359] regulations. When incinerated, PLA produces fewer by-products than traditional polymers, having also a comparable 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[358].

The latter issue points to a negative environmental impact of biotechnology-based polymers. Ideally the difference to oil-based polymers is not recognisable for end consumers, which prevents them to collect biotechnology-based polymers separately. As a result, oil- and biotechnology-based polymers 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.

3.4.3.5 Production of other biotechnology-based chemicals

Chemical production in the EU is resource intensive in terms of energy and water, and leads to emissions of CO_2, CH_4 and N_2O. Additionally, the production of chemicals leads to by-products and pollutants which need special treatment. Today, a large number of chemicals are produced through biotechnological processes. These processes are so heterogeneous and data are so scattered that a consistent picture of the environmental impacts of the application of modern industrial biotechnology in the production of chemicals cannot be drawn.

One well documented example is the production of acrylamide, which is one of the few biotechnologically produced bulk chemicals in the several 100 000 tonnes range. A comparison of the energy consumption and CO_2 emissions is presented in Table 58 and Table

[357] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.
[358] OECD (2001). The application of biotechnology to industrial sustainability. OECD, Paris, p. 88. http://www.oecd.org/bookshop?pub=932001061P1.
[359] DIN: Deutsches Institut für Normung, Germany; ISO: International Organization for Standardization; CEN: European Committee for Standardisation; ASTM: American Society for Testing and Materials.

59. The comparison shows a 30% lower energy consumption, and CO_2 emissions are reduced by 25%.

Table 58: Comparison of energy consumption in the production of acrylamide (MJ/kg acrylamide)
Source: OECD 2001[360]

	Catalytic process	Enzymatic process
Steam	1.6	0.3
Electric power	0.3	0.1
Raw materials	3.1	3.1
Total	**5.0**	**3.5**

Table 59: Comparison of GHG emissions in the production of acrylamide (kg CO_2/kg acrylamide)
Source: OECD 2001[360]

	Catalytic process	Enzymatic process
Steam	1.25	0.2
Electric power	0.25	0.1
Raw materials	2.3	2.3
Total	**3.8**	**2.6**

Another example for which some data is available is the production of cephalosporins (see also Section 2.4.2.4). Concerning the 7-ACA process, no information concerning the changes in energy use and GHG emissions compared to the chemical synthesis is available. The input of solvents is reduced by almost 100%. The waste streams from the 7-ACA production process are reduced by 10% in the case of waste water, which additionally does not contain heavy metals or hazardous chemicals. Incineration material is reduced by almost 100%. In the case of 7-ADCA production, waste water generation is reduced by 90%. The CO_2 emissions from the energy production as well as from the fermentation process decrease by 75%. Energy consumption is reduced by 37% (electricity) respectively 92% (steam production)[361].

In the context of the Bio4EU study, industry provided information on the biotechnological production of a number of other substances, such as amino acids. For these amino acids, used as animal feed additives for pig feed replacing inorganic feed supplements, a number of environmental impact categories have been analysed: global warming, acidification, nutrient enrichment and photochemical ozone formation. It turned out that the biotechnology-based amino acids were superior in all analysed categories, with the reduction in nutrient enrichment being the most significant difference due to a reduced phosphate content in pig manure. However, environmental benefits were not only achieved indirectly through changes in pig feed, but also through the production process of the supplement. As a small quantity of the amino acids replaced a large quantity of the inorganic supplement, environmental impacts

[360] OECD (2001). The application of biotechnology to industrial sustainability. OECD, Paris, p. 74. http://www.oecd.org/bookshop?pub=932001061P1.
[361] ETEPS (2006). Bio4EU Task 2, case studies report: industrial biotechnology applications.

from the respective production processes differed widely. Studies carried out analysing the environmental impact of amino acids in poultry feed came to similar conclusions.

These examples show similarities to the application of modern biotechnology in other industrial processes as discussed above in the sense that generally the use of energy in the process and the emission of GHG is reduced. It can be assumed that in other biotechnological production processes in the chemical industry the impacts are similar.

3.4.4 Summary

Industrial biotechnology is mainly applied in the manufacturing sector. It impacts on the environment through changes in GHG emissions, energy use, waste generation and reduction of other non-renewable resources. The share of manufacturing sectors using enzymatic processes in GHG emissions is around 2.1%. This share consists of a 1.1% contribution to CO_2 emissions and a 1% contribution to N_2O emissions. The latter are almost exclusively produced by the chemicals industry (production of nitric and adipic acid). For both substances, no large scale biotechnological production is in use, so that the impact of modern biotechnology in industrial applications on N_2O emissions can be assumed to be zero.

The transport sector is one of the largest GHG contributors with 21% of total emissions. 37% of this share is generated by petrol combustion, which corresponds to 7.9% of total GHG emissions. The blending of transport fuels with bioethanol could help to improve the environmental impact of this sector. The environmental impacts of bioethanol compared to fossil fuel depend on a variety of factors, such as import share (and origin of imports), chosen biomass and production pathway. First-generation biofuels, produced in the EU using the most economically attractive production method, have been estimated to result in GHG emissions of 35 - 50% lower than the conventional fuels they replace. Applied to the 7.9% share of petrol in overall GHG emissions this means that a 100% replacement of petrol with bioethanol would lower GHG emissions by around 4%. Accordingly, compliance with the 5.75% replacement target of the EU[362] will lead to a GHG emissions reduction of around 0.23%. Recently the replacement target was increased to 10% by 2020[363]. Calculations for a higher share in 2020 show that with a 7% contribution (petrol and diesel) 48 $MtCO_2eq$ can be saved, and with a 14% target, around 100 $MtCO_2eq$ can be saved[364].

Power generation is the largest GHG emitting sector: 29% of all GHG are generated in energy generation industries themselves, 17% in fuel combustion in other sectors (non energy and non industrial, e.g. residential, agriculture), and 13% in industrial fuel combustion, i.e. energy generated for industrial processes. The GHG emissions from industrial fuel combustion are more than 50% higher than the GHG emissions from industrial processes themselves (8%). Power generation experiences two environmental impacts through the application of modern

[362] Directive 2003/30/EC of the European Parliament and of the Council of 8 May 2003 on the promotion of the use of biofuels or other renewable fuels for transport. OJ L 123/42, 17.5.2003. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:123:0042:0046:EN:PDF.

[363] Brussels European Council, 8 and 9 March 2007, Presidency conclusions. http://www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/ec/93135.pdf.

[364] European Commission SEC (2006) 1721: Commission staff working document. Review of economic and environmental data for the biofuels progress report. http://ec.europa.eu/energy/energy_policy/doc/08_biofuels_progress_report_annex_en.pdf.

biotechnology. A direct impact through a switch from non-renewable resources such as oil to renewable resources such as biomass as the input material, and an indirect impact through reduced energy demand from industrial processes. This indirect effect, which cannot be quantified, emerges because the application of enzymatic processes in industrial production leads, as a general rule, to reduced energy consumption in the respective processes.

In addition to reductions in energy consumption (and thus GHG emissions, mostly CO_2), the application of modern biotechnology in industrial processes (detergents, pulp and paper, textiles) lead, as a general rule, to savings in water consumption, and chemicals input. Also usually the process time is reduced.

In the case of biotechnology-based polymers, three environmental impacts can be observed. In most of the cases, the energy usage and related GHG emissions are reduced. The same is true for process related GHG emissions. However, the values differ depending on the oil-based polymer taken as a benchmark. For PHA, environmental indicators show negative environmental impacts compared to oil-based polymers.

Other biotechnology-based chemicals cannot be depicted in the entirety of their environmental impacts, as information for a lot of processes is not available or accessible. Information concerning known examples indicates environmental impacts which are similar to those of the application of modern biotechnology in other industrial sectors, i.e. reductions in energy use, GHG emissions and waste generation.

4 Contribution of modern biotechnology to public health

4.1 General outline and the overall contribution of modern biotechnology

The programme of Community action in the field of public health describes the respective EU policy objectives[365]. This programme goes hand in hand with the Lisbon Strategy as good health is considered crucial to economic growth and sustainable development. Moreover, in the context of 'health and food safety' the general principles and requirements of food law must also be considered[366], as far as the provision of safe and high quality food is concerned and taking into account the protection of animal health and welfare, as well as the European Environment and Health Strategy[367].

The assessment of the contribution of modern biotechnology to public health was based on relevant case studies and was structured along the following guiding policy objectives: improved warning, monitoring and control of communicable diseases, reduction of (major) non-communicable disease incidence, reduction of disease burden, and reduction of healthcare and social costs.

The case study analysis presented in this section shows that modern biotechnology applications in the human health sector have a direct impact on the overarching public health policy objective of reducing the disease burden. This is achieved through the provision of effective treatments, unique solutions for treatment and diagnosis (e.g. enzyme replacement therapy for Gaucher's disease or HIV/AIDS diagnostic tests), potentially safer treatments or unlimited supplies of pharmaceuticals (e.g. human recombinant insulin or recombinant hepatitis B vaccine). Additionally, modern biotechnology enables further development of drugs with the aim of increasing the quality of patients' lives (e.g. human insulin analogues). Similarly to modern health biotechnology, the public health effects of modern biotechnology applications in the agro-food sector build on the availability of new and better diagnostics and vaccines. Especially the monitoring and control of some of the most important zoonoses and food safety concerns (e.g. salmonellosis and BSE) help in safeguarding EU-wide food safety but also in assuring consumer confidence in the food chain and facilitating the continuity of related trade activities. Hence, modern biotechnology directly contributes to the control and monitoring of diseases, thus improving quality of life and potentially reducing burden of disease.

The contribution of modern health biotechnology applications for reducing healthcare and social costs is less clear. Whereas in some cases these applications increase efficiency in the

[365] Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September 2002 adopting a programme of Community action in the field of public health (2003-2008). OJ L 271/1 9.10.2002. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF. *And:* Decision No 1350/2007/EC of the European parliament and of the Council of 23 October 2007 establishing a second programme of Community action in the field of public health (2008-2013).OJ L 301/3 20.11.2007. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:301:0003:0013:EN:PDF.

[366] 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 in matters of food safety. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:EN:PDF.

[367] European Commission COM (2003) 338 Communication from the Commission to the Council, the European Parliament and the European Economic and Social Committee – A European Environment and Health Strategy. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2003:0338:FIN:EN:PDF.

healthcare sector, thus contributing to the objective of reducing healthcare costs, in other cases a new treatment puts an over-proportional strain on healthcare resources. While the latter case is not specific to biotechnology-based therapies but applies also to conventional approaches, it nevertheless emphasises the ethical question of how to allocate scarce resources in healthcare, when efficiency considerations could prevent patients' access to potentially life-improving or even life-saving therapies. However, a more general assessment of the cost-effectiveness of health biotechnology applications is still pending, given that in many cases results of pertinent studies are only preliminary and further studies need to be carried out. The cost-effectiveness of modern biotechnology applications is also relevant for applications in the agro-food sector which may impact public health indirectly. It has been reported, for example, that the use of the modern biotechnology-based vaccines for Aujeszky's disease in pigs is the most cost-effective option for the 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, which, however, may be achieved at a high monetary cost. Yet, like with health applications, 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 and it is relevant for several of the policy objectives identified in this study, such as the reduction of disease burden and the reduction of social costs. Modern biotechnology may have several and contrasting implications for animal health and welfare. On the one hand some modern biotechnology applications may present new issues in terms of animal welfare, potentially necessitating a case-by-case assessment. On the other hand, modern biotechnology 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.

4.2 Human health biotechnology

Probably the most important – but difficult to measure – impact of a new technology in the health sector is its contribution to people living healthier, better, longer and more productive lives, thus increasing social welfare and individual well-being as well as economic growth. Another impact of a new technology in the health sector is the potentially improved efficiency within the healthcare system. Thus, these two potential impacts of health technologies are directly linked to EU public health policy objectives, namely "Improved warning, monitoring and control of communicable diseases (including medical product safety)" and "Reduction of (major) non-communicable disease incidences (e.g. mental illnesses, cancer, cardio-vascular diseases, diabetes)", which principally relates to the effectiveness of health interventions, and the "Reduction of healthcare and social costs and the reduction of disease burden", which principally refers to the efficiency of these interventions.

For modern health biotechnology applications to have an impact, it is obviously necessary that the related products (therapeutics, vaccines and diagnostics) have achieved a certain level of diffusion, on their respective markets and in the clinics. The analysis of the underlying economic indicators and of their economic performance has been carried out in Section 2.2.

The impact of modern biotechnology on the incidence of zoonoses will be discussed in the section on agro-food (Section 4.3).

In the following sections, the health policy objectives and related aspects will be discussed and the impact of modern biotechnology will be illustrated by means of eight case studies describing modern health biotechnology applications including biopharmaceuticals, diagnostics and preventives. The case studies are presented and the effectiveness of the respective biotechnology applications is examined, including their potential impact on the burden of disease within the EU and on the quality of life of its citizens. Likewise, the cost-effectiveness of these applications is evaluated, and some ethical implications of cost-effectiveness analysed are highlighted.

The following Section 4.2.1 looks at the impact of health biotechnology in the field of therapeutics, while Section 4.2.2 evaluates its impact in the field of diagnostics and Section 4.2.3 considers preventives; Section 4.2.5 extrapolates some more general tendencies from the case studies.

4.2.1 Therapeutics

The following case studies regarding biopharmaceuticals have been analysed and will be discussed below: recombinant human insulin for diabetes, interferon-beta for multiple sclerosis, genetically engineered glucocerebrosidase enzyme for Gaucher’s disease and CD20 monoclonal antibodies for Non-Hodgkin’s lymphoma.

4.2.1.1 Recombinant human insulin for diabetes

Diabetes is a chronic disease for which there is currently no cure; the disease is caused by a loss of the insulin regulatory process, which is vital for the regulation of glucose levels in the blood. Over time, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves, in some cases leading to blindness, limb amputation, kidney failure, stroke and overall increased mortality. There are two main types of diabetes: type 1 diabetes is characterised by a lack of insulin production; without daily administration of insulin, type 1 diabetes is fatal. Type 2 diabetes results from the body's ineffective use of insulin. Type 2 diabetes comprises 90% of patients with diabetes around the world, and is largely the result of excess body weight and physical inactivity[368].

The World health Organisation (WHO) estimates that currently more than 180 million people worldwide have diabetes and that this number is likely to exceed 360 million by 2030[368]; the International Diabetes Federation (IDF) reports similar figures, with 194 million cases of diabetes in 2003 and projected 333 million cases for 2025. For Europe (including all the countries of the former Soviet Union, Turkey and Israel) the IDF reports 48.4 million people with diabetes in 2003 and projects that 58.6 million people will have diabetes in 2025[369]. Another study estimates that in the year 2000 in the same region (without Israel) 5% of all deaths, i.e. 602 800 deaths, were attributable to diabetes[370]. Within the EU, diabetes is responsible for about 5 - 10% of total healthcare spending; a share that is projected to rise significantly because the average age of the EU population is expected to increase and so is the prevalence of obesity. To these direct costs, further indirect costs need to be added, like loss of productivity due to sickness, disability, premature retirement or premature mortality; intangible costs include inconvenience, pain, loss of leisure time or loss of mobility[371].

The existence and role of insulin, which is essential for the treatment of diabetes, was discovered in 1921. This discovery found an immediate use when insulin was extracted from animal pancreases to treat diabetes. Although changes in lifestyle and proper diet management can help to alleviate the consequences of the disease, type 1 diabetic patients generally require insulin throughout their lives, while also some patients with type 2 diabetes may need insulin at more severe stages or when dietary approaches and weight reduction attempts fail.

To circumvent issues of potential contamination and of immune reaction against animal insulin with prolonged use, a genetic engineering approach was used to produce recombinant human insulin, which was the first genetically engineered product on the market (launched in 1982). According to a survey of the IDF in 2002 on the access to, and availability of, insulin in its member countries, 70% of the insulin that is currently available in the world is recombinant human insulin, followed by porcine insulin with 17%, bovine insulin with 8% and porcine-bovine mixtures with 5%, with most of the animal insulin used outside the industrialised countries. However, this survey also finds that despite its spread, recombinant human insulin is considerably more expensive in most countries where both human and animal insulin are commercially available, e.g. within European countries, the average price

[368] WHO (2006). Diabetes. Fact sheet 312. World Health Organisation, Geneva. http://www.who.int/mediacentre/factsheets/fs312/.
[369] IDF (2003). Diabetes Atlas, 2nd ed. International Diabetes Federation, Brussels. http://www.idf.org/e-atlas/.
[370] Roglic, G. et al. (2005). Diabetes Care **28**: 2130-2135. http://care.diabetesjournals.org/cgi/content/abstract/28/9/2130.
[371] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

of human insulin was twice as high as the price of porcine insulin[372]. Yet, in its position statement the IDF writes that 'there is no overwhelming evidence to prefer one species of insulin over another' and '[modern highly purified] animal insulins remain a perfectly acceptable alternative'[373]. Similarly, a recent review article finds 'no relevant differences in efficacy and adverse effects between human and purified animal (mainly porcine) insulin. [...] In our systematic review we could not identify substantial differences in the safety and efficacy between insulin species' [374]. Therefore, on the face of it, human insulin is more widely used than animal insulins even though it is equally effective but more expensive.

An explanation for this situation could be that human insulin is preferred by clinicians because they perceive that it avoids the risk of immune reactions and of contamination – a view that has been confirmed in selected interviews with health professionals[375]. Moreover, according to a study for the US, the actual cost of insulin (and delivery supplies) only amounts to 7.6% of total diabetes-related healthcare expenditures[376]. Hence, in the eyes of physicians who decide on which insulin species to give to their patients, the perceived safety of human insulin may come at a small cost. Also, while there are diabetic patients who prefer animal insulins, other patient groups may – for ethical reasons – prefer not to consume animal products. Yet, many such patient-oriented outcomes relating to quality of life, as well as effects on diabetic complications were never investigated scientifically[377]. Regarding the costs of recombinant human insulin vs. animal insulins, a further question would be to what extent the production of animal insulin could be limited by the availability of appropriate pancreases and at what point such a limitation would drive up the price of animal insulins if less recombinant human insulin would be consumed.

However, the development of recombinant human insulin opened the way for the engineering of another form of insulin: insulin analogues. While the first generation of recombinant insulins was designed to be identical to human insulin, insulin analogues were designed to improve the control of insulin requirements. Today there are several analogue products available, like fast-acting insulins that may take effect within five minutes of injection and last up to 3-4 hours, or slow-acting insulins that help prevent the building-up of blood glucose over the longer term. Hence, these products help diabetic patients manage their insulin requirements in different situations (like before mealtimes or at night-time). While the advantages of insulin analogues to patients – e.g. for the less constrained timing of their meals – is obvious, the generally higher prices of these products may reduce their cost-effectiveness, especially when used in the therapy of type 2 diabetic patients. Apart from their cost-effectiveness, also the long-term effects of insulin analogues need to be investigated in more detail[378].

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[372] IDF (2003). Diabetes Atlas, 2nd ed. International Diabetes Federation, Brussels. http://www.idf.org/e-atlas/.

[373] IDF (2005). Position statement: animal, human and analogue insulins. International Diabetes Federation, Brussels. http://www.idf.org/home/index.cfm?node=1385.

[374] Richter, B. and. Neises G (2005). Cochrane Database of Systematic Reviews **1**, Art. CD003816. http://dx.doi.rg/10.1002/14651858.CD003816.pub2.

[375] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[376] ADA (2003). *Diabetes Care* **26**: 917-932. http://care.diabetesjournals.org/cgi/content/abstract/26/3/917.

[377] Richter, B. and Neises G. (2005). Cochrane Database of Systematic Reviews **1**, Art. CD003816. http://dx.doi.org/10.1002/14651858.CD003816.pub2.

[378] IQWiG (2006). Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2. Institute for Quality and Efficiency in Healthcare, Cologne. http://www.iqwig.de/iqwig-publications.114.en.html. *And:* Warren, E. et al. (2004). Health Technology Assessment **8** (45). http://www.ncchta.org/execsumm/summ845.htm.

While recombinant human insulin and insulin analogues are effective in the treatment of diabetes, these products do not seem to *add* to the efficacy of conventional animal insulins. Hence, the contribution of biotechnology-derived insulin products to the reduction of the burden of diabetes may need to be considered marginal. However, especially insulin analogues may improve the quality of life of diabetes patients, which could be seen as the major contribution of recombinant insulins. The effectiveness and quality aspect of recombinant insulins also needs to be contrasted with their price. While more detailed studies are lacking, the generally higher price of recombinant human insulin vs. animal insulins seems not to be reflected in greater clinical efficacy. Because of the marginal impact on the burden of diabetes, substantial productivity gains due to more healthy and active patients cannot be expected.

Judging such qualitative improvements requires more specific cost-utility analyses and more fundamental ethical decisions; any current assessment cannot come to a conclusive evaluation. It should also be noted that, in early 2007 it was announced that plant-produced recombinant human insulin (compared to recombinant human insulin from yeast) has been demonstrated to be equivalent to human insulin. The company that developed this new process believes it can help to accommodate the rising demand for insulin, which may be further increased through the commercialisation of alternative delivery technologies that require several times more insulin per dose than administration through injection; it also believes product costs may be reduced by 40% or more[379].

4.2.1.2 Interferon-beta for multiple sclerosis

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 is characterised by lesions that occur throughout the brain and spinal cord. These lesions cause alterations in the transmission of messages by the nervous system, which has severe consequences like loss of memory or the loss of balance and muscle coordination (which makes walking difficult); other symptoms include slurred speech, tremors, stiffness or bladder problems. MS is categorised by one of five disease subtypes: benign, monosymptomatic, relapsing-remitting (RRMS), secondary-progressive (SPMS) or primary progressive (PPMS). However, about 75% of all MS patients suffer from either the relapsing-remitting or the secondary-progressive form of the disease[380].

Because there are no national registries for the disease, there is uncertainty regarding the number of MS patients and estimates can vary substantially[380]. According to the WHO, in 2002 there were 454 400 people who suffered from MS in Europe, 256 500 of which lived in Western Europe[381,382]. However, according to the Multiple Sclerosis International Federation,

[379] DrugNewswire (2007). SemBioSys' plant-produced insulin chemically and physiologically equivalent to commercial insulin in animal studies. DrugNewswire, 15 January. http://www.drugnewswire.com/11185/. *And:* SemBioSys (2007). Insulin, Pharmaceutical Products. SemBioSys Genetics, Calgary. http://www.embiosys.com/Main.aspx?id=14.

[380] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[381] The WHO region "Europe" consists of the three subregions EUR-A, EUR-B and EUR-C, where EUR-A comprises Andorra, Austria, Belgium, Croatia, the Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, the Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom; *EUR-B* comprises Albania, Armenia,

there are currently over 563 400 cases of MS within the EU alone[383]. Given the number of people who suffer from MS and the fact that it primarily affects young adults who may not only be building their families but who are also generally at an economically very productive stage of their lives, the individual consequences of this disease are severe and the economic and social costs are substantial[384]. This is also reflected in the high share of indirect costs, i.e. of costs that occur outside the healthcare system, such as productivity losses, costs for informal healthcare or estimates of intangible costs. Economic analyses of the costs of MS estimate that indirect costs usually make up more than half of total costs[385]. Annual total costs are, for instance, estimated to reach several billion euros in some bigger EU countries and in the US, and still hundreds of millions of euros in other European countries with smaller populations[386].

Prior to 1993, when the US Food and Drug Administration (FDA) licensed interferon-beta-1b for the treatment of certain patients with MS in the US[387], the only MS therapy was a treatment with corticoids to accelerate recovery[388]. Even though interferon-beta is not a cure for MS, it may slow down the development of some disabling effects and decrease the number of relapses of the disease. The mechanism by which interferon-beta acts on MS is not fully understood[389], but it is explained by the repression of inflammatory processes in the body. In the meantime more drugs for MS were developed, but most are still only at development or clinical trial stage; altogether worldwide there are 172 products available or under development for the therapy of MS[388].

Azerbaijan, Bosnia And Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan and Yugoslavia; and *EUR-C* comprises Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation and Ukraine. (Mathers, C.D. et al. (2002). Global Burden of Disease 2000: version 2 methods and results. Global Programme on Evidence for Health Policy Discussion Paper No. 50. World Health Organisation, Geneva. http://www.who.int/healthinfo/boddocs/.)

[382] WHO (2006). Point prevalence for selected causes: by sex, age and WHO subregion: 2002. Health statistics and health information systems. World Health Organisation, Geneva. http://www.who.int/entity/healthinfo/tatistics/gbdwhosubregionprevalence2002.xls.

[383] MSIF (2006). European map of MS database. Multiple Sclerosis International Federation, London. http://www.europeanmapofms.org/query.aspx. (The figure reported for the EU does not contain data on Cyprus, Lithuania and Malta.)

[384] Phillips, C.J. (2004). CNS Drugs **18**: 561-574. http://cnsdrugs.adisonline.com/pt/re/cns/abstract.00023210-200418090-00002.htm. *And:* Kobelt, G., et al. (2006). Journal of Neurology, Neurosurgery, and Psychiatry **77**: 918-926. http://jnnp.bmj.com/cgi/content/abstract/77/8/918. *And:* Orlewska, E. (2006). Expert Review of Pharmacoeconomics & Outcomes Research **6**: 145-154. http://dx.doi.org/10.1586/14737167.6.2.145. *And:* APF (2006). Le Livre Blanc de la sclérose en plaques. Etats Généraux de la SEP, Association des Paralysés de France, Paris. http://www.sclerose-en-plaques.apf.asso.fr/actualites_rubrique/evenements_etudes_sep.htm.

[385] Amato, M.P. (2004). Expert Opinion on Pharmacotherapy **5**: 2115-2126. http://dx.doi.org/10.1517/4656566.5.10.2115. *And:* Kobelt, G. and Pugliatti M. (2005). European Journal of Neurology **12**: S63-S67. http://dx.doi.org/10.1111/j.1468-1331.2005.01193.x.

[386] Kobelt, G. and Pugliatti M. (2005). European Journal of Neurology **12**: S63-S67. http://dx.doi.org/10.1111/j.1468-1331.2005.01193.x. *And:* Whetten-Goldstein K. et al. (1998). Multiple Sclerosis **4**: 419-25. http://www.ingentaconnect.com/content/sage/ms/1998/00000004/00000005/3500379a. *And:* Svendsen, B. et al. (2006). The cost of multiple sclerosis in Norway (and how certain can we be?) Department of Finance and Management Science, Discussion Paper 12. Norwegian School of Economics and Business Administration, Bergen. http://www.nhh.no/for/dp/2006/1206.pdf.

[387] FDA (1993). FDA licenses interferon beta-1b. News 07/23/1993. Food and Drug Administration, Rockville, MD. http://www.fda.gov/bbs/topics/NEWS/NEW00424.html.

[388] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[389] McCormack, P.L. and Scott L.J. (2004). CNS Drugs **18**: 521-546. http://dx.doi.org/10.2165/00023210-200418080-00004.

However, the use of interferon-beta in the treatment of MS is not without controversy. In 2002 the UK's National Institute for Health and Clinical Excellence (NICE) issued the guidance that 'on the balance of their clinical and cost-effectiveness neither interferon-beta nor glatiramer acetate is recommended for the treatment of MS', but that patients currently receiving either drug could suffer loss of well-being if their treatment is discontinued and that they, therefore, should have the option to continue treatment[390]. As a result of this guidance, the UK government has reached an agreement with the manufacturers of the drugs on a risk-sharing scheme for the supply of interferon-beta (and glatiramer acetate) to its National Health Service (NHS)[391]. Nevertheless, the guidance has still effects: the prescription rate of interferon-beta in the UK, at around 2 - 3% of MS patients, is far lower than the rate in other EU countries, where it is about 12 - 15%[392]. Pending data from the risk-sharing scheme, a planned review of the original guidance was deferred from 2004 until November 2006[393]. Yet, more recent evaluations of the cost-effectiveness of interferon-beta that have been carried out in the meantime do not (yet) show a very different picture: the impact of interferon-beta on the progression of MS seems to be rather limited, at least in the short to medium term for which there are factual data of treatment successes, and for the modest benefits the drug is considered too costly[394].

4.2.1.3 Genetically engineered glucocerebrosidase enzyme 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 to accumulate in the spleen, liver, lungs, bone marrow and sometimes in the brain, where it causes functional abnormalities of these organ systems. The resulting course of the disease can be quite variable, ranging from no outward symptoms to severe disability and death. The accumulation of the lipid (glucocerebroside) in some of the body's cells and tissues is putting this disease into the family of lipid-storage disorders. The genetic predisposition for the disease needs to be inherited from both parents for the disease to manifest itself. There are three types of Gaucher's disease, according to when in life the symptoms appear and how severe the course of the disease is. Patients who have the most common type 1 Gaucher's disease usually bruise easily and experience fatigue due to anaemia. However, while they have enlarged livers and spleens and suffer from skeletal disorders and sometimes from lung and kidney impairment, their brains are not affected; type 2 and 3 are more severe and usually lethal[395]. Type 1

[390] NICE (2002). Guidance on the use of beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology Appraisal No. 32, National Institute for Clinical Excellence, London. http://www.nice.org.uk/page.aspx?o=TA032guidance.

[391] NICE (2002). Risk-sharing scheme. National Institute for Clinical Excellence, London. http://www.nice.org.uk/page.aspx?o=27673.

[392] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[393] NICE (2002). National Institute for Clinical Excellence, London. http://www.nice.org.uk/page.aspx?o=246259.

[394] Prosser, L.A. et al. (2004). Value in Health **7**: 554-568. http://dx.doi.org/10.1111/j.1524-4733.2004.75007.x. *And:* Phillips, C.J. (2004). CNS Drugs **18**: 561-574. http://pt.wkhealth.com/pt/re/cns/abstract.00023210-200418090-00002.htm. *And:* Amato, M.P. (2004). Expert Opinion on Pharmacotherapy **5**: 2115-2126. http://dx.doi.org/10.1517/14656566.5.10.2115. *And:* Hoch, J.S. (2004). Expert Review of Pharmacoeconomics & Outcomes Research **4**: 537-547. http://dx.doi.org/10.1586/14737167.4.5.537. *And:* McCormack, P.L. and Scott L.J. (2004). CNS Drugs **18**: 521-546. http://dx.doi.org/10.2165/00023210-200418080-00004.

[395] NINDS (2006). Gaucher's Disease. Disorder Index. National Institute of Neurological Disorders and Stroke, Bethesda, MD. http://www.ninds.nih.gov/disorders/gauchers/. *And:* NGF (2006). Gaucher's disease. National

Gaucher's disease affects one in about 50 000 individuals in the general population, while type 2 and 3 each affect even less, namely fewer than one in 100 000 individuals[396]. 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[397]. Given these prevalence rates, for a EU population of 458 973 024 in 2004[398], there could be around 5000 to 18 000 individuals who suffer from Gaucher's disease in the EU.

Historically, Gaucher's disease has been treated by the removal of part of the spleen, which can however accelerate bone disease and is not done any more except in extreme cases. Another option was bone marrow transplantation, which however required matching donors and carried a high mortality rate. Given these alternatives, the current treatment of choice is enzyme replacement therapy[399]. This therapy compensates the deficiency in the respective enzyme by its administration at an appropriate rate and dosage. While the involvement of glucocerebrosidase in Gaucher's disease had been established by the 1970s, the breakthrough in a corresponding therapy came with the modification of the glucocerebrosidase enzyme. This was first done by modifying a placenta extract. However, 22 000 human placentas are required to supply this product (Ceredase) to one patient for one year The subsequent product was a recombinant enzyme (Cerezyme, an analogue of the human enzyme (beta)-glucocerebrosidase), which proved to be as effective as Ceredase in treating Gaucher's disease, but was more easily available and free of potential contamination[400]. This drug was launched in the US in 1994 and authorised in the EU in 1997[401]. A more recent alternative intervention to enzyme replacement therapy is substrate reduction, i.e. a reduction of the creation of cerebroside, whose accumulation is the clinical cause of Gaucher's disease. The respective enzyme inhibitor (miglustat; product name Zavesca) was approved in the EU in 2002 and in the US in 2003[402]. It is currently being marketed for patients 'for whom enzyme replacement therapy is not an option'[403], because the drug is less effective and can have undesirable side-effects[400].

Enzyme replacement therapy in Gaucher's disease has proven to be efficacious from a clinical point of view, with only few mild adverse reaction, and it also improves the quality of life

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Gaucher Foundation, Harpers Ferry, WV. http://www.gaucherdisease.org/. *And* ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[396] Genzyme (2006). Gaucher's disease's approximate frequency, onset, and course by type, overview table. Gaucher's disease Information, Healthcare Professionals. Genzyme Therapeutics, Cambridge, MA. http://www.cerezyme.com/healthcare/disease/cz_hc_disease.asp.

[397] GOLD (2006). Gaucher's disease, Disease Information Search. Global Organisation for Lysosomal Diseases, Buckinghamshire. http://www.goldinfo.org/disease_search.aspx.

[398] Eurostat (2006). Population by sex and age on 1. January of each year. Theme: Population and Social Conditions. European Commission, Eurostat, Luxembourg. http://epp.eurostat.ec.europa.eu/.

[399] ETEPS (2006). Bio4EU Task2, case studies report: human health applications. *And:* NINDS (2006). Gaucher's Disease. Disorder Index. National Institute of Neurological Disorders and Stroke, Bethesda, MD. http://www.ninds.nih.gov/disorders/gauchers/.

[400] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[401] Genzyme (2006). Genzyme timeline, Corporate Info. Genzyme Corporation, Cambridge, MA. http://www.genzyme.com/corp/structure/timeline_genz.pdf. *And:* EMEA (2003). Committee for Proprietary Medicinal Products' meeting of 20 to 22 May. EMEA/CPMP/2848/03/Rev 1. European Medicines Agency, London. http://www.emea.eu.int/pdfs/human/press/pr/284803en.pdf.

[402] Actelion (2006). All milestones, company information. Actelion Pharmaceuticals, Allschwil. http://www.actelion.com/uninet/www/www_main_p.nsf/Content/All+Milestones.

[403] Actelion (2006). Zavesca: balance by substrate reduction, homepage. Actelion Pharmaceuticals, Allschwil. http://www.zavesca.com/.

from the patients' perspective[404]. Estimates of the simple costs of procuring the quantities of the drug for one patient per year range from about EUR 100 000 to several times that amount[405]. Gaining one 'quality-adjusted life year' (QALY the weighted equivalent of one healthy life year) with the enzyme replacement therapy may cost anything between EUR 150 000 and 2 million, beyond any usually applied cost-effectiveness thresholds[406]. This highlights the specific ethical questions surrounding 'orphan drugs' [407], namely whether scarce public money in the healthcare sector should be spent according to equity (all individuals are entitled to the same minimum quality of healthcare) 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)[408].

4.2.1.4 CD20 monoclonal antibodies for non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is a type of cancer in which malignant cells form in the lymph system. The latter is part of the immune system and consists of the tissues and organs that produce, store and carry white blood cells to fight infections and other diseases. Because 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. This spreading of the cancer is divided into four stages (I-IV), depending on where the cancer is found and how it has spread[409]. NHL is more common in men and older age groups than in women and younger age groups (see Figure 38). 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[410]. In 2001 there were over 30 000 deaths within the EU due to NHL[411].

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[404] Whittington, R. and Goa K.L. (1992). *Drugs* **44**: 72-93. Abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1379912. *And:* Whittington, R. and Goa K.L. (1995). Pharmacoeconomics **7**: 63-90. Abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db =PubMed&list_uids=10155294. *And:* Damiano1, A.M. et al. (1998). Quality of Life Research **7**: 373-386. http://dx.doi.org/10.1023/A:1008814105603.

[405] Whittington, R. and Goa K.L. (1995). Pharmacoeconomics **7**: 63-90. Abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10155294. *And:* Clarke, J.T.R. et al. (2001). Canadian Medical Association Journal **165**: 595-596. http://www.cmaj.ca/cgi/content/full/165/5/595. *And:* Connock, M. et al. (2006). Health Technology Assessment **10** (24). http://www.hta.ac.uk/ProjectData/ 3_project_record_published.asp?PjtId=1414.

[406] Whittington, R. and K.L. Goa (1995). Pharmacoeconomics **7**: 63-90. Abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10155294. *And:* Connock, M. et al. (2006). Health Technology Assessment **10** (24). http://www.hta.ac.uk/ProjectData/3_project_record_published.asp? PjtId=1414.

[407] Orphan drugs are medicinal products to diagnose, prevent or treat a life-threatening, seriously debilitating or serious and chronic condition affecting less than five in 10 000 persons (in the EU). Because these conditions occur so infrequently that the cost of developing and bringing to the market a corresponding drug 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. See also Regulation (EC) No 141/2000 of the Euroepan Parliament and of the Council of 16 December 19999 on orphan medical products. OJ L 18/1 22.1.2000. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF.

[408] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[409] NCI (2006). Non-Hodgkin's's Lymphoma. Cancer Topics. National Cancer Institute, Bethesda, MD. http://www.cancer.gov/cancertopics/types/non-hodgkin'ss-lymphoma.

[410] Trümper, L. et al. (2004). Maligne Lymphome. In: Hiddemann, W. et al. (eds.) (2004). Die Onkologie, Teil 2. Springer Verlag, Berlin, pp. 1709-1774. http://www.springer.com/3-540-64648-5. *And:* Morgan, G. et al. (1997). Annals of Oncology **8**: S49-S54. http://www.springerlink.com/content/r07442h1n6225553/.

Lymphomas were classically treated with radiotherapy and systemic chemotherapy (like 'CHOP', a specific combination of anti-cancer drugs). Over the last years these treatments have been supplemented by autologous and allogeneic stem cell transplantation and by immunotherapy with monoclonal antibodies. This increase in available therapies makes it possible to better differentiate therapeutic strategies and aim for curative treatment[412]. The various therapies can also be combined, e.g. existing systemic chemotherapy regimes can be delivered with monoclonal antibodies, or monoclonal antibodies can be used for the delivery of targeted radiotherapy to tumour tissue[413].

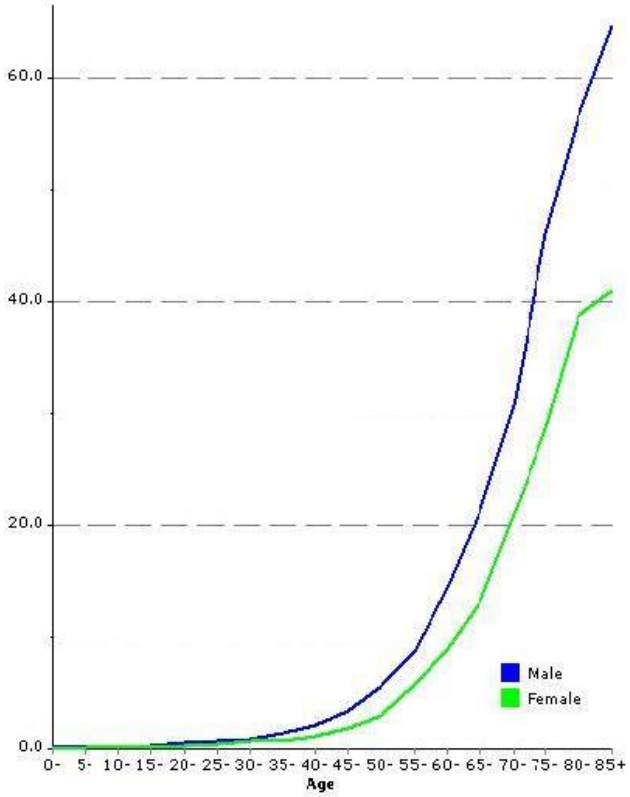

Figure 38: Incidence of non-Hodgkin's lymphoma in the EU by age (2001)
Source: IARC 2006[414].
Note: Does not include Belgium and Cyprus.

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 attack the malignant cells while sparing most normal tissue. Hence, such antibodies are 'targeted' drugs.

[411] IARC (2006). CANCERMondial, update of July 2006. Descriptive Epidemiology Production Group, International Agency for Research on Cancer, Lyon. http://www-dep.iarc.fr/. (Does not include Cyprus; data for Belgium from 1997.)
[412] Trümper, L. et al. (2004). Maligne Lymphome. In: Hiddemann, W. et al. (eds.) (2004). Die Onkologie, Teil 2. Springer Verlag, Berlin, pp. 1709-1774. http://www.springer.com/3-540-64648-5.
[413] Dunleavy, K, and W.H. Wilson (2006). Lymphomas: Non-Hodgkin's Lymphoma. In: Dale D.C. (ed.) (2006). ACP Medicine Online. WebMD Professional Publishing, New York. http://www.medscape.com/viewarticle/534542.
[414] IARC (2006). CANCER*Mondial*, update of July 2006. International Agency for Research on Cancer, Lyon. Available online at http://www-dep.iarc.fr/ (accessed 15 December 2006).

The need for engineering these antibodies arises from the fact that patients generally do not produce effective antibodies against the relevant antigens[415].

To date, studies on the effectiveness and cost-effectiveness of CD20 antibodies (rituximab) are scarce; the drug was approved in the US for the treatment of NHL in 1997 and in the EU in 1998[416]. A systematic review that was carried out in the UK could identify only one randomised controlled trial, which however confirmed the effectiveness of rituximab in the treatment of aggressive NHL (in combination with CHOP) in certain patient groups. In the same review, a cost-effectiveness analysis was carried out. This analysis showed that the addition of rituximab to the CHOP treatment regime may extend the patients' lives by about one QALY at a cost of about GBP 10 000 (about EUR 15 000), which qualifies as a cost-effective intervention. These results also confirm the data provided by industry[417]. Given this scarcity of information, for instance NICE has recommended the (general) use of rituximab only in some cases of NHL[418]. 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 to come to a more comprehensive assessment of the various effective treatments, including CD20 antibodies, that have been developed for NHL[419].

4.2.2 Diagnostics

Diagnostics are gaining increasing importance for healthcare, constituting an invaluable set of tools for diagnosis, but in the recent years even more so for prognosis and prevention. As they are often a central part of first-line clinical decisions, diagnostics are a critical component of healthcare with growing social implications in terms of their impact on health outcomes but also healthcare delivery and costs[420].
Recent advances in biotechnology, and in particular genomic technologies, have greatly improved the understanding of disease mechanisms, and have, as a result, contributed to the development of new and improved diagnostics. These can be applied to early detection (e.g. for infectious diseases such as HIV/AIDS, SARS[421]), predisposition testing (e.g. breast

[415] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.
[416] FDA (1997). Rituximab: product approval information, drug information. Food and Drug Administration, Rockville, MD. http://www.fda.gov/cder/biologics/products/ritugen112697.htm. *And:* Roche (2004). MabThera receives positive opinion for first-line use in indolent non-Hodgkin's lymphoma, investor update. Hoffmann-La Roche, Basel. http://www.roche.com/inv-update-2004-06-28.
[417] Knight, C. et al. (2004). Rituximab (MabThera) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. Health Technology Assessment **8** (37). http://www.hta.nhsweb.nhs.uk/execsumm/summ837.htm.
[418] NICE (2003). Rituximab for aggressive non-Hodgkin's lymphoma. Technology Appraisal No. 65, National Institute for Clinical Excellence, London. http://www.nice.org.uk/page.aspx?o=TA065guidance. *And:* NICE (2002). Guidance on the use of rituximab for recurrent or refractory Stage III or IV follicular non-Hodgkin's lymphoma. Technology Appraisal No. 37, National Institute for Clinical Excellence, London. http://www.nice.org.uk/page.aspx?o=37193.
[419] van Agthoven, M. et al. (2004). Expert Opinion on Pharmacotherapy **5**: 2529-2548. http://dx.doi.org/10.1517/14656566.5.12.2529.
[420] The Lewin Group (2005). The value of diagnostics, innovation, adoption and diffusion into healthcare. AdvaMed, Washington, DC. http://www.advamed.org/publicdocs/july2005hillbriefing.shtml.
[421] HIV/AIDS: Human immunodeficiency virus/acquired immunodeficiency syndrome; SARS: Severe Acute Respiratory Syndrome

cancer) and prevention (e.g. early diagnosis of phenylketonuria to prevent mental retardation), but also in disease management and personalised 'real time' treatment (e.g. therapeutic drug monitoring tests to select drugs for resistant HIV strains), an important emerging trend in healthcare.

Diagnostics based on modern biotechnology fall in two main categories. Nucleic acid-based tests are used to identify alterations in the genetic make-up of an individual correlating with a disease or a higher risk for developing a disease. Protein-based tests on the other hand can be used to identify changes in the levels of proteins during disease (e.g. hepatitis, cancer, etc.) or an infection (e.g. HIV). In general, this involves the detection of a protein by a specific antibody (e.g. immunoassays).

In an era of increasing healthcare expenditures, the use of sophisticated diagnostics based on biotechnology is costly and may therefore pose a further economic strain on healthcare systems in spite of their potential positive role in improving public health through earlier diagnosis and prevention. In this context, assessing their impact on quality of life but also on healthcare delivery and costs is essential. This impact is evaluated based on three case studies, covering a broad spectrum of important communicable and non-communicable conditions. These include HIV testing, cardiac diagnostic assays and genetic testing.

4.2.2.1 Biotechnology-based HIV testing

The first case of an HIV infection was reported more than 20 years ago and by the end of 2005, HIV was estimated to have affected 38.6 million people worldwide (Sub-Saharan Africa is the most affected region; however, the prevalence is high in other regions as well)[422]. In 2005 an estimated 4.1 million people became newly infected with HIV and between 2.4 million and 3.3 million people lost their lives to HIV/AIDS. Overall, the proportion of people who have become infected with HIV is believed to have peaked in the late 1990s and to have stabilised subsequently. However, recent projections confirm that the number of HIV/AIDS infections will continue to increase in the coming years although the magnitude will depend on how many people will have access to therapy and, more importantly, on the extent to which prevention strategies are efficiently applied[423].

According to UNAIDS, about 1.2 million people in the US 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[424], it has been estimated that 2.2 million people were living with the

[422] UNAIDS (2006). Report on the global AIDS epidemic 2006. UNAIDS, Geneva. http://www.unaids.org/en/HIV_data/2006GlobalReport/.

[423] Mathers, C.D. and Loncar D. (2006). PLoS Medicine **3**: 2011-2029. http://dx.doi.org/10.1371/journal.pmed.0030442.

[424] WHO European Region: Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, the Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, the United Kingdom and Uzbekistan.

virus[425] in 2005. The majority of these are in Eastern Europe and central Asia, where the overall rates of newly diagnosed HIV infections has increased significantly since 1998. In the same report, it is predicted that 100 000 - 580 000 people will need antiretroviral therapy by 2010, indicating the growing implications of HIV/AIDS for healthcare.

HIV belongs to the group of retroviruses, which are typically characterised by the long interval between infection and symptom development (patients may be asymptomatic for years after infection, although acute onset occurs within days). Individuals infected by the virus suffer from gradual but severe deterioration of their immune system, mainly as a result of the destruction of a subset of immune cells (known as CD4+ lymphocytes). Antiretroviral therapy was launched a decade ago and has made an important contribution to patient survival. However, the high mutability of the virus which in turn leads to drug resistance remains the pivotal challenge for the efficiency of available therapies used for the treatment of chronic patients and of the efficacy of post-exposure prophylaxis. A recent study indicates that in Europe drug-resistant HIV variants are frequently present in patients who have been recently infected or in patients suffering from a chronic infection and who have never been exposed to therapy before (baseline drug resistance)[426]. The early identification of such mutations is critical for monitoring the progression of the disease but more importantly for adjusting therapy accordingly[427].

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 applied for the diagnosis of an infection or screening of blood donations. Some immunoassays have been designed to give rapid results in a non-laboratory setting.

NATs detect DNA (or RNA) sequences which are highly specific to the virus. These tests can detect genetic HIV material from very small quantities and with a quick turnaround, which makes them a critical tool for the early detection of an infection and in identifying mutated strains (genotyping). This application is crucial for monitoring drug resistance and disease management (e.g. applying appropriate therapy, monitoring of transmissions, etc.) and is widely applied. NATs display additional advantages over phenotypic assays in the context of HIV testing and drug resistance[427]. For example, their ability to identify emerging mutations before the phenotypic onset of drug resistance is another crucial advantage for a timely change in therapeutic strategy.

[425] WHO (2005). HIV/AIDS in Europe: overview. Fact sheet EUR/14/05. WHO Regional Office for Europe, Copenhagen. http://www.euro.who.int/Document/Mediacentre/fs1405e.pdf.
[426] Wensing, A.M.J et al. (2005). The Journal of Infectious Diseases **192**: 958-966. http://www.journals.uchicago.edu/JID/journal/issues/v192n6/34030/brief/34030.abstract.html.
[427] Blum, R.A. et al. (2005). Pharmacogenomics **6**: 169-179. http://dx.doi.org/10.1517/14622416.6.2.169.

Table 60: Cost-effectiveness of drug resistance testing – a comparison of US studies

Reference	Type of study	Target population	Main Results
Weinstein et al. 2001[1]	Modelling cost-effectiveness	HIV-infected patients in the US with a defined baseline of CD4 cell counts	Primary resistance testing for guiding initial therapy was cost-effective at USD 22 300 per QALY gained with 20% prevalence, but at USD 69 000 per QALY gained if the prevalence of resistant variants is lower (4%)
Sanders et al. 2005[2]	Modelling cost-effectiveness	Symptomatic patients who started treatment when CD4 cell counts dropped below a defined number	With a 1% prevalence of unidentified HIV infection, testing was cost-effective at a ratio of USD15 078 per QALY. But the ratio increased in populations with lower prevalence
Paltiel et al. 2006[3]	Modelling cost-effectiveness	US patients, low to moderate prevalence (0.05% to 1.0%)	Routine HIV screening was cost-effective at USD 30 800 per QALY (one-time screening) or USD 32 300 per QALY (screening every five years), in a population with 1.0% prevalence and 0.12% annual incidence Cost-effectiveness is not observed if prevalence of undiagnosed HIV infection is below 0.2% and thus routine HIV testing is not recommended Main limitation: determining prevalence and incidence of undetected HIV infection

[1] Weinstein, M.C. et al. (2001). Annals of Internal Medicine **134**: 440-450. http://www.annals.org/cgi/content/short/134/6/440.
[2] Sanders, G.D. et al. (2005). The New England Journal of Medicine **352**: 570-585. http://content.nejm.org/cgi/content/abstract/352/6/570.
[3] Paltiel, A.D. et al. (2006). Annals of Internal Medicine **145**: 797-806. http://www.annals.org/cgi/content/abstract/145/11/797.

The likelihood of early detection of mutated HIV strains is greatly enhanced if genotyping is applied at the onset of care. Further to this, the chance to detect mutations in patients before they revert to normal (wild-type) is also increased. Thus, resistance testing is now recommended for treatment-naive patients, and for patients who are not responding to therapy or during pregnancy (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)[428]. However, as these tests are relatively expensive, their widespread application is debated. Several studies have investigated the cost-effectiveness of routine use of genotyping for drug resistance in different scenarios (e.g. treatment failure or treatment-naive patients, prevalence, etc.). In the studies reviewed, genotyping was proven cost-effective although at different ratios (see Table 60), and still more cost-effective than, e.g. screening for colon cancer[429] or prophylaxis against other infections[430]. Moreover, cost-effectiveness persisted even when the prevalence was low. Although most of the studies reviewed investigated the situation in the US (testing is already reimbursed in all but two states of the US) one European study reports a similar result, i.e. that the routine use of genotypic antiretroviral resistance testing (GART) after each treatment

[428] Blum, R.A. et al. (2005). Pharmacogenomics **6**: 169-179. http://dx.doi.org/10.1517/14622416.6.2.169.
[429] CEVR (2002). Cost-utility ratios 1976-2001. Center for the Evaluation of Value and Risk in Health, Boston. http://www.tufts-nemc.org/cearegistry/data/.
[430] Saag, M.S. (2001). Annals of Internal Medicine **134**: 475-477. http://www.annals.org/cgi/content/short/134/6/475.

failure increases both life expectancy and healthcare costs per patient[431]. The use of GART after treatment failures is considered cost-effective and GART before the first treatment with Highly Active Anti-Retroviral Therapy (HAART) would also be cost-effective if it could lower the failure probability by a third. The cost-effectiveness of immunoassays is not clear.

The uptake of HIV genotyping in routine clinical practice is considered to have been influenced by the wide availability of such testing by reference laboratories and patient awareness, but is predicted to be further driven by the high costs of new drugs. As monitoring drug resistance is essential for the effective management of HIV-infected patients, the application of these biotechnology tests may have a significant impact on the epidemic (projections suggest that by 2015 in the 60 countries most affected by HIV/AIDS, the total population will be diminished by 115 million because of HIV/AIDS). In addition, studies support the fact that routine testing (mainly using NATs) would be cost-effective considering the costs that can be saved through early diagnosis of HIV carriers.

4.2.2.2 Cardiac diagnostic assays

Cardiovascular disease (CVD) was estimated to have contributed to a third of global deaths in 1999 and it is predicted to become the leading cause of death in developing countries by 2010[432]. In the EU, CVD causes more than 1.5 million deaths and is the main cause of years of life lost due to premature deaths[433]. The overall cost of CVD in the EU was recently estimated to be EUR 169 billion annually[434].

The term CVD collectively refers to a class of diseases affecting the heart or the blood vessels. Theses include, for example, arteriosclerosis, heart failure, endocarditis, hypertension and congenital heart disease. Individuals suffering from CVD, particularly arteriosclerosis, are at high risk for an Acute Myocardial Infarction (AMI, heart attack)[435], which currently represents the leading cause of death in the adult population in the US (one out of every five deaths[436]). The rapid diagnosis of an AMI episode (and its distinction from other non-critical conditions with similar symptoms) is critical for the effective management of the disease[437].

Tests for the diagnosis of AMI are based primarily on the detection of a defined set of biomarkers associated with this condition. Troponin, a protein found in the heart muscle, is a

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[431] Corzillius, M. et al. (2004). Antiviral Therapy **9**: 27-36. http://www.intmedpress.com/general/contents.cfm?JournalTypeID=1&SectionID=2&SectionSubID=1&SectionSubSubID=1.

[432] WHO (2007). Strategic priorities of the WHO Cardiovascular Disease programme. World Health Organisation, Geneva. http://www.who.int/cardiovascular_diseases/priorities/.

[433] Petersen, S. et al. (2005). "European cardiovascular disease statistics." British Heart Foundation, London. http://www.heartstats.org/1570/.

[434] Leal, J. et al. (2006). European Heart Journal **27**: 1610-1619. http://eurheartj.oxfordjournals.org/cgi/content/abstract/27/13/1610.

[435] A heart attack is caused by blocking the supply of blood and oxygen to the heart. This is typically a result of a clot in the coronary artery.

[436] AHA (2007). Heart attack and angina statistics. American Heart Association, Dallas, T.X. http://www.americanheart.org/presenter.jhtml?identifier=4591.

[437] AHA (2003). Heart and stroke facts. American Heart Association, Dallas, T.X. http://www.americanheart.org/presenter.jhtml?identifier=3000333.

very common biomarker with high prognostic and diagnostic value[438]. These assays are based on the use of monoclonal antibodies and can be grouped in two major categories: rapid tests which are used in the emergency care (point of care) and more quantitative tests used in a laboratory setting for a more detailed analysis. Their use in the clinic has allowed the rapid identification of patients suffering an AMI episode, as well as for the distinction of patients who display similar symptoms but are not actually in danger of an AMI (e.g. chest pains as a result of chronic indigestion). Additionally, these assays can be applied in monitoring disease progression in response to specific therapies.

The economic benefit for healthcare 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 the treatment of patients who are not in danger (it is estimated that only 15% of people admitted to hospitals with chest pains are actually experiencing a heart attack)[439]. Certain studies support this estimation. For instance, one investigation explored the cost-effectiveness of various diagnostic strategies for patients suffering from chest pains (one of the main symptoms of AMI but also of other non-life threatening conditions). These strategies included either cardiac enzyme testing alone or in combination with admission to the hospital for observation over a few hours or overnight. The study showed that immediate cardiac enzyme testing alone has incremental cost-effectiveness compared to enzyme testing combined with overnight hospital admission for further observation[440]. In further support of the potential cost-effectiveness of cardiac enzyme testing, certain hospitals have reported savings from the use of troponin assays (mainly as a result of minimising the number of days a patient might spend in the hospital just for observation), in spite of the high cost of the test[439,441].

4.2.2.3 Genetic testing

Modern biotechnology and genomic technologies 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 may predict disease (or risk thereof) through the analysis of a person's genetic make-up. Genetic testing has been defined by the OECD[442] as 'testing for variations in germline DNA sequences, or for products/effects arising from changes in heritable sequences, which are predictive of significant health effects'. This definition indicates that the analysis of genetic information may be made through varying methods including cytogenetic and biochemical testing. However, as the association of specific DNA sequences with a disease phenotype has greatly improved, particularly following the completion of the human genome project, DNA testing has expanded to be considered the main type of genetic testing. In this context, it is estimated that DNA testing is currently available for over 1000 genetic disorders and the methods rely mainly on detecting specific mutations (often at the single nucleotide level) through polymerase chain reaction (PCR) and

[438] Eggers, K.M. et al. (2004). American Heart Journal **148**: 574-581. http://pt.wkhealth.com/pt/re/amhj/abstract.00000406-200410000-00004.htm.
[439] ETEPS (2006). Bio4EU Task2 Case studie report – Human Health Applications.
[440] Goodacre, S. and N. Calvert (2003). Emergency Medicine Journal **20**: 429-433. http://emj.bmj.com/cgi/content/abstract/20/5/429.
[441] Polanczyk, C.A. et al. (1999). Annals of Internal Medicine **131**: 909-918. http://www.annals.org/cgi/content/bstract/131/12/909.
[442] OECD (2000) Workshop on Genetic Testing: Policy Issues for the New Millennium, Vienna http://www.oecd.org/document/16/0,2340,en_2649_37407_1895632_1_1_1_37407,00.html.

DNA sequencing[443]. Another recent report estimates that about 700 000 tests per year are performed in the EU, whereas information regarding the US points to a 30% increase in the number of genetic tests carried out between 1995 and 1996[444], although more recent data are scarce.

Genetic tests may be classified based on the purpose for which they are performed. The most common application is diagnostic testing typically carried out to complement the clinical diagnosis of a patient with symptoms that have a suspected genetic cause (e.g. the test for fragile X syndrome in children with learning difficulties). In this case, the test is used either for confirmation or exclusion of the diagnosis already made in the clinic. Predictive testing is the second most common application of genetic testing and comes in two varieties: presymptomatic testing, which is performed on healthy individuals who have a condition of delayed onset (e.g. Huntington's disease) and predisposition testing which informs medical staff of the increased or decreased risk of developing a certain condition. One such example is testing for mutations in the *BRCA1* and *BRCA2* genes, which confer susceptibility to breast cancer, although it is important to note that a positive result does not translate to 100% risk of developing cancer.

Genetic testing may also be utilised in reproductive decision-making and is usually pertinent when parents are at high risk or who have previous experience of a family member with a serious genetic disorder. This application includes carrier testing, prenatal testing and preimplantation genetic diagnosis (done in conjunction with *in vitro* fertilisation). The latter is only an emerging application which has expanded considerably in the recent years. Genetic screening is an extended application of predictive testing (i.e. prenatal or carrier testing) carried out for a specific population. This type of testing is organised and implemented by national or regional health authorities.

Pharmacogenetics is a newer application of genetic testing referring to the study of varied drug responses as a result of the differences in the genetic makeup of different patient populations. In 2002, the OECD estimated that pharmacogenetic tests represented about 5% of all testing carried out in laboratories in five EU countries (Italy, Austria, Finland, Portugal and the UK), the US and Canada. However, the availability of such tests has increased since then. Examples of currently marketed tests include tests for hereditary colon cancer, periodontitis, breast cancer (HER2), warfarin and 6-mercaptopurine poor metabolisers[445]. The ultimate aim of pharmacogenetic tests is to facilitate tailored therapy according to an individual patient's needs, thus reducing potential adverse drug reactions which represent a considerable burden on healthcare expenditure. Consequently, the application of pharmacogenetics is predicted to have a major impact on cost-savings. However, the overall potential contribution of pharmacogenetics to improving the efficiency of the healthcare systems requires further investigation.

Perhaps less visible, but quite common applications of genetic testing include paternity testing and forensics. Additionally, it is applied in disease stratification. Other applications, which are

[443] McPherson, E. (2006). Clinical Medicine and Research **2**: 123-129. http://www.clinmedres.org/cgi/content/abstract/4/2/123.
[444] Ibarreta, D. et al. (2003). Towards quality assurance and harmonisation of genetic testing services in the EU. European Commission, IPTS, EUR 20977. http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1124.
[445] Higashi, M.K. and Veenstra D.L. (2003). The American Journal of Managed Care **9**: 493-500. http://www.ajmc.com/article.cfm?ID=2.

only indirectly related to human health, include testing for animal diseases and food testing. The potential impacts of the latter are discussed in Section 4.3.3.

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 are well established which potentially contributes to 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[446].

However, a broader clinical implementation of genetic testing is still largely missing. For instance, the case study on phenylketonuria (PKU), a genetically inherited metabolic disease, indicates that testing is carried out primarily through 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[447]. Genetic testing based on DNA analysis is also not widespread for haemochromatosis, another common metabolic disorder characterised by iron overload, in spite of the clear knowledge of the causing disease mutations (two specific mutations have been identified with strong correlation)[448]. As only a few carriers actually require treatment, testing can be performed efficiently with biochemical techniques, although genetic testing may be applied e.g. to confirm an unclear biochemical diagnosis.

Table 61: Examples of marketed genetic tests and their approximate cost
Source: Higashi et al. 2003[449], adapted by IPTS

Gene	Clinical outcome	Test provider and approximate cost
Pathogenomics		
Mismatch repair genes	Prediction of risk for colon cancer (hereditary non-polyposis colorectal cancer HNPCC)	Available from multiple testing facilities: cost includes patient counselling USD 1300 - 3600
BRCA1	Prediction for risk of breast cancer	Myriad Genetic Laboratories, Inc USD 2760
Pharmacogenomics		
CYP2C9	Avoidance of major bleeding events	Genelex USD 135
TPMT	Reduced haematopoietic toxicity	DNA Sciences, Inc. USD 395

[446] McPherson, E. (2006). Clinical Medicine and Research **2**: 123-129. http://www.clinmedres.org/cgi/content/abstract/4/2/123.
[447] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.
[448] Pietrangelo, A. (2004). New England Journal of Medicine **350**: 2383-2397. http://content.nejm.org/cgi/content/extract/350/23/2383.
[449] Higashi, M.K. and Veenstra D.L. (2003). The American Journal of Managed Care **9**: 493-500. http://www.ajmc.com/article.cfm?ID=2

The frequent lack of clear genotype-phenotype associations results primarily from the complex nature of the human genome but also from the fact that several gene-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 and associated costs (both direct and indirect, e.g. for genetic counselling)[450]. For instance, *BRCA1* and *BRCA2* testing and counselling for breast cancer was estimated to cost more than USD 2000 per test in 2001[451]. However, in another case, the test may be relatively inexpensive but the accompanying therapy very costly, as is observed for HER2 testing[452]. A list of examples of marketed genetic tests and their approximate cost is provided in Table 61.

The cost-effectiveness of genetic testing depends on many factors such as the prevalence of the genetic mutation and the disease in the population and the penetrance[452]. However, only few economic analyses of genetic testing exist, and those available have covered a limited number of diseases. One study reports that screening of high-risk (Ashkenazi Jewish) women for *BRCA1/2* is cost-effective only when all women who test positive undergo prophylactic surgery[453]. However, the overall scarcity of cost-effectiveness studies for genetic testing impedes the evaluation of their potential impact on the efficiency of healthcare systems. An economic evaluation is further complicated by the unclear reimbursement situation and the limited information on patients' views related to these diagnostic technologies (e.g. are patients willing to pay for these tests even if their benefit is not clear). More research would be required to clarify these aspects influencing 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[454]. 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[455].

The social, legal and ethical implications of genetic testing must be taken into account when considering the overall benefit of technological advances in the area of diagnostics. DNA-based testing and genotyping are being increasingly applied to the prediction of drug response and risk for diseases such as breast cancer (facilitated by the continuous identification of relevant biomarkers). Thus genetic testing offers a unique opportunity for improved and early diagnosis of monogenic and complex disorders facilitating prevention and (more

[450] Higashi, M.K. and D.L. Veenstra (2003). The American Journal of Managed Care **9**: 493-500. http://www.ajmc.com/article.cfm?ID=2.

[451] Lawrence, W.F. et al. (2001). Cancer Epidemiology Biomarkers & Prevention **10**: 475-481. http://cebp.aacrjournals.org/cgi/content/abstract/10/5/475.

[452] Phillips, K.A. et al. (2004). The American Journal of Managed Care **10**: 425-432. http://www.ajmc.com/Article.cfm?Menu=1&ID=2651.

[453] Grann, V.R. et al. (2004). Journal of Clinical Oncology **22**: 494-500. http://jco.ascopubs.org/cgi/content/abstract/17/2/494.

[454] Smith, G.D. et al. (2005). The Lancet **366**: 1484-1498. http://dx.doi.org/10.1016/S0140-6736(05)67601-5.

[455] 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. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML.

personalised) therapy. However, the increasing collection of individual genetic information raises several concerns related to patient privacy, the potential misuse of a patient's genetic data and access to healthcare. The incidence of genetic discrimination as a result of such data misuse (e.g. in the form of employment termination or limitation/refusal of health insurance provision) is being increasingly addressed by regulators and policy-makers[456]. In this context, the European Group on Ethics in Science and New Technologies published an opinion regarding the ethical aspects of genetic testing in the workplace[457], based on which initiatives to protect employees' personal data have been announced by the Euroepan Commission[458]. The issue of preferential treatment of a specific subgroup of patients based on a genotypic test merits serious attention, as it may lead to racial discrimination[459]. This is particularly important for medical practice and healthcare management as, in certain cases, the predictive value of some genetic tests is not clearly demonstrated.

Additional ethical concerns are raised in the context of reproductive medicine. In this respect, the application of prenatal or preimplantation genetic diagnosis for establishing an unaffected pregnancy or identifying a genetic defect in the case of high-risk families, and the decisions connected to such diagnoses naturally raise questions related to the status of the embryo and the potential for eugenics[460,461], as the technology could be potentially applied for the selection of desirable traits in an embryo. However, there are other dimensions to this issue, in that the same technology can be utilised for the identification of an embryo that could serve as a donor of stem cells for the treatment of an existing person[462]. In such cases, immune rejection of the cells by the recipient is a critical factor for the success of the therapy, and genetic diagnosis for the identification of appropriate donors (HLA typing) is becoming increasingly important and is gaining support (through regulation).

In summary, it appears that diagnostics based on modern biotechnology are gaining importance in all aspects of clinical practice, including disease diagnosis, monitoring and prevention. However, their actual implementation in the clinic is widely varied ranging from routine (e.g. HIV testing for monitoring drug resistance) to limited use (e.g. genetic testing for PKU). Moreover, although these diagnostic tools may offer clinical benefits they also potentially pose economic strains to healthcare systems mainly due to their direct and indirect costs. Further cost-effectiveness studies would help elucidate their actual overall benefit. In

[456] The Lewin Group (2005). The value of diagnostics, innovation, adoption & diffusion into healthcare. AdvaMed, Washington, DC. http://www.advamed.org/publicdocs/july2005hillbriefing.shtml.

[457] European Group on Ethics in Science and New Technologies to the European Commission (2003). Ethical aspects of genetic testing in the workplace. Opinion No 18, 28 July 2003. http://ec.europa.eu/european_group_ethics/docs/avis18_en.pdf.

[458] 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. http://ec.europa.eu/biotechnology/pdf/com2005286final_en.pdf.

[459] Phillips, K.A. et al. (2000). Health Services Research **35**: 128-140. Abstract at http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1383600.

[460] The term refers to the improvement of human genetic traits through various interventions.

[461] Soini, S. et al. (2006). European Journal of Human Genetics **14**: 588-645. http://dx.doi.org/10.1038/sj.ejhg.5201598.

[462] Boyle, R.J. and Savulescu J. (2001). British Medical Journal **323**: 1240-1243. http://www.bmj.com/cgi/content/extract/323/7323/1240.

this context, it is important to note that some experts highlight the use of these diagnostic tools to complement, rather than to replace, clinical medicine[463].

4.2.3 Preventives

Recombinant hepatitis B vaccine, the first modern biotechnology vaccine authorised for humans, was selected as a case study for the assessment of the effectiveness of biotechnology in preventives. The results of this case study are discussed in the following.

4.2.3.1 Recombinant hepatitis B vaccine

Hepatitis is an inflammation of the liver that is caused by a virus, and while there are five different hepatitis viruses, the hepatitis B virus (HBV) is the most serious type: HBV can cause an acute disease with symptoms lasting several weeks including the yellowing of skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain. It can take several months to a year to recover, but HBV can also cause chronic infection and many years later this can develop into cirrhosis of the liver or liver cancer – diseases that kill about one million persons each year worldwide and can hardly be treated. HBV is transmitted by contact with blood or body fluids of an infected person; the main ways of getting infected with HBV are from mother to child at birth (perinatal), from child to child contact in household settings, from unsafe injections or transfusions and from sexual contacts. But while the former ways of infection are more frequent in developing countries, in industrialised countries the majority of infections are acquired during young adulthood by sexual activity, and injecting drugs; HBV is also the major infectious occupational hazard of health workers[464].

According to the WHO, currently more than 350 million people worldwide are infected with HBV and have to live with chronic infections, i.e. about 6% of the global population carries the virus. For Europe in 2004 (including the countries of the former Soviet Union, Turkey and Israel), the WHO reports an incidence rate of 5.95 new cases of hepatitis B per population of 100 000 (down from an incidence rate of 19.20 in 1995), while for the EU the reported incidence rate for 2004 was only 3.49 (down from 6.55 in 1996), even though for the EU this amounts to a small increase over 2003 when the incidence rate was only 3.43[465]. Given that the EU had a population of 458 973 024 in 2004[466], this corresponds to 16 018 new hepatitis B cases in 2004. However, half of all hepatitis B infections may go unreported and two-thirds of the infections are asymptomatic[467]. Under this premise, there may have been almost 100 000 new infections in 2004. Furthermore, given the high prevalence of HBV carriers in the rest of the world, HBV infections remain a risk.

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[463] McPherson, E. (2006). Clinical Medicine and Research **2**: 123-129. http://www.clinmedres.org/cgi/content/abstract/4/2/123.

[464] WHO (2000). Hepatitis B. Fact sheet 204. World Health Organisation, Geneva. http://www.who.int/mediacentre/factsheets/fs204/.

[465] WHO (2006). European Health for All Database (HFA-DB), June 2006. WHO Regional Office for Europe, Copenhagen. http://data.euro.who.int/hfadb/.

[466] Eurostat (2006). Population by sex and age on 1 January of each year. Theme: Population and Social Conditions. European Commission, Eurostat, Luxembourg. http://epp.eurostat.ec.europa.eu/.

[467] Van Damme, P. et al. (1995). Vaccine **13**: S54-S57. http://dx.doi.org/10.1016/0264-410X(95)80053-G.

The first vaccine against HBV became available in 1982. The agent for vaccination against hepatitis B contains a surface protein of the virus that triggers the development of antibodies and, thus, neutralises the infectivity of HBV. This protein is produced in the liver of chronically infected persons from where it spills into the blood. Consequently, for the first generation of vaccines, these agents were extracted from the plasma of infected persons, purified and inactivated. These plasma vaccines are still used in those parts of the world where biotechnological know-how is missing and where the incidence of hepatitis B is high (so that chronically infected donors of plasma are readily available). However, plasma vaccines have been largely replaced in the industrialised countries since 1986 when recombinant vaccines became available. These vaccines are produced in recombinant yeast and, therefore, are free from human plasma particles and potential contamination of the vaccine with infectious material. In the EU, the last plasma vaccine was taken off the market in 1991. Factors fuelling the transition from plasma to recombinant hepatitis B vaccines were not only the availability of the technological know-how, but – following the experience with HIV contaminated blood products in the 1980s – the fears of new safety hazards[468].

Either way, hepatitis B vaccines have an outstanding record of safety and effectiveness. Only about 1 - 6% of those who receive the vaccine develop a mild fever that lasts one or two days after injection of the vaccine, and more severe reactions and complications due to the vaccine are rare: allergic reactions occur about once every 600 000 doses and no fatal allergic reaction has been reported so far[469]. Since 1982, over one billion doses of hepatitis B vaccine have been used worldwide, and studies have shown that the vaccine is 95% effective in preventing chronic infection if the patients have not yet been infected[470].

Because plasma vaccines have by and large been replaced by recombinant vaccines in the industrialised world in the early 1990s, there is little comparative information on the production of plasma vaccines available (in the context of industrialised countries). The plasma vaccines were relatively expensive and testing was time-consuming because of the routine testing of the vaccine's safety (innocuity) in chimpanzees, and because the availability of plasma from chronically infected persons was limited in low-endemicity industrialised countries[471]. In contrast, in these countries the biotechnological know-how and the genetically modified yeast strains were readily available and, therefore, the production of recombinant hepatitis B vaccines was relatively easy. Still, because of the need to demonstrate the safety and efficacy of the new vaccines in clinical studies, these new vaccines were initially substantially more expensive than the traditional products, also because the companies carrying out the underlying research had to protect their economic interests through the application of patents for their discoveries[472].

Nevertheless, after the introductory period of the new vaccine, i.e. by the mid-1990s, the sterile production of the agents from plasma in the EU had probably already become more expensive than the production of the antigen in recombinant yeast, and (in Germany) about half the end price of the vaccine could be attributed to sales and distribution costs and not to

[468] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.
[469] WHO (2006). Hepatitis B: the vaccine. IVB Topics. World Health Organisation, Geneva. http://www.who.int/immunization/topics/hepatitis_b/.
[470] WHO (2000). Hepatitis B. Fact sheet 204. World Health Organisation, Geneva. http://www.who.int/mediacentre/factsheets/fs204/.
[471] Stephenne, J. (1988). Vaccine **6**: 299-303. http://dx.doi.org/10.1016/0264-410X(88)90173-9. (Information quoted in ETEPS (2006). Bio4EU Task2, case studies report: human health applications.)
[472] Poirot, P. and Martin J.F. (1994). Cahiers Santé **4**: 183-187. http://www.john-libbey-eurotext.fr/fr/revues/sante_pub/san/e-docs/00/04/1F/9A/resume.md?type=text.html.

the actual production of the vaccine[473]. While easier production and more competition may have driven down factory prices over time, nominal list prices for the hepatitis B vaccine in Germany have not changed much since 1983 and are still at a level of about EUR 60. However, available price information is inconsistent and some sources report considerably lower vaccine costs[474]. For example, the UNICEF Supply Division procures a dose of hepatitis B vaccine at the price of about EUR 0.20, excluding transportation and distribution costs[475]. The cost of a recombinant hepatitis B vaccine from producers of generic drugs in developing countries may be as little as one per cent of the price of a corresponding vaccine from multinationals in industrialised countries (e.g. the Indian company Shantha Biotechnics charges about EUR 0.95 for one course of the vaccine, while elsewhere international pharmaceutical companies may charge as much as about EUR 95)[476]. Yet, part of these differences may also be due to the fact that the production and use of vaccines is not only influenced by technical and economic factors, but also by changes in healthcare systems and vaccination strategies, or by national pricing and reimbursement policies.

It seems to be plausible that, apart from the clinical benefits in terms of higher (perceived) safety, there may also have been a production-based advantage of recombinant hepatitis B vaccines over the corresponding plasma vaccines. One may also suspect that the improved supply of hepatitis B vaccines has had a share in the above-mentioned decline in the incidence rates of hepatitis B. Therefore, hepatitis B vaccines have not only improved efficiency in the healthcare system, they have also contributed to more effective disease prevention and, thus, generated more widespread social benefits in terms of safeguarded work capacities and general well-being. Yet, given the lack of an appropriate counterfactual situation in which plasma vaccines have been used, it is difficult to judge how many of these benefits have to be attributed to *recombinant* hepatitis B vaccines in contrast to hepatitis B vaccines as such.

There have been several specific studies on the cost-effectiveness of various hepatitis B vaccination strategies – irrespective of whether the vaccines used are plasma or recombinant vaccines. The studies considered only cover industrialised countries to ensure comparability, because the social and economic effects of vaccination programmes depend on the underlying prevalence of the disease: the higher the prevalence is, the cheaper it is to avoid a new case. However, these studies give a mixed picture. While no study doubts the effectiveness of hepatitis B vaccines, sometimes the studies seem to be biased in favour of one particular vaccination strategy or the study's scientific quality seems questionable. The studies generally support the cost-effectiveness of one vaccination strategy or the other, i.e. the question is less whether hepatitis B vaccine as such can contribute to more efficiency in the healthcare system, but which vaccination strategy to choose[477].

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[473] Caspari, G. and Gerlich H.W. (1997). Deutsches Ärzteblatt **94**(26): A-1768. http://www.aerzteblatt.de/v4/archiv/artikel.asp?src=suche&id=6882.

[474] ETEPS (2006). Bio4EU Task2, case studies report: human health applications.

[475] Blanchet, S. (2006). Personal communication. Communication Officer, UNICEF Supply Division, Copenhagen (e-mail on 7 December 2006).

[476] DNM (2007). New Hep C drug means treatment for the masses. In-PharmaTechnologist Newsletter, Materials & Formulation, 04/01/2007. Decision News Media, Montpellier. http://www.in-pharmatechnologist.com/news/ng.asp?n=73091. *And:* Shantha (2007). Shanvac-B. Products. Shantha Biotechnics, Hyderabad. http://www.shanthabiotech.com/shanvac_b.htm.

[477] Miller, M.A. and McCann L. (2000). Health Economics **9**: 19-35. http://www3.interscience.wiley.com/cgi-bin/abstract/69502209/. *And:* Diel, R. (2003). Evaluation aktueller Impfstrategien gegen Hepatitis A und B. Heinrich-Heine-Universität, Düsseldorf. http://deposit.ddb.de/cgi-bin/dokserv?idn=974297135.

Given the available information discussed so far, it is difficult to assess the impact of recombinant vs. plasma hepatitis B vaccines. Mainly due to safety concerns (whether substantiated or not) within the EU, recombinant hepatitis B vaccines have now been used exclusively for 15 years. During the same period the incidence rates of hepatitis B within the entire EU have experienced a substantial decline. Although the contributing factors cannot be disentangled easily, the trust in the vaccine and its ease of availability may have had their share in this success. Moreover, the quick adoption of recombinant hepatitis B vaccines could also indicate their economic profitability over plasma vaccines. While the end-price of hepatitis B vaccines has not fallen considerably in the EU countries for which such information is available, this may have been due to other costs (like the sales and distribution cost of the product and national regulations).

4.2.4 The use of animals in research

Animals are being increasingly 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 a range of 75-100 million vertebrates are used worldwide per year in research, mainly related to drug development, the testing of vaccines and cancer research[478]. Most commonly, animals are used as research models for the study of a specific biological/molecular process associated with a disease or a genetic condition in humans, with the ultimate aim of developing a new therapy or of improving existing treatments[479]. The use of animal models has been particularly enhanced by the similarity of important molecular pathways between human and non-human species as uncovered by sequencing and comparing their genomes. For instance, mice and rats have a high homology to the human genome which may at least partly contribute to their frequent use as research models[478].

The contribution of animal models in medical advances may be illustrated by several examples, including their use in the development of the polio vaccine or techniques improving kidney transplantation, and the development of potential therapies for genetic conditions such as cystic fibrosis[479]. Additionally, animals may be used in compound screening and toxicity testing, as part of the drug development process. In spite of this, the use of animals in research has also raised concerns regarding the suitability of animals as models for human disease as it is argued that the differences that exist between humans and animals compromise the validity of these models in the study of disease or drug safety. At the same time, it is also recognised that careful design of the model could play a critical role in the outcome of the research. One illuminating example for this notion is that of thalidomide, a drug having been prescribed to pregnant women as an antiemetic (now withdrawn). The drug induced foetal malformations, which were not predicted by the mouse model used to test this drug initially. However, these side effects were later demonstrated when the drug was retested in pregnant mice.

Additional concerns relate to the welfare of the animals themselves (additional animal welfare issues are discussed in the previous section). Some reports indicate that experimental animals may experience discomfort ranging from minor (e.g. due to a procedure such as single blood

[478] Baumans, V. (2005). Scientific and Technical Review **24**: 503-514. http://www.oie.int/eng/publicat/RT/2402/A_R2402_BAUMANS.htm.

[479] Bateson, P. et al. (2004). The use of non-human animals in research: a guide for scientists. The Royal Society, London. http://www.royalsociety.org/displaypagedoc.asp?id=11514.

sampling) to moderate and severe (resulting, for example, from recovery from anaesthesia or toxicity testing). The latter two categories represent a respective share of 30% and 20% of all laboratory animals[480]. Specific animal models are most typically developed through genetic modification (e.g. gene insertion or deletion, introduction of targeted mutations), which has been suggested to have a potentially negative impact on the welfare of laboratory animals as a result of either the procedures employed to achieve the modification (e.g. microinjection of transgene) or of the modification itself. For instance, the introduction of a new gene may impact the health of the mouse[481]. It has also been suggested that experimental animals may be compromised immunologically which might, in turn, render them inappropriate for research (leading to unreliable conclusions)[482]. The increasing production of genetically modified animals for research (increase of more than 23% per year) further contributes to these welfare concerns[480].

Overall the use of animals in research has made a recognised contribution to both scientific and medical advances, but welfare issues potentially related to this use cannot be ignored. The '3Rs principle'[483] (i.e. 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 if available (e.g. *in vitro* techniques using cells or tissues), reduction refers to the decrease of the number of animals used in research to the minimum possible (e.g. by standardising procedures) and refinement aims at minimising animal discomfort. Modern biotechnology applications may facilitate these objectives. For instance, the increasing use of *in vitro* methods for toxicity testing or as screening tools could contribute to the reduction of animal use (full replacement may not be possible as *in vitro* systems cannot completely reflect the complexity of living systems). At the same time, the knowledge gained through genomics allows a better (more refined and standardised) experimental design which could, in turn, impact the number of animals used per experiment. The 3Rs principle has been acknowledged by the existing EU legislation on animal protection (Directive 86/609/EEC[484]) and is also a key component of the recently adopted Community Action Plan on the Protection and Welfare of Animals, which outlines specific measures for the promotion of animal welfare in the EU until 2010[485].

[480] Baumans, V. (2005). Scientific and Technical Review **24**: 503-514. http://www.oie.int/eng/publicat/RT/2402/A_R2402_BAUMANS.htm.

[481] Osborne, N. (2006). The impact of modern biotechnology on animal welfare. Submission by the EuroGroup for Animal Welfare in the context of this study's stakeholders dialogue (http://bio4eu.jrc.ec.europ.eu/stakeholders.html). *And:* Baumans, V. (2005). Scientific and Technical Review **24**: 503-514. http://www.oie.int/eng/publicat/RT/2402/A_R2402_BAUMANS.htm.

[482] Poole, T. (1997). Laboratory Animals **31**: 116-124. Abstract at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9175008.

[483] Russell, W.M.S. and Burch S.L. (1959). The principles of humane experimental techniques. Methuen & Co., London. Updated edition at http://altweb.jhsph.edu/publications/humane_exp/het-toc.htm.

[484] 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 L358/1 18.12.1986. http://ec.europa.eu/food/fs/aw/aw_legislation/scientific/86-609-eec_en.pdf.

[485] European Commission COM (2006) 13 final: 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. http://ec.europa.eu/food/animal/welfare/com_action_plan230106_en.pdf.

4.2.5 Summary

In the previous sections the impact of modern health biotechnology on public health policy objectives has been illustrated by means of eight case studies. The results of these analyses only allow generalisations to some extent. In all cases, the biotechnology applications have some advantages, either by providing for better clinical interventions (like in the case of glucocerebrosidase, monoclonal antibodies, cardiac testing or HIV testing) or by improving perceived safety and quality of life of the individuals concerned (like in the case of human insulin, testing for PKU or hepatitis B vaccinations). In addition, the cost-effectiveness of some applications could not yet be established because the necessary long-term trials have not yet been carried out, but there is preliminary evidence of cost-effectiveness (like in the case of interferon-beta). Therefore, it seems to be warranted to conclude that modern biotechnology can indeed contribute to improved warning, monitoring and control of communicable diseases and to a reduction of non-communicable diseases incidence by improving the effectiveness of health interventions, reducing the burden of disease and/or improving the quality of life of those suffering from disease.

Regarding the second policy objective of achieving a reduction of healthcare and social costs as well as a reduction of disease burden, the results are less clear. In some cases, the application of modern biotechnology in fact increases efficiency in the healthcare sector, while in other cases it has simply become the standard application without in-depth evaluation of its cost-effectiveness (like in the case of human insulin or the recombinant hepatitis B vaccine). In some cases the assessment is only preliminary in nature (like for interferon-beta or monoclonal antibodies), or the new drug actually puts a strain on healthcare resources, even though this may be justified from an ethical point of view (like in the case of glucocerebrosidase). Given the relative novelty of most of these applications, further cost-effectiveness studies need to be carried out to assess the contribution of modern biotechnology to efficiency within healthcare systems.

Modern biotechnology also has implications for animal health and welfare (see also Section 4.3). On the one hand the use of animals in research has made a recognised contribution to both scientific and medical advances. On the other hand, the use of animals in research also implies animal welfare issues. Modern biotechnology, e.g. through the development of *in vitro* methods may help to contribute to the replacement, refinement and reduction of animal-based tests in research.

4.3 Agro-food biotechnology

4.3.1 The relevance of primary production and agro-food to public health

The agro-food sector has both direct and indirect relevance to the EU public health policy objectives: on the one hand, it is responsible for the provision of a large share of the food products consumed by EU citizens; on the other hand, there is an inherent interaction between primary sector activities and the natural environment. The major EU public health policy objectives relate to the protection of the EU citizen against health threats and to disease prevention, as well as to ensure that healthcare and related social costs are at a minimum, and that the objectives are attained cost-effectively. The agro-food sector activities have public health implications, mainly in terms of the following:

- major zoonoses (e.g. BSE and salmonellosis)
- chemical contaminants in the food chain (e.g. pesticides)
- food quality (e.g. related to the nutrient profile of the products)
- animal health and welfare
- healthcare and related social costs (e.g. public spending on animal disease eradication and monitoring).

The importance of food safety within the context of public health has been widely recognised by the EU society and EU policymakers. Food safety has emerged as an issue of utmost importance in the EU agenda, especially following a series of food scares in the late 1990s, which stressed the need for action at EU level. All of the above culminated in the review of the general food law at EU level and the creation of the European Food Safety Authority[486].

Modern biotechnology applied to the agro-food sector may have implications for all the public health issues identified above. For example, modern biotechnology applications in the propagation and breeding of plants, animals and fish, may aid in the selection of animals for better food quality, whereas modern biotechnology-based inputs to primary production, the food processing sector and the food chain in general, are of direct relevance for the health management of the farmed populations, as well as for the monitoring of the safety of the final product offered to consumers.

4.3.2 Breeding and propagation

Modern biotechnology currently applied in animal breeding and propagation mainly have animal health and welfare implications, and the discussion will therefore be limited to these aspects. A number of recent R&D projects, however, are now aiming at other public health objectives, such as targeting the development of disease resistant animals (e.g. the development of BSE resistant cattle via genetic modification) or the selection for nutritional quality traits (e.g. through marker assisted selection).

[486] 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 in matters of food safety. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:EN:PDF.

4.3.2.1 Animal health and welfare[487]

Animal welfare has been receiving increased attention by society and the EU policy agenda in recent years. Modern biotechnology may have several and contrasting implications for animal welfare. On the one hand there are issues with negative connotations, such as the use of what are perceived as intrusive techniques or techniques that may involve additional risks for animals; on the other hand, modern biotechnology provides solutions that improve animal 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.

Modern biotechnology applications that have been associated negatively in terms of animal welfare mainly concern those that are applied directly to animals such as embryo technologies in livestock and ploidy and sex manipulation in fish. A baseline concern of some stakeholders is the artificial aspect of these technologies, with respect to natural selection and reproduction, which however is a common feature of the mainstream agricultural practices in general. As regards embryo transfer (ET), ovum pick-up (OPU), which is part of ET methods, is an invasive method and may have a negative impact on the welfare of individual animals that needs to be balanced by the benefits obtained by the technology. The acceptance by animal welfare organisations of these and other related assisted reproduction technologies (e.g. artificial insemination - AI, *in vitro* fertilisation - IVF, culture of embryos, cloning, and others) was reviewed by Kolar and Rusche[488]. Of the six organisations surveyed, two did not accept ET and *in vitro* embryo production (IVP), while only two generally accepted AI. Overall, of importance to most organisations was the specific context of each application, e.g. regarding the objectives and potential side effects. Public perception of reproduction techniques was also considered for France and the UK in the SEFABAR project[489]. It was found that AI had unanimous acceptability in these two countries with the author interpreting this to be as a consequence of both its length of service and its successful application in human reproduction. 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 the means of addressing concerns.

ET is considered a very safe method of disseminating genetic characteristics from an infectious disease point of view (under regulations established by IETS[490] and OIE[491]). Thus, on a global level it is thought of by some as contributing positively to animal welfare in terms of animal health. The effective use of ET in breeding programmes means that there is an

[487] Non-referenced information is based on expert opinion and data from (ETEPS (2006). Bio4EU Task 2 Case studies report – Primary Production and Agro-food Applications).
[488] Kolar, R. and Rusche B. (2003). Animal welfare aspects of farm animal breeding and reproduction: chances for a sustainable future? In: Liinamo, A.E. and Neeteson-van Nieuwenhoven A.M. (eds.). SEFABAR: Sustainable European Farm Animal Breeding And Reproduction. Proceedings of the final workshop, 4 September 2003, Rome. European Forum of Farm Animal Breeders, Oosterbeek, p. 17-35. http://www.sefabar.org/component/option,com_docman/task,doc_view/gid,28/Itemid,33/.
[489] Ouédraogo, A.P. (2003). Symbolic goods in the market place, public perceptions of farm animal breeding and reproduction in France and the UK. In: Liinamo, A.E. and Neeteson-van Nieuwenhoven A.M. (eds.). SEFABAR: Sustainable European Farm Animal Breeding *And* Reproduction. Proceedings of the final workshop, 4 September, Rome. European Forum of Farm Animal Breeders, Oosterbeek, p. 36-46. http://www.sefabar.org/component/option,com_docman/task,doc_view/gid,28/Itemid,33/.
[490] IETS: International Embryo Transfer Society.
[491] OIE: World Organisation for Animal Health.

overall reduction in the number of cows required to produce candidate bulls. Sexed semen may also be viewed positively from a welfare point of view, as it will mean that replacement heifers can be produced from a smaller number of cows, so that the number of unwanted bull calves will be significantly reduced. Lastly, it is argued that ET is a key tool for keeping the EU cattle sector competitive in the global arena, and that maintaining a production industry ensures that production complies with the social requirements within the countries of the EU. This will include the development of (animal breeding) approaches that fit into sustainable land use programmes (holistic approaches to food chain production).

As far as ploidy and sex manipulation in fish are concerned, both positive and negative views on their impacts to animal welfare have been expressed. 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 induced through early maturation, and its associated characteristics, such as reducing the need for chemotherapeutics. The induction of triploidy, has been associated with increased deformity and disease susceptibility (low stress tolerance) but also the beneficial avoidance of maturity related stressors.

Assisted breeding through the use of modern biotechnology (molecular markers) has also been discussed regarding its impact on animal welfare, although to a smaller extent. Marker assisted selection (MAS) is not considered to be different in qualitative terms from the classic quantitative genetics-based breeding as the means and targets are similar. The major difference brought about by MAS is on the improved efficiency in driving genetic selection. Direct impacts to animal welfare will depend on the trait targeted: conventional breeding through quantitative genetics has been already criticised for selecting production traits without due concern for specific animal welfare issues[492]; therefore, the relevance of MAS to animal welfare depends more on the targeted trait than the technology itself.

A positive aspect for animal welfare is the fact that MAS is directed more towards selecting for multi-gene dependent traits that were difficult to address before through conventional genetic selection. The focus is therefore moving away from the clearly productivity-related attributes to disease resistance and product quality, which have positive animal welfare implications. A look at the identified traits targeted in pigs indicates that MAS has already been directly applied in favour of animal welfare traits: an example which, according to expert opinion, has been extensively applied already in pig production is the selection against the 'Halothane' gene which has reduced preslaughter mortality in pigs from between 4-16 per 1000 pigs to nearly zero. Similarly, a survey of two Spanish commercial abattoirs suggested that preslaughter deaths (during transport and time in lairage) could be reduced from 0.22% to 0.02% through selection against the 'Halothane' gene[493]. Another example given was the K88 marker indicating resistance to diarrhoea in pigs. This disease can result in a large number of deaths of young pigs. The interviewee noted that the disease could be controlled cheaply by the use of antibiotics but this would result in a loss of public good will and it was therefore appropriate to use MAS rather than antibiotics. However, some of the traits targeted, such as

[492] See for example: European Commission (2000). The welfare of chickens kept for meat production (broilers). Report of the Scientific Committee on Animal Health and Animal Welfare, Adopted 21 March 2000. http://ec.europa.eu/food/fs/sc/scah/out39_en.pdf.

[493] Fàbrega, E. et al. (2002). Animal Welfare 11(4): 449-452. http://www.ingentaconnect.com/content/ufaw/aw/2002/00000011/00000004/art00007.

increased litter size, would also require the consideration of potentially negative indirect animal welfare effects[494].

4.3.3 Modern biotechnology-based diagnostics and vaccines

Modern biotechnology-based diagnostics and animal health products have a direct relevance for the achievement of major public health policy objectives. As already presented in Section 2.3.5.2 and Section 2.3.5.3 there are a number of diagnostic and vaccine products available on the market while an even larger number is currently under development.

4.3.3.1 Zoonoses and food safety

4.3.3.1.1 Diagnostics[495]

Diagnostics are essential for supporting the operation of the food chain through early and quick identification of pathogens, thus avoiding animal suffering from diseases and supporting food safety. Furthermore, diagnostics also support the monitoring and compliance with regulatory obligations as well as consumers' freedom of choice, e.g. in the case of traceability of genetically modified organisms (GMOs). Contagious diseases such as foot and mouth disease are of minor danger for humans but, if not controlled, spread rapidly and involve the suffering of many animals, apart from causing 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.

Modern biotechnology-based diagnostics are characterised by several advantages over conventional diagnostics, the main ones being: i) a decrease in the time needed to conduct an analysis, ii) enabling their incorporation in pen-side tests, thereby facilitating on-site testing, iii) improving the accuracy and/or sensitivity of an analysis, iv) providing a cost-effective solution and iv) providing the sole alternative for the diagnosis of a disease. Overall, the main impacts arising from the use of modern biotechnology diagnostics are mainly related to faster and accurate diagnosis, thereby indirectly reducing the impact of a potential zoonoses outbreak. Moreover, the availability of modern biotechnology diagnostics may be the only practical and/or cost-effective option towards meeting regulatory requirements within the context of disease surveillance and food safety, thereby indirectly ensuring functional trade regimes, trade exchanges and public confidence. Illustrative examples are provided in the following paragraphs.

[494] See for example Weary, D.M. et al. (1998). Applied Animal Behaviour Science 61: 103-111. http://dx.doi.org/10.1016/S0168-1591(98)00187-7.

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

Foot and mouth disease (FMD)

FMD is one of the most contagious diseases of mammals and has a great potential for causing severe economic losses. Since the last outbreak in 2001, there have been no new cases of FMD reported across the EU Member States. Since 2001, Member States have increased their focus on FMD and their surveillance activities, as well as the development of biotechnological tests for the earlier and more rapid confirmation of FMD, mainly for the avoidance of misdiagnosis (that is linked to extensive animal culling) and for facilitating testing the large numbers of samples. While this may be contributing to the fact that no new cases of FMD have been reported since 2001, it is not possible to attribute this fall in incidence to new biotechnological approaches for the early diagnosis of FMD. The potential impact arising from the avoidance of new outbreaks may be illustrated based on analyses of the last outbreak in the UK, where the UK government alone is estimated to have lost GBP 2.4 billion over two years (mainly due to compensation payments and lower tax returns following a decline in economic activities). However, this sum does not include the more drastic losses incurred by agricultural export, transport, tourism, hotels and restaurants in the UK[496]. Moreover, the European Commission provided compensation, under an Emergency Veterinary Fund, estimated for the period 2001-2002 at EUR 800 million. Last but not least, the eradication efforts for the 2001 outbreaks included the killing and destruction of over 4 million animals. This illustrates the considerable social cost of not detecting FMD early enough.

Bovine spongiform encephalopathy (BSE)

In the case of BSE, modern biotechnology provides the only method for a rapid processing of samples and diagnosis and thus enables the level of surveillance required by EU legislation[497]. BSE monitoring and eradication became very important after the public health risk to nvCJD (new variant Creutzfeldt-Jakob Disease) from the consumption of BSE-infected meat was identified in 1996. Until end of 2006, approximately 162 cases of nvCJD were identified in the UK and 36 more in the rest of the world (of which 30 were in the EU). However, the largest impact relates to the loss of consumer confidence, trade implications and the high cost of monitoring and eradication. For example, in the UK, sales of beef fell by 40%, the price of beef fell by more than 25%, export markets were lost (trade estimated to be about GBP 520 million), and there were effects on employment, as abattoirs temporarily closed or reduced their working hours. It was estimated that, in the year following the start of the BSE crisis, the total economic loss to the UK was between GBP 740 million and GBP 980 million (0.1 - 0.2% of the UK's GDP)[498]. 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

[496] Blake, A., Sinclair, M.T, and Sugiyarto, G. (2001) The Economy-Wide Effects of Foot and Mouth Disease in the UK Economy, Discussion Paper 2001/3, Nottingham University Business School, UK https://www.nottingham.ac.uk/ttri/pdf/2001_3.PDF.

[497] Regulation (EC) No 999/2001 of the European Parliament and of the Council of 22 May 2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies. http://ec.europa.eu/food/fs/bse/bse36_en.pdf.

[498] Atkinson, N. (1999). The impact of BSE on the UK economy. Meeting on transmissible spongiform encephalopathies (TSE), 9-11 August. Inter-American Institute for Cooperation on Agriculture, San Jose. http://www.iica.org.ar/Bse/14-%20Atkinson.html.

at EUR 92 billion[499]. Thirteen different immunoassays have now been approved in the EU for BSE testing of slaughtered animals before they enter the food chain, thereby reducing the risk of contamination and increasing consumer trust in beef meat. However, food safety and consumer confidence come at a cost, which in this case is mainly borne by public authorities at the EU and the Member States levels, as well as by the cattle industry and consumers. Between 2001 and 2004 around 44.7 million cattle were tested at overall costs of EUR 1835 million. Considering only healthy animal stock, around EUR 1.56 million were spent per identification of a BSE case, whereas EUR 0.07 million per identification of a BSE case were spent in at-risk animal stock. Nevertheless, the introduced measures were essential for eradication, and restoring public confidence and markets, while the development of rapid test kits were necessary in order to cope with the large numbers of samples which were necessary to process.

Salmonellosis

A new generation of modern biotechnology-diagnostic methods could also enable a faster detection of the food pathogen *Salmonella* bacterium. Salmonella cause food poisoning and is the second most prevalent food pathogen after *Campylobacter*. In 2004, on average 42.2 cases per 100 000 inhabitants were registered in the EU. While studies indicate that more than 80% of all salmonellosis cases occur individually rather than as outbreaks, early diagnosis may allow rapid preventative action in cases of large-scale contamination of the food chain, such as in the removal of tainted foods thereby reducing the human incidence of salmonellosis. An issue of increasing concern is the reporting of antimicrobial resistance in Member States, which is a concern as effective treatment may be compromised; rapid and serotype-specific diagnosis through modern biotechnology-based testing may prove especially helpful here.

While there has been a small declining trend in the human incidence of salmonellosis in the EU in recent years[500], it is difficult to attribute changes in reported disease incidence to emergent biotechnology applications for pathogen detection as, in several cases, better enforcement by an EU Member State and 'therapeutic' or 'preventative' techniques such as heat-treatment of eggs or vaccination of poultry are identified by the respective Member State's regulatory agencies as the key cause of the falling incidence of human zoonotic cases. However, methods using salmonella cultures, dominantly applied, require 4 to 7 days for presumptive evidence of salmonella in foodstuffs. This is often too long a time from a public health perspective when an outbreak can get expensive and serious in this timeframe. Methods that aim to shorten this timeframe often require techniques that combine preenrichment or selective enrichment with time saving genetic or immunological tests.

Rapid detection methods for the presumptive identification of salmonella usually rely on enrichment times of at least 40 hours. Overall, it is expected that rapid tests reduce testing times by 1 to 5 days. The costs for ensuring salmonella control and safety, are borne mainly by the food industry (farmers, retailers, processors), while the costs in the cases of human

[499] Cunningham, E.P. (ed.) (2003). After BSE: a future for the European livestock sector. EAAP Series no. 108, Wageningen Academic Publishers, Wageningen. http://cms2.ibvision.nl/_clientFiles/{7E09414A-876D-45D3-9E9C-D4BF7C1C6DD8}/more/EAAP108.pdf.

[500] EFSA (2006). The community summary report on trends and sources of zoonoses, zoonotic agents, antimicrobial resistance and foodborne outbreaks in the European Union in 2005. The EFSA Journal **94**. European Food Safety Authority, Parma.
http://www.efsa.europa.eu/en/science/monitoring_zoonoses/reports/zoonoses_report_2005.html.

salmonellosis outbreaks are borne by the patients and public health budgets. To this end, a US cost assessment in 2005 provided an estimate of the annualised cost of salmonellosis at about USD 2.4 billion with an average cost of USD 1709 per case, of which 89% related to premature deaths, 8% to direct medical costs and 3% to costs of productivity loss[501].

Genetically modified organisms (GMOs)

Modern biotechnology also enables the identification and quantification of genetically modified (GM) ingredients in raw material and food. It thus facilitates compliance with EU regulations regarding traceability and labelling of food[502] and transparency and consumer choice regarding GM food. Moreover, the ability to detect and quantify GMOs also provides the possibility for the long-term monitoring of the commercial use of GM products. Traceability requirements for GM food and feed and the corresponding documentation and traceability systems would therefore facilitate the withdrawal of products where unforeseen adverse effects on human and animal health or the ecosystems are detected.

4.3.3.1.2 Vaccines[503]

Prevention of diseases in farm animals plays an important role in terms of economics, animal welfare and public health (zoonoses). 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 the so-called marker vaccines, which allow the distinction 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 live vaccine against pseudorabies or Aujeszky´s disease is one example, which is also the first GMO authorised in the EU.

Aujeszky´s disease primarily affects pigs, a major livestock species produced in the EU. It is caused by a virus and results in nervous disorders of affected animals, increased mortality of piglets and reduced fertility. The biotechnological vaccine was developed in the early 1980s with two main objectives: to develop a live vaccine (known to be more effective than inactivated viruses) and to develop a vaccine which allows the distinction between vaccinated and infected animals, thus facilitating the eradication of the disease. Genetic engineering was used to produce a modified virus, which was approved in 1989, that is not infectious and where, due to the deletion of a specific surface protein, vaccinated pigs can be distinguished serologically from pigs infected with the natural virus. The vaccine therefore enabled the cost-effective EU eradication programme of Aujeszky´s disease to take place, with arguably

[501] ERS (2006). Foodborne illness cost calculator: salmonella. Economic Research Service, US Department of Agriculture, Washington, D.C. http://www.ers.usda.gov/Data/FoodborneIllness/salm_Intro.asp.

[502] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. OJ L 268/1 18.1.2003. http://europa.eu/eur-lex/pri/en/oj/dat/2003/l_268/l_26820031018en00010023.pdf. *And:* Regulation (EC) No 1830/2003 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 L 268/24 18.10.2003. http://europa.eu/eur-lex/pri/en/oj/dat/2003/l_268/l_26820031018en00240028.pdf.

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

positive implications to the livestock sector, but also to the public budget due to less compensation payments. 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 their vaccination programmes and three are currently vaccinating the endemically affected population.

4.3.3.2 Animal health and welfare

Besides the implications of modern biotechnology applied directly to animals to animal welfare, other modern biotechnology applications may have a range of interactions with animal welfare. Modern biotechnology provides improved or novel diagnostics, with positive animal welfare effects. For example, modern biotechnology-based diagnostics facilitate early diagnosis for a number of animal diseases, which is instrumental in their control and eradication, and therefore in the reduction of the number of animals that suffer from diseases or that are culled (e.g. FMD, salmonellosis, etc.) or may even provide the sole option in detecting a disease (e.g. BSE). Similarly, modern biotechnology-based vaccines are beneficial for animal welfare for a number of reasons. For example, vaccines are in general the most efficient strategy for the eradication of any disease and they rely on prevention, thus avoiding the need for chemical treatment. Moreover, marker vaccines (such as Aujeszky's disease vaccine) have the added benefit in that they allow disease monitoring during the eradication programme and therefore targeted animal culling before symptoms appear (they may also be the only approved vaccine product available on the market). While some biotechnology-based inputs to animal production have received some criticism regarding animal welfare, such as the potential risks to animal health through the feeding of GM feed or additives, all commercially available products in the EU are placed on the market only after they have gone through the obligatory pre-market safety assessments.

4.3.4 Summary

Modern biotechnology provides essential tools, mainly through diagnostics and vaccines, towards the assurance of EU-wide food safety and consumer confidence in the food chain. Areas where the highest impacts have already been realised include the monitoring and control of some of the most important zoonoses and food safety concerns. Besides the direct impacts towards food safety and public health, these modern biotechnology applications have indirect implications in the assurance of consumer confidence and the related trade, which may manifest themselves in the avoidance of negative economic consequences. On the other hand, there are a number of animal welfare issues regarding animal production techniques, some of which relate to the use of modern biotechnology. A case by case evaluation may therefore be needed when such challenges arise, as they may be specific to particular applications.

5 Conclusion

Biotechnology, and in particular modern biotechnology, is considered one of the key enabling technologies of the 21st century. Its potential for providing economic growth and jobs in a wide range of sectors, as well as for sustainable development, has been widely recognised[504]. This study confirmed the considerable diffusion of modern biotechnology, mainly in three major areas: human and animal health, agro-food and industrial manufacturing processes. Modern biotechnology products and processes are, for example, used in the cultivation of crops, in animal husbandry and fisheries (aquaculture), in food processing, in the manufacture of textiles and leather, in the production of pulp and paper, in fuel production, in the manufacture of chemicals (including pharmaceuticals), in healthcare, and in research.

5.1 Contributions of modern biotechnology to the Lisbon Strategy

5.1.1 Economic significance of modern biotechnology applications

The broad diffusion that modern biotechnology has experienced as an enabling technology is also reflected in the fact that it is estimated to contribute – just through its applications in industrial manufacturing processes including food processing – to about 0.88% of EU Gross Value-added (GVA). The significance of this figure becomes clearer if compared to, e.g. the share of GVA of 2% that is generated by the entire agricultural sector. On a more disaggregate level, for instance, biotechnology-based products for human health contributed over 5% to the GVA of the pharmaceutical industry, or 0.04% to the EU GVA; this surpassed the contribution of other industrial subsectors such as man-made fibres, and points to the significant economic value of the corresponding products.

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 health sector, where modern biotechnology is widely applied, for example in *in vitro* diagnostics, biotechnology applications contribute about 30% to overall turnover in the EU, whereas in therapeutics, biopharmaceuticals have a 9% share of the EU's total pharmaceuticals turnover. Regarding industrial manufacturing, modern biotechnology adoption diverges even more; this is reflected in the turnover shares of individual applications, which range from less than 1% in the case of biotechnology-based polymers, to 10% in pulp and paper and 30% in detergents, all the way up to 100% in some food production processes (e.g. fruit juice). In the agro-food sector, modern biotechnology is estimated to directly contribute to 13 - 23% of the overall turnover of input sectors such as breeding or feed additive production. Furthermore, the use of these biotechnology-based inputs affects more than 30% of the agro-food sector's total turnover. Still, the economic significance of modern biotechnology in this sector also depends very much on the specific application. Some modern biotechnology applications are thought to have reached their peak in terms of adoption, while, e.g. genetic engineering in crop seed production has thus far only played a minor role within the EU. In other cases, such as embryo transfer in cattle, the direct adoption rate may be small, but it is economically

[504] European Commission COM (2002) 27: Communication form 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. http://ec.europa.eu/prelex/detail_dossier_real.cfm?CL=en&DosId=171079.

significant because it is used for high value production at the top of the breeding pyramid. Given these different degrees of adoption, future growth potential exists and the related turnover is expected to grow insofar as modern biotechnology enables the provision of new or better products or enhances efficiency. For instance, such dynamic developments can be discerned in health biotechnology, where the EU market for biopharmaceuticals grows an average of 23% annually, twice as much as the overall EU pharmaceuticals market average growth rate (11%).

Overall, modern biotechnology applications relate to the generation of about 1.43 - 1.69% of EU GVA.

5.1.2 Effects of modern biotechnology on employment

In terms of employment, the contribution of modern biotechnology is mainly seen in the creation of 'better jobs'. More highly qualified employment also potentially contributes to higher labour productivity. 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 probably corresponds to the overall diffusion of biotechnology applications. Just as with the diffusion of biotechnology applications, it can be assumed that a portion of the newly-generated jobs substitutes existing ones.

5.1.3 Effects of modern biotechnology on competitiveness

Modern biotechnology also contributes to higher labour productivity via efficiency gains. Industrial manufacturing processes that apply modern biotechnology are estimated to have an average of 10% to 20% higher labour productivity. This potentially improves competitiveness, as well as the development of new products that stem from the application of modern biotechnology. However, in other countries several applications of modern biotechnology have experienced more comprehensive and quicker adoption, i.e. these countries could increase their competitiveness relative to the EU. More specifically, in terms of the adoption of modern biotechnology, in many cases the US has now become the benchmark. For instance, while the US embarked later than the EU on the production of bioethanol, corresponding policy support helped its enterprises gain a large share of world production within a few years. Developments in China and India indicate that, at least in terms of market size, these countries may also soon outpace the EU. Regarding the market for biotechnology-based polymers, here the US also has a strong position, although Japan is the world market leader in producing acrylamide. In the field of health biotechnology, for instance, only 15% of the biopharmaceuticals on the market were developed by EU companies, compared to the more than 50% that were developed by US companies. In the agro-food sector, however (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 those markets for which biotechnology-based products are relevant. This is supported by a considerable share in the export market for breeding and propagation material, as well as in the markets for veterinary products, diagnostics and feed additives.

5.2 Contributions of modern biotechnology to environmental sustainability

Modern biotechnology applications in the agro-food sector mostly aim to improve the production efficiency of primary production, and thereby contribute to the reduction of resource use and the emission of harmful substances. Yet, while these impacts are mostly of an indirect nature, direct impacts have been also realised. Examples include replacing drug and antibiotic treatments with the use of vaccines in animal production (many of which are produced using modern biotechnology), and reducing 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 for considering specific aspects or potential risks (e.g. in relation to GMOs or feed additives). To this end, the EU has enacted specific legislation that requires comprehensive risk assessments to be carried out before placing such products on the EU market.

In the case of industrial production processes, modern biotechnology applications mitigate greenhouse gas emissions (mainly carbon dioxide), waste generation and the use of non-renewable resources. Moreover, modern biotechnology applications also lead to savings in energy and water usage, as well as to reductions in the use of chemical inputs. In particular, reduced energy demand could lead to a decrease in greenhouse gas emissions, considering that industrial fuel combustion for energy generates more than 50% more greenhouse gases than the industrial production processes themselves. While the environmental impacts of biotechnologically produced chemicals cannot be depicted in their entirety because information for many processes is not available or accessible, exemplary information indicates that the environmental effects are similar.

Another, indirect impact of modern biotechnology could materialise through the use of biofuels in the transport sector, which, with 21% of total greenhouse gas emissions, is one of the largest greenhouse gas contributors. More than a third of this share (7.9%) is generated by petrol combustion. Hence, the blending of petrol with bioethanol could help to improve the environmental impact of this sector. Although the environmental impacts of bioethanol compared to fossil fuel depend on a variety of factors, the use of bioethanol currently produced in the EU was estimated to lead to greenhouse gas reductions of 35 - 50% compared to the conventional fuels they replace.

5.3 Contributions of modern biotechnology to public health and food safety

Modern biotechnology applications in the field of human health have major public health implications. The case studies presented in this report show that modern health biotechnology may provide various benefits, such as better clinical interventions (in the case of enzyme replacement therapies, monoclonal antibodies, cardiac testing or HIV testing) or potentially improved safety and a higher quality of life for the individuals concerned (in the case of human recombinant insulin or recombinant hepatitis B vaccine). Hence, modern health biotechnology contributes to improvements in monitoring and controlling communicable diseases and also to enhancing the effectiveness of medical interventions, thereby reducing the burden of disease or improving the quality of life of those suffering from disease.

The contribution of health biotechnology applications to reducing healthcare and social costs is not as clear: in some cases, these applications increase efficiency in the healthcare sector,

thus contributing to the objective of reducing healthcare costs; but in other cases, a new drug puts an overproportionate strain on healthcare resources. While the latter case is not specific to biotechnology-based therapies because it also applies to conventional approaches, it nevertheless emphasises the ethical question of how to allocate scarce resources in healthcare when efficiency considerations could prevent patients' access to potentially life-improving or even life-saving treatments. Yet, 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 need to be carried out. Moreover, as the technology matures and generic biopharmaceuticals (biosimilars) reach the market, product prices may be driven down, thus improving the cost-effectiveness of the related health interventions.

Similar to health biotechnology, the public health effects of modern biotechnology applications in the agro-food sector build on the availability of new and better diagnostics and vaccines. The monitoring and control of some of the most important zoonoses and food safety concerns (e.g. salmonella and BSE) especially help in safeguarding EU-wide food safety and in assuring consumer confidence in the food chain. Moreover, as some modern biotechnologies may present new issues in terms of animal welfare, a case-by-case assessment based on robust indicators and guidelines may be needed.

5.4 Outlook

Modern biotechnology has been widely diffused in the EU economy through a large variety of applications. Many of these are being further developed and improved, e.g. bioethanol production from lignocellulosic biomass, thus potentially enhancing their performance in economic, environmental and social terms. Many more applications are in the research and development stages, e.g. animal cloning, gene therapy or novel biocatalysts, which further enlarges the application range of modern biotechnology, but also potentially raises new issues. Thus, today's modern biotechnology significantly contributes to the EU economy and sustainable development, but its potential has not yet been fully exploited. The availability of data is a critical issue for the assessment of modern biotechnology applications. In particular, there is a considerable lack of relevant, statistical data regarding the agro-food sector and industrial manufacturing processes. To facilitate monitoring, the development and adoption of modern biotechnology applications and their impacts, e.g. for evidence-based policy making, a continuous statistical collection of data needs to be established.

Annex 1 – Methodology

Objectives

The Analysis Report of the Bio4EU study aims at the identification and quantification (as far as possible) of the contributions of modern biotechnology to achieve major EU policy objectives, formulated in the Lisbon Strategy and in the Sustainable Development Strategy. This concerns in particular:

- economic growth, competitiveness and employment
- environment and energy
- public health (including food safety, animal health and welfare)

Scope

Modern biotechnologies

Major modern biotechnologies were identified at the preparatory step of the study[505].

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'[506]. This definition includes traditional biotechnological processes that have been used for a very long time in the food and drink industry as well as modern biotechnological processes. The study focuses on major modern biotechnologies. These encompass DNA- , protein- and cell-based technologies utilised in the modification of living or non-living materials for the production of goods and services. Under this definition, traditional biotechnologies, such as fermentation and conventional animal and plant breeding, are not included. However, modern biotechnologies used in combination with traditional biotechnologies, e.g. fermentation processes using recombinant organisms, are considered modern biotechnology.

Table 62 provides a list-based definition of the key technologies used in modern biotechnology research and production. The list includes four general categories for nucleic acid, protein, metabolite, and cell-related technologies, plus a fifth category for supporting tools. Some of these tools include a number of technologies.

Biotechnology application areas included

Modern biotechnology applications in the following areas were analysed, as these were considered the main application areas:

- human health
- primary production and agro-food
- industrial processes, environment and energy

[505] 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.ec.europa.eu/documents/Bio4EU-Task1.pdf.

[506] OECD (2005). A framework for biotechnology statistics. Organisation for Economic Co-operation and Development, Paris. http://www.oecd.org/document/3/0,2340,en_2649_33703_34962243_1_1_1_1,00.html.

Table 62: List-based definition of modern biotechnology

Biotechnology	Applications
Nucleic acid-related technologies (DNA/RNA)	• high-throughput sequencing of genomes, genes, DNA • DNA synthesis and amplification • genetic engineering • anti-sense technology
Protein-related technologies	• high throughput protein/peptide identification, quantification and sequencing • protein/peptide synthesis • protein engineering and biocatalysis
Metabolite-related technologies	• high throughput metabolite identification and quantification • metabolic pathway engineering
Cellular- and subcellular-related technologies	• cell hybridisation/fusion • tissue engineering • embryo technology • stem cell-related technologies • gene delivery • fermentation and downstream processing
Supporting tools	• bioinformatics

Geographic area

The analysis focuses on the EU, and competitors, in particular the US and Japan, For specific application areas, additional countries have been included if relevant information was available.

Assessment

General

The impact assessment is based on the use of indicators that were selected after a careful review of indicators and data availability[507]. The impacts of biotechnology were then grouped into two categories: direct and indirect. In the context of this study, direct impacts relate to effects at the level of biotechnology technique users, while indirect impacts concern the effects realised at the level of the users of biotechnology-derived products (downstream sectors).

[507] 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.ec.europa.eu/documents/Bio4EU-Task1.pdf.

The direct impacts, therefore, aim to measure the various impacts (sector and EU-wide economy) arising from the activity of the producer of modern biotechnology products such as pharmaceutical companies producing modern biotechnology-derived products (vaccines, therapeutics, etc.), breeding companies employing modern biotechnology for the production of seeds or embryos, diagnostic companies producing modern biotechnology-based test kits, companies employing modern biotechnology for the production of enzymes, etc.

Table 63: List of Bio4EU case studies

Application area	Case study
Human health	
Therapeutics	Insulin for the treatment of diabetes
	Interferon-beta for the treatment of multiple sclerosis
	Enzyme replacement therapy for Gaucher's disease
	Anti-CD20 monoclonal antibodies for the treatment of Non-Hodgkin's lymphoma
Preventives	Hepatitis B vaccine
Diagnostics	Cardiac diagnostic assays
	HIV testing
	Genetic testing for phenylketonuria
Animal health	
Diagnostics	Foot and mouth disease diagnostics
Preventives	Animal vaccines (Aujeszky's disease)
Primary production/agro-food	
Diagnostics	BSE testing
	Detection of *Salmonella* in food
	GMO traceability
Breeding and propagation	Marker assisted selection in livestock breeding (pigs)
	Marker assisted selection in maize
	GM crops
	Livestock propagation (cattle)
	Fish breeding and propagation
	Micropropagation in plants (horticulture)
Industrial production	
Processing of biomass to biological feedstock as a renewable resource	Bioethanol production from biomass
	Biopolymer production from biomass
Industrial processes using biological systems	Use of enzymes in detergents
	Use of enzymes in fruit juice clarification
	Use of enzymes in the pulp and paper industry
	Use of enzymes in the textile industry
	Production of the amino acid lysine
	Production of the vitamin riboflavin/vitamin B2
	Production of the antibiotic cephalosporine
Bioremediation	Biosensors and bio-based analytical tools used in environmental monitoring

Indirect impacts mainly relate to the impacts arising from the use of biotechnology-derived products, and, depending on the application, may include several levels upstream or downstream the production chain. For example, the use of a modern biotechnology-based feed enzyme may generate impacts both upstream (raw material producers in the primary sector, feed ingredient producers) and downstream (feed producers, the farm gate, through processing or even through final retail sale).

The aim of the analysis was to provide results at the most aggregated level possible, both in terms of indicators, as well as in terms of the sectors. In addition, a representative set of 29 case studies was used to analyse in depth the current economic, social or environmental impact (see Table 63). The case studies were selected to cover all relevant application areas and to cover those applications of modern biotechnology in each of the parts that are considered to have the highest current impact in economic, environmental or social terms.

Indicators

At the preliminary phase of the study, an assessment was carried out on the availability of data for potential indicators[507]. At the second stage, the useable indicators were selected based on whether and how much they were related with the major EU policy objectives.

There is no standard methodology for linking the indicators to EU policy objectives. However, a structured approach was developed, based on the identification of the major policy objectives and linking indicators to these policy objectives (quantitatively or qualitatively). A table illustrating the approach is provided at the end of Annex 2 (see Table 64).

Data

Data were obtained from a number of sources depending on their availability, and were prioritised based on their perceived quality as follows (in descending order): official statistics and reports (provided by public institutions); peer reviewed publications; surveys and interviews of industry and technical experts; market reports and other available publications; and other web-based available information. This information was sourced either through direct desk research or through the various ETEPS reports.

Overall, data availability was of the highest quality for the human health sector, followed by the industrial sector and lastly by the agro-food sector. While the overall focus was on a quantitative analysis, a qualitative analysis was performed when the first was not feasible. Where robust data were not available, an effort was made anyway to provide estimates for illustrative purposes.

Methodological remarks

Sector classification

The sectors in which modern biotechnology is known to be applied were identified. This identification was made using the NACE classification framework[508] where feasible. For the agro-food sector, the sector classification provided by Eurostat was mainly used (e.g. based on the European Economic Accounts for Agriculture and Forestry). Where needed, sectors at a more disaggregated level were identified, and sourced with estimated data from variable sources.

For each identified biotechnology application, the closest matching sector category was chosen as a benchmark (using NACE where available), e.g. "NACE D 24.51 Manufacture of soap, detergents, cleaning and polishing" as the benchmark for detergents containing enzymes. Available data for each individual biotechnology application were then put into context with the benchmark sector data.

Economic and employment indicators

Gross value-added (GVA) is the main economic indicator used throughout the analysis (for the most recent year; therefore, 2004 was used in the majority of cases, with some exceptions); value-added was chosen as an indicator because as an economic measure it works as well as turnover and GDP figures, but more information is available in public databases, particularly in Eurostat. For the analysis of the agro-food sector, especially at more disaggregated levels, turnover was used instead, as GVA data were not available. Other economic indicators where used were available in quantitative or qualitative terms. Competitiveness is discussed in a qualitative manner throughout the analysis and where relevant information is available.

The number of direct employees was used as the main employment indicator. If the employee figure for a biotechnology application is not known, but the employee number and rate of diffusion into the benchmark sector is known (for example: 30 - 50% of all detergents are produced using enzymatic processes), then the relation ‘employee number x diffusion rate’ is applied to calculate employment figures for the relevant biotechnology application.

If no basis for calculating value-added or employee figures is available, plausible estimates are looked for. These might stem from an overview of company reports or market research reports, as far as available. The emphasis in this sub-optimal solution lies on the feasibility. Where relatively solid estimates could not be obtained, this information is omitted.

The resulting figures are put in relation to statistical totals of the overall economy, in order to learn:

- what the contribution of each individual biotechnology application to GVA of the EU is

[508] NACE is the statistical classification of economic activities in the European Community. Version 1.1 of 2002 is used in this report. http://ec.europa.eu/eurostat/ramon/nomenclatures/.

- what the contribution of each individual biotechnology application to GVA (or turnover) of the various benchmarks used is (e.g. at the most aggregated sector level or to the closest matching sector)

For the industrial sector analysis, the following results where also estimated:

- what the labour productivity of each industrial biotechnology application is, calculated as

$$\frac{Contribution\ of\ each\ industrial\ biotech\ application\ to\ EU-25\ employment}{Contribution\ of\ each\ industrial\ biotech\ application\ to\ EU-25\ Gross\ Value-Added}$$

- how this labour productivity of manufacturing sectors using enzymes relates to the respective NACE sector labour productivity
- how this labour productivity of manufacturing sectors using enzymes relates to the labour productivity of overall EU manufacturing.

This analysis is carried out for direct impacts, i.e. the producers of biotechnology products, and for indirect impacts, i.e. the users of biotechnology-derived products. The analysis of the contributions of modern biotechnology to the EU economy does not calculate the change in economic or employment terms induced through the adoption of modern biotechnology, but calculates the economic and employment output that uses biotechnology. Where modern biotechnology (direct) or derived products (indirect) are used at some step(s) of a production process, the entire output is calculated as an impact of modern biotechnology, even if the modern biotechnology-based process is only one production step amongst several non-biotechnological steps. Therefore the calculated indicator provides a relative measure of the diffusion and importance of modern biotechnology to the EU economy rather than an absolute measure of the positive and/or negative effects to the EU economy. An additional assumption behind this is that modern biotechnology production has been taken up by the producer in order to be and remain competitive in the respective product market.

Where more information is available, the changes influenced by the modern biotechnology adoption are also presented, i.e. how efficiency increases, decreases, or remains the same, when modern biotechnology is applied.

Environment and energy, and public health indicators

The assessment of the contribution of modern biotechnology to the environment and energy, and public health, is based on a range of indicators, namely:

- environment and energy: resource productivity, waste prevention, air-soil-water quality, biodiversity, greenhouse gas emissions and energy supply security
- public health: protection against health threats and disease prevention, healthcare and social costs.

Due to the inherent differences among the different sectors and the different applications within the context of environment and public health, the exact assessment varies for the three sectors, and therefore, the details of the assessment are provided in the respective chapters. The most relevant indicators were used on a case-by-case basis.

Table 64: Concept for the selection of indicators according to policy objectives

convergence

Policy	Sub-themes	Policy objectives	Policy indicators	Output and impact indicators
Lisbon Strategy	Competitiveness and economic growth	Competitiveness and economic growth	Market shares and adoption rates	Number and share of companies in the respective sectors active in biotechnology
				Total production and shares (area, weight, value) of conventional and biotechnology products (by application area)
				Share of biotechnology turnover in each application out of total turnover in each application
				Share of biotechnology turnover in each application out of total biotechnology turnover
				Share of biotechnology turnover out of total turnover of biotechnology active firms in the relevant sector or the case study
			Trade	Changes in international market shares of European products
				Changes in shares of imports in total domestic consumption
			Gross margin and production costs	Gross margin of biotechnology product per unit output compared to alternative conventional product, in each application
				Total production costs of biotechnology product per unit output compared to alternative conventional product, in each application
			Labour productivity	Biotechnology turnover per biotechnology employee compared to turnover of alternative conventional products per employee, in each application
			GDP growth	Total sector specific biotechnology related GDP out of total sector specific GDP
	Employment	Employment	Employment growth and rates	Number of biotechnology active employees per application out of total employees in each application
				Shares of employment in each application out of total biotechnology employment
				Total biotechnology active employees out of total employment in biotechnology active firms, in the relevant sector
				Number of jobs created through specific biotechnology applications (direct and spillover effects)

Policy	Sub-themes	Policy objectives	Policy indicators	Output and impact indicators
Sustainable development strategy	Environment	Improve resource productivity	Change of energy, water and material inputs Change of the use of non-renewable resources	Change of energy, water and material inputs Change of the use of non-renewable resources
		Waste prevention	Change of resulting waste streams in different environmental media	Change of resulting waste streams in different environmental media, in each application
		Improve air quality	Change of (risk of) emissions to the air	Change of emissions to the air: direct and/or indirect via change in the use of inputs responsible for emissions to the air (e.g. fossil fuels)
		Improve soil quality	Change of (risk of) emissions to the soil and reduced land use	Change of emissions of nutrients/fertilisers, pesticides to the soil, change of tillage and of land use: direct and/or indirect via change in use of inputs responsible for emissions to the soil (e.g. nutrients)
		Improve water quality	Change of (risk of) emissions to the water	Change of emissions of nutrients/fertilisers, pesticides direct and/or indirect via change in use of inputs responsible for emissions to the water (e.g. nutrients)
		Preserve biodiversity	Preservation of genetic resources and landscape diversity	Preservation of genetic resources and landscape diversity
	Energy	Climate change: (reduction of GHG emissions by 8% by 2012, compared to 1990)	Change of (risk of) GHG emissions	Change of GHG emissions: direct and/or indirect via change in use of inputs responsible for GHG emissions (e.g. fossil fuels)

Policy	Sub-themes	Policy objectives	Policy indicators	Output and impact indicators
		Supply security: (2010 targets) • 12% energy from renewable resources • 25% of electricity • 5.75% biofuels share	Change in the use of non-renewable resources	Change in the use of non-renewable resources Change in biofuel production
	Public health (including food safety)	Improved warning, monitoring and control of communicable diseases (including medical product safety)	Availability and use of: • diagnostics for communicable diseases (including novel pathogens) • vaccines for communicable diseases • medicines for communicable diseases	Market shares of human health biotechnology products (e.g. molecular diagnostic tests, biopharmaceuticals, vaccines) already on the market in terms of absolute numbers and revenues
				Adoption by end-users (e.g. number and share of prescriptions, number and share of laboatories using biotechnology-based diagnostics)
				Number and share of products in the pipeline (e.g. drugs in clinical trials)
				Number and share of clinical studies (or equivalent for animal health products) for emerging biotechnology applications
				Share of processes that use biotechnology for small molecule drug development related to chemical processes for the same purpose
			Efficiency of diagnostics and vaccines	Cost-effectiveness/cost-utility of biotechnology products
			Incidence of major diseases	Change in burden of diseases in relation to diagnostic/treatment with biotechnology products
				Impact on food safety: change in numbers of contamination cases; number and share of food-related diseases diagnosed through modern biotechnology-based diagnostics
			Incidence of zoonoses	Animal health: change in number of animals becoming ill and/or dying; changes in number/risk of human zoonotic cases
		Reduction of (major) non-communicable disease incidences (e.g. mental illnesses, cancer, cardio-vascular diseases, diabetes)	Availability and use of diagnostics and medicines for non-communicable diseases	Market shares of human health biotechnology products (e.g. molecular diagnostic tests, biopharmaceuticals, vaccines) already on the market in terms of absolute numbers and revenues
				Adoption by end-users (e.g. number and share of prescriptions, number and share of labs using biotechnology-based diagnostics)
				Number and share of products in the pipeline (e.g. drugs in clinical trials)
				Number and share of clinical studies (or equivalent for animal health products) for emerging biotechnology applications

Policy	Sub-themes	Policy objectives	Policy indicators	Output and impact indicators
				Share of processes that use biotechnology for small molecule drug development related to chemical processes for the same purpose
			Efficiency of diagnostics and treatments	Cost-effectiveness/cost-utility of biotechnology products
			Incidence of (major) diseases	Change in burden of diseases in relation to diagnostics/treatment with biotechnology products
	Development of more effective and efficient healthcare systems	Reduction of healthcare and social costs and reduction of disease burden	Cost-effectiveness/cost-utility of biotechnology products	Cost-effectiveness/cost-utility of biotechnology products
			Reduction of disease burden	Change in burden of diseases in relation to diagnostics/treatment with biotechnology products
				Change in burden for public health budget
			Improvement of animal health and welfare	Change in animal health and welfare

Annex 2 – Human Health Biotechnology

Table 65: Biopharmaceuticals originated in the EU 1995 - 2005

Generic Name	Originator	Originating Country	Primary therapy description	Any therapy description
Factor VIIa	Novo Nordisk	Denmark	Recombinant, other	Recombinant, other Blood fraction Haemostatic
Glucagon	Novo Nordisk	Denmark	Recombinant, other	Recombinant, other Antidiabetic Glucagon
Somatropin	Novo Nordisk	Denmark	Recombinant hormone	Recombinant hormone Growth hormone Vulnerary Fertility enhancer Musculoskeletal Anabolic
Insulin Aspart, biphasic	Novo Nordisk	Denmark	Formulation, other	Formulation, other Recombinant hormone Insulin Antidiabetic
Insulin glargine	Sanofi-Aventis	France	Recombinant hormone	Recombinant hormone Insulin Antidiabetic
Lepirudin	Sanofi-Aventis	France	Recombinant, other	Recombinant, other Antithrombotic Haematological Antianginal Cardiovascular
Rasburicase	Sanofi-Aventis	France	Recombinant, other	Recombinant, other Antigout Radio/chemoprotective
Somatropin	Sanofi-Aventis	France	Recombinant hormone	Recombinant hormone Growth hormone
Alpha-1, antitrypsin	Bayer	Germany	Recombinant, other	Recombinant, other COPD treatment
Factor VIII-2	Bayer	Germany	Recombinant, other	Recombinant, other Blood fraction Haemostatic
Interferon, BI (alpha2c)	Boehringer Ingelheim	Germany	Recombinant interferon	Recombinant interferon Anticancer, interferon Antiviral, interferon Cytokine
Nateplase	Bayer	Germany	Recombinant, other	Recombinant, other Fibrinolytic
Tasonermin	Boehringer Ingelheim	Germany	Recombinant, other	Recombinant, other Anticancer, immunological Cytokine
Scintimun	Bayer	Germany	Immunoconjugate, other	Immunoconjugate, other Imaging agent
RecFSH	Akzo Nobel	Netherlands	Recombinant hormone	Recombinant hormone Fertility enhancer
Interferon	Crucell	Netherlands	Recombinant interferon	Recombinant interferon Cytokine Antiviral, interferon

Generic Name	Originator	Originating Country	Primary therapy description	Any therapy description
Agalsidase alpha	Shire	UK	Recombinant, other	Recombinant, other Metabolic and enzyme disorders
131I-tositumomab	GlaxoSmithKline	UK	Immunoconjugate, other	Immunoconjugate, other Anticancer, immunological
Alemtuzumab	BTG	UK	Monoclonal antibody, humanised	Monoclonal antibody, humanised Anticancer, immunological Multiple sclerosis treatment Immunosuppressant
Adalimumab	AstraZeneca	UK	Monoclonal antibody, human	Monoclonal antibody, human Antiarthritic, immunological GI inflammatory/bowel disorders
Epoetin delta	Shire	UK	Recombinant growth factor	Recombinant growth factor Antianaemic Radio/chemoprotective

Table 66: Case studies summary of economic data

	Companies	Turnover	Market share
Biopharmaceuticals (products)			
Insulin	EU: Novo Nordisk (NN) EU: Sanofi Aventis (SA) US: Eli Lilly (EL)	NN: EUR 2 billion (41% of company's total, 2006) – insulin analogues: 26% of the company's total (2005) SA: EUR 0.162 billion (0.75% of total) – insulin analogue: 5.45% of company's total (2005) EL: EUR 0.798 billion (converted from USD) EUR 0.367 billion estimated to be sold in the EU (humulin 2005) – humalog: EUR 0.882 billion Total EU turnover (human insulin): 6.8% (out of total turnover of NN and SA) 2005	EU: 42% of global (EUR 1.89 billion) 2004 US: 47% of global (EUR 2.115 billion) 2004 World: (EUR 4.5 billion) 2004
Interferon-beta	EU: Schering EU: Sanofi Aventis (SA) CH: Serono US: Biogen Idec	Schering: EUR 0.867 billion (16% of company's total, 2005) SA: EUR 0.902 billion (3% of company's total, 2005) Serono: EUR 0.872 billion (42% of company's total, 2005) Biogen: EUR 0.56 billion (2005) Total EU turnover: 5.4% (out of total turnover of Schering and SA) 2005 *(estimated by IPTS)*	
Enzyme replacement therapy for Gaucher's disease (Cerezyme)	US: Genzyme	Genzyme: EUR 0.932 billion (35% of company's total, 2005)	
CD20 monoclonal antibodies (Rituxan (rituximab), Mabthera (rituximab), Zevalin, Bexxar)	US: Biogen, Genentech, Corixa (acquired by GSK in 2005) CH: Roche (not a producer, just marketing the product)	Roche: EUR 2.6 billion (11.7% of company's total, 2005)	

	Companies	Turnover	Market share
Preventives			
Hepatitis B vaccine	EU: GlaxoSmithKline (GSK) EU: Sanofi-Aventis (SA) And Merck	GSK: EUR 0.662 billion (32% of company's total turnover of vaccines, and 2.1% of total sales, 2005) SA: EUR 0.167 billion (8.1% of company's total turnover of vaccines, and 0.6% of total sales, 2005) "other vaccines" (includes HBV)	
Diagnostics			
Cardiac assays	CH: Roche Diagnostics US: Dade Behring, Abbott Diagnostics, Bayer Diagnostics, Beckman Coulter, Diagnostics Products Corp.	Roche Diagnostics: EUR 0.055 billion (1% of company's total, 2005)	EU: 30% of global (EUR 0.141 billion estimated) 2005
HIV testing	EU: BioMerieux, Trinity biotech CH: Roche Diagnostics US: Dade Behring, Abbott Diagnostics, Bayer Diagnostics, Beckman Coulter, Gen-Probe, OraSure Technologies	Share of biotech/total turnover : 18% (firms producing HIV diagnostics in the EU)	
PKU testing		Share of biotech/total turnover : 1%	

Annex 3 – Agro-Food Biotechnology

Table 67: Economic data on the EU agro-food sector
Note: Numbers in italics are IPTS estimates; the most likely relationship between GVA and turnover was used in the respective sectors[509].

2003 data	NACE sectors	Turnover (EUR million)	GVA (EUR million)	Relation GVA/ Turnover	Share of EU GVA (in %)	Employment	Share of EU employment (in %)
EU			8 782 817			200 000 000 [510]	
Core production							
Agriculture[511]	*A 01: Agriculture and hunting*	314 160	157 403	0.50	1.79		
Forestry[512]	*A 02: Forestry*	*40 000*	20 000	*0.50*	0.23		
Agriculture and forestry	*A: Agriculture, hunting and forestry*	*354 015*	177 371	*0.50*	2.02	9 757 100	4.88
Fishing, EU-15	*BA 05.01Fishing*	6185	2412	0.39	0.03	208 852[513]	0.10
Aquaculture, EU	*BA 05.02 Fish Farming*	2769	*1387*	*0.50*	0.02	65 365[513]	0.03
Fisheries	*B: Fishing*	8954	*3799*	*0.42*	0.04	274 217[513]	0.14
Primary production sub-total		**362 969**	**181 170**	**0.50**	**2.06**	**10 031 317** [514]	**5.02**
Food processing	*DA 15 Manufacture of food products and beverages*	797 069	181 220	0.23	2.06	4 434 100	2.22
Core production total		**1 160 039**	**362 390**	***0.31***	***4.13***	**14 465 417**	**7.23**

[509] The data have been obtained from EUROSTAT (dataset available online at http://epp.eurostat.ec.europa.eu/), and from reports published by the European Commission, DG Agriculture and Rural Development (2006): Agriculture in the European Union – Statistical and Economic Information 2005. http://ec.europa.eu/agriculture/agrista/2005/table_en/2005enfinal.pdf; *And*: Rural Development in the European Union - Statistical and Economic Information Report 2006. http://ec.europa.eu/agriculture/agrista/rurdev2006/RD_Report_2006.pdf. *And*: P. Salz et al. (2006) Employment in the fisheries sector: current situation. http://ec.europa.eu/fisheries/publications/studies/employment_study_2006.pdf.

[510] Rounded-up from 192 615 000

[511] The data are based on the Economic Accounts for Agriculture and Forestry, providing complementary information and concepts adapted to the particular nature of the agricultural industry. However, the EAA agricultural industry differs in some respects from the branch as defined for national accounts purposes.

[512] Estimated as the difference between the estimate for NACE A and the value for NACE A 01.

[513] P. Salz et al. (2006) Employment in the fisheries sector: current situation. http://ec.europa.eu/fisheries/publications/studies/employment_study_2006.pdf. The report also estimates the employment of the fish processing sector at 147 102.

[514] The sum of the most recent estimates was used. It was estimated at 10 149 000 in the report "Agriculture in the European Union - Statistical and economic information 2005", European Commission, DG Agriculture and Rural Development (2006). http://ec.europa.eu/agriculture/agrista/2005/table_en/2005enfinal.pdf .

2003 data	NACE sectors	Turnover (EUR million)	GVA (EUR million)	Relation GVA/ Turnover	Share of EU GVA (in %)	Employment	Share of EU employment (in %)
Related sectors							
Input sectors (products and services) specific to primary production and the agro-food chain							
Fertilisers	*DG 24.15: Manufacture of fertilisers and nitrogen compounds*	13 323	2672	0.20	0.03	51 200	0.03
Pesticides	*DG 24.2: Manufacture of pesticides and other agro-chemical products*	*12 201*	2767	0.23	0.03	29 500	0.01
Veterinary products	Values are estimated at the turnover provided under "veterinary services"[515]	*5200*	*1768*	*0.34*	0.02	14 966	0.01
Diagnostics	Estimated from various sources (see Section 2.3.5)	*700*	*238*	*0.34*	0.005		
Food and feed additives	DG 24.66: Manufacture of other chemical products (enzymes, amino acids, vitamins, organic acids)[516]	*2300*	*600*	*0.26*	0.01	2700	
Input sectors sub-total		***33 724***	***8045***	***0.24***	***0.09***	***98 366***	***0.05***
Total of production sectors (agro-food economy)		**1 193 763**	***370 435***	***0.31***	**4.21**	***14 563 783***	**7.28**
Wholesale and retail							
	GA 51.2 Wholesale of agricultural raw materials and live animals	*175 754*	13 723	0.08	0.16	321 600	0.16
	GA 51.3 Wholesale of food, beverages and tobacco (except GA 51.35)	*653 812*	57 779	0.09	0.66	1 600 200	0.80

[515] Due to a lack of disaggregated information in NACE DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products.

[516] The totals are not comprehensive as they only include specific product categories (turnover: food and feed related amino acids, vitamins, organic acids, antibiotics and xanthan, see Section 2.3.5.3; employment: refers only to food enzymes related production, assuming that 45% of all enzymes are food related, see Section 2.3.5.3).

2003 data	NACE sectors	Turnover (EUR million)	GVA (EUR million)	Relation GVA/ Turnover	Share of EU GVA (in %)	Employment	Share of EU employment (in %)
	GA 52.11 Retail sale in non-specialised stores with food, beverages or tobacco predominating	*740 498*	102 423	0.14	1.17	4 654 800	2.33
	GA 52.2 Retail sale of food, beverages and tobacco in specialised stores (except GA52.26)	*101 789*	20 363	0.20	0.23	1 287 500	0.64
	HA 55.3 to 55.5: Restaurants; bars; canteens and catering.	*258 241*	101 127	0.39	1.15	6 194 200	3.10
Wholesale and retail sub-total		***1 930 094***	***295 415***	**0.15**	**3.36**	***14 058 300***	**7.03**
Related sectors total		***1 963 818***	***303 460***	**0.15**	**3.45**	***14 165 432***	**7.08**
Total		***3 123 857***	***665 850***	**0.21**	**7.58**	***28 630 849***	**14.31**

Table 68: Main modern biotechnology applications in the agro-food sector

Biotechnology application in		Biotechnology techniques	Biotechnology producers – direct impacts (most disaggregated NACE/EAA sectors if available)	Biotechnology users – indirect impacts
Breeding/propagation in primary production	*Plants*	*Marker assisted selection in plant breeding*	Plant breeders, seed companies: -seeds and planting stock -nursery plants and flowers	Plant growers: AA 01.1: Growing of crops; market gardening; horticulture
		Genetic modification in plant breeding	Plant breeders, seed companies: -seeds and planting stock	Plant growers: AA 01.11 Growing of cereals and other crops n.e.c. (includes seed multiplication)
		Micropropagation in plant breeding	Specialised laboratories, young plant companies, etc: -nursery plants and flowers	Plant growers: AA 01.12 Growing of vegetables, horticultural specialities and nursery products
	Animals	*Marker assisted selection in livestock breeding*	Livestock breeders, specialised genetics companies: AA 01.42 Animal husbandry service activities, except veterinary activities NA 85.20: Veterinary activities	Livestock growers: AA 01.2 Farming of animals

Biotechnology application in		Biotechnology techniques	Biotechnology producers – direct impacts (most disaggregated NACE/EAA sectors if available)	Biotechnology users – indirect impacts
		Embryo techniques in livestock breeding	Livestock breeders, specialised genetics and embryo transfer companies: AA 01.42 Animal husbandry service activities, except veterinary activities NA 85.20: Veterinary activities	Livestock growers: AA 01.2 Farming of animals
	Fish/ Shellfish	*Marker assisted selection in fish/shellfish breeding*	Fish/shellfish breeders, specialised genetics companies: B 05.02 Fish farming	Fish/shellfish growers: B 05.02 Fish farming
		Sex/ploidy manipulation in fish/shellfish breeding	Fish/shellfish breeders: B 05.02 Fish farming	Fish/shellfish growers: B 05.02 Fish farming
Inputs -diagnostics used throughout the food chain (primary production, food manufacturing, through retail sale)		*Modern biotechnology-based diagnostics*	Specialised laboratories, veterinary laboratories, specialised chemical/pharmaceutical companies: KA 74.30: Technical testing and analysis (as relevant for diagnostics in the food chain) NA 85.20: Veterinary activities 19050 Veterinary expenses (incl medicines and fees) DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products (as relevant for veterinary products) DG 24.66: Manufacture of other chemical products (diagnostic reagents)	*1st level:* Analytical laboratories (if not direct producer) KA 74.30: Technical testing and analysis (as relevant for diagnostics in the food chain) NA 85.20: Veterinary activities *2nd level: Food/feed and beverages processing* DA 15 Manufacture of food products and beverages *3rd level: Wholesale and retail sale* GA 51.2 Wholesale of agricultural raw materials and live animals GA 51.3 Wholesale of food, beverages and tobacco (except GA51.35) GA 52.11 Retail sale in non-specialised stores with food, beverages or tobacco predominating GA 52.2 Retail sale of food, beverages and tobacco in specialised stores (except GA 52.26)
Inputs used in primary production		*Veterinary products (based on modern biotechnology)*	Pharmaceutical companies, biotechnology companies, fermentation, enzyme producers, etc. DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products DG 24.66: Manufacture of other chemical products (enzymes)	*1st level: Pharmaceutical companies* DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products *2nd level: Livestock and fish/shellfish producers* AA 01.2 Farming of animals B 05.02 Fish farming

Biotechnology application in		Biotechnology techniques	Biotechnology producers – direct impacts (most disaggregated NACE/EAA sectors if available)	Biotechnology users – indirect impacts
		Other chemical products (based on modern biotechnology (e.g. amino acids, vitamins,enzymes, etc.)	Fermentation, enzyme producers, speciality chemical producers (amino acids, vitamins) DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products DG 24.66: Manufacture of other chemical products (enzymes) DG 24.66: Manufacture of other chemical products (amino acids, vitamins, etc.)	*1st level: Chemicals producers (amino acids, vitamins, etc.)* DG 24.4: Manufacture of pharmaceuticals, medicinal chemicals and botanical products DG 24.66: Manufacture of other chemical products *2nd level: feed additive and feed producers* DA 15.Manufacture of prepared feeds for farm animals *3rd level: Livestock and fish producers* AA 01.2 Farming of animals B 05.02 Fish farming
Food manufacturing		*Modern biotechnology derived microorganisms/enzymes applied in food processing*	Fermentation-enzyme producers, DG 24.66: Manufacture of other chemical products (enzymes)	Food and beverage processors DA 15 Manufacture of food products and beverages

This list is not exhaustive as there are other techniques and applications, as well as other users, relevant to primary production and agro-food. Furthermore, products, such as biopesticides and biofertilisers, are not included, as it is still an emerging application area and these applications may not always fall within the scope of the modern biotechnology definition used in this study. However, it is believed that the large share of modern biotechnology applications and users are captured in this table.

Annex 4 – Industrial Biotechnology

Table 69: Carbon dioxide emissions by industry in 2001
Source: IPTS calculation based on Eurostat data[517]; n.e.c.: not elsewhere classified

	Carbon dioxide emissions by industry (1000 tonnes)						
NACE section		**Denmark**	**Germany**	**Italy**	**UK**	**Total**	**Share (in %)**
DA	Manufacture of food products; beverages and tobacco	1800.55	9117.77	2236.28	9519.30	**22 673.90**	**6.74**
DB	Manufacture of textiles and textile products	101.42	892.35	1819.23	2521.76	**5334.76**	**1.59**
DC	Manufacture of leather and leather products	4.84	70.09	368.75	129.72	**573.40**	**0.17**
DD	Manufacture of wood and wood products	502.67	1056.94	595.00	3914.6	**6069.21**	**1.80**
DE	Manufacture of pulp, paper and paper products; publishing and printing	260.97	7920.85	6359.01	5522.57	**20 063.40**	**5.97**
DG	Manufacture of chemicals, chemical products and man-made fibres	570.95	2030.02	1955.43	16691.96	**39 520.36**	**11.75**
DH	Manufacture of rubber and plastic products	130.03	1670.29	1454.67	4524.89	**7779.88**	**2.31**
DI	Manufacture of other non-metallic mineral products	3259.25	33126.36	37716.19	15455.06	**89 556.86**	**26.63**
DJ	Manufacture of basic metals and fabricated metal products	384.25	58 552.19	22 235.16	31 121.79	**112 293.39**	**33.39**
DK	Manufacture of machinery and equipment n.e.c.	227.19	3119.51	2030.54	1609.13	**6986.37**	**1.82**
DL	Manufacture of electrical and optical equipment	97.81	3476.56	980.63	1573.60	**6128.60**	**1.82**
DM	Manufacture of transport equipment	65.08	6571.19	2215.72	3336.13	**12 188.12**	**3.62**
DN	Manufacturing n.e.c.	221.42	1564.82	741.59	4573.60	**7101.43**	**2.11**
	Total					**396 344.07**	**100.00**

[517] Eurostat data from online database. http://epp.eurostat.ec.europa.eu/.

Table 70: Methane emissions by industry in 2001
Source: IPTS calculation based on Eurostat data[518]; n.e.c.: not elsewhere classified

	Methane emissions by industry (1000 tonnes)						
NACE section		**Denmark**	**Germany**	**Italy**	**UK**	**Total**	**Share (in %)**
DA	Manufacture of food products; beverages and tobacco	0.41	0.48	33.75	0.61	**35.25**	**34.40**
DB	Manufacture of textiles and textile products	0.02	0.04	4.08	0.14	**4.28**	**4.18**
DC	Manufacture of leather and leather products	0.00	0.00	0.07	0.01	**0.08**	**0.08**
DD	Manufacture of wood and wood products	0.34	0.15	0.07	0.51	**1.07**	**1.04**
DE	Manufacture of pulp, paper and paper products; publishing and printing	0.07	0.43	1.18	0.39	**2.07**	**2.02**
DG	Manufacture of chemicals, chemical products and man-made fibres	0.11	0.67	27.29	3.09	**31.16**	**30.41**
DH	Manufacture of rubber and plastic products	0.03	0.07	0.17	0.30	**0.57**	**0.56**
DI	Manufacture of other non-metallic mineral products	0.38	1.22	1.54	1.16	**4.30**	**4.20**
DJ	Manufacture of basic metals and fabricated metal products	0.08	2.24	11.53	7.42	**21.27**	**20.76**
DK	Manufacture of machinery and equipment n.e.c.	0.05	0.16	0.28	0.10	**0.59**	**0.58**
DL	Manufacture of electrical and optical equipment	0.03	0.18	0.16	0.12	**0.49**	**0.48**
DM	Manufacture of transport equipment	0.02	0.31	0.20	0.22	**0.75**	**0.73**
DN	Manufacturing n.e.c.	0.11	0.07	0.10	0.30	**0.58**	**0.57**
	Total					**111.90**	**100.00**

[518] Eurostat data from online database. http://epp.eurostat.ec.europa.eu/.

Table 71: Nitrous oxide emissions by industry in 2001
Source: IPTS calculation based on Eurostat data[519]; n.e.c.: not elsewhere classified

	Nitrous Oxide emissions by industry in 2001 (1000 tonnes)						
NACE section		**Denmark**	**Germany**	**Italy**	**UK**	**Total**	**Share (in %)**
DA	Manufacture of food products; beverages and tobacco	0.05	0.21	0.40	0.29	**0.95**	**1.16**
DB	Manufacture of textiles and textile products	0.00	0.02	0.26	0.07	**0.35**	**0.43**
DC	Manufacture of leather and leather products	0.00	0.00	0.05	0.01	**0.06**	**0.07**
DD	Manufacture of wood and wood products	0.02	0.03	0.07	0.30	**0.42**	**0.52**
DE	Manufacture of pulp, paper and paper products; publishing and printing	0.01	0.19	0.14	0.18	**0.52**	**0.64**
DG	Manufacture of chemicals, chemical products and man-made fibres	2.87	21.76	28.85	17.76	**71.24**	**87.36**
DH	Manufacture of rubber and plastic products	0.00	0.03	0.12	0.24	**0.39**	**0.48**
DI	Manufacture of other non-metallic mineral products	0.06	0.49	2.63	0.31	**3.49**	**4.28**
DJ	Manufacture of basic metals and fabricated metal products	0.01	1.24	0.59	0.67	**2.51**	**3.08**
DK	Manufacture of machinery and equipment n.e.c.	0.01	0.10	0.23	0.07	**0.41**	**0.50**
DL	Manufacture of electrical and optical equipment	0.00	0.09	0.11	0.06	**0.26**	**0.32**
DM	Manufacture of transport equipment	0.00	0.13	0.16	0.12	**0.41**	**0.50**
DN	Manufacturing n.e.c.	0.01	0.05	0.11	0.37	**0.54**	**0.66**
	Total					**83.10**	**100.00**

[519] Eurostat data from online database. http://epp.eurostat.ec.europa.eu/.

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Abstract

Biotechnology is generally considered one of the key technologies of the 21st century, with a potentially wide range of applications in e.g. healthcare, agriculture, and industrial production processes. However, this notion has not yet been substantiated, as the diversity of sectors in which biotechnology is applied makes it difficult to investigate its actual degree of diffusion. Against this background and following a request from the European Parliament, the European Commission initiated the Biotechnology for Europe Study (Bio4EU Study). The study's objectives are to assess the contributions of modern biotechnology to the achievement of major European policy goals, and to increase public awareness and understanding of modern biotechnology. This report presents an analysis of the collected data with a view to assessing the contributions of modern biotechnology to major EU policy goals such as economic growth and job creation (Lisbon Agenda), and environmental sustainability and public health (Sustainable Development Strategy). As such, the study can be considered a background document of the Bio4EU synthesis report, which sets out the main findings of the study.

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