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Review

The impact of industrial biotechnology

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In this review, the impact of industrial (or "white") biotechnology can have on our society and economy is discussed. An overview is given of industrial biotechnology and its applications in a number of product categories ranging from food ingredients, vitamins, bio-colorants, solvents, plastics and biofuels. The use of fossil resources is compared with renewable resources as the preferred feedstock for industrial biotechnology. A brief discussion is also given of the expected changes in society and technology, ranging from the shift in the supply of resources, the growing need for efficiency and sustainability of the production systems, changing consumer perception and behaviour and changing agricultural systems and practices. Many of these changes are expected to speed up the transition from a fossil-based to a bio-based economy and society.

Keywords: Biocatalysis · Biofuels · Fermentation · Fine and bulk chemicals · Industrial biotechnology

1 Introduction

Presently, a third wave of biotechnology – industrial biotechnology – is strongly developing. Industrial biotechnology (also referred to as white biotechnology) stands apart from red biotechnology, aimed at the medical sector, and green biotechnology, focussing on genetically modified crops. Industrial biotechnology uses biological systems for the production of chemicals, materials and energy. This technology is mainly based on biocatalysis (the use of enzymes to catalyse chemical reactions) and fermentation technology (directed use of microorganisms), in combination with breakthroughs in molecular genetics, enzyme engineering and metabolic engineering.

The term "White biotechnology", recently proposed by EU decision making bodies, is also gaining momentum now; it covers the field of industrial biotechnology; with "white" also referring to the positive environmental aspects linked to the application of industrial biotechnology.

This new biotechnology has developed into a main contributor to the so-called green chemistry, in which renewable resources such as sugars or vegetable oils are transformed into a wide variety of chemical substances such as fine and bulk chemicals, pharmaceuticals, biocolourants, solvents, bioplastics, vitamins, food additives as well as biofuels such as bioethanol and biodiesel [1].

The implementation of industrial or "white" biotechnology offers significant ecological advantages. Renewable agricultural crops are the preferential starting materials, instead of dwindling fossil resources such as crude oil and natural gas. This technology consequently has a beneficial effect on greenhouse gas emissions and at the same time supports the agricultural sector, delivering these raw materials. Moreover, industrial biotechnology frequently shows significant performance benefits compared to conventional chemical technology, such as a higher reaction rate, increased conversion efficiency, improved product purity, lowered energy consumption and significant decrease in chemical waste generation. The combination of these factors has led to the recent strong penetration of industrial biotechnology in all sectors of the chemical industry, particularly in fine chemicals but equally so for bulk chemicals such as plastics and fuels. At

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present, the penetration of biotechnological production processes in the chemical industry is estimated at 5%, and is expected to increase to 10–20% by the year 2010 [2].

This development is now mainly driven by the laws of market economy, in view of the higher efficiencies obtained by biotechnological production processes. In the near future, a number of societal and technological changes are expected to reinforce this trend even further, such as the depletion of crude oil reserves, the increased demand of a growing world population for raw materials and energy, the demand for sustainability and efficiency in chemical production systems and changes in agricultural policy [3].

The strong development of industrial biotechnology is of immediate interest to the economically important chemical and agro-industry. From the collaboration of these two industries, entirely new chemical activities can be created in the form of bio-refineries. Also, industrial biotechnology may contribute significantly to the future of European agriculture.

Furthermore, efforts to increase the public awareness about industrial biotechnology are needed, with the added benefit that this is likely to improve the consumer's perception of biotechnology as a whole, in view of the clear link between industrial biotechnology and the sustainable development of our society [4].

2 Sustainable chemistry

The chemical industry produces a broad range of compounds that can roughly be divided into the following groups: fine chemicals, pharmaceutical products, bulk chemicals, plastics and fuels. The chemical industry is a very important production sector, but at the same time a big user of fossil resources and a significant source of waste.

Researchers, chemists and chemical engineers face major challenges for developing sustainable chemical processes that respect the environment, improve our quality of life and at the same time are competitive in the marketplace. This includes the development of new production processes, which reduce or eliminate the use of dangerous or hazardous substances, minimise energy consumption and waste generation and start as much as possible from renewable raw materials. The ultimate goal is the development of a clean chemical technology, starting from renewable raw materials and energy, with minimal waste generation, and maximal productivity and competitiveness.

Sustainable chemistry is based on a range of different technologies, ranging from more efficient conventional chemical processes, the use of better catalysts, innovative separation methods such as membrane processes, recycling technology and last but not least, the use of industrial biotechnology. The latter technology is increasingly impacting the chemical sector, a reflection of the fact that biotechnology is naturally suitable for sustainable chemistry [5]. Whereas the use of renewable raw materials is rather difficult in conventional chemical processes, industrial biotechnology can handle these renewable raw materials with amazing ease. Low waste generation and energy consumption, the use of non-hazardous, harmless and renewable raw materials and the high efficiency guarantee the sustainability of this technology. Industrial biotechnological processes increasingly penetrate the chemical industry, with very positive results with regard to sustainability as well as industrial competitiveness.

It is important to stress that industrial biotechnology is not the sole technology in this quest for sustainability. The most sustainable chemistry consists of an interplay between different technologies. In fact, it is common to obtain the best results from a suitable combination of conventional chemical technology and industrial biotechnology. New processes increasingly seem to consist of so-called combi-syntheses, consisting of a number of chemical and biotechnological steps. Also innovative separation technologies such as membrane technology and the use of super-critical solvents are being increasingly integrated and help to increase the eco-efficiency of this "green chemistry".

3 Industrial biotechnology

Industrial biotechnology is a multidisciplinary technology and includes the integrated application of disciplines such as biochemistry, microbiology, molecular genetics and process technology to develop useful processes and products, based on microbial, animal or plant cells, their organelles or enzymes as biocatalysts. Particularly microorganisms have received a lot of attention as a biotechnological instrument and are used in so-called fermentation processes. Numerous useful bacteria, yeasts and fungi are widely found in nature, but seldom find the optimum conditions for growth and product formation in their natural environment. In artificial (*in vitro*) conditions, the biotechnologist can intervene in the microbial cell environment (in a fermentor or bio-reactor), as well as in their genetic material (DNA), to better control and direct the cell metabolism during these fermentation processes. Because of their extremely high synthetic versatility, ease of using renewable raw materials, great speed of microbial reactions, quick growth and relatively easy to modify genetic material, many microorganisms are extremely efficient and in many cases indispensable workhorses in the various sectors of industrial biotechnology.

Industrial biotechnology has been practised for a long time in a number of sectors of health care, food industry and fine chemistry. At present, this technology increas-

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ingly penetrates into areas such as bulk chemistry and energy supply, in a world where sustainable development is the key word.

A McKinsey study has indicated that the market share of industrial biotechnology will strongly increase in all areas by 2010, but particularly in fine chemicals production [2]. The estimated penetration degree in 2010 is estimated to lie between 30% and 60% for fine chemicals and between 6% and 12% for polymers and bulk chemicals. Taken over the whole of the chemical industry, the penetration of biotechnology is presently estimated at 5% and this is expected to increase to 10–20% by 2010, and strongly increase even further afterwards. The penetration speed will depend mainly on a number of factors such as the prices of crude oil and agricultural raw materials, technological developments and the political will to support and structure this new technology.

4 Renewable *versus* fossil resources

The use of renewable resources as raw material for technical (non-food) purposes is certainly not new [6]. People already used such materials from the first civilisations onwards. To meet their basic needs, people have employed plant- and animal-based raw material, from natural fibres for clothing, wood for heating, animal fat for lighting to natural dyes for textiles and art works, etc.

The first industrial activities were also largely based on the use of renewable resources and this continued until the industrial revolution. In the 19th century there was a fundamental change, brought about by the emergence of carbochemistry (based on coal, aromatics and synthesis gas) and in the 20th century by the development of petrochemistry. The use of renewable raw materials declined significantly, mainly as a consequence of the extremely low prices for petrochemical resources. During this period, the strongly developing chemical industry was nearly systematically based on petrochemical resources. Nowadays, a large part of the chemical industry is based on petrochemical resources and our energy needs are also largely met by fossil fuels such as coal, petroleum and natural gas. Currently, 95.8% of all organic chemical substances produced in Europe (including fuel) are based on fossil resources.

Nevertheless, a fair number of important industries are still based on renewable raw materials. Half of the fibres used in the textile industry are natural fibres (cotton, wool, flax,..), the oleo-chemical industry supplies our daily hygienic needs for soap and detergents based on vegetable oils, the building industry still uses a lot of wood and other natural fibres as construction material, etc. Moreover, petrochemistry does not offer a realistic alternative for the use of renewable raw materials in several important applications. For example, almost all antibiotics are made by fermentation processes, starting from natural sugars and about half of our drugs are still isolated from living organisms.

The oil crisis between 1973 and 1979, when OPEC raised oil prices from 2 to 30 $ per barrel (1 barrel = 159 l), gave rise to a renewed interest in renewable resources. As a result of this crisis, serious concern grew about our increasing dependency on fossil resources and the fact that these are not infinitely available. This concern was largely channelled politically into the energy question and resulted in many studies concerning the development of alternative energy sources. The results of these studies underlined that renewable raw materials were not (yet) competitive and the enthusiasm for renewable raw materials quickly disappeared when the oil price dropped again and the economy turned back to business as usual.

In the nineties, the discussions around sustainable development and the greenhouse effect as well as the emergence of the green political parties provided new impulses. The problems related to the food surpluses in the European Union were also an important driving force. Because of the huge costs arising from these food surpluses, the EU strongly intervened into the European Common Agricultural Policy (CAP). For this purpose, the European Union developed the „set-aside" land concept in 1992. According to this principle, subsidies were given to farmers for not planting anything on parts of their land, in order to limit overproduction. Then, within the European Common Agricultural Policy, possibilities were created to use this land for non-food applications. Thus, farmers could earn additional revenue from this land.

With the increasing awareness and concern about industrial waste and its effects on the environment, the need arose for better biodegradable intermediates and final end products. These biodegradable products can naturally degrade into components that are absorbed back into the natural cycle, in contrast to persistent products that do not (or only after an unacceptably long period) disappear from the environment or from the food chain. Biodegradability was the focal point of many products and these were frequently based on renewable resources, in view of their intrinsic biodegradability. Such applications are, for example, chemical substances that will almost certainly end up in the environment, like lubricating oils for tree saws and agricultural machinery, detergents, etc. Green detergents like alkylpolyglucosides have already achieved a significant market share and are made entirely from renewable resources (fatty acid alcohols and glucose).

The world's crude oil reserves will not last forever [7]. With regard to fossil reserves, we are now faced with the paradoxical situation that, while crude oil (petroleum) is being consumed faster than ever, the "proven oil reserves" have remained at about the same level for 30 years as a consequence of new oil finds. Nevertheless, these "proven oil reserves" are located in increasingly difficult to reach places. Therefore, the cost for extracting the crude oil rises continuously, reflected in increasing oil prices. In sharp contrast to this, agricultural raw materials such as wheat and corn are becoming cheaper as a fundamental consequence of the rising agricultural yields. This trend will most likely continue for some time, also as a consequence of the realisations of the "green" bio-technology. This long-term trend may be perturbed by the transitory effects of market imbalances and politics but for a growing number of applications the economic balance is tipping towards the use of renewable resources, also in the segment of (inexpensive) bulk chemicals.

On a weight basis, renewable resources are about half as expensive as fossil resources (Table 1). Agricultural byproducts such as straw are even 10 times less expensive than petroleum. It is also quite remarkable that the current world market prices for petroleum and sugar are about the same, despite the fact that sugar is a very pure (99.8%) and refined product and petroleum is a non-refined crude raw material, consisting of a very complex mixture of hydrocarbons and other compounds. On an energy base, as renewable resources have about half the energy content of fossil resources, renewable and fossil resources are roughly equal in price.

Table 1. Average world market price of some fossil and renewable resources

Fossil	Price (€/ton)	Renewable	Price (€/ton)
Petroleum	250	Corn/wheat	100
Coal	40	Straw	20
Ethylene	500	Sugar	250

At the time of writing (April 2006), the oil price has even increased to over 70 $ per barrel, which is 380 € per ton, nearly four times as much as the price of agricultural commodities such as wheat or corn (around 100 €/ton). It is increasingly becoming clear that we are faced with a long-term trend in the price of petroleum instead of a transitional effect (Fig. 1). For the simple reason of the price of raw materials, it is clear that the use of renewable raw materials has significant growth perspectives.

5 Renewable raw materials for the industry

Renewable raw materials are essentially based on the use of "biomass", the sum of all substances that the living world is made of. Renewable raw materials thus have a biological origin. Its fundamental basis is the plant growth and production, which is fuelled by the photosynthesis process, and possibly via the intermediate step of animal production results in a large variety of available biomass.

The total annual biomass production on our planet is estimated at 170 billion tons and consists of roughly 75% carbohydrates (sugars), 20% lignins and 5% of other substances such as oils and fats, proteins, terpenes, alkaloids, etc. [8]. Of this biomass production, 6 billion tons (3.5%) are presently being used for human needs, distributed as:

- 3.7 billion tons (62%) for human food use, possibly via animal breeding as an intermediate step;
- 2 billion tons of wood (33%) for energy use, paper and construction needs;
- 300 million tons (5%) to meet the human needs for technical (non food) raw materials (clothing, detergents, chemicals,..).

The rest of biomass production is used in the natural ecosystems (feed for wild animals), is lost when biomass is obtained for humans (especially by burning) or is lost as a result of the natural mineralization processes.

The renewable raw materials discussed here are almost all provided by agriculture and forestry. The animal breeding sector and fisheries also contribute (mainly ani-

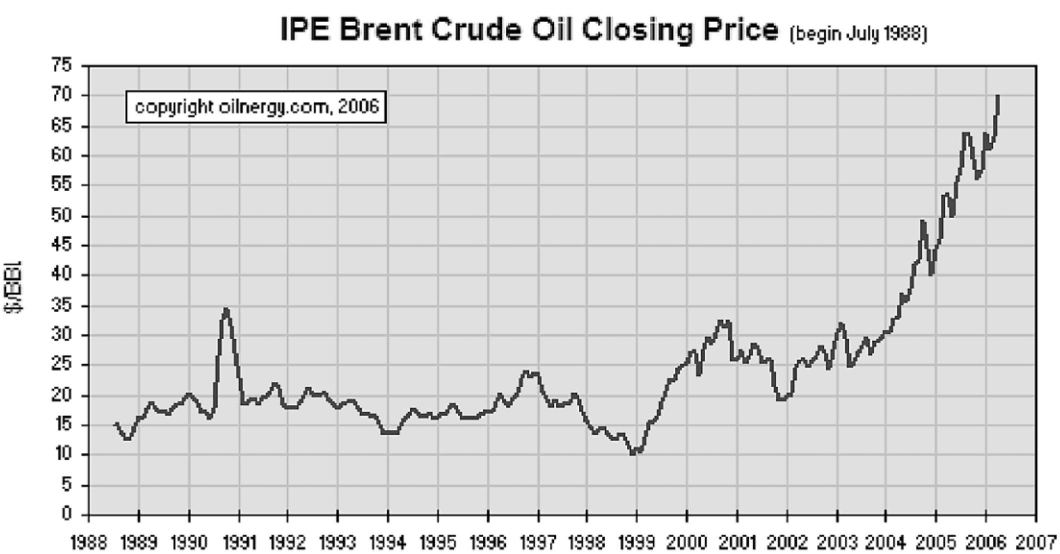

Figure 1. Crude oil price from 1988 to 2006. Copyright oilenergy.com

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mal fat), but are clearly less significant, also in view of the low conversion efficiencies of plant to animal (about 10–25%).

A range of different technologies can be used to industrially convert this available biomass into renewable raw materials or energy carriers. This industrial activity is often linked or connected to the food sector, in view of the fact that food ingredients and renewable raw materials for technical use can be made within the same factory from the same agricultural raw materials. For example, sugar or glucose are produced for human food use and are also the most important raw materials for industrial fermentation processes.

The following industrial sectors supply the most important renewable raw materials:

– the sugar and starch sector: it produces carbohydrates such as sugar, glucose, starch and molasses from plant raw materials such as sugar beet, sugar cane, wheat, corn, potatoes, sweet cassava, rice, etc.;
– oil and fat processing sector: it produces numerous oleo-chemical intermediates such as triglycerides, fatty acids, fatty alcohols and glycerol from plant raw materials like rape seeds, soybeans, palm oil, coconuts and animal fats;
– the wood processing sector, particularly the cellulose and paper industry: it produces mainly cellulose, paper and lignins from wood.

These industries process plant raw materials in order to break them down into separate components such as sugar, starch, cellulose, glucose, proteins, oils, and lignins. They make use of two technological pillars:

– fractionation technology: this technology is primarily based on physical and chemical separation methods to separate agricultural raw materials into their separate components.
– enzymatic technology: this aspect of industrial biotechnology intervenes during the transformation of agricultural raw materials. In practice, mainly hydrolytic enzymes are used, for example amylases, that hydrolyse starch to glucose.

Although both technologies are clearly very different in nature, the interaction between them is particularly decisive for success. For example, the fractionation technology is strongly influenced by the use of hydrolytic enzymes.

The obtained pure basic products (sugar, starch, cellulose, oils) are then converted into a very broad range of products, employing physical, chemical and biotechnological processes. For example, starch and cellulose are chemically modified to derivatives that find many uses in our daily lives. Sugars like sucrose and glucose are chemically coupled to oleo-chemicals to obtain detergents and emulsifiers.

With respect to industrial biotechnological processes, the fermentation technology needs to be specifically mentioned. This very important key technology makes use of microorganisms (bacteria, yeasts, and fungi) to convert basic raw materials such as sugars and oils into an almost unlimited range of products. By simple use of another production organism, the raw material (for example sugar) can be converted to totally different products, ranging from products with a chemical structure that is very close to the raw material (*e.g.*, gluconic acid from glucose) to products that have virtually nothing in common with the starting material (for example, antibiotics, enzymes,…).

This whole chain of different process steps, implying the use of very different technologies often takes place within the same factory or industry complex. These are increasingly referred to as “biorefineries”, analogous to the petrochemical crude oil refineries.

For orientation, the estimated world production figures and indicative world market prices of a number of renewable and petrochemical raw materials are given in Table 2. The comparison clearly shows that their volumes and prices are quite comparable.

Table 2. Estimated world production figures and indicative world market price of a number of renewable and petrochemical raw materials

	World production (million tons/year)	World market price (€/ton)
Renewable raw material		
Cellulose	320	500
Sugar	140	250
Starch	55	250
Glucose	30	300
Bio-ethanol	38	400
Glutamic acid	1	1500
Petrochemicals		
Ethylene	85	500
Propylene	45	350
Benzene	23	400
Terephthalic acid	12	700
Isopropanol	2	700
Caprolactam	3	2000

6 Bioprocesses in industrial biotechnology

6.1 Fermentation processes

Industrial biotechnology is used to produce a wide variety of bulk and fine chemicals like alcohol, lactic acid, citric acid, vitamins, amino acids, solvents, antibiotics, biopolymers, bio-pesticides, industrial enzymes, biocolourants, bio-surfactants, alkaloids, steroids, etc. Industrial fermentation is the main technology here, whereby microorganisms (bacteria, yeasts, and fungi) are cultivated that efficiently convert sugars into useful products. It is the only industrial production method for several of these products and some are produced in very significant quantities. Table 3 compiles the production figures and prices for a number of these fermentation products. The range varies from inexpensive bulk products to very expensive fine chemicals.

Table 3. World production figures and prices for a number of fermentation products

	World production (ton/year)	World market price (€/kg)
Bio-ethanol	38 000 000	0.40
L-Glutamic acid (MSG)	1 500 000	1.50
Citric acid	1 500 000	0.80
L-Lysine	350 000	2
Lactic acid	250 000	2
Vitamin C	80 000	8
Gluconic acid	50 000	1.50
Antibiotics (bulk products)	30 000	150
Antibiotics (specialities)	5 000	1 500
Xanthan	20 000	8
L-Hydroxyphenylalanine	10 000	10
Dextran	200	80
Vitamin B_{12}	3	25 000

Thanks to recombinant DNA-technology, one can now specifically intervene into the genetic material of these microorganisms. On the one hand, the metabolism of microorganisms can be modified or even completely changed (so-called “metabolic engineering”). On the other hand, genes from higher organisms (plants and animals) or other microorganisms (yeast, bacteria, virus, algae) can be inserted into industrial microorganisms and brought to expression. Thus, new direct gene products can be made or new metabolic pathways can be created to produce chemical substances with high efficiency via industrial fermentation processes.

In practice, well-known, productive and harmless production organisms are used that, equipped with the new genetic information, will produce the desired chemical products in high yield and efficiency. A major advantage is that these genetically modified microorganisms do their work under controlled conditions in a fermentor or bio-reactor, carefully contained and separated from the outside world. They cannot escape from the factory and ecological problems or concerns with regard to the release of genetically modified organisms in the environment are thus avoided altogether.

6.2 Enzymatic processes

Enzymes are catalytically active proteins that have evolved and were perfected over billions of years of evolution. As very specific and efficient catalysts, they direct the chemistry of life without needing extreme temperatures, high pressures or corrosive conditions as often required in chemical synthetic processes. Enzymes are the machinery of the living world and their amazing properties are increasingly used for industrial applications. This technical discipline is referred to as biocatalysis.

Enzymes have become very important in a wide range of industrial sectors to carry out biocatalytic reactions. Typically microbial enzymes are used, produced by the previously mentioned fermentation processes. New technologies for enzyme engineering such as directed evolution allow new enzymes to be tailor-made, whereas metagenomics vastly expand the range of natural enzymes to be exploited. These developments can strongly improve this technology or even expand it to totally new applications.

Conventional applications are the large scale use of enzymes in the starch sector, not coincidentally the sector at the source of glucose, one of the most important renewable raw materials. A key enzyme is α-amylase, a very thermostable enzyme used to hydrolyse starch at a temperature of 105°C. Such thermostable enzymes allow bioreactions to take place at high temperatures, considerably increasing the reaction rate. Glucose isomerase is another important enzyme in this sector. This enzyme converts glucose to fructose. It is used in immobilised form and maintains its catalytic activity up to 2 years when used industrially. The world production glucose and fructose syrups with the help of this enzyme has passed the mark of 15 million tons per year.

The detergent sector is another big application area for enzymes. Here, proteases and lipases are used to break down protein and fat stains on clothing.

The animal feed industry is another important market. For example, phytase from the fungus *Aspergillus niger* is employed to release phosphate from phytic acid in animal feed. Thus, less additional phosphate has to be added to animal feed, with considerable environmental benefits. Other enzymes strongly improve food conversion, with equally positive ecological benefits.

Enzymes are increasingly penetrating the chemical industry to catalyse numerous reactions. The specificity of the enzymatic reaction is very important here. When compared with conventional chemical catalysts, this specificity is often very high. Besides a high degree of reaction specificity, chirality has also provided strong impulses to the application of biocatalysts in the chemical industry. The use of enzymes (used in free or immobilised form) for very specific organochemical reactions is rapidly developing. These are mostly one-step reactions, carried out with high efficiency, specificity and reaction rate. This scientific domain is often referred to as “biocatalysis” and the processes used are described as “bioconversions” or “biotransformations”. These bioconversions are normally performed at normal temperatures and pressures, whereby no dangerous intermediate products are needed nor dangerous waste products generated. Typically, the reactions take place in” green” solvents such as water,

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ethanol or supercritical CO_2, though enzymes are also active in "conventional" chemical solvents such as methanol, acetone, chlorinated solvents, etc. It should also be mentioned here that the enzymes used in industrial biotechnology and biocatalysis are practically all derived from microorganisms via fermentation. Industrial enzymes represent a two billion dollar sector in industrial biotechnology [9].

7 Products from industrial biotechnology

7.1 General

A vast range of useful products can be produced by industrial biotechnology. These fall within the categories of fine chemicals, pharmaceuticals, food additives and supplements, colourants, vitamins, pesticides, bio-plastics, solvents, bio-plastics, bulk chemicals and biofuels. These products range from very cheap bulk chemicals (*e.g.*, ethanol: 38 million ton/year at 400 €/ton) to extremely expensive fine chemicals (*e.g.*, vitamin B_{12}: a few ton/year at 25 000 €/kg). Whereas industrial biotechnology is already well established in the production of fine chemicals and pharmaceuticals, also bulk chemicals, biofuels and bio-plastics are now increasingly produced by industrial biotechnology [10, 11]. In some cases a polymer building block is produced from fossil resources using enzymatic technology. In other cases a completely biodegradable bio-plastic can be obtained from renewable resources, e.g., the biodegradable bio-plastic PLA can be produced from corn. Industrial biotechnology can either intervene in a single step in a chemical synthesis route or replace an entire cascade of chemical synthesis steps with one single fermentation or biocatalysis step. Some demonstrative examples are discussed hereafter.

7.2 Vitamins

Vitamins are important fine chemicals that are produced in relatively large quantities. Whereas a number of vitamins can be prepared only via biotechnology such as vitamin B_{12}, an extremely complicated compound, other more simple vitamins can be produced by either a chemical route or a biotechnological route and quite often by a combination of both.

The synthesis of vitamin B_2 (riboflavin, 4000 tons/year) is a good example of this. The conventional process consisted of the synthesis of the building block D-ribose by fermentation with *Bacillus* bacteria, followed by a sequence of chemical reactions to obtain riboflavin. Thus, this was a combined chemical-biotechnological synthesis route of no less than eight steps. This combined synthesis route has been recently replaced by the complete biotechnological synthesis of riboflavin in one single fermentation step with the help of bacteria, yeast or fungi. The productivity of these fermentation processes is so high that the product already crystallises out during the fermentation itself! The production cost of the new biotechnological process is 40% lower than the conventional process.

Another example is the synthesis of vitamin C (ascorbic acid), that is made conventionally via the Reichstein-Grüssner synthesis, a synthesis process starting with glucose and consisting of one fermentation step and 5 chemical steps. A new process has been developed in which a fermentation process takes over the greatest part of the chemical steps. The new synthesis route consists of one fermentation step and two simple chemical steps (via 2-keto-L-gulonic acid). Moreover, much effort is being put in to develop a fully biotechnological route that will convert glucose to vitamin C in a single fermentation step.

7.3 Fine chemicals and pharmaceuticals

Today, industrial biotechnology has the greatest degree of penetration in the fine chemical and pharmaceutical sector (15%), with further strong development underway. Antibiotics and their intermediates are among the most important fine chemicals, with a world market value of about 20 billion euro. They are almost exclusively made by fermentation processes with the help of specially selected microorganisms. The structural complexity of most antibiotics is so great that chemical synthesis has never been a serious alternative. Only in the case of so-called semi-synthetic antibiotics are the building blocks obtained by fermentation, and subsequently chemically modified to obtain new antibiotic derivatives with improved effectiveness. Nowadays, these chemical modifications are increasingly replaced by biotechnological methods, with excellent economic and ecological benefits.

Another example in the pharmaceutical sector is the synthesis of Captopril™, a so-called ACE inhibitor used to treat high blood pressure. Captopril™ is built from two building blocks D-β-hydroxy-isobutyric acid and L-proline. These building blocks are both synthesised by fermentation, respectively with the yeast *Candida rugosa* and the bacterium *Corynebacterium* sp. Both building blocks are then linked by conventional chemistry, resulting in Captopril™.

In the fine chemical sector, Lonza has developed a biotechnological route, starting with 3-cyanopyridine to nicotinamide (niacin or vitamin B_3), nicotinic acid and 6-hydroxynicotinic acid. At present, these intermediate products for many chemical syntheses are made via industrial biotechnology. Conversions are done by means of enzymatic hydrolysis with nitrile hydratase from *Rhodococcus* bacteria or by bioconversion with living bacterial cells. The reactions are very specific and the yields are almost quantitative.

In the sector of enzymatic conversions, Novozymes has introduced an extremely thermostable lipase from the yeast *Candida (Pseudozyma) antarctica* (Novozyme 435). It is excellently suitable for carrying out specific esterifications in organic solvents. This enzyme is widely used today in different sectors of the chemical industry.

7.4 Food additives and food supplements

Amino acids are very important natural building blocks of proteins. They are increasingly used as supplements for human food and animal feed. Previously, only a small number of amino acids were made by industrial biotechnology, Nowadays, almost all 20 natural L-amino acids are produced by fermentation or enzyme technology.

These are very large-scale industrial productions. The world-wide production of L-glutamic acid is over 1.5 million tons a year. It is one of the most important fermentation products with a tonnage comparable with many petrochemical products. Glutamic acid is used in the form of monosodium glutamate (MSG) as a taste enhancer in many foods. L-Lysine (350 000 tons/year) is another large-scale produced amino acid, mainly used in animal feed.

L-Phenylalanine is yet another amino acid, taking part in the synthesis of L-aspartame. Aspartame is an artificial sweetener that is 200 times sweeter than sugar. It is used in many foodstuffs, such as "light" beverages. Worldwide, around 15 000 tons of aspartame are produced each year at an approximate world market price of 35 €/kg. The initial synthetic process for aspartame was based on chemical synthesis. However, in the mean time, it is now strongly based on industrial biotechnology. For example, the most important building blocks, L-phenylalanine and L-aspartic acid, are produced by fermentation and biocatalysis, respectively. The Holland Sweetener Company uses enzymatic technology to connect the two building blocks: the amino acids phenylalanine and aspartic acid are very specifically linked to one another by the bacterial enzyme thermolysine. After that, a few more chemical steps are needed to obtain the sweetener aspartame.

L-Carnitin is a vitamin-like natural component in animal tissues that stimulates lipid metabolism. Initially, L-carnitin was produced via chemical synthesis, but now it is entirely made through a fermentation process, starting from renewable raw materials. The L-carnitin obtained is very pure and is increasingly used. People and animals use L-carnitin as a food supplement to stimulate their fat catabolism (more energy, less fat synthesis and more growth).

Erythorbic acid or iso-ascorbic acid is an anti-oxidant used in food. It is made by a fermentation process from glucose. It is a chemical analogue of vitamin C, but has no vitamin action. By fermentation with bacteria, glucose is almost quantitatively converted to 2-keto gluconic acid that is then chemically cyclised to erythorbic acid.

These are just a few examples from an ever increasing list, not in the least due to the more positive image that such biotechnologically made food additives enjoy, contrary to their chemically prepared counterparts.

7.5 Bio-colourants, flavours and aroma compounds

Bio-colourants are increasingly produced by industrial biotechnology, in particular when these are employed for food, pharmaceutical or cosmetic applications. These substances can often be made by both chemical synthesis and industrial biotechnology, with comparable production costs. Bio-colourants produced by biotechnology have an important marketing advantage with respect to entering the market because consumers disapprove of synthetic substances.

β-Carotene (or provitamin A) is produced by organic synthesis, extraction from roots as well as by fermentation with the fungus *Blakeslea trispora*. Optically active hydroxycarotenoids such as zeaxanthin and astaxanthin are important as animal and human food, and are mainly used in the fish and animal feed industry. The pink pigment astaxanthin is, for example, added to the feed of sea-farm-raised salmon to obtain the beautiful pink salmon meat. In nature, salmons get the pigment from their natural diet. Until recently, astaxanthin was mostly synthetically produced, via a complex synthesis route using a combination of chemical and enantio-selective bioconversion steps. Recently, there has been growing interest in the direct fermentative synthesis of this pigment with the help of the red yeast *Xanthophyllomyces rhodochrous*, because the synthetic variant has been criticised in view of the fact that it differs slightly from natural astaxanthin. A blue food pigment, phycocyanin, is produced in Japan with the cyanobacterium *Spirulina* sp. Also the orange red food/drink pigment, monascin, is produced with the fungus *Monascus purpureus* via a fermentation process.

Flavours and aroma compounds can also be produced by fermentation or enzymatic technology. The German company BASF recently started with the microbial synthesis of 4-decalactone, a peach aroma. It is based on a fermentation process with the yeast *Yarrowia lipolytica,* whereby 12-hydroxy-19 octadecenic acid is released from ricinus oil and subsequently metabolised to the desired 4-decalactone.

Unilever in England makes the butter aroma, R-δ-dodecanolide, starting from 5-ketododecanoic acid with the help of baker's yeast as the biocatalyst. Butyric acid and its ethylester have been obtained by fermentation for a long time and are used in cheese aroma, fruit aroma, etc.

7.6 Solvents

The most important "green" solvent today is ethanol, obtained by fermentation from sugar or glucose. Ethanol is a widely used solvent in the chemical industry because it is available in large quantities, is very pure, inexpensive, not toxic and perfectly biodegradable. The world production in 2005 is 38 million tons, of which about 80% was used as a biofuel and the rest for human food and beverages and in the chemical sector. It is produced for the most part by fermentation.

Ethyllactate is a strong newcomer solvent. Ethyllactate is made from ethanol and lactic acid, both produced from glucose or sugar by fermentation processes. It is also non-toxic, inexpensive and has other solvent properties than ethanol. A great future is expected for this new solvent but its availability is still a limiting factor, given that it just recently entered the market. Also, the acetone-butanol fermentation, practised since World War I in Europe and the USA, but in decline in the Western World since the 1950s at the expense of petrochemical production, is becoming important again worldwide.

7.7 Plastics or bio-plastics

Recently, numerous plastics have been commercialised on a large scale, in which industrial biotechnology has a significant part in their synthesis. The production process typically consists of an intelligent combination of conventional chemical polymer technology and industrial biotechnology. Industrial biotechnology usually participates in the synthesis of monomer building blocks of these plastics. These monomer building blocks are then converted to plastics by means of conventional (chemical) polymerisation technology.

Mitsubishi Rayon produces acrylamide from acrylonitrile with the help of an immobilised bacterial enzyme nitrile hydratase. Acrylamide is then polymerised to the conventional plastic polyacrylamide. This process was one of the first large-scale applications of enzymes in the bulk chemical industry and replaces the conventional production process that uses sulphuric acid and inorganic catalysts. The enzymatic process has clear advantages with respect to the chemical alternative as indicated in Table 4. The efficiency of enzymatic conversion leads to less waste, higher yields and significantly lower energy consumption with consequently reduced CO_2 production (Table 4). Surprisingly, the main reason for introducing the biotechnological route was the much better product quality. No undesired polymerisation occurs when the biotechnological route is employed, resulting in a purer acrylamide that can be better polymerised for high-quality applications. Today, about 100 000 tons of acrylamide are produced yearly via this method in Japan and other countries. In this case, a conventional plastic is produced from petrochemical raw materials with the help of industrial biotechnology; renewable raw materials are not involved here, apart from the enzyme used.

Table 4. Comparison of the chemical and the enzymatic process for the production of acrylamide

	Chemical	Enzymatic
Reaction temperature	70°C	0–15°C
Single-pass reaction yield	70–80%	100%
Acrylamide concentration	30%	48–50%
Product concentration	Necessary	Not required
Energy demand (MJ/kg acrylamide)	1.9	0.4
CO_2 production (kg CO_2/kg acrylamide)	1.5	0.3

Sorona™ 3GT is a new polyester synthetic fibre produced by DuPont. 1,3-propanediol is one of the monomers for the production of this polymer. It is made by fermentation from renewable raw materials, *i.e.*, glucose, derived from corn (Table 5). In a collaborative project between Genencor and DuPont, an *E. coli* production strain has been equipped with four foreign genes from other microorganisms. As a result, the recombinant production organism converts glucose to 1,3-propanediol, which it does not naturally produce. This is a fine example of so-called "metabolic engineering". The monomer is usually produced from the petrochemical raw materials ethylene oxide or acrolein via conventional chemical synthesis, but can now also be produced at comparable cost using biotechnology from renewable resources. The new polymer Sorona™ is mainly used as a synthetic fibre in the textile industry. It is not biodegradable and is thus a conventional plastic in that sense.

Natureworks™ bio-plastic (Poly Lactic Acid; PLA) has been made (140 000 tons/year) in the USA by Cargill since 2002 from glucose, derived from corn. In a first step, glucose is converted to lactic acid by fermentation, which is subsequently polymerised to PLA. The properties of the polymer are quite comparable to conventional polymers such as polyethylene or polypropylene and it is used in the packaging and textile industry. The polymer is completely biodegradable (compostable) so that packaging, plastic cups, etc. can be simply put on the compost heap after use, together with the organic waste. In this case, one closely approaches the ideal situation: a completely biodegradable plastic is produced from a renewable raw

Table 5. Characteristics of some (bio-)plastics

Plastic	Biodegradable?	Raw material	Renewable?	Monomer	Technology
Polyacrylamide	No	Acrylonitrile	No	Acrylamide	Biocatalysis
Sorona™ polyester	No	Glucose	Yes	Propanediol	Fermentation
Natureworks™ PLA	Yes	Glucose	Yes	Lactic acid	Fermentation

material with the help of industrial biotechnology. The new biodegradable plastic has technological properties very comparable to those of the conventional polymers, greatly facilitating its market introduction. Several other biopolymers, produced directly from glucose mainly by bacteria as extracellular capsular cell material, such as dextran, xanthan, hyaluronan, cellulose gellan, etc., are already used in the food, medical and technical sector. Others are built up completely intracellularly (*i.e.*, poly-β-hydroxybutyrate, poly-β-hydroxyvalerate) and display interesting properties.

Thus, industrial biotechnology penetrates into the production of plastics, with either a single step in a conventional polymer synthesis to completely new biodegradable polymers, produced from renewable raw materials. In all cases, these are large-scale productions of inexpensive plastics, a sector, in which renewable raw materials in combination with industrial biotechnology appear to be competitive (Table 5).

7.8 Bio-energy

In our society, a large proportion of the available resources are used to generate energy. At present, 79% of the global energy consumption is met by fossil energy sources, divided over crude oil (35%), natural gas (23%) and coal (21%). Hydraulic power and nuclear energy provide 9%, and the remaining 12% is met by renewables, particularly conventional firewood, wind energy and solar energy.

The use of these resources for energy production is subjected to the conditions already mentioned, *i.e.*, the depletion of these raw materials and their negative environmental effects, particularly the greenhouse effect [12]. Consequently, there is an intensive search for renewable energy sources, such as hydraulic power, solar energy, wind energy, tidal energy, geothermal energy and also energy from biomass.

A number of conversion processes based on industrial biotechnology seem to be particularly important for transforming biomass into useful fuel. The value of a fuel is not only defined by its energy content, but also by its physical form and ease of use. For example, in principle cars could run on firewood. However, this would be quite inefficient and not at all user friendly. In contrast to that, the production of bio-ethanol from, for example, sugar beet leads to a compact and user friendly liquid fuel that can be mixed with normal gasoline and employed without having to adapt the car engine. The use of bio-ethanol thus fits perfectly into the current concept of mobility based on motorised vehicles, powered by liquid fuel and supplied over gasoline stations. In addition to that, the current agricultural practice (sugar beet cultivation) remains essentially unchanged.

These conversion processes are essential and are performed with the help of industrial biotechnological processes in "biorefineries". Again, the analogy with the petrochemical industry is striking: an automobile does not run on petroleum, but on a refined product derived from it, *i.e.* gasoline. The production of biofuels is expected to provide a strong stimulus for the development of biorefineries [13]. Once the infrastructure for the production of biofuels has been created in the biorefineries, new possibilities will open up for producing more complex chemical substances. This is very similar to the early development of the petrochemical industry: initially it produced primarily fuel but subsequently an entire chemical industry developed around it.

7.8.1 Bio-ethanol

Bio-ethanol (alcohol or ethyl alcohol) is produced by fermenting sugars, usually with the help of yeasts. These sugars can be obtained from numerous raw materials such as sugar beet, sugar cane, wheat, corn or organic waste. In Europe, most alcohol is produced from sugar beet or wheat, leading to an easily fermentable substrate. More research is now directed towards producing alcohol from more difficult substrates such as organic waste, either from agro-industry or domestic waste (*e.g.*, vegetable, fruit and garden waste).

On the one hand, by genetic modification, a number of microorganisms have been modified such that they can convert substrates like pentose (C5) sugars and cellulose to alcohol. These "superbugs" are used to convert more complex substrates, like bagasse, domestic waste, straw, and paper, to ethanol. A lot of work has been invested in this technology, particularly in the USA. The whole field has been strongly stimulated by the US government, already providing several pilot installations and some industrial realisations.

On the other hand, much effort has been put into biotechnological research for inexpensively producing and improving the required celllulase enzymes. These "supercellulases" must hydrolyse cellulose to glucose that can be easily fermented.

After the fermentation process, alcohol is usually obtained by simple distillation from the fermentation liquid, resulting in a very pure product. This alcohol must be freed of remaining water before it can be used in motor fuel, usually by membrane processes. This pure alcohol is then commercialised as so-called bio-ethanol and can be used in motor fuels in different forms, typically in mixtures with normal gasoline. On the one hand, bio-ethanol can be converted with the petrochemical intermediate isobutylene, and the ETBE (ethyl tertiary butyl ether) obtained added to normal gasoline. On the other hand, bioethanol can be directly added to normal gasoline without any further elaboration, usually up to a maximum percentage (5% is permitted in Europe). In the current European practice, it is mostly added in the form of ETBE. In the USA and Brazil, ethanol is frequently directly added to gasoline and in higher percentages (*e.g.*, E85 or a 85% ethanol blend). The use of these ethanol/gasoline mix-

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tures does not require any engine adaptations up to an addition percentage of 15%. In fact, adding bio-ethanol or ETBE increases the oxygen content of fuel, leading to a greatly improved combustion. Moreover, ETBE is often added to gasoline to serve as a lead substitute. Thus, ecological advantages are achieved also in this respect.

About 38 million tons of ethanol was produced worldwide in 2005, mainly in Brazil and the USA, with Europe seriously lagging behind with only about 2 million tons.

7.8.2 Bio-diesel

Bio-diesel is produced from fats and vegetable oils. Except for recovered fats and oils (*e.g.*, used frying fat), most bio-diesel in Europe is made from rape seed oil. Essentially, bio-diesel consists of methyl esters of C_{16}-C_{18} fatty acids [14]. After so-called transesterification with methanol, the fat fraction of rape seed oil is separated into its components, bio-diesel and glycerol, that has other useful applications. The technology is based on a simple chemical process (base catalysed trans-esterification). Biotechnology is normally not implicated here, although work is performed on a biotechnological alternative for the current chemical production. Lipase enzymes might circumvent the use of alkaline agents, which can make the whole production process considerably more environmentally acceptable.

The bio-diesel obtained can be directly mixed to normal diesel fuel, typically up to 5%. In France, a 30% mixture is also used (referred to as diester) and in Germany and Austria even pure bio-diesel is used. Bio-diesel addition requires absolutely no adaptation of the diesel engines. Quite the contrary, the addition of bio-diesel is well appreciated because of its engine-lubricating action. When pure bio-diesel is used, some problems may occur in winter due to cold crystallisation. The production of bio-diesel is growing rapidly and has passed the mark of 2 million ton per year in 2005, mainly produced in Germany, France and Italy.

7.8.3 Biogas

Biogas usually is the result of methane fermentation of biomass. This process uses a consortium of different microorganisms that can transform complex organic material to carbon dioxide (CO_2) and methane gas (CH_4). These molecules distil spontaneously from the liquid and this biogas normally contains about 70% of methane and has an energy content of approximately 20–25 MJ/m^3. This biogas can be burnt and used for the production of electricity and heat. Typically, 1 kg of dry organic matter (sugar, plants, etc.) corresponds to 1 kWh of electricity and 2 kWh of thermal energy, produced on the basis of biogas.

It must be stressed that this process is very efficient in the sense that around 90% of the energy content of the raw material is recovered by the collected biogas, even starting with liquid waste such as manure and sludge, which cannot be burnt under normal conditions. The remaining product after methane fermentation contains only minerals released from the organic material, as well as some residual recalcitrant organic molecules such as lignin. These residues can be brought back to the soil as a fertiliser for plants and as a source of humus. This concept of biomass to biogas has been fully developed and tested in practice. One hectare of corn can produce 48 000 kWh of biogas that can be transformed into 14 500 kWh of electrical energy and 24 000 kWh of useful thermal energy. Also organic waste can be efficiently converted to biogas. This process is widely employed to process waste water (mainly from the food industry), excess sludge and vegetable, fruit and garden waste. Various processes have been developed and these are applied on a large scale all over the world. After methanisation, the remaining waste water must be processed, typically by means of an aerobic wastewater treatment.

7.8.4 Hydrogen

Renewable hydrogen can be produced biologically by dark fermentation of low-cost substrates or by photosynthetic splitting of water. Though promising, the yields of hydrogen obtained so far preclude realistic applications [13].

8 The economical and ecological advantages of industrial biotechnology

Introducing biotechnological process steps into chemical syntheses often results in significant ecological advantages such as considerably reduced waste generation, reduced energy requirement, decreased use of solvents, elimination of dangerous intermediate products, etc. However, these ecological advantages are typically not the reason for the technology switch. The technological process improvements and accompanying cost reduction are almost always the driving force for such decision. The ecological advantages are a pleasant side effect. By themselves, they are not sufficient to motivate decision makers to introduce a new technology (with associated failure risk). The way industrial biotechnology combines both economical and ecological progress is quite typical: the increased efficiency and reduced production cost of such biotechnological processes nearly always results in a greatly decreased ecological impact and generally leads to an improved competitiveness.

In a 2001 OECD report, 21 such case studies were presented [15]. Each case study convincingly illustrates the economic and ecological advantages offered by industrial biotechnology. It should be mentioned that in most cases, the processes described have been implemented in industrial practice and are competitive, and in no way limited to theoretical studies or research projects.

9 Expected changes in society and technology

Several changes in both society and technology are expected to happen in the coming years that may seriously modify the present order. Admittedly, these changes are likely to come about gradually, but may nevertheless give rise to some real “shock waves”. If we are to overcome these changes, the technological basis of our society will have to change radically.

9.1 Changes in the supply of primary raw materials

Currently, most organic chemical substances are based on petrochemical resources and our energy needs are also largely met by fossil fuels such as coal, petroleum and natural gas. This is mainly a consequence of the very low prices for petrochemical resources in the past. However, the world’s crude oil reserves will not last forever. The increasing demand for crude oil from a growing world population is now faced with a stagnating production rate. Even though the known oil reserves have remained at about the same level for 30 years as a consequence of new oil findings, these oil reserves are increasingly located in difficult to reach places. Therefore, the costs for extracting the crude oil rise continuously, as reflected in increasing oil prices.

In sharp contrast to this, locally produced agricultural raw materials such as wheat and corn are becoming continually cheaper as a fundamental consequence of the rising agricultural yields, gradually tipping the economic balance towards the use of renewable resources. This trend will most likely continue for some time.

Today, on a weight basis, fossil resources are about two to three times as expensive as comparable renewable resources such as corn. Agricultural by-products such as straw are even ten times less expensive than petroleum. Renewable resources thus offer excellent perspectives as a raw material for both our chemical needs and our energy needs (biofuels), for reasons of cost, self-sufficiency, sustainable development and the conservation of natural resources. However, the technologies for the efficient conversion of these renewable resources into useful products are still a major limitation and industrial biotechnology is the key technology in that respect. Whereas conventional chemical processes have reached a high technological maturity and efficiency in using fossil resources, they typically have serious difficulties in using renewable raw materials. Industrial biotechnology processes on the contrary can handle these renewable resources with amazing ease as microorganisms have no difficulties in converting raw materials, such as, for example, carbohydrates into a wide variety of useful products. Industrial biotechnology is thus an essential technology that needs to be developed for the transition from the present-day fossil-based society to a future sustainable bio-based society.

9.2 Increased demand of a growing population for raw materials and energy

Currently, around 80% of all available raw materials and energy are used by approximately 20% of the world population. Naturally, it can be expected that the other 80% of the world population will do everything possible to improve their living standards and thus require much more raw materials and energy than before. Also, one should not forget that the world population keeps growing at an alarming rate. The often cited and erroneously interpreted assertion of “reduced population growth” will only take effect in a few generations at the earliest, an unfortunate consequence of the peculiarities of population growth dynamics. For the time being, the world population continues to grow faster than ever. In particular, the dynamics of China and India must be taken into consideration, in view of the fact that these population-rich countries are expected to improve their living standards in the short term.

All these effects will inevitably lead to a strong increase in the demand for raw materials and energy. A fair redistribution of the available raw materials is unlikely, so that in the end far more raw materials will be used globally. This will deplete the remaining fossil reserves and other raw materials even faster and bring renewable raw materials and energy to the forefront of attention.

9.3 Increased demand for efficiency in chemical production systems

The laws of the market economy provide strong pressures to continuously improve the efficiency of all production systems. Wasteful production systems that produced large quantities of waste were still economic in the past, either because this waste could be dumped into the environment or the cost of clean-up was shifted to the society. Nowadays, the principle of “the polluter pays” means such processes are doomed. Waste costs money, firstly to get rid of it and secondly, waste essentially means a yield loss with all its associated extra costs. Consequently, a high degree of efficiency and performance is required of all chemical processes today. Biocatalytic methods are particularly efficient, specific, with less waste, raw material use and energy consumption as a result. The penetration of industrial biotechnology into the chemical industry is almost always motivated by normal economic principles such as cost saving, increased efficiency, etc.

Furthermore, as it can be expected that the factors discussed previously will inevitably result in further price increases for raw materials and energy, the need for efficient chemical processes will grow even stronger. The further penetration of industrial biotechnology into the chemical industry and its synergistic cooperation with conventional chemical technology will no doubt be strongly stimulated.

9.4 Growing need for sustainability of the production systems

The world is faced with the major challenge of developing clean and sustainable production processes that respect the environment, improve our quality of life and at the same time are competitive in the marketplace. This includes the development of new production processes that reduce or eliminate the use of dangerous or hazardous substances, minimise energy consumption and waste generation and ideally start from renewable raw materials. Industrial biotechnology is particularly well positioned to play a key role in this quest for sustainability. Bioprocesses generally produce less waste and the use of toxic and dangerous chemicals can sometimes be completely eliminated by using an enzyme. In general, industrial biotechnology typically leads to a significantly reduced environmental footprint of industrial manufacturing.

Since the Kyoto treaty, most industrialised nations have been obliged to respect a number of base criteria with respect to raw material use and energy policy. Many countries have undertaken efforts within the framework of the Kyoto treaty. The negotiability of CO_2 emission rights is now a fact. The first penalties for exceeding the norms soon will become effective. This is expected to result in a fundamental perception change of the use of raw material and energy consumption. It is clear that renewable raw materials that are CO_2 neutral, such as biomass, will benefit from this development.

9.5 Changing consumer perception and behaviour

In most developed societies, there is a growing demand from consumers for information about the products they buy and this goes beyond quality and price. Nowadays, a growing segment of consumers also care more about the production systems by which their products are made (*i.e.*, organic farming, animal welfare,…) and about what happens with them after their use (waste, degradability,…). Production systems that cause ecological damage or animal suffering, are based on inequitable trade or exploitation (such as child labour), etc. are being increasingly rejected by consumers, even if they happen far away and strictly speaking do not directly burden or harm them. Consumers are looking for goods and services that are obtained and used under socially and economically acceptable circumstances, and do not raise any ethical or emotional dilemmas.

The European public's refusal of genetically modified crops is of this nature. It must be emphasized that often exactly the same consumers that reject genetically modified crops, use without grumbling and even enthusiastically products made by means of fermentation processes, such as fermented milk products or Quorn, a mycoprotein from fungi. The consumers' perception of chemical products in their food (preservatives, colourants, anti-oxidants) is also very negative and natural alternatives are demanded. One can therefore expect increasing replacement of these "chemical" products by products obtained by industrial biotechnology.

Industrial biotechnology has the potential to be perceived as working in concert with nature. People generally like the idea of using biomass instead of petroleum and biological processes instead of more conventional synthesis. So bio-processes are not only cost-competitive and offer ecological benefits, they also have a public acceptance edge over classical processes. Furthermore, industrial biotechnology and its processes are mostly performed in contained production systems and the used microorganisms are harmless or cannot survive in nature.

9.6 Changes in the agricultural system

It is clear that the agricultural sector will have to adapt continuously to new needs and problems, under the pressure of consumers, governments as well as foreign forces that wish to reduce import restrictions [16]. Particularly in Europe, the expansion of the European Union with a large number of new member states from Eastern Europe will put a lot of additional pressure on the system.

Some guidelines for the change can be clearly distinguished:

- one wants an agriculture that is less oriented to (mass) production but more directed towards high quality agricultural products;
- one wants an agriculture with more respect for the environment;
- one wants to reduce or abolish altogether production-related subsidies for farmers;
- one wants to reduce import taxes for a number of agricultural products to allow developing countries to market their products in Europe;
- more diversity of agricultural systems is desired, such as new agricultural crops and new production systems, such as organic agriculture;
- one wants to stimulate the production of agricultural crops for non-food purposes.

The use of agricultural raw materials as a renewable raw material for the chemical industry and for fuel clearly meets the many expectations. Consequently, these developments are warmly welcomed, particularly by the agricultural community that has clearly understood the importance of industrial biotechnology.

10 Conclusions and perspectives

Industrial biotechnology can synthesise a broad range of chemical substances, usually using useful microorganisms and their enzymes. The recent wave of new applications seems to indicate that only the tip of the iceberg has been touched. The microbiologist Jackson Foster already predicted in 1964: „Never underestimate the power of the microbe" and has been proven right so far.

For now, some bottlenecks still remain. It is self-evident that replacing a "hydrocarbon economy" with a "carbohydrate" economy is not easy or cheap! In addition to convincing the petrochemical sector, it remains important to know the total production cost and return of biomass production and use for the different applications, before investments can be made. The potential for valorisation of waste biomass and by-products from other bioprocesses may in many cases have a significant impact on economic feasibility.

This technology, already strongly developed in conventional domains of the food and health care industry, now also strongly penetrates the chemical industry with applications in fine and bulk chemistry, polymer synthesis, pharmaceutical industry and the energy sector. As these processes and products are largely based on renewable raw materials and possess substantial ecological benefits, this provides them with a major advantage in the perspective of sustainable development.

Science, industry and policy people alike should give more attention to this green chemistry and its bio-products. Successful innovation by a biotechnological product or process is never solely defined by technology and science but equally by other factors such as acceptance by the general public, the innovation climate and support by the authorities through a consistent Research and Development policy.

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