Overcoming hurdles for innovation in industrial biotechnology

Research and Development Roadmap

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Contents

1 Introduction

Despite being able to tackle some of today's global societal challenges including climate change, dwindling fossil fuel resources and the need for the development of a more sustainable and resource-efficient industry, several hurdles continue to hamper the full exploitation of Industrial Biotechnology's (IB) potential today.

In order to create customer value, new industries and work for the present and the future, it is essential to interface fundamental science with innovation and applications to create new markets. This requires major advances in the key area of biocatalysis which is the foundation of industrial biotechnology.

The BIO-TIC project was a solutions-centred approach that comprehensively examined these many innovation hurdles in IB across Europe and formulated action plans and recommendations to overcome them.

Three roadmaps have been developed, based on a literature study, more than 85 interviews with experts and on the information collected through several regional and business case workshops.

- The *market roadmap* relates to current markets for five IB business cases for Europe, and market projections extending to 2030. It aims to obtain a comprehensive overview of the market potential for industrial biotechnology, the current and potential future value chain composition and stakeholders, including segmented market opportunity assessment and projections.
- The *technology roadmap* revolves around the setting of R&D priorities and identifying needs for research, pilot and demonstration plant activities. This was centred on obtaining a clear overview and insight into the R&D related hurdles for realising Europe's IB market potential. The analysis focuses on the identification of R&D bottlenecks that will require breakthroughs across a broad range of technological domains. It seeks to identify key areas of research to focus on, and to selectively highlight those areas that can be best aligned with current and foreseen end-user market requirements. The technology roadmap also seeks to identify the strength of research areas in different European countries and to gather evidence where duplication of resources exists.
- The *non-technological roadmap* is aimed at identifying regulatory and non-technological hurdles that may prevent IB innovation from taking advantage of market opportunities. The roadmap identifies and subsequently proposes solutions for key market entry barriers, going beyond recommendations already formulated by other initiatives and projects on biobased products.

The BIO-TIC roadmaps show how the various stakeholders can work together to overcome the major issues that hamper the huge potential for IB in Europe. The roadmap *'The bioeconomy enabled: A roadmap to a thriving industrial biotechnology sector in Europe'* shows the relationship between potential market developments, R&D needs, regulatory and non-technological aspects impacting upon IB innovation. All roadmaps can be downloaded from the project website at http://www.industrialbiotech-europe.eu/.

1.1 Reader's Guide to this Roadmap

The scope of the project will be discussed in Chapter 2. The methodology of the project can be found in Annex 3. Chapter 3 presents the vision on the development of industrial biotechnology in Europe in 2030, and the vision of the five business cases or product segments studied in this project. Subsequently, Chapter 4 gives an overview of the state of the art of the different business cases. Chapter 5 discusses the results of the literature study, interviews, regional workshops and business case workshops in terms of a description of R&D hurdles for further development of industrial biotechnology in Europe and actions to overcome these hurdles.

2 Scope of the Roadmap

The scope of the BIO-TIC-project is the industrial biotechnology (IB) value chain. While BIO-TIC aims to develop roadmaps with a scope that covers the wider IB market and value chains, it takes a focused approach in analysing the main hurdles, enablers and required actions towards realising IB's potential for Europe. The analyses will focus on five complementary "business cases for Europe", each of which represent different products and application areas, such that they enable the project partners to discover the widest possible hurdles and enablers that are relevant for the European IB market.

The business cases were selected based on a product group-specific rating carried out by an expert panel comprised of BIO-TIC partners and validated by the Project Coordination Committee and the Advisory Committee of the project. More information on the selection process can be found in Annex 2.

The 5 business cases represent product groups that can make a major contribution to an accelerated uptake of IB into the market place. The selected business cases are:

- Advanced biofuels: bioethanol and biobased jet fuels;
- Chemical building blocks[1];
- Biobased polymers[2];
- 2G or microbial biosurfactants;
- CO_2 as a feedstock: Using IB as tool for reducing CO_2 generated from processes using fossil or biobased raw materials (Carbon Capture and Utilisation).

The BIO-TIC roadmaps have been developed in three stages as shown in Figure 1. See Annex 3 for the roadmap methodology. The first versions of the roadmaps were published in May 2013 and mostly based on literature reviews. The second draft of the roadmaps were published in month 20 of the project and based on further analysis and on the validation of the project partners' findings by means of 8 regional workshops and various stakeholder interviews. This is the third and final version of the roadmap and was developed after further validation and information gathered from an additional 5 business case workshops to fine-tune the BIO-TIC partners analysis on the selected product categories. More information on the project can be found at http://www.industrialbiotech-europe.eu/.

[1] A decision was made to have a closer look at 5 platform chemicals and these were later defined as Succinic acid; Isoprene; 3-hydroxypropionic acid (3-HPA); 1,3-propanediol (1,3-PDO); and Furfural.
[2] For biopolymers the decision was made to focus on PHA (polyhydroxyalkanoate) and PLA (polylacticacid)

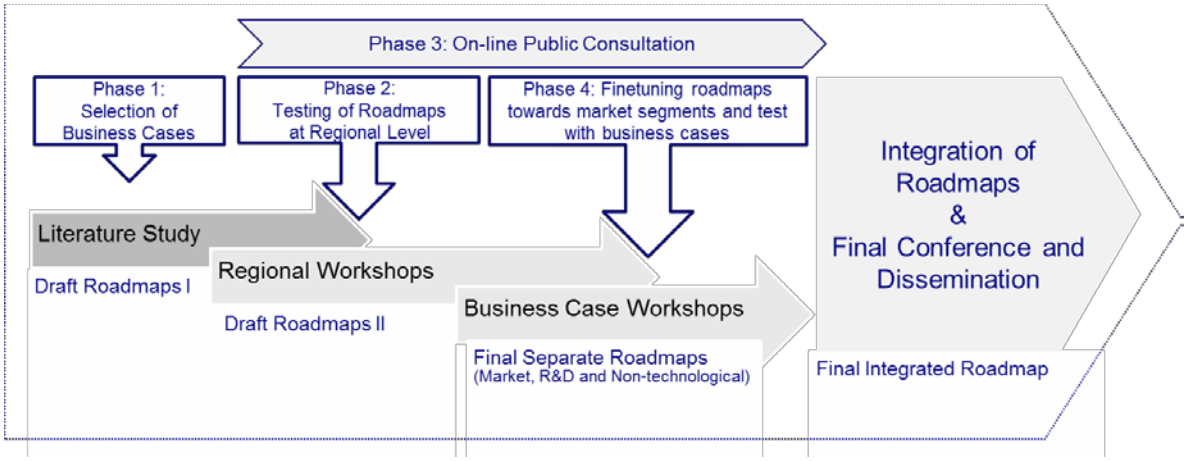


Figure 1. Roadmapping Process

3 Vision

In this chapter the vision on Industrial Biotechnology in general up until 2030 for the five selected business cases or product segments are described. These visions have been developed and refined throughout the project. Detailed information on the market development of industrial biotechnology and the business cases can be found in the market roadmap available at www.industrial-biotechnology.eu

3.1 General IB Vision

Industrial biotechnology has the potential to save energy in production processes and can lead to significant reductions in GHG emissions. Furthermore, it can lead to improved performance and sustainability for industry and higher value products. And also via IB – compared to fossil processes – capital investment can be reduced and more employment realised.

BIO-TIC looks at a world where Industrial Biotechnology plays a significant role in realising the biobased economy through biorefineries, but also through novel IB processes for the production of valuable substances (chemicals and biochemicals, surfactants, building blocks for pharmaceuticals, agrochemicals, flavors and fragrances, fuels etc.) through e.g. cell-factories, direct enzymatic transformation as well as using novel feedstock streams such as CO_2 from flue gas or directly from the atmosphere.

The development of organisms as optimised biotechnological production systems cannot only replace petro-based products and processes, but also lead to new products and processes, for instance through bio-catalysts, which opens up the market for technology providers.

These developments will lead to new feedstock demands and related new technology developments. Synergies between different research fields are expected, as the combination of biotechnology, nanotechnology, process engineering and information & computing technologies can open new technological paradigms.

All over, BIO-TIC's vision is that Industrial Biotechnology will play a major role in transforming our world, contributing to drastically lower CO_2 footprints of our society, and generating significant economic value and jobs for Europe.

According to the BIO-TIC projections, the IB market is estimated to develop from 28 billion EUR in 2013 to 40 billion EUR in 2020, and up to 50 billion EUR in 2030 (Figure 2). This development represents an annual compound average growth rate (CAGR) of 7% between 2013 and 2030 (excluding antibiotics and biogas).

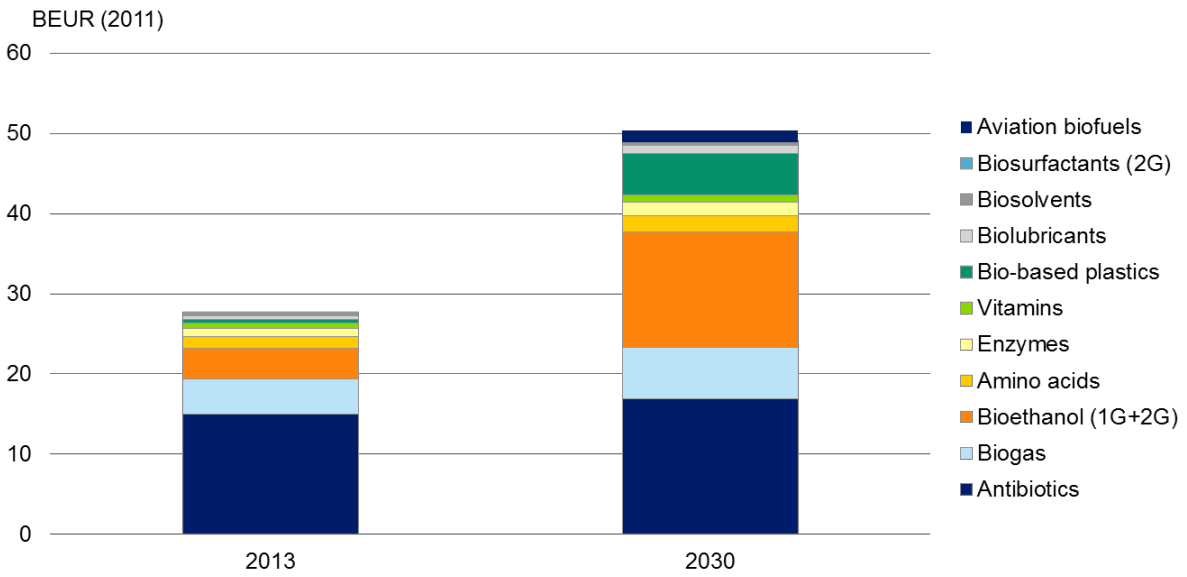


Figure 2. Estimated IB Market Demand in the EU up to 2030

3.2 Advanced Biofuels

In 2030, diverse sustainable feedstocks will be available on a large scale and there will be a performing biofuels supply chain in Europe and globally. However, the governments must guarantee stable policies, investments and prices that can support the development of the sector.

3.2.1 Lignocellulosic Ethanol

Ambitious greenhouse gas emission reduction targets for 2030 will continue to drive the development for low-carbon means of road transport, particularly if separate quotas for renewable energy and advanced biofuels in transport are implemented for 2030. Emission limits have been imposed to new cars, but due to the long turnover time of car fleet, drop-in biofuels are also needed. This contributes to an increasing consumption of 1G/2G biofuels, even though they will unlikely be cost competitive with fossil fuels in the EU by 2030.

In 2030, the EU has a flourishing 1G and 2G bioethanol industry resulting in considerable GHG emission reductions in transport. Thanks to advancements in cultivation and increased use of bioenergy in ethanol production, the GHG emission savings from 2G bioethanol make it a competitive means to reduce GHG emissions in road transport. For 2030, it has been assumed that in the reference scenario 10% of road transportation fuels are 2G biofuels. In the high and low scenarios, the shares are 15% and 5%, respectively. The reference scenario would equal to 1.4 million ton 2G ethanol demand in 2020 and 13.1 Mt in 2030. This market would be valued at approximately 1.1 BEUR in 2020 and 14.4 BEUR in 2030.

3.2.2 Aviation Fuel

In 2030, diverse sustainable feedstocks will be available on a large scale and there will be a performing aviation biofuels supply chain in Europe and globally. The EU governments will have supported the scaling-up of biojet production capacity. Thanks to major efforts on reducing the price for feedstocks, development of more efficient production processes and economies of scale, the aviation biofuel cost disadvantage will have decreased. However, the cost for CO_2 in EU ETS is not likely to fully cover the price gap to fossil kerosene. Therefore, only an international agreement on CO_2 emission reductions in aviation will make it possible to progress towards the goals set in Flightpath 2050. Without such an international agreement (and with severe international hub competition in place), it will be difficult for the market to grow except on a voluntary basis, relying on air passengers' willingness to pay for additional biofuel costs in their ticket prices. Much will depend on the member states' strategies on transport decarbonisation and allocation of incentive regimes between aviation and road transport, too.

The energy demand in aviation is expected to grow from current 52 Mtoe to 59 Mtoe in 2030[3], but the potential of biofuels and that of IB in particular is very unclear. Assuming 1%, 2% and 10% biofuel blend in low, reference and high scenarios in 2030, the 2030 bio jet fuel market would total 0.7, 1.4 and 6.8 BEUR, respectively, but no specific estimates can be given for IB processes because of their early stage of development and unclear competitive advantage compared to other bio jet fuel processes.

3.3 Biopolymers Vision (PHA & PLA)

In 2030, both biodegradable and non-biodegradable bio-based polymers will have a considerable share in the so-called construction or structural polymers market. In 2011 the worldwide production of bio-based polymers was about 3.6 million tonnes (235 million tonnes total) and is expected to rise to 12 million tonnes by the year 2020. The highest growth rates are expected in the non-biodegradable (drop-in) biopolymers like PET and PE, which could be processed and recycled using existing infrastructure. These are followed by the new biodegradable biopolymers PHA and PLA, since infrastructure has to be developed alongside improvements in performance.

Since PHA and especially PLA are commodity market products, without policies to support the use of biodegradable (bio-based) polymers, an enormous price pressure will raise the demand for more cost effective products. Therefore, 2nd generation raw materials (in particular (lignocellulose, agricultural wastes and by-products, as well as by-products from the food industry) will be preferably used in biopolymers production in by 2030. Consumers are widely aware of the environmental benefits of biopolymers and familiar with EU-wide labels indicating bio-based content, biodegradability and recyclability of biopolymers. The market value of biopolymers is expected to reach approx. 5.2 billion BEUR in 2030.

3.4 Chemical Building Blocks Vision

By 2030, the EU will have succeeded in attracting investments in fermentation-based chemicals despite limited access to low-cost feedstocks and challenges in the competitiveness of production

[3] EU energy, transport and GHG emissions trends to 2050. Reference scenario 2013.

costs. In other words, the EU has succeeded in speeding up market entry of new IB-based CBBs by capitalising on its strengths in R&D, demonstration facilities and market for final products.

In 2030, the cost and security of supply will still be the dominant sourcing criteria in commodity chemicals, making fermentation-based production more feasible in the value-added fine and specialty chemical markets than in commodity building blocks. Nevertheless, there will be several building block products available at a cost competitive price and at equal quality. Cost competitiveness will be achieved either 1) by reducing production costs by decreasing the number of steps in the production chain (e.g. succinic acid) or 2) as a result of increased chemical market price due to tight fossil-based supply (e.g. aromatics as a result of ethane cracking). In the case of novel bio-based chemicals, by 2030 industrial biotechnology will allow the realisation of commodity products which have not been possible with traditional chemical technologies.

The increasing uncertainty and volatility of crude oil and shale gas markets will result in commodity chemical companies bringing in new feedstock alternatives to allow stable product supply to their customers. In 2030, there is more flexibility in feedstock; both 1st and 2nd generation raw materials will be widely used in industrial biotechnology while algae and waste feedstocks will move to large scale production.

Being business-to-business market with little or no bio-based premium, the IB-based chemical building block market is expected to follow the overall GDP development and the development of bio-based chemical demand in Europe. Despite a decreasing EU trade surplus in commodity chemicals, there will be an increasing demand for bio-based alternatives. Much of the downstream production will remain in Europe thanks to strong operational and technological knowhow, good co-operation in application development and location of leading brands. One of the key end-uses for bio-based building blocks will be in the production of bio-based plastics. Due to a closer co-operation with consumer markets, a bio-premium may be accepted in the bio-based plastics industry. The market value of IB-based CBBs in 2030 is expected to reach 3.2 BEUR.

3.5 Biosurfactants Vision

2G bio-surfactants are surfactants produced by fermentation. The bio-based carbon content is equal or higher than 95%. In 2030, 2G bio-surfactants produced via industrial biotechnology will be available for a wide range of applications, however, still as niche products due to their limited cost competitiveness compared to conventional surfactants. On a global scale, Europe will remain as the largest consumer of bio-surfactants.

The main contributing factors for the success of the European bio-surfactant market are increased environmental awareness and opportunities for new product properties at a competitive cost. In 2030, European eco-labels include the use of bio-based or bio-surfactants as one of the criteria in consumer goods. GMM fermented bio-surfactants are widely accepted by consumers in many applications e.g. household detergents.

In 2030, bio-surfactants will be produced from a variety of feedstocks including plant oils, fats and sugar biomass but also algae and waste streams. The cost of renewable raw materials, e.g. vegetable oils, will keep the production costs of bio-surfactants at a higher level than conventional surfactants because of increasing demand in e.g. animal feed, biofuels and bio-lubricants. Another factor hindering market growth is the limited number of bio-surfactant suppliers. In order for brand owners

to switch product formula to include bio-surfactants there need to be multiple suppliers of the same surfactant to secure a steady supply at a competitive price.

The demand for bio-surfactants will depend strongly on household spending and industrial activity in detergents and cosmetics where environmental concerns are more evident. The development of the detergent and cosmetic industries can be characterised by general economic development and the 2G bio-surfactants market is estimated to grow from 1.3 MEUR in 2013 to approximately 3.1 MEUR in 2030. In high and low case scenarios, the market value is expected to reach 4.0 and 2.2 MEUR, respectively.

3.6 CO_2 as a Feedstock

In 2030, carbon dioxide offers opportunities for new cost competitive chemical processes and applications, allowing some complex chemical production chains to be reduced to one or two step microbiological conversions and opening windows for completely new chemical compounds.

Moreover, Europe has succeeded in integrating CO_2 bioconversion into existing energy and chemical infrastructures making green energy available for CO_2 technologies and allowing the transformation of energy at peak load periods into chemicals and fuels. At the same time, competitive renewable energy prices have attracted leading CO_2 technology developers to set up commercial facilities in Europe thus making Europe a forerunner in this industry.

Bacterial fermentation and microalgae technologies are expected to be ready for commercial production by 2030. Realisation of industrial scale facilities will depend strongly on the cost of CO_2 capture, on the future political climate, and on the development of energy prices and hydrogen in particular. Advanced biotechnological processes, bio-electrochemical systems and artificial photosynthesis technologies are forecast to develop significantly from today to 2030 reaching demonstration scale production. A key challenge related to all CO_2 based IB process development is the success of scale-up, both from laboratory to demonstration and from demo to commercial capacity.

4 Introduction to State of the Art of the Business Cases

In this chapter the state of the art for each of the business cases in terms of R&D is presented. Some market size elements have also been included as considered relevant to give an overview of the technology development. These will be merged with the two other roadmaps later in the consolidation of the individual road maps process. Furthermore, some companies are listed as examples. It should not be seen as giving an exhaustive picture of the current state of the art.

4.1 Advanced Biofuels

4.1.1 Second Generation Ethanol

The value chain of cellulosic ethanol from hydrolysed lignocellulosic biomass is shown in Figure 3 below.

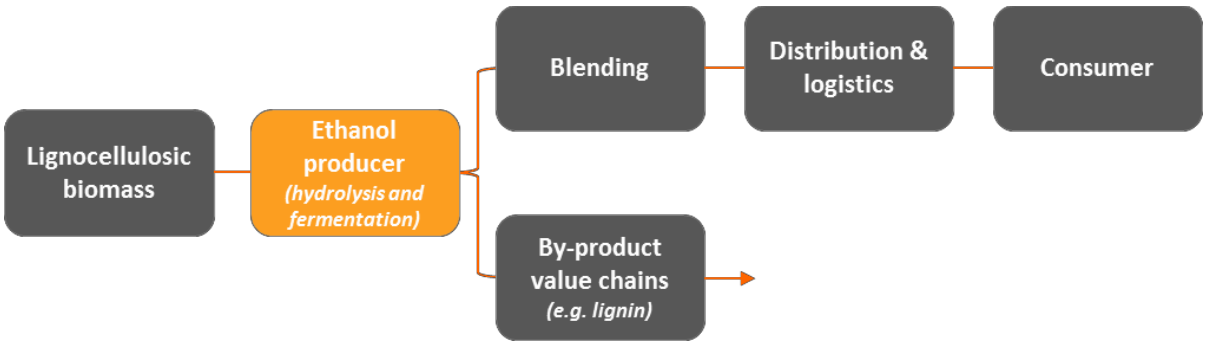


Figure 3 Representation of a value chain of lignocellulosic ethanol from sugar production

The most developed route to produce ethanol from lignocellulosic biomass is fermentation of the sugars, which become accessible by pre-treatment of the lignocellulose and subsequent hydrolysis of the sugar containing cellulose fibre and hemicellulose fraction.

Different chemical, physical and biological pre-treatment methods are known:

- Acid pre-treatments with concentrated or diluted sulphuric acid. Using diluted acids, an additional enzymatic hydrolysis step of the fibre is necessary (process applied by Iogen), while concentrated acids will hydrolyse the fibre as well (process applied by Arkenol)
- Well established pre-treatments as used in the pulp & paper industry like the Kraft pulping or sulfite pulping processes
- Other chemical pre-treatment processes using e.g. ammonia, lye, mixtures of alcohols or organic acids with water (Organosolv) and ionic liquids are under development.
- Physical methods like steam explosion are used in different pilot plants (e.g. Clariant). Methods using supercritical water or supercritical CO_2 are under development.
- Biological pre-treatments using enzymes or organisms (fungi, bacteria) are under research.

The current state-of-art method is enzymatic hydrolysis of the cellulose fibre fraction by fungal cellulases. These enzymes are commercially available or can be produced on-site using side streams of the pre-treatment process (like the hemicelluloses fraction). The application of highly efficient intricate multi-enzyme machines (cellulosomes) from bacteria is still in the state of basic research. .

The common biochemical conversion of the C6-sugar fraction to ethanol is via classical brewing with yeasts. Fermentation to ethanol by bacteria is also possible though there are disadvantages in handling (e.g. sterilisation of the media is necessary). Due to the biochemical pathway, one third of the carbon bound in the sugar will be lost as CO_2 during fermentation.

Alternatively, to avoid the loss of carbon, the sugars can be fermented by homo-acetic bacteria. The product of the fermentation, acetic acid, can be chemically converted to ethanol. The hydrogen required for the process should be generated from biological sources for sustainability reason.

The hydrolysis of hemicelluloses is much easier and may be performed by diluted acids, bases or by appropriate hemicellulase enzymes. In several process set-ups, the hydrolysis already happens in the pre-treatment step.

For co-fermentation of the resulting C5-sugar fraction to ethanol either genetically modified yeast strains are necessary or other microorganisms have to be used which are able to utilise the C5 sugars (xylose). Normally, the utilisation of C5-sugars is much slower while co-fermenting, which can reduce the space-time yield.

Nevertheless, while using the sugars from lignocellulose an alternative application for the lignin fraction must be developed, since lignin cannot be fermented to ethanol. Commonly, the lignin fraction will serve as a source for energy and heat production for the process. It could also be used as a source for hydrogen by gasification (see below). Thermoplastic and duroplastic applications are under development to use lignin as a source for phenols. The whole process chain can be integrated in a biorefinery concept.

Cellulosic Ethanol: Gasification of Lignocellulosic Biomass and Fermentation of Crude Syngas

The value chain of cellulosic ethanol from syngas is shown in Figure 4 below.

Figure 4 Representation of a Value Chain of Lignocellulosic Ethanol from Syngas Production

A completely different way to produce ethanol from lignocellulosic feedstock is the gasification of biomass to syngas and subsequent fermentation of the gas to ethanol. The advantage of the combination of biomass gasification with fermentation instead of chemical liquefaction (e.g. Fischer- Tropsch, Methanol-Synthesis) is that the crude syngas can be used for fermentation regardless of Sulphur- or CO_2-content and without adjustment of the H_2/CO-ratio. The main disadvantage is the limited gas-to-liquid mass transfer rate. Bacteria which are able to use Syngas as a source of carbon and energy belong to the genus *Clostridia*.

Algae-based ethanol

The value chain of algal-based ethanol is shown in Figure 5 below.

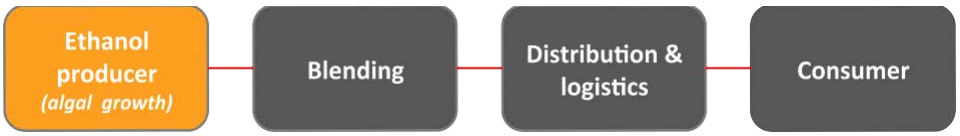


Figure 5 Representation of a Value Chain of Algal-based Ethanol Production

Using genetically engineered algae for the production of ethanol from 'almost' only CO_2 and sunlight is another alternative. Today, some start-up companies are in the market producing ethanol directly from algae derived oils with high lipid content (from genetically modified algae) or bio crude oil by hydrothermal treatment of algae biomass.

However, none of them are today on an industrial scale. An approach is the direct-to-ethanol process of Algenol, who have engineered algae which produces ethanol directly from photosynthetically-fixed CO_2. Since ethanol is excreted by the algae, no energy consuming harvest of the algae is necessary which makes the process more feasible. In a recent announcement Algenol stated they have reached 9.000 gal/acre/year (75.000 l/ha/year)[4]. The Algenol process many similarities with the process of Photanol.[3] This process produces lactic acid and butanol with the same type of cyanobacteria but with significantly lower concentrations

Pilots, demonstration facilities and commercial plants

According to IEA Bioenergy Task 39's report 'Status of Advanced Biofuels Demonstration Facilities in 2012' in Europe there are 12 pilot and demonstration facilities and two commercial plants operational to produce ethanol based on cellulosic sugar fermentation with a capacity of about 100.1 tonne ethanol per year. Three facilities were scheduled for commissioning in 2014 with an annual capacity of 50.000 tonne per year ethanol.

4.1.2 Aviation Fuels

All aviation fuels must comply with the requirements of ASTM D1655 "Standard Specification for Aviation Turbine Fuels", which is extended in ASTM D7566 to cover also Fischer-Tropsch hydrocarbons (BtL-FT) up to 50 %. A revision of ASTM D7566 in 2011 now certifies HEFA (hydroprocessed esters and fatty acids) up to 50 % and in June 2014 ASTM D7566 was revised again to certify Farnesane (2,6,10-trimethyldodecane) up to 10 % in jet fuel. Aviation biofuels must be 'drop-in' replacements for conventional kerosene as the development of new engines, aircraft and infrastructure is very expensive and the existing infrastructure has a long lifespan. IB and non-IB routes to aviation biofuels exist and these are explained briefly below. The value chain for aviation biofuels is shown in Figure 6 below.

4 http://www.biofuelsdigest.com/bdigest/2013/03/11/algenol-hits-9k-gallonsacre-mark-for-algae-to-ethanol-process/

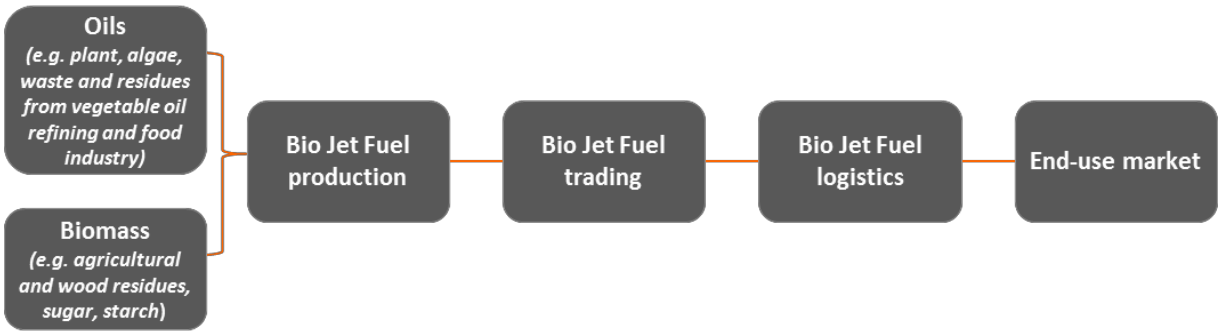


Figure 6. The Value Chain for Aviation Biofuels

BtL-FT is based on the (i) gasification of dry biomass, (ii) gas upgrading to syngas and (iii) the subsequent production of hydrocarbons by Fischer-Tropsch synthesis.

- The pre-treated biomass (torrefaction or pyrolysis, size reduction) is gasified and transformed into crude syngas (composed of mainly H_2 and CO, but also CO_2, CH_4 and short chain hydrocarbons and other gases, depending on the gasification process (autotherm vs. allotherm) and the oxidising agent (O_2 vs. air vs. steam).
- After removing all impurities the ratio of the remaining H_2 and CO have to be adopted for the Fischer-Tropsch-Process. While biomass typically yields a H_2/CO ratio of 0.7 to 1.8, a ratio of 2 is needed to synthesize hydrocarbons. The additional hydrogen can be gained during gasification using the water-gas-shift reaction. Remaining short chain hydrocarbons can also be converted into H_2 and CO using the gas reforming reaction. Also pressure and temperature of the synthesis gas has to be adopted.
- The Fischer-Tropsch Synthesis leads to alkanes of different chain lengths. Therefore, the raw product needs to be upgraded via distillation to split it into fractions; via hydration and isomerisation of the C5 – C6 fraction and reforming of the C7 – C10 fraction in order to increase the octane number for petrol use; and via cracking to convert long-chain fractions (waxes) into petrol and diesel fractions.

The Fischer-Tropsch-Synthesis is itself a well-established technology, which is used for liquefaction of coal and gas into CtL and GtL, respectively. The challenge in the BtL-technology is the gasification of biomass which is much more inhomogeneous than coal or gas and in upgrade of the product gas into synthesis gas. Due to these challenges and the high investment costs, BtL is not commercially available at present. Industrial Biotechnology is not involved in BtL-FT and could potentially only play a role in feedstock supply.

Hydro-processed esters and fatty acids (HEFA) are produced by reducing vegetable oils (also from non-food resources), animal-based waste fats, as well as by-products of vegetable oil refining and fatty acids with hydrogen to expel hetero atoms like oxygen. The products of the process are long chain hydrocarbons with propane as co-product. Either the oils can be treated in the hydro-treating stage of a common oil refinery (to a certain extend), or in separate hydro-treating plants. The Finnish company NesteOil is currently producing more than 1.3 million tonne of NExBTL[5] in four commercial plants across Europe. Industrial Biotechnology is currently not involved in HEFA production but could potentially play a role in feedstock supply (e.g. algae production).

Fast pyrolysis of lignocellulosic biomass with subsequent hydro-processing of the pyrolysis oil

fraction is also an option for generating jet compatible drop-in fuels. A drawback is that pyrolysis oil contains up to 40 % oxygen, which is bound in organic acids, phenols, aldehydes und ketones. Therefore large amounts of hydrogen are necessary to reduce and neutralise the oil constituents to hydrocarbons. Of advantage is that pyrolysis-derived biofuels still contain aromatics produced from the conversion of the phenolics in the lignin component of biomass. Aromatics in jet fuels are mandatory for elastomers in the fuel system to enable their 'swell and seal' properties at low temperature.

Hydrothermal liquefaction is another option for thermochemical treatment of (wet) biomass. The resulting bio-oil-fraction could be upgraded after separation to fuel quality hydrocarbons by hydro-processing comparable to HEFA and pyrolysis oil. One potential feedstock for hydrothermal liquefaction is algal biomass. Sapphire Energy is currently building the world's first commercial demonstration scale algae-to-energy farm to produce "green crude" from algae by hydrothermal liquefaction, which is ready for upgrading/refining in the hydro-processing step. Since generation is part of the concept, industrial biotechnology is integrated into the process development for algal strain development and cultivation.

Alcohol to Jet (ATJ) is a combined biotechnological/chemical synthesis process. In principle fermentatively derived alcohols (e.g. ethanol, isobutanol) could be upgraded in three well-established chemical steps (Dehydration, oligomerisation and hydrogenation) to paraffins of kerosene quality. Ethanol could be achieved from sugar or carbon monoxide fermentations as mentioned above in the advanced ethanol section. The company Lanzatech has already an ATJ process based on carbon monoxide fermentation, Byogy on sugars.

In contrast to ethanol, fermentation to isobutanol needs genetic engineering advances to effect this. The biosynthesis of isobutanol was first discovered in bacteria *(Clostridia)* and has been genetically engineered into several species including yeasts. Companies like Gevo and Butamax have business models developed to convert ethanol facilities to produce isobutanol as a platform.

The ATJ process has good opportunities for industrial biotechnology, since existing ethanol facilities can be converted/extended to produce jet fuels. By-products of the process could be used as platform chemicals in the chemical industry, bringing the biorefinery concept into life.

The direct sugar to hydrocarbons (DSHC) fermentation uses bacteria or yeast to produce straight hydrocarbons. The company Amyris has taken DSHC production to a commercial scale. Amyris uses a genetically modified yeast to ferment sugars to farnesene, a C15 hydrocarbon (isoprenoid). Farnesene is accredited for use as an aviation fuel-blending component at blends of up to 10 %. Industrial biotechnology plays a major role in DSHC. There is still space for further strain optimisation and the development of alternative isoprenoids (like bisabolene) for aviation fuel blending.

Nevertheless aside from DSHC all mentioned processes are dependent on hydrogenation steps, which requires large amounts of hydrogen. Hydrogen can either be produced by reforming fossil sources (like methane gas) or by reforming the biological source itself (like the water-shift-reaction of syngas), which will decrease the yield of the biological product. Nevertheless hydrogen-sourcing will play a major role in future commercialisation of all drop-in fuels like aviation fuels.

4.2 Chemical Building Blocks

The roadmap focuses on 3HPA, succinic acid, PDO, furfural, and isoprene. The value chain of chemical building blocks is shown in Figure 7 below.

Figure 7 Representation of Value Chain of Chemical Building Blocks

4.2.1 3HPA

3HPA (or 3-hydroxypropionic acid) can be produced using sugar fermentation using bio-engineered micro-organisms. Potential applications are the subsequent transformation of 3HPA into valuable chemical derivatives, including acrylic acid. Acrylic acid is a high volume chemical used in a wide range of materials: plastics, coatings and paints.

OPXBIO, a US based company is currently developing technology to produce 3HPA using fermentation processes. The core technology of OPXBIO is its EDGE technology platform, which enables them to rapidly and robustly engineer microbes. Together with The Dow Chemical Company they are developing an industrial scale bioprocess for bio-acrylic acid. The fermentation process was demonstrated at the 3.000 litre scale in mid-2012.

Succinic Acid

Several companies are currently developing processes to produce bio-based succinic acid. A production process based on bacterial fermentation allows a large reduction of production cost (in comparison to petrochemical alternatives) that allows access to larger volume commodity markets. Potential intermediates to be produced based on succinic acid are 1,4-butanediol, tetrahydrofuran or maleic acid. Potential applications are textiles, coatings and engineering plastics.

Table 1. Overview of the Current Production Facilities

Company	Plant capacity	Location	Remarks
Myriant	14.000 tonne/yr	Lake providence (USA)	Operational since 2013
BioAmber	3.000 tonne/yr	France	Fully operational since 2010
BioAmber	30.000 tonne/yr	Sarnia (Canada)	Expected for 2016
Succinity	10.000 tonne/yr	Montmeldo (Spain)	Operational
Reverdia	10.000 tonne/yr	Cassano Spinola (Italy)	Modified existing installation operational in 2013.

More capacities are planned for the future; especially BioAmber who have announced plans for several potential new plants for the coming years.

4.2.2 PDO

PDO (or 1,3 propanediol) is produced by fermentation of sugar, which leads to lower operating costs and capital investment over conventional petrochemical processes. Potential applications are textiles, coatings and engineering plastics. A joint venture between DuPont and Tate & Lyle is currently operating a plant with a capacity of 45.000 tonne per year in Tennessee in the US. Metabolic Explorer, a French company, supported by the BioHub program, is currently planning to build a PDO plant in Malaysia together with Bio-XCell[5].

4.2.3 Furfural

Furfural offers a promising, rich platform for lignocellulosic biofuels. These include methylfuran and methyltetrahydrofuran, valerate esters, ethylfurfuryl and ethyltetrahydrofurfuryl ethers as well as various C_{10}–C_{15} coupling products. Furfural is produced by the hydrolysis and dehydration of xylan contained in lignocellulose. The conventional furfural processes rely on feedstocks rich on hemicelluloses, such as corncobs or sugarcane bagasse, and yield approximately 10 wt% of furfural (typically only 50–60% of the theoretical yield), which is stripped from the reactor with a large quantity of steam. The resulting residue after furfural production is used to generate the required steam for the reactor and downstream separation. Hence, the overall yield of valuable products does not exceed 18–21 wt% including co-products. Improved technologies will need to operate at a much larger scale (20 to 100 times the current processes) with improved yields (e.g., >80 mol% based on xylose) and reduced energy consumption (e.g., <10 t_{steam} $t_{furfural}$) to leave residual biomass to generate power or for producing biofuels. Worldwide furfural production is approximately 400 kt, most of which is converted to furfuryl alcohol for the subsequent production of furan resins[6][7].

4.2.4 Isoprene

A major proportion of the world's isoprene is made via separation from the petrochemical C5 stream. C5 components are found in pyrolysis gasoline. However, in order to extract isoprene a complex series of separations are needed to remove first cyclopentadiene as its dimer-DCPD, as well as piperylene, culminating in extractive distillation for isoprene recovery.

Isoprene produced via an IB process, utilises glucose sourced from biomass which is converted to isoprene via microbial fermentation. However this process is not yet implemented on an industrial scale. Several companies are currently at the forefront of this process technology development. The biotransformation process requires microbial strain development to provide a microorganism with sufficient capabilities to support the fermentation of glucose into isoprene. The bio-derived isoprene

[5] http://www.duponttateandlyle.com/fact_06-2007_sustainability | http://www.metabolic-explorer.com/contenu.php?rub=company&ssrub=1

[6] Furfural—A Promising Platform for Lignocellulosic Biofuels <http://onlinelibrary.wiley.com/doi/10.1002/cssc.201100648/pdf>

[7] Large Scale Furfural Production (from Bagasse) | DalinYebo: Biomass to Chemicals & Energy <http://www.dalinyebo.com/item/315-large-scale-furfural-production-from-bagasse>

generated needs to be recovered and purified to a specification suitable for high cis polyisoprene, where the specification is tightest. As with butadiene, isoprene is reactive and requires stabilisation with an inhibitor, such as tertiary-butyl-catechol. Strain development researchers have developed a microbial cell culture that drives sugar conversion through engineered biosynthetic pathways, to produce isoprene at very high yields through an aerobic biotransformation. With a boiling point of 34°C, isoprene is very volatile and can be removed from the fermentation broth with relative ease such that it does not accumulate at sufficient concentration as to poison the microorganism that makes it. However, isoprene makes explosive mixtures with air when in a 2%-9% concentration, so care is required to ensure that the air feed to the fermentation ensures all oxygen is converted, leaving isoprene to vaporise into an atmosphere of carbon dioxide and nitrogen[8].

4.3 Biopolymers

The term biopolymer refers to (i) biodegradable bio-based or (ii) biodegradable petrol-based or (iii) non-biodegradable (partly) bio-based polymers. Within the group of the bio-based polymers, the non-biodegradable drop-in (partly) bio-based polymers, which are chemically identical to their petrol-based counterparts, represent the single largest sector of the global bioplastics production. These are commodity plastics such as PE or PET, and benefit from the well-established infrastructure on production, processing and recycling of their conventional counterparts.[9]

The second largest sector of global bioplastics production is that of the new biodegradable bio-based polymers like PLA and PHA. The market development of both are strongly dependent on efforts in industrial biotechnology to enhance production efficiency.

Therefore this roadmap focuses on PLA and PHA. Below we provide a short description of the state of the art and the value chain of biopolymers. The value chain for biopolymers is shown in Figure 8 below.

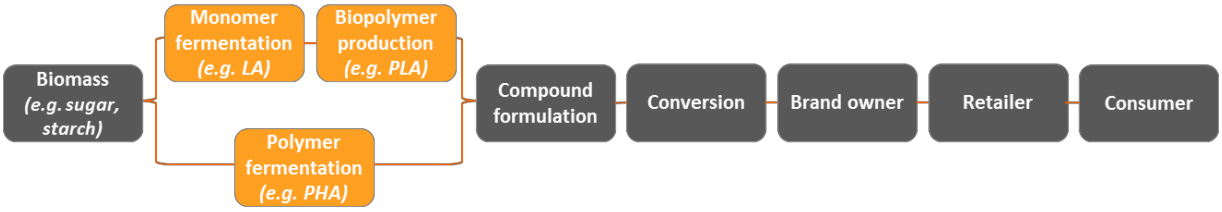


Figure 8 Representation of value chain of biopolymers

4.3.1 Polylactides (PLA)

In terms of volume, currently the most important biopolymer produced by IB technologies is polylactide (PLA) with a worldwide production capacity of about 185,000 tonnes per year in 2013[10].

[8] The Potential for Bio-Isoprene <http://www.chemweek.com/chem_ideas/Guest-Author/Biomaterials-The-Potential-for-Bio-Isoprene_39990.html>
[9] European Bioplastics, 2014. Bioplastics - facts and figures
[10] Material share of biopolymer production capacity sorted by material grade 2013. http://ifbb.wp.hs-hannover.de

According to their own forecasts, existing PLA producers are planning to considerably expand their capacity to reach around 710,000 tonnes per year by 2020. There should be at least nine sites with a capacity of at least 50,000 tonnes per year by that time. A survey of lactic acid producers (the precursor of PLA) revealed that production capacity could even rise to roughly 950,000 tonnes per year, mainly L-(+)-lactic acid, to meet confirmed demand.

PLA is produced by chemical polymerisation of lactic acid, which is a fermentation product of lactic acid bacteria and some filamentous fungi. In contrast to chemical synthesis, fermentation leads to either optically pure L-(+)- or D-(-)-lactic acid, which are the desired sources for the polymerisation. Impurities by its counterpart enantiomer lead to more amorphic polymers with different properties, which are relevant for processing and use[11].

Despite the environmental advantages of PLA (bio-based, biodegradable under composting conditions), the biopolymer is still a player in the commodity market which is influenced by strong economic pressure. The selling price of lactic acid is dependent on many factors of which the cost of feedstock is very significant. The microbial conversion requires the presence of carbon, complex nitrogen and phosphorus sources:

- The carbon source for microbial production of lactic acid can be either sugar in pure form such as glucose, sucrose, lactose etc. or sugar-containing materials such as molasses, whey or starch. Alternative sources, like by-products (glycerol) and residues from agricultural materials (e. g. hydrolysates of straw, cottonseed hulls, corncob, corn stalks, rapeseed residues, wheat bran and brewer's spent grains) are of considerable interest and under investigation. Recent research papers address new wild type strains of lactic acid bacteria which are for example able to utilise glycerol, the by-product of the biodiesel production, or pentoses, which are a considerable fraction of hydrolysates from 2nd generation lignocellulosic feedstocks like wood or straw. Additionally NatureWorks and Calysta Energy are working on a pathway for using C1 sources like CO, CO_2 or methane for the lactic acid production in future proposed for 2018[12].

- The nitrogen source is essential for the conversion of glucose to lactic acid. A complex nitrogen source like yeast extract contains all necessary amino acids and other organic nitrogen compounds needed to maintain cell development and lactic acid formation. However, yeast extract, is too expensive for cost-efficient industrial production. Cheap complex nitrogen sources are rare, because organic materials with high nitrogen/protein contents are mainly used in food and feed productions. Grass press juice is a promising complex nitrogen source and also under investigation as nitrogen source for PHA production.

- It is likely, that one of the future trends in lactic acid production will end up in mixtures of different low-cost feedstocks in order to avoid the use of expensive complex supplements. As a consequence the phosphorus content of the fermentation broth has to be maintained, since the phosphorus content of the different may vary.

  Other factors which affect the economics of lactic acid production are yield, optical purity of the desired enantiomer, tolerance against by-products of hydrolysis of 2nd generation feedstocks, as

[11] Sven Jacobsen, 2000. Polylactide – Biologisch abbaubare Kunststoffe aus nachwachsenden Rohstoffen für neue Anwendungen. Universität Stuttgart

[12] http://www.natureworksllc.com/News-and-Events/Press-Releases/2013/06-18-13-Calysta-Energy-NatureWorks-RandD-Collaboration

well as optimum pH of the organisms.

- The yield of lactate is dependent on the fermentation type of the organism and the carbon source. Homofermentative lactic acid bacteria convert hexoses to L(+)-lactate as a single product, while heterofermentative lactic acid bacteria convert hexoses to D(-)-lactate, ethanol and CO_2. Growing on other carbon sources like pentoses, glycerol or methane could lead to undesired by-products like acetate, which reduces the yield of lactate and also enhances downstream processing. In recent research papers new wild type homofermentative lactic acid bacteria are described, which are able to convert to lactate solely.
- Optical purity could be enhanced by genetic engineering. The strategy is to delete either the D- or L- lactate dehydrogenase genes of the organisms.
- Tolerance against the by-products of hydrolysis of 2nd generation feedstocks could be achieved by selecting high tolerant strains or by using enzymatic instead of acid based hydrolysis.
- The pH-optimum of the organisms is also crucial for economics. Most lactic acid bacteria have a pH-optimum around neutral pH with the consequence that the fermentation broth has to be pH-controlled with lime (calcium hydroxide). Sulfuric acid is used to acidify the calcium salt of lactic acid, results in stoichiometric production of calcium sulfate (gypsum). Using organisms with a lower pH-optimum leads to lower gypsum production. The strategy of NatureWorks as the main global PLA producer is directed on the (genetically engineered) yeast fermentation at lower pH. Recently, *Pichia stipitis*, a yeast that naturally ferments xylose, was genetically engineered for L-(+)-lactate production.[13]

4.3.1 Polyhydroxyalkanoates (PHA)

In contrast to PLA, which is chemically synthesised from a biobased monomer (lactic acid), PHAs are a group of biodegradable biobased linear polyesters which are produced directly via biochemical routes in the fermentation process. The worldwide production capacities today are about 34,000 tonnes/year[14] and according to the forecasts of PHA producers and several experts is will be expanded to about 350.000 tonnes/year by 2020.

PHA are intracellular storage substances of microbes, which are mainly build from saturated and unsaturated hydroxyalkanoic acids. Aside from unbranched 3-hydroxyalkanoic acid, also 4-, or 5-hydroxyalkanoic acids and branched or even side chain substituted hydroxyalkanoic acids are possible mononers. With regard to the diversity of monomers and constitutional isomers and the varying molecular weights of the polymers a high potential of biobased polymers arises all with different properties[15]. The most common type of PHA is the homopolymer of 3-hydroxybutyrate (PHB), which became available in the 1980s.

The aerobic biosynthesis of PHB is usually induced under conditions of limiting essential nutrients (like nitrogen or phosphorus) or oxygen while the carbon sources are in excess. The production can

[13] Ilmén et al. 2007. Appl. Environ. Microbiol. Vol. 73, No. 1, p. 117–123

[14] Material share of biopolymer production capacity sorted by material grade 2013. http://ifbb.wp.hs-hannover.de

[15] Endres et al. 2014. Biobasierte Kunststoffe und biobasierte Verbundwerkstoffe. *In:* Marktanalyse nachwachsende Rohstoffe, Schriftenreihe Nachwachsende Rohstoffe, Band 34, FNR, p. 202-312

account for as much as 80% of the cell's dry weight. PHB is accumulated in intracellular granules by a wide variety of Gram-positive and Gram-negative organisms, but for potential industrial applications many different expression systems have already been developed like *E. coli*, *S. cerevisiae* and also transgenic plant cells.

Since PHAs are highly biodegradable in different environments (not just in composting plants) and also due to their good thermochemical and barrier properties, they offer great potential for packaging applications[16]. Like PLA, PHA is also a commodity and therefore has to compete against the strong economic pressure within this market.

In contrast to bio-based polymers, where the monomer is produced by industrial biotechnology, which has to be (optically) purified before chemical polymerisation processing (like PLA), down-stream processing is just limited to isolate the granules after fermentation. This enhances the possibilities of industrial biotechnology to reduce the high production costs of by using 2nd and 3rd generation feedstocks, complex waste streams, mixed culturing and even by fermentation under unsterile conditions. Moreover, PHA can be acquired as a by-product of biofuels or platform chemicals in a biorefinery context to enhance sustainability.

4.4 2G /Microbial Bio-surfactants

This roadmap focusses on the technical issues surrounding the production of 2G/microbial biosurfactants, that is to say, surfactants produced by fermentation. The bio-based carbon content is equal or higher than 95%. The value chain for 2G / microbial biosurfactants is shown in Figure 9 below.

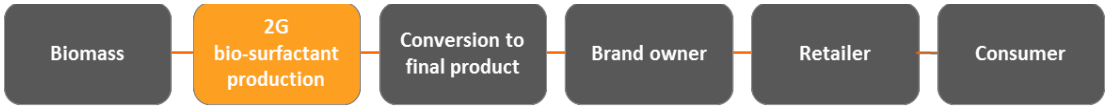


Figure 9 Representation of the Value Chain for 2G/ Microbial Biosurfactants

Surfactants are compounds that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid. Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants

Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their *tails*) and hydrophilic groups (their *heads*). Therefore, a surfactant contains both a water insoluble component and a water-soluble component. Surfactants will diffuse in water and adsorb at interfaces between air and water or at the interface between oil and water, in the case where water is mixed with oil. The water-insoluble hydrophobic group may extend out of the bulk water phase, into the air or into the oil phase, while the water-soluble head group remains in the water phase.

[16] Bugnicourt et al. 2014. eXPRESS Polymer Letters Vol.8, No.11, p. 791–808

World production of surfactants is currently estimated at 15 million tonnes/year, of which about half is destined for soaps. Other surfactants produced on a particularly large scale are linear alkylbenzenesulfonates (1700k tonnes/year), lignin sulfonates (600k tonnes/year), fatty alcohol ethoxylates (700k tonnes/year), and alkylphenol ethoxylates (500k tonnes/year).

Biosurfactants are surface-active substances in much the same way as chemically synthesised fossil surfactants. The noticeable difference being the feedstocks used and/or the mode of synthesises employed:

- Conventional biosurfactants like APG (green surfactants) are made entirely from renewable feedstocks (starch, vegetable oil...etc) via classical chemical synthesis. This kind of biosurfactant is now well established and can be found in personal care and cleaning products amongst others.
- 2G or microbial biosurfactants like Rhamno- or Sophorolipids are produced from renewable feedstocks via microbial fermentation. Such biosurfactants can be produced in high yield (typically 400 g/L). Another point to note is currently microbial biosurfactants are expensive and command a premium typically >10x that of fossil-based surfactants. As microbial biosurfactant manufacture is in its infancy, limited product variation is achievable due to the limitations of the microorganisms used. However this fast evolving area will benefit from genetic engineering, which will allow for the utilisation of a wider feedstock library, which in turn will generate a larger portfolio of microbial derived biosurfactants. Examples of popular microbial biosurfactants and the producing organisms include:
    - Emulsan produced by *Acinetobacter calcoaceticus*
    - Sophorolipids produced by the yeast *Starmerella bombicola*
    - Rhamnolipids produced by *Pseudomonas aeruginosa*

These definitions of a biosurfactant are generally accepted throughout the industry, although ubiquitous acceptance is needed across all business sectors.

2G / microbial biosurfactants potentially have many advantages over chemically synthesised fossil surfactants; they are environmentally friendly, less toxic and non-hazardous. They have better foaming properties and higher selectivity and may be active at extreme temperatures, pH and salinity and can be produced by industrial by-products. This last feature will be a key in driving down the price of commercially available microbial biosurfactants while utilising unwanted waste streams at the same time, although downstream processing (purification) needs to be addressed. Large-scale production of some biosurfactants is now in place; a leading exemplar of such is the Bio Base Europe Pilot Plant in Ghent. The Bio Base Europe Pilot Plant is a flexible and multipurpose pilot plant for the production of biobased products like tailor-made biosurfactants and the development of advanced processes.

One of the major domestic product applications of green surfactants is in the area of laundry products. Currently, the most commonly used class o f surfactant in washing products is the alkyl sulfonates, such as linear alkylbenzene sulfonates (LAS). However, the glycolipid biosurfactants, like sophorolipids, rhamnolipids and mannosylerythritol lipids, are possible

candidates to be used, at least as partial replacements for LAS. Table 2 lists the most important current 2G / microbial biosurfactants and describes the major technological challenges to overcome for each of them.

Table 2 State of the Art Review for Bio-Surfactants.

Microbial biosurfactant class		Technical Challenge	Microorganism	Application
Glycolipids	Rhamnolipids	Fermentation production reservation lies with rhamnolipids and the main organism that produces them, P. aeruginosa, which in the UK is classified as a class II pathogen.	*P. aeruginosa and P. putida*	Bioremediation
			P. chlororaphis	Biocontrol agent
			Bacillus subtilis	Antifungal agent
			Renibacterium salmoninarum	Bioremediation
	Sophorolipids	Difficult downstream process (involves solvent extraction which is complicated and long downstream process)	*Starmerella (Candida) bombicola and Candida apicola*	Emulsifier, MEOR, alkane dissimilation
	Trehalose lipids	Difficult downstream processing	*Rhodococcus sp.*	Bioremediation
			Tsukamurella sp. and Arthrobacter sp.	Antimicrobial agent
	Mannosylerythritol lipids	Difficult downstream processing	*Candida antartica*	Neuroreceptor antagonist, antimicrobial agent
			Kurtzmanomyces sp.	Biomedical application
Lipopeptides	Surfactin	Difficult downstream processing	*Bacillus subtilis*	Antimicrobial agent, biomedical application
	Lichenysin	Difficult downstream processing	*B. licheniformis*	Hemolytic and chelating agent

4.5 CO_2 as a Feedstock for Biochemicals

The value chain of CO_2 as a feedstock is shown below.

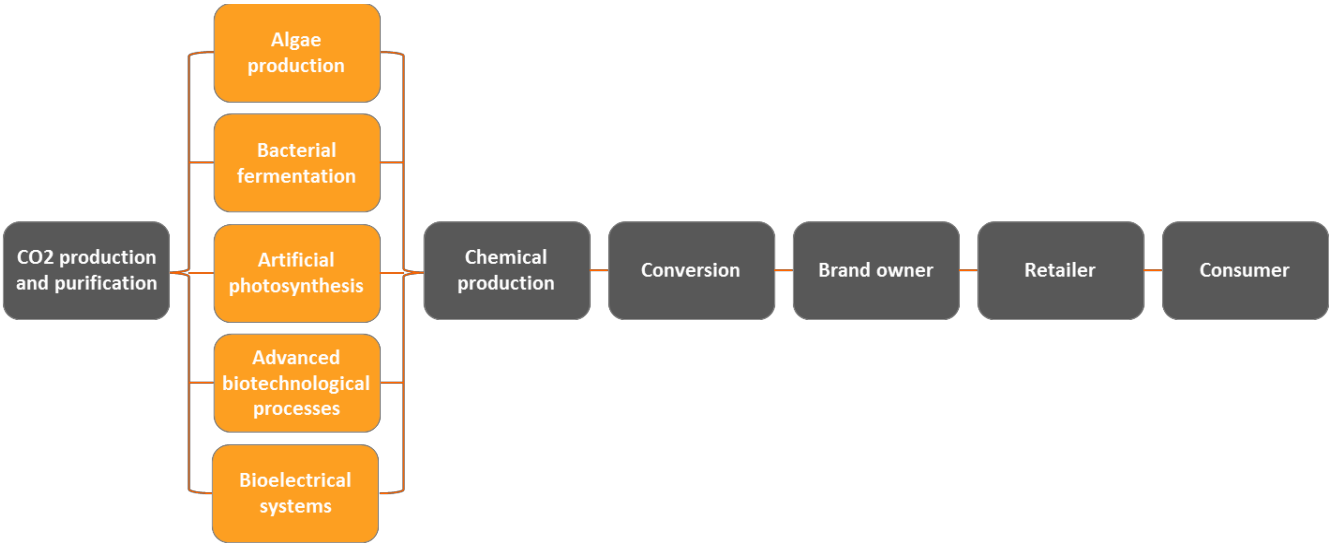


Figure 10 Representation of the Value Chain of CO_2 as Feedstock for Chemicals

The first demonstration and commercial applications of waste gas fermentation processes to produce ethanol and 2,3-BDO (LanzaTech, IneosBio, Coskata, opxbio, Kiverdi) are already commissioned. In the case of LanzaTech the CO_2 feedstock comes from waste gases from coal fired power plants and steel mill plants. The CO_2 preparation is done, and the design of the fermenter is optimised for the use of gaseous feedstocks. Microorganisms are optimised for the use of CO and CO_2 as is the production of the first aimed products (Ethanol, Acetic acid, 2,3-BDO). Also the CO_2 uptake and capture is demonstrated in a continuous fermentation process.

A generic prerequisite of the success for CO_2-based chemicals is the need to produce cost effective chemical intermediates. All technologies are in early stages and need substantial R&D but the costs for the production processes need to be competitive with conversion processes available for nonrenewable hydrocarbons. It must be less energy intensive with respect to the on-stream processes that it aims to replace or energy and especially hydrogen costs have to be much lower than today.

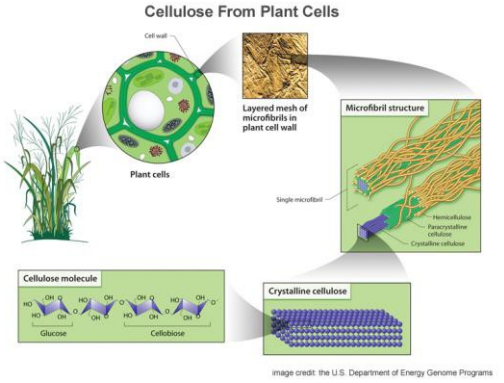
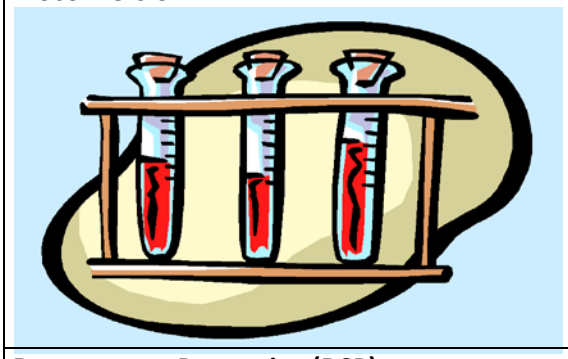
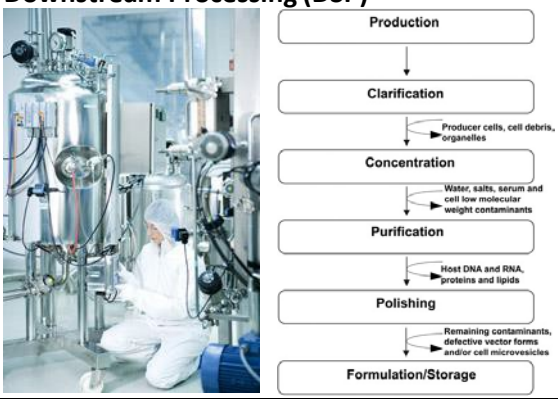
In addition to cost effective chemical intermediates, it is important to develop new synthetic routes based on CO_2 leading to novel products which have so far not been produced.

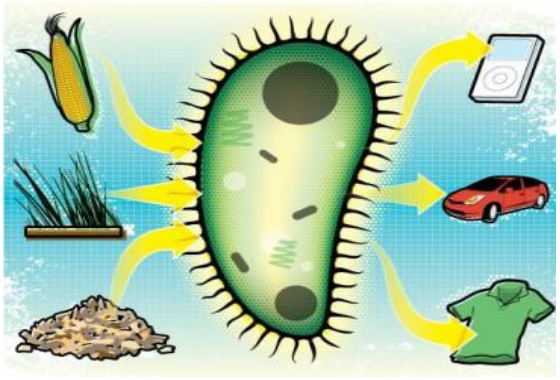
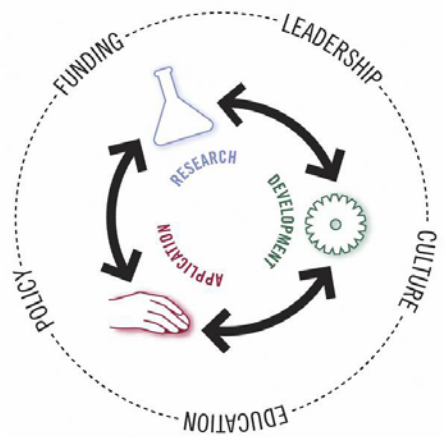
5 Hurdles, Enablers and Actions for R&D for Industrial Biotechnology in Europe

In this chapter an overview is given of hurdles, enablers and actions for R&D for industrial biotechnology in Europe. The overview is based on literature research, eight regional and five business-case related workshops and several interviews with stakeholders.

To categorise the hurdles, enablers and actions, we defined six R&D topics as shown in Table 3.

Table 3 R&D Topics as Distilled from a Broad Range of Literature Sources

R&D topic	Definition
Feedstock Supply 	Topics related to biomass cultivation, logistics, pre-treatment.
Bioconversion 	Topics related to biochemical conversion through biocatalysts, microorganisms.
Downstream Processing (DSP) 	Topics related to biotech process development, e.g. product recovery, water management.

Products & Markets 	Topics related to valorization, commercialisation and development of products.
R&D Tools 	Topics related to development of tools supporting R&D, like the development of models and databases.
Knowledge Infrastructure – Hard 	Topics related to installation of pilot facilities, connections to existing physical infrastructure.
Knowledge Infrastructure – Soft 	Topics related to funding, entrepreneurial climate, presence of knowledge sharing and open innovation models.

The above-mentioned R&D topics are further explained as well as the hurdles, enablers and actions for the further development of Industrial Biotechnology in Europe.

Hurdles are defined as characteristics/activities that are currently in place (or will be in the very short term) and (potentially) contribute negatively to (R&D) developments/the development of the business case. Hurdles are seen as **the main bottlenecks in the development of the business case within Europe**.

Enablers are defined as characteristics or activities that are currently in place (or will be in the very short term) and (potentially) contribute positively to (R&D) developments/the development of the business case. Enablers are seen **as incentives and/or preconditions for potential breakthroughs for the development of the business cases within Europe**.

Chapter Structure

The structure of this chapter is as follows:

- Overview of the key hurdles and enablers for R&D for the development of IB in Europe according to literature, the regional and the business-case related workshops;
- Discussion of hurdles, enablers and actions for each R&D topic.

Per R&D topic the hurdles and actions are discussed according to the following structure.

Novel (and newly applied) Technology	-	New technical innovations and developments needed to produce new equipment and processing methodologies for the field of industrial biotechnology
Process capability, yield and optimisation	-	Process capability refers to the operational limits of equipment/processes and the ability of the equipment/process to meet its purpose and control to specifications. Process yield and optimisation focuses on maximising throughputs and production and achieving the most cost effective and efficient performance for equipment/processes.
R&D / pilot / demo scale	-	Research and development of new products, processes and technologies. Particular focus is around scale-up from lab to large-scale volume manufacturing on new and existing facilities.
Economic viability	-	Capital and production costs associated with manufacturing products in the field of industrial biotechnology
Quality assurance	-	The requirement to ensure raw materials, final products, by-products and wastes meet the required specifications and performance criteria

5.1 Key Hurdles and Enablers Regarding R&D

In this section the key hurdles and enablers for R&D for industrial biotechnology development in Europe are given. The experts in the field will notice that many R&D issues raised in this chapter are determined in previous roadmaps on Industrial Biotechnology and have been well known for some years as well as the actions that should be taken to overcome the hurdles.

R&D issues that are partly novel and/or require attention in our view:

- Feedstock variability is a hurdle for the development of robust bioconversion processes and should be addressed more pronounced;
- Transfer of knowledge of the chemical industry to the biobased chain can provide a breakthrough;
- Co-cultivation[17] in bioconversion and continuous bioconversion processes as a solution to hurdles like poor performance in terms of yield;
- The issue of water use and water recycling is very specific for the IB value chain. All processes are water-rich.

Within this section, an overview of the literature findings is presented in Table 4 and an overview of the results from the regional workshops is presented in Table 5.

Results of the Literature Review

The following table provides a comparative quantitative estimate of hurdles present across business cases based on a literature search. The number of - signs indicates the severity of hurdles as recognised by the BIO-TIC project partners.

[17] The idea of co-cultivation in bioconversion means that two or more strains are cultivated at the same time in the bioreactor. One strain is efficient in conversion of 2nd generation feedstock in a particular product, which is then subsequently converted by another microbe in the target product.

Table 4. Summary of Key Hurdles and Enablers from the Literature

Comparison	Feedstock supply	Bio-conversion	Downstream processing	Products & Markets	Knowledge infrastructure
Biofuels	- --	--	0	-	- - (funding for demo)
Chemical Building Blocks (*)	- -- (process yields have to increase and toxic by-products are still a problem)	-- (several molecules close to max yield. Opportunities from novel enzymes, novel bioconversion conversion routes, Interfacing chemical synthesis and biocatalysis)	- - (current chemical models are used, however not applicable in all cases. Yields have to be improved. Opportunities from new product recovery and purification tools)	-/- - (depends on drop-in or not. Opportunities for high quality products, enantiomerically pure building blocks, cost savings in molecular economy)	- - (funding for demo, transfer of knowledge. Opportunities for providing the required bioinformatic tools and directing the ICT innovation and infrastructure towards the needs of biocatalysis and IB)
Biopolymers PHA and PLA	- -	- (PLA/PHAs close to max yield)	- / - - (depends on LA/PLA or PHAs)	-	-
Biosurfactants	- - (process yields have to increase and toxic by-products are still a problem)	- - - (state-of-the-art is less developed)	- - - (very complicated and requires high innovative process)	- (Bio products has a better performance and lower toxicity compare to petrochemical ones)	- - - (R&D required)
CO_2-based chemicals	- (mainly CO_2 capture and storage)	- - - (state-of-the-art is less developed. Fundamental biocatalysis R&D needed)	- - (same as in building blocks)	- / - - (same as in building blocks)	- - - (funding for demo, transfer of knowledge)

- - - Improvement highly required
- - Improvement moderate required
- Improvement required
0 Improvement not required

(*) Average value. Actual value differs per building block.

Advanced biofuels is the business case that requires the least development, compared to the other business cases. For all business cases feedstock supply requires some to moderate improvements. Apart from the advanced biofuels, all business case require moderate to high improvement for bioconversion and downstream processing. Funding of the valley of death (from pilot plant to flagship plant) requires moderate to high improvement for all business cases.

Table 4 has been validated in the second phase of development of the R&D roadmap via the regional workshops and stakeholder interviews. In this chapter the results of this validation will be discussed in more detail.

Overview of the Results from the Regional Workshops

In the regional workshops the hurdles were prioritised. See Figure 11 for an overview of the categories of hurdles prioritised in each of the eight regional workshops. As can be seen, the majority of the hurdles voted for by participants are related to market and non-technological issues. Research and development received 25% of the given votes on the EU level, market entry 38%, policies and regulations 32%. R&D challenges were emphasised in Italy and UK & Ireland, while market entry and the issue of economic viability in particular were most questioned in France, Germany, the Nordic countries, and Spain. Policy barriers were emphasised in Germany and Spain.

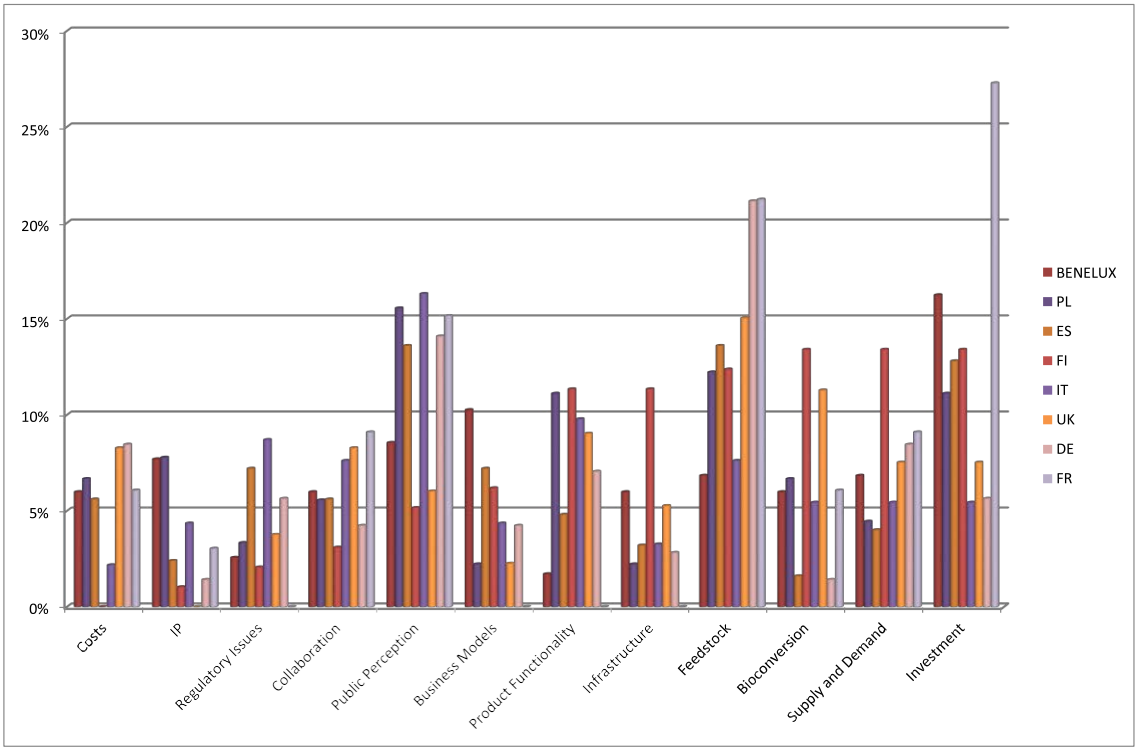


Figure 11. Overview of hurdles most voted for in the regional workshops

Table 5 below gives the specific R&D hurdles and solutions most voted for in the regional workshops.

Table 5. The R&D Hurdles Most Voted for in the Regional Workshops*

HURDLES

Topic	Details	Votes
Bioconversion	Process performance is currently poor – need to increase yield, productivity	25
Bioconversion	It is very difficult to extrapolate lab scale results to large scale processes	13
DSP	Bioconversion systems produce many impurities, which are separated in the DSP which represents 2/3 of the total process cost	12
Feedstock	Uncertainty regarding feedstock availability	10
Feedstock	Current raw material competes with the food chain	8

POSSIBLE SOLUTIONS

Topic	Details	Votes
Product Functionality	Value-adding co-product streams	11
Bioconversion	Increased performance of bio-catalysts and micro-organisms	10
Product Functionality	Developing new biobased products with specific functionalities, taking full advantage of the native properties of biomass	8
DSP	Innovative DSP-technology transfer from the chemical industry makes it possible to learn from their continuous process experience	8

**Participants at the regional workshops voted on the specified R&D hurdles listed on posters*

.

Overview of the participants ranking of the five business cases and the extent to which technological innovation is needed.

The participants of three of the eight regional workshops (Italy, Germany, France) were asked to give their expert opinion per business case on what they think is required for the different R&D topics for the further development of IB in Europe in terms of breakthrough technologies (score 3)/incremental technological innovation (score 2)/no technological innovation (score 1). Table 6 summarises the

results obtained by 25 participants of three regional workshops in total. An average per business case and per R&D topic was calculated.

Table 6. Average Rating of Need for Technology Development Based on Six Regional Workshops

R&D topics: Case:	Feedstock supply	Bio-conversion	Downstream processing	Products& Markets	Knowledge & infrastructure	Average
Advanced biofuels	**2,1**	**1,9**	**1,6**	**1,4**	**1,7**	**1,8**
Building blocks	**2,7**	**2,5**	**2,0**	**1,8**	**1,8**	**2,1**
Biopolymers PHA and PLA	**2,0**	**1,9**	**0,9**	**2,1**	**2,0**	**1,8**
Bio-surfactants	**1,6**	**2,0**	**2,0**	**1,9**	**2,0**	**1,9**
CO_2-based chemicals	**2,1**	**2,6**	**1,9**	**1,6**	**2,4**	**2,1**
Average	**2,0**	**2,2**	**1,7**	**1,7**	**2,0**	

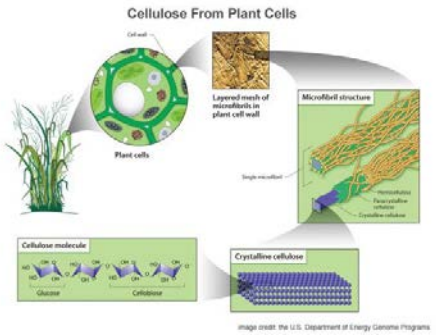
3 Breakthrough technologies required
2 Technological developments required
1 No technical innovation required

The table gives an impression of where the participants think (breakthrough) innovation is needed and where not. According to the participants questioned, generally the most technological development is required in feedstock supply; bioconversion for chemical building blocks and CO_2-based chemicals. Downstream processing for biopolymers like PHA and PLA scores below 1, meaning the participants assess this topic as not requiring technical innovation.

5.2 Introduction to the Business Case Workshops

For each business case in the BIO-TIC project a workshop was held in which stakeholders were invited to discuss hurdles and required actions for the uptake of IB for the manufacture of specific product group. As preparation for each workshop a survey was circulated to the participants of the different business cases workshops and a request made to submit the results before the commencement of the workshop. The purpose of the survey was two-fold; to provoke thought on the issue prior to the workshop so that participants came to the workshop with fresh ideas of business hurdles and enablers and secondly to gather first and uninfluenced thoughts from those unfamiliar with the BIO-TIC project.

In the workshops themselves, currently identified hurdles for the uptake of biotechnology within the BIO-TIC project were presented to the audience and then the attendees were invited to select the most critical hurdles that prevent or slow down the development/uptake of industrial biotechnology within the EU. The issues receiving the most votes were to be discussed in detail by the workshop participants in three breakout sessions (each session was moderated and discussion points captured by members of the BIO-TIC project team). The results of the business case workshops have been integrated into each of the following sections.



5.3 Feedstock Supply

The R&D topic feedstock supply refers to R&D topics related to biomass cultivation, logistics and pre-treatment. Based on a literature study and discussion with stakeholders during regional workshops and expert interviews, this section describes the hurdles, enablers and actions concerning feedstock supply and R&D.

Overview of the Main Hurdles in Terms of Feedstock Supply

The stakeholder interviews and workshops have in large confirmed the findings of the literature study. The feedstock prices were commonly considered as a major hurdle for IB because they are too high for the bulk chemical market compared to fossil alternatives. Both literature and stakeholders highlighted the availability of sufficient feedstock amounts as an issue. This is due to the fact that IB is currently based on classical food plants and that most of the biomass is imported. Finally, another recurring issue consists in the fluctuating feedstock quality that can have a potential impact on the whole value chain. As IB is moving towards using waste-streams as feedstock, this hurdle is even more relevant. In addition to the above-mentioned hurdles, the desk study has also raised the question of food security because it is argued that the currently available feedstocks for IB compete with the food chain. However, this point was not validated during the discussions with the stakeholders.

The considered IB business cases (BC) 'biopolymers', 'chemical building blocks', and the hydrocarbon based Jet biofuels (ATJ, DSHC) in the BC 'advanced biofuels' are dependent almost exclusively on 1st generation sucrose and starch-based feedstocks for industrial biotechnology. The BC 'Bio-surfactants' depends on plant oils/fatty acids as well as sugars. The BC 'CO_2 based chemicals' is not named regarding to the products but to the feedstock CO_2.

The majority of cost-specific hurdles in feedstock supply are seen in the BCs 'biopolymers' and 'chemical building blocks' respectively, since these are in direct competition for market share with their petrochemical counterparts. Moreover, the BCs 'biopolymers' and 'chemical building blocks' and 'biosurfactants' also compete with any biofuels/bioenergy business case for the same feedstock in a market, which is highly supported by policies (tax incentives, blending quota from the Fuel Quality Directive (98/70/EC), GHG counting from the Renewable Energy Directive (2009/28/EC) and its proposed amendment on the promotion of the use of energy from renewable sources

(COM(2012) 595 final)). The direct consequences of these regulations are raising feedstock prices and creating an unlevel playing field in feedstock competition. See also the Market and Non Technological Roadmap of IB for more details.

'Advanced biofuels', and 'CO_2 based chemicals' are facing more technical hurdles. In case of 'advanced biofuels' sugars produced from non-food feedstock are mandatory, but the treatment of non-food feedstock for the production of sugars (or biofuels) is just entering industrial scale (see also page 47 on Bioconversion).

CO_2 delivered in flue gas could be a cheap carbon feedstock. However, as flue gas is still considered as waste, many hurdles regarding logistics, composition and quality assurance are actually hindering its utilisation as a feedstock.[18] For the use of CO_2 rich flue gases normally some cleaning is needed, but for industrial biotechnology use, impurities and poisoning are not that big an issue as in chemical catalysis. Bacteria can tolerate certain amounts of impurities better than chemical catalysts. A main issue however will be the logistics, since there is the need to concentrate, collect and transport CO_2 gas to the fermentation process plant. In this case a system of pipelines is needed and the fermentation plants have to be near the CO_2 producing industries. An alternative could be the direct air capture of CO_2 via concentrating atmospheric carbon dioxide – this technology is undergoing feasibility studies by several companies (like Climeworks in Switzerland, Kilimanjaro Energy or Carbon Engineering in the US and Canada) and is proving to be a very expensive alternative. In addition the need for cheap energy coming from renewable sources and especially low cost hydrogen is another topic to be solved in the future to realise the opportunities of CO_2 as feedstock.

Special hurdles regarding feedstock supply are not mentioned in literature and by the consulted experts related to BC 'bio-surfactants'. Reasons postulated could be that the amounts of sugar and lipids needed are low compared to the world markets (that keeps the prices more stable) and that the products belong to the fine chemical sector and are of higher value and selling price.

Structure of the Chapter

The following sections will provide a more detailed description of the hurdles related to feedstock supply. More importantly, a series of technological solution pathways to overcome these bottlenecks are presented. As mentioned at the beginning of this chapter, the input gathered from the workshops and stakeholder interviews can be structured along five subject matters:

- Novel (and newly applied) technology;
- Process capability, yield and optimisation;
- R&D / pilot / demo scale;
- Economic viability;
- Quality assurance.

In order to derive comprehensive results, business case specific hurdles and solutions will also be highlighted. The section closes with a summary table of all stakeholder suggested actions to overcome feedstock supply issues.

[18] However, waste policy is more an enabler in this case, since directives like 2010/75/EU on industrial emissions (integrated pollution prevention and control) regulates quality (dust, heavy metals, other pollutants) which are able to disrupt upgrading and/or fermentations.

5.3.1 Feedstock Supply: Novel (and newly Applied) Technology

Novel (and Newly Applied) Technology Feedstock Supply*: *Horizontal hurdles

The main worrisome hurdles mentioned in the interviews and workshops refer to the supply of sufficient amounts of feedstock that compete on price with fossil derived feedstocks. To overcome this hurdle technical developments are required and new (non-food) feedstock is requested. Alternatively, feedstock that creates more added-value for the business cases which serve in the high volume, bulk chemical market should be developed. These refer to business cases like 'biopolymers', 'chemical building blocks', and 'advanced biofuels'.

Microalgae are promising candidates to serve as new feedstock since they are highly diverse photosynthetic organisms, with very high growth rates, and lipid content generally higher than terrestrial plants. In some interviews and workshops, algae were mentioned to be very attractive for the production of advanced biofuels, including jet fuels, as they do not compete for land used in food and feed production. However, production chains with net energy output need yet to be identified, and costs in all segments of the production spectrum still need to be reduced significantly. Cultivation, harvesting and drying of algal biomass is not yet economically and environmentally sustainable, research is needed to optimise cultivation systems with optimal use of light and other resources. Quality, availability and price of the carbon dioxide source is an important hurdle, which links microalgae production to the business case 'CO_2 based chemicals'.

The use of waste streams of biological content as feedstock could be another option to minimise feedstock costs and to enhance sustainability. But in order to use waste streams, either its constant quality must be ensured, or the processes of bioconversion and downstream processing must be flexible enough to handle its variability. Potential biomass waste streams could be lignocellulosic residues (straw, bagasse, residual wood from forestry like logging slash), or even residues from food and processing industries. In any case, valuable waste streams are already occupied and not disposed as garbage. They could only be taken over by IB if its utilisation creates higher value added. While lignocellulosic residues value is relatively low as it is used in composting, fertiliser, animal breeding (litter), or biomass burning, non lignocellulosic residues from food industry are processed to more valuable fodder. However, for new waste streams logistics will have to be established regarding storage and transport especially for perishable waste streams.

Novel (and Newly Applied) Technology Feedstock Supply*: *Business Case Specific Hurdles

CO_2-based Chemicals

A technical hurdle in the use of flue gases from power plants as feedstock is its commonly low CO_2-fraction of about 9 vol-% to 14 vol-% in wet exhaust flue gas[19]. When air is used in combustion and gasification processes the largest part in flue gases is nitrogen. Since 80 vol-% to 90 vol-% CO_2 in the gas stream is needed for optimal feed in fermentations, CO_2 upstream processes (gas separation and cleaning) are required. Of course, the balance between using this CO_2 from flue gas and the energy consumption and CO_2 emission required by the upstream processes should be taken into account.

[19] http://en.wikipedia.org/wiki/Flue-gas_emissions_from_fossil-fuel_combustion

Exhausts from biological sources like anaerobic fermentation processes lead to gas emissions with a higher CO_2 part. Biogas (product of anaerobic digestion) consists of about 50 % CO_2, depending of its digestion source). Especially, if biogas is upgraded to natural gas quality, CO_2 has to be separated and can be subsequently used as building block commodity. The exhaust from ethanol fermentation contains almost pure CO_2 (with some H_2O). Both, anaerobic digestion and anaerobic fermentations could be parts of integrated biorefinery concepts.

In principal this hurdle of concentrations and impurities is the same in chemical catalysis processes using CO_2 as feedstock and normally a pre-treatment and concentration of the flue gases is less demanding for bioconversion, although some purification may be necessary for some sources.

Enablers

- *The use of CO_2 as feedstock is completely outside the food value chain.*
- *CO_2 is the only raw material that the EU has everywhere in abundance.*

Hurdles

- *The use of CO_2 as feedstock for fermentation should be coupled to purification and preparation of the CO_2 stream. This is because the sources of CO_2 can be very heterogeneous and thus can carry different kind of impurities that can either lower the productivity of the fermentative or chemical processes or even to completely inactivate them. This aspect it is very similar to any other fermentative or chemical standardisation of the feedstock prior to any conversion technology.*

Advanced Biofuels

The use of advanced biofuels in the EU is driven by policy and therefore an increasing demand is expected in the near future due to blending quota and "multiple counting" stemming from the Fuel Quality Directive and Renewable Energy Directive and its proposed amendment. Since advanced biofuels are by definition dependent on non-food biomass, new high volume but sustainable feedstocks have to be exploited. Aside from lignocellulosic biomass of waste origin mentioned above a more realistic scenario for high volume feedstock is the use of lignocellulosic biomass from forestry, since logistics for harvest, transport, storage and pulping are well established in the pulp & paper industry. In fact at present there is a declining world paper market.

Moreover, it will be crucial to utilise all possible value streams from lignocellulosic feedstocks. These can bring in additional revenues and potentially reduce the cost of the biofuel. In addition, several additional product streams can be produce in the biofuel process, which could be marketed and appropriate incentives should be in place to affect this. It was stressed during the business case workshop that regardless of the technology-readiness level of biofuels production technologies, R&D should continue to be funded from basic to applied levels to allow continuous improvements in technologies over time.

Advanced biofuels based on HEFA[20] or biodiesel are also dependent on new non-food feedstocks, since most of the oil plants currently used for biodiesel are food plants. A promising plant seems to be Jatropha, which is able to grow on arid land in tropical and subtropical areas. But on one hand the

[20] Hydroprocessed Esters and Fatty Acids

optimisation of the plant by breeding is still on-going and on the other hand the experiences with the entire value chain from planting to biodiesel production and use of by-products is still marginal.

As mentioned above algae could serve as feedstock for advanced biofuels if the process chain gets more sustainable. Today, some start-up companies are in the market producing:
(i) ethanol directly by genetically modified algae
(ii) oils from algae with high lipid content, or
(iii) bio crude oil by hydrothermal treatment of algae biomass

However, none of them today are on an industrial scale. See also Chapter 4 on the state of the art of advanced biofuels.

Enablers

- *Fuel blending quotas and CO_2 taxes in aviation*
- *Exploitation of new non-food renewable feedstocks like lignocellulosic waste streams, CO_2 streams and algal based biomass*

Hurdles

- *Especially the production of bio-based jetfuels will have a high demand on hydrogen to gain pure hydrocarbons, which are suitable for use in jet engines. Possible sources for the hydrogen could beside others the lignin fraction of lignocellulosic feedstocks (gasification and water-gas shift reaction) or any Power-to-Gas solution, which has the means to produce the hydrogen without generating CO_2.*

5.3.2 Feedstock Supply: Process Capability, Yield and Optimisation

Process Capability, Yield and Optimisation: Horizontal hurdles

As stated before the hurdles of main concern mentioned in literature, stakeholder interviews and workshops refer to the supply of sufficient amounts of feedstock which have to be price competitive with fossil feedstocks. To overcome this hurdle some suggestions regarding 'process capability, yield and optimisation' are discussed.

For higher efficiency the combination of feedstock production and bioconversion into integrated (multi-feedstock) biorefinery concepts are needed to decrease costs for transport and logistics. Further backwards integration which includes feedstock development should allow an optimisation of the feedstock for the bioconversion step and *vice versa*. Examples of possible optimisation steps are the cloning of starch-hydrolysing enzymes into grain or the manipulation of the lignin structure and lignin content in wood for a better efficiency in the pre-treatment steps. Both approaches are related to genetic engineering of plants, which is a non-technical hurdle for itself due to public acceptance and regulations of authorisation in the European Union.

In order to use lignocellulosic biomass, more efficient processes taking its full constituent into account are necessary, because the dry matter of wood consists to only about 45 % to 50 % of cellulose, which can be almost quantitatively hydrolysed to glucose after pulping for its use in IB. But high value applications are still needed for the residual 50 % hemicelluloses and lignin, whose usage is essential for the sustainability (efficiency and economic viability) of the process. Genetic

manipulation is currently underway to enable baker's yeast to utilise the C5-sugars of hydrolysed hemicelluloses.

Another hurdle in using hemicelluloses is depending on the pulping conditions the hemicelluloses may be hydrolysed to a certain extent and become soluble in the pulping broth. Recovery of pure hemicelluloses from the broth is difficult and cost-intensive. Also applications using the lignin fraction for other than energy purpose are under development. But these applications are strongly depended on the quality and origin of the lignin. For example the widely used Kraft-pulping process leads to a lignin containing sulphur, which due to its inherent odour limits its applications, as such it is only burned today. Either (sulphur-free) lignin can chemically be downgraded to an oil of mixed aromatics (phenols) for chemical applications or used directly in duromeric (resins) or thermoplastic (compounding) material applications.

Process Capability, Yield and Optimisation Feedstock Supply: Business Case Specific Hurdles

Advanced Biofuels

It has been discussed during the business case workshop that the principal hurdle to develop the biofuel industry in Europe is the high production cost of 2nd generation ethanol. The main solution to overcome this hurdle is to develop more economical conversion processes with higher yields and less waste on cheap biomass feedstock.

It was stated that although some technologies may be at higher technology readiness levels (TRLs) than others, basic research into process improvement should continue (for example research into conversion efficiency) to ensure that technologies do not simply stagnate and are increasingly competitive over time. Grants for taking research to demonstration scale should be encouraged, ensuring that the whole value chain approach is kept in mind.

5.3.3 Feedstock Supply: R&D / Pilot / Demo Scale

R&D/Pilot/Demo Scale Feedstock Supply: Horizontal hurdles

In the field of feedstock supply the technologies to process food plant feedstock for sugar and oil production are well established and efficient and therefore not seen as a hurdle.

Hurdles are seen in the fact that there are now competitive uses of crops that were traditionally destine for food feedstocks (food, feed, fuel, bio-based products) which results in uncertainties in feedstock supply and ultimately prices. Another hurdle, which is especially true for annual plants, is the dependence on weather conditions for availability and impacting the quality of the feedstock.

An option to overcome these hurdles is to extend the feedstock basis of certain business cases by enabling facilities to process multiple feedstocks. Examples already exist for successful multiple feedstocks in sugar biorefineries which are able to use sugar beet and grain in parallel to produce ethanol, CO_2 and fodder (e.g. DDGS). Different sugar feedstocks may require convergent process routes (different pre-treatments and upstream processing) to get the common substrate for industrial biotechnology, but also downstream processing and by-products may vary. Though it is possible to combine the different process routes as early as at the fermentation stage for higher process efficiency (e.g. CropEnergies, Zeitz, Germany), keeping the fermentation routes separated may also be a reasonable option to obtain process flexibility (e.g. CRISTANOL, Bazancourt, France),

since the (fodder) by-products gained from sugar beet fermentation and grain fermentation are different. Therefore, the integration level of the biorefinery will be a compromise of efficiency and flexibility, which need to be evaluated at pilot or demonstration scale. To date there are not enough studies focusing on which scale the plant efficiency reaches it's maximum according to different feedstocks.

Another option is to include wood and other perennial plants to lower the weather dependent risks. However, pre-treatment technologies for wood are well established in the pulp and paper industry with the aim to produce cellulose fibres as single main product. The production of 2nd generation sugars for applications in industrial biotechnology is only at the demonstration to early commercial scale if straw (annually grown) is the feedstock. IEA Bioenergy Task 39 provides an overview of demonstration facilities for 2nd generation biofuels using straw[21]. Pre-treatment technologies for wood as feedstock used in biorefineries are currently available only in the pilot stage. Examples are the Lignocellulose Biorefinery pilot plant at CBP Leuna, Germany[22] and the CIMV Biorefinery pilot plant, Pomacle, Champagne-Ardenne, France[23]

Algae based feedstocks are also an option to overcome the hurdles mentioned above. Not only is algae production almost independent of weather risks, it also is independent of arable land. Algae are highly diverse, single- or multi-cellular organisms comprised of mostly lipids, protein, and carbohydrates[24], and in contrast to terrestrial plants they do not comprise of lignin, which makes classical pre-treatment obsolete. They can utilise salt and wastewater sources that cannot be used by conventional agriculture. Many algae farms exist around the world manly in subtropical and tropical area with the aim to produce food and food additives. However, since algae cultivation and harvest is cost and energy intensive, many production sites of algal biomass for chemicals like advanced biofuels are still in demonstration scale to prove and optimise processes for sustainable production.

R&D/Pilot/Demo Scale Feedstock Supply: Business Specific Case Hurdles

Advanced Biofuels

When lignocellulosic sugars are used for the production of aviation fuels or ethanol, this will, as a consequence, produce lignin in very large quantities. Lignin research is not new and there has been much research for the past 20 years on lignin from paper production process. However, it is also acknowledged that lignin from different sources can vary quite significantly in terms of chemical properties (and therefore its appropriateness for different downstream uses). The largest application today for lignin is in its heating value, however there are many higher value potential uses for lignin, like as a phenol substitute in duromeric resins, as thermoplast, and also as source of aromatic mixtures in the chemical industry. The market is not yet developed with low volumes and unstable quality.

Since these applications are in the commodity market demonstration facilities are needed to produce enough volumes at a meaningful scale for industrial applications and to assess the quality differences at different biorefineries. This could be funded under Horizon 2020, LIFE or through the BBI-JU with a

[21] http://demoplants.bioenergy2020.eu/

[22] http://www.cbp.fraunhofer.de/en/Projects/Project_1.html

[23] http://www.cimv.fr/

[24] O'Connor, D. (2011) Algae as a Feedstock for Biofuels – An Assessment of the Current Status and Potential for Algal Biofuels Production, IEA Bioenergy Task 39 (http://task39.org/files/2013/05/Algal-Biofuels-IEA-Task-39-and-AMF-Joint-Summary.pdf)

call from 2016/2017 and would cost around 30 MEUR for a demonstration facility using lignin derived from an existing biorefinery. The technology is at a too early stage for a standalone flagship plant.

The valorisation of lignin would enable better fermentation processes (higher sugar yield), as well as overcoming the problems of dealing with the huge quantity of lignin side streams envisaged from the use of lignocellulosic materials for biofuels and biochemical production. Such a facility could build upon calls from the BBI on 'Advanced products from lignin and cellulose streams of the pulp and paper industry' and 'Fibres and Polymers from Lignin' and build upon the work of the Biorizon project.

Chemical Building Blocks

Feedstock amounts for manufacturing chemical building blocks have to be high in order to meet the market needs. Moreover, biobased industries are competing in an international environment, but due to import tariffs and quotas the EU market is non-globalised. This creates high prices for sugars from biomass, thus hindering the production of chemicals from sugars. Therefore, there is an urgent need to establish a better collaboration between farmers and the feed sector. Governments should install a win-win scheme for buyers and producers (farmers) in order to bring the feedstock market into a more competitive situation. This was a major conclusion in the business case workshop on Chemical Building Blocks. See also the Non-Technological Roadmap.

5.3.4 Feedstock Supply: Economic Viability

Economic Viability Feedstock Supply: Horizontal Hurdles

An important hurdle for economic viable biobased bulk chemicals are high feedstock prices, since the politically preferred Biofuel/Bioenergy industry competes for the same feedstock. It is therefore necessary to create more added-value from certain feedstocks. The biomass should therefore be refined into a range of valuable products, such as fuels, chemicals, power, materials, fuels, power and also animal feed. The rationale behind this is to valorise the biomass as much as possible.

The co-production of high value products may enhance the viability of the feedstock, since it can compensate loss-making production of bulk chemicals and high feedstock costs. Not only must the production of added value by-products fit into the concept of the facility, also the market volumes of the by-products have to match the production scale of the main products. Therefore all parts of the process chain have to be involved to integrate other feedstocks or by-products.

Another action for lowering prices on feedstocks may be a reduction in transportation costs and post-harvest losses by transportation. This can be realised by a change in logistics from centralised large-scale plants to decentralised small units directly on the field, which are able to proceed as a primary refinery step. The produced intermediate will have advantages in stability and transportability and can therefore be further processed in centralised (larger) units to the final product(s). This concept is now followed by the BtL[25] pilot plant Bioliq[26], Karlsruhe, Germany, where wheat straw is pyrolysed in decentralised units before transported to the gasification plant for producing syngas based fuels.

[25] BtL - Biomass to Liquid

[26] http://www.bioliq.de/english/index.php

Economic Viability Feedstock Supply: Business Case Specific Hurdles

CO_2-Based Chemicals

Though CO_2 in flue gas is considered as waste and therefore a cheap feedstock source, it's transport to a CO_2 consuming facility is extremely inefficient, since the content of the CO_2 in the flue gas is low and if not transported by pipeline the gas has to be transported compressed in gas flasks. This hurdle limits its application to over-the-fence located consumers.

Only if flue gas is upgraded (by enrichment/concentrating and cleaning of CO_2) to a valuable product, its distribution and logistics over long distances may become economically feasible. One positive example is a CO_2network in The Netherlands, where greenhouses between Rotterdam and Amsterdam are supplied with CO_2 from a Shell refinery near Rotterdam via an 85 km long transport pipeline and a circa 300 km long distribution network[27].

In the business case workshop a group of experts discussed the topic to enable cost-effective CO_2 capture, pre-treatment and direct in-situ conversion, at a single point CO_2 source, to a higher value product, using IB (possible combined with chemical catalysis) in an integrated process to minimise the feedstock and pre-treatment costs via the integration to a single CO_2 source. In this case the reduction of logistic costs and the simplification of production planning could be an advantage. Also some precursors lead to an efficient conversion process.

In one interview it was claimed that it might make sense in some cases to use IB for CO_2 pre-treatment (eliminating impurities) before feeding CO_2 to chemo-catalytic systems. In this case the IB will only be the purification step and the conversion will be chemical catalysis.

Chemical Building Blocks

In the business case workshop the following solutions were discussed to overcome the hurdle of high prices of feedstock for the production of chemicals in Europe.

- Remove import quotas and tariffs (trade policies, CAP-policies) to enable cost effective import of sugar feedstocks;
- Amend trade policy allowing the import of low cost sugars into the EU from world markets;
- Research is needed, especially in the area of cost effective extraction of C5 and C6 sugars from cellulosic sources. Also, on a long-term basis, conduct research into technology for processing multiple types of feedstock at one facility to overcome the issue of crop variety in the EU).
- Local sugar processing capacity that has been lost in the EU over the last decade should be reinstalled. Perhaps encouraged by government grants or fiscal incentives. This would also reduce costs associated with the transportation of biomass.

5.3.5 Feedstock Supply: Quality Assurance

Quality Assurance Feedstock Supply: Horizontal Hurdles

[27] http://www.the-linde-group.com/en/clean_technology/clean_technology_portfolio/co2_applications/greenhouse_supply/index.html

In the stakeholder interviews and workshops the fluctuating quality of biological feedstocks has been identified as a hurdle. This is not limited to the feedstock itself, but also includes the production chain of the feedstock with regard to sustainability standards.

To overcome the hurdle it was suggested to certify the entire value chain of feedstock production in-line with certification schemes such as RSB and ISCC+. On one hand certification of sustainability regarding economic, ecologic and social criteria of cultivation and also certification of feedstock quality, e.g. drying technologies, physico-chemical processes. While several tools and standards for sustainability certification are available, certification systems regarding feedstock quality should still be developed.

A hurdle for using waste as feedstock is the risk of fluctuating quality, since the process that generates the waste stream may have to adapt to regulate the final product quality. This could of course be solved when the waste is considered as one of the products as soon as its commodity price rises and ensures a set product quality. In any case this will influence the price of the feedstock. Apart from that the demand for waste streams as feedstock will rise when technology is available to process such ‘waste’. Consequently, the price of waste streams as feedstock is expected to rise.

5.3.6 Overview of R&D Hurdles and Actions Regarding Feedstock Supply

Table 7 summarises the R&D hurdles and actions discussed concerning feedstock supply.

Following abbreviations have been used: EA = European Authorities; IO = intermediary organisations; I = investors; LCo = large companies; NA = national authorities, NGO = non-government organisation; RTO = Research and Technology Organisations; SME = small medium enterprise; U = universities. / = no action suggested

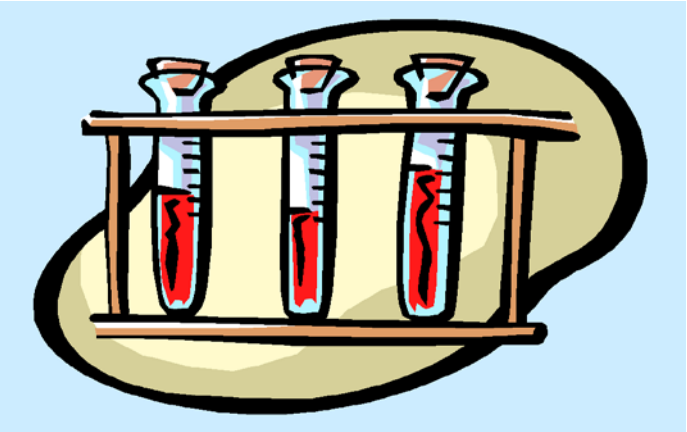
Stakeholders mentioned in brackets of the action columns are those involved in overcoming the identified hurdles.

Table 7. Overview of the R&D Hurdles and Actions Regarding Feedstock Supply

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
Feedstock price is too high for bulk chemical market	IO, LCo	• Co-production of high value products *[RTO, SME, U]* • Reduction in transportation costs and post-harvest losses by transportation *[IO, LCo, RTO]* • Valorize the biomass as much as possible *[IO, RTO, SME, U]*	/	• Integrate feedstock production and bioconversion for tailor made feedstock plants *[RTO, U]*
Low CO_2-fraction in flue gases to use as feedstock	IO, LCo	• Use flue gas from anaerobic fermentation and digestion processes *[IO, LCo, SME]* • Upgrade flue gas to CO_2 rich product gases *[IO, LCo, RTO]*	/	/
Insufficient supply of sufficient amounts of	IO, LCo, SME	/	• Facilities should process multiple feedstocks • Microalgae biomass feedstocks	• New (non-food) feedstocks *[IO, NGO, SME, RTO, U, EA, NA]* • Use of waste streams *[IO,*

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
feedstocks			*[IO, LCo, RTO, SME, U]*	*NGO, LCo, SME, RTO, U, EA, NA]* • Develop perennial non food crops for agriculture on arid land *[IO, NGO, SME, RTO, U, EA, NA]* • Microalgae biomass feedstocks *[IO, LCo, RTO, SME, U]*
Fluctuating feedstock quality	LCo, SME	/	• Certification of feedstock production • Waste should be considered as one of the products *[EA, IO, LCo, NA, NGO, SME]*	/
Process capability, yield and optimisation	LCo, SME, RTO, EU	• Research on processes with higher productivity *[RTO, LCo, SME]* • Make funding available to promote research activities [EU]	/	/

5.4 Bioconversion



Based on a literature study and discussions during regional workshops and stakeholder interviews, this section describes the hurdles, enablers and actions concerning bioconversion and R&D.

Bioconversion involves the conversion of biological or chemical substances into useful products including the advanced biofuels, biopolymers, chemical building blocks and biosurfactants that were chosen as business cases. Other examples are enzymes, antibiotics, food additives and pharmaceuticals. However, bioconversion can also involve biocatalysis where microbiologically-produced enzymes are used to catalyze industrial chemical reactions. Products may be produced by microorganisms via conversion of biological feedstocks, including edible biomass containing sugars (1st generation feedstock), non-edible biomass containing lignocellulose (2nd generation feedstock) and possibly also the greenhouse gas CO_2 (3rd generation feedstock), the potential of which was discussed with experts and stakeholders.

The production of useful products through bioconversion involves several processes that need to be developed, integrated and reiteratively optimised during scale-up (see Annex 4 for a more detailed description of microbial process development). These processes include strain development, process optimisation, purification, separation and downstream processing. The usage of enzymes in biocatalysis of industrial chemical processes is also a process that needs to be optimised. Strain development, process optimisation and biocatalysis are discussed in this chapter, while purification and separation will be focused on in the Down Stream Processing chapter of this roadmap.

Overview of the Main Hurdles in Terms of Bioconversion

The literature study done on the subject of bioconversion indicates that its main hurdles are the poor process performance in terms of yield, productivity and robustness. The stakeholders who described the problematic points of the identified hurdles largely confirmed this issue:

1. The performance of microbes and biocatalysts is often poor;
2. The bioconversion of substances is often poor;
3. The (fermentation) process performance is poor;
4. Advanced bioreactors are lacking;
5. Water management systems for biocatalysis are lacking or perform poorly.

In addition it was found in the literature that IB is currently not effective at high concentrations. This was validated, but not seen as most important hurdle in bioconversion by the surveyed experts.

Chapter Structure

The following sections will provide a more detailed description of the hurdles related to bioconversion. More importantly, a series of technological solution pathways to overcome these bottlenecks will be presented. The input gathered from the workshops and interviews have been structured along five subject matters:

- Novel (and newly applied) technology;
- Strain development, fermentation, secretion and biocatalysis;
- R&D / pilot / demo scale;
- Economic viability;
- Quality assurance.

In order to result in a comprehensive analysis, business case specific hurdles and solutions will also be pointed out. The topic section closes with a summary table of all stakeholder suggested actions to overcome bioconversion issues.

5.4.1 Bioconversion: Novel (and Newly Applied) Technology

Novel (and Newly Applied) Technology Bioconversion: Horizontal Hurdles

Experts and stakeholders generally agreed that the yield and productivity of current microbial production strains and robustness of fermentation and biocatalysis is often insufficient to enable cost-effective production of biobased products. It was generally agreed that novel microbial production systems, novel tools to modify microbes and novel process methods have to be developed to overcome these hurdles.

A key limitation in current bioconversions is that most industrial microbial production strains can only convert relatively pure and non-complex feedstocks. This is typically 1st generation feedstocks such as sugar, the price of which has tripled over the last decade, because of a growing demand for usage in food production. As the high sugar price is a burden in the production costs of biobased products and large-scale usage of sugar would interfere with food production, microbes that can convert other feedstock are required. Stakeholders suggested potential usage of 2nd generation feedstock such as lignocellulose, lignin, municipal waste or potential usage of 3rd generation feedstock of C1 molecules such as CO_2, methane or syngas¸ a fuel gas mixture consisting primarily of hydrogen, carbon monoxide, and very often some CO_2. In order to process 2nd and 3rd generation feedstocks, microorganisms used for product processes by fermentation should be further optimised. In addition, these microbes have to be tolerant against potentially growth-inhibiting compounds in the feedstock. For example, microbial growth is notoriously sensitive to lignocellulosic-derived sugar stream impurities like furfural and hydroxymethylfurfural, which are produced in pre-treatment technologies that use extreme acidic and temperature conditions. An alternative strategy to the development of new microbial production systems is the modification of 2nd or 3rd generation feedstocks in a way that they can be converted by current microbial production systems. Finally, some stakeholders have suggested using immobilised enzymes instead of whole cells to convert substances derived from feedstock in a bioconversion reaction to useful products.

Another frequently encountered hurdle is that the by-products or target products produced during fermentation inhibit productivity and complicate product recovery. The formation of by-products requires more complex purification steps, and thus imposes additional costs for product recovery.

For example, production of many chemical building blocks including lactic acid induces acidity of the fermentation growth medium, which in turn inhibits microbial growth. The acidity of the fermentation medium is typically neutralised with calcium hydroxide. After fermentation the medium is acidified with sulphuric acid to gain the free lactic acid. This produces gypsum as a by-product. Disposal of gypsum can lead to additional costs. Fortunately, there are new technological advances, which prevent production of gypsum and produce ammonium sulphate instead that is itself a valuable by-product for fertilisers. In general, R&D should focus on developing novel microbial production organisms that are tolerant to by-products and target products.

Microbial strains are often not very amenable to genetic modification. In many cases, protocols for genetic transformation are lacking. Without the availability of genetic transformation tools microbes cannot be optimised for acquisition of the key features mentioned above. In industrial fermentations, the usage of anaerobic microbes has clear advantages as the dependency on oxygen limits fermenter size and requires oxygen infusion. This adds up significantly to production costs. Despite these clear advantages of anaerobic microbial production systems, there are only limited methods available to modify anaerobic microbes. Thus, R&D efforts should focus on developing such methods. Platform technologies could be developed for improved strain engineering (e.g. improved -omics methods for system understanding, high-throughput engineering), high-throughput screening in variable fermentation conditions including non-conventional reaction systems and media.

For many industrially relevant chemical processes discovery of novel enzyme reactions is required before efforts can be taken to enhance efficiency of the chemical conversion. In addition, the efficiency of existing bioconversion enzyme reactions is low, due to intrinsic enzyme characteristics but also due to poor productivity of some of the required more complex enzymes. The poor performance of some of the bioconversion reactions may, in part, also be explained by the fact that the reaction conditions including pH and temperature are unfavourable for enzymatic performance and in many cases additional co-factors such as the energy provider adenosine triphosphate (ATP) are required. Thus, R&D should focus on identifying and developing novel and more robust enzymes. In addition, the knowledge required in specific industrially relevant areas of enzymology are not well covered by research organisations. Related to this scattered knowledge base, biocatalyst database should be developed to help stakeholders find existing enzymes for their chemical processes. Based on the above-mentioned efficiency and thus cost-prize hurdles alternatives for the modification of microbes for production of specific enzymes used in biocatalysis is sought. Some stakeholders have suggested developing synthetic production systems to produce enzymes. Such synthetic production systems consist of engineering of parts of natural biological systems. An important advantage is that such systems are fully dedicated to production of useful products and do not require growth for their integrity. One problem of intact microbes is that they are focussed on using feedstocks for biomass growth, which means that there is less feedstock available for conversion in target products. This can already be done on lab scale but requires substantial optimisation to reach demonstration scale. Thus, R&D efforts should focus on developing new tools for synthetic biology.

Another very important generic hurdle for any enzymatic biocatalysis process, thus requiring novel technological solutions is the way that the large amounts of water which is driving these processes is dealt with. In particular, new water management technologies are needed.

Novel (and Newly Applied) Technology Bioconversion: Business Case Specific Hurdles

Chemical Building Blocks

Some chemical building blocks are inherently easier to purify than other chemicals. However, this will be more of an issue with lignocellulosic feedstocks, given that these contain more impurities. Therefore, more robust microorganisms have to be developed and most cost effective technologies for downstream processing have to be created.

Biosurfactants

Other major production concerns relate to the yields of biosurfactants produced, the substrates needed to produce them. The application of economic technologies based on utilisation of waste substrates for biosurfactant production and the utilisation of cheaper renewable substrates may significantly contribute to cost reduction. One attractive option as a substrate is glycerol, which is now available in large quantities (c.f feedstock availability).

CO_2 as Feedstock

Despite the fact that 35% of Europe's patents involves low carbon technology in terms of CO_2 emissions, little progress has been made in the use of these technologies at demonstration or even pilot scale. Bioconversion chemicals based on CO_2 as a substrate were generally conceived as most challenging and score the lowest in terms of technology readiness. Current technologies are unable to support industrially relevant conversion of CO_2 into chemicals.

A major hurdle is the inability to supply sufficient reduction equivalents to enable an energetically favourable biochemical reaction. It was therefore suggested that it would be easier to use energy-rich syngas or biogas to produce these chemicals.

5.4.2 Bioconversion: Strain Development, Fermentation, Secretion and Biocatalysis

Strain Development, Fermentation, Secretion and Biocatalysis: Horizontal Hurdles

The yield, productivity and robustness of many bioconversions are low. In general, more than 50% of the feedstock needs to be converted to achieve commercially relevant productivity. This has been achieved for many bioconversions involving 1st generation feedstock. However, for bioconversions involving 2nd generation feedstocks, a conversion efficiency of only 10% is often achieved. This is in sharp contrast with traditional chemical processes, in which a conversion efficiency of 80-90% is often attained. The cause of the problem is that most of the feedstock is used by microbes for growth and biomass production, not for production of the target compounds. In addition, microbes typically require more feedstock to ensure viability and growth in challenging conditions such as low pH, suboptimal temperatures, high (by)product concentrations. Process intensification takes place in this critical zone. Strains are sometimes not robust enough to survive the whole process. Microbes need to be engineered to maximise conversion of feedstock into target molecules while minimising usage of feedstock for cell growth. However, this has proven to be a costly and time-consuming process, mainly due to the complexity of microbial cell factories. Developing a centre of expertise to help increase the effectiveness of strain development and improved sharing of information through public databases is essential. Finally, combinations of microbes might also be used to improve process development. For example, it might be able to co-cultivate one strain which is efficient in

conversion of 2nd generation feedstock in a particular product, which is then subsequently metabolised by another microbe into the target molecule.

In addition, process conditions require optimisation and careful monitoring. For example, large amounts of water in fermenters are required to ensure microbial viability. Thus, problems with water management results in problems with the product yield. Stakeholders agreed that current water management systems often fail to ensure optimal conditions and on that fact, new water management systems are needed.

Business Case Specific Hurdles

There are no notable exceptions for the frequently observed poor yield of bioconversions. In the case of lactic acid for the production of polylactic acid (PLA), yields are high enough to enable cost-effective production. In fact, the production costs of bio-based PLA are lower than petrochemical derived PLA.

Bioconversion issues least affect the bioethanol business case as these processes are already established and very efficient if using 1st generation feedstocks.

5.4.3 Bioconversion: Scale-up: Lab / Pilot / Demo Scale

Scale-up of Bioconversion: Horizontal Hurdles

Numerous bioconversions have been demonstrated at small scale, but up-scaling has proven to be difficult. The major hurdles are:

(1) Integration of bioconversion, product recovery and downstream processing
(2) Lack of continuous fermentation systems
(3) Lack of expertise and predictive models
(4) Insufficient capital investments

Experts and stakeholder generally agree that a major hurdle towards scale-up is that pre-treatment, bioconversion; product recovery and downstream processing are now often developed and optimised independently from each other. This leads to difficulties in integration of these processes during scale-up. It was suggested that pre-treatment and enzymatic hydrolysis can be tailored to achieve a hydrolysate quality for maximised microbial conversion and improved process yields. In addition, the flow of these various production steps is often batch-wise. Integration of these processes in continuous systems should lead to a substantial reduction of production costs. This would require integrated optimisation of process intensification, *in-situ* product recovery (ISPR), continuous fermentation and downstream processing systems. In addition to integration of processes, new industrial physicochemical processes should be developed and tested in a variety conditions, for example making use of other solvents and process pressure.

Microbial processes should be developed by optimising bioconversion and ISPR together. In addition, currently used batch fermentation systems, in which products are purified afterwards, should be replaced by continuous fermentation systems, in which the product is recovered during the fermentation process were suggested to be key. However, such advanced bioreactors are currently lacking. It was suggested that more funding should be made available and funding models should be developed to encourage joint and integrated research between universities, research organisations and industry. Chemical engineers were mentioned as having the essential skills for integration of

biochemical and chemical processes. Unfortunately, there is currently a lack of chemical engineering graduates working in industrial biotechnology. Developing new masters programs, Ph.D programs and apprenticeships focussed upon combining chemistry and chemical engineering disciplines with the life sciences were suggested as possible solutions by stakeholders. In the U.K., the lack of skills in industrial biotechnology was successfully addressed by improving basic skills in maths and physics at school and university level and introduction of the industrial biotechnology subject.

Another hurdle towards scaling up production is the lack of predictive scale-up models and scale-up expertise and microbes that can sustain high productivity in large scale conditions. The EU is lagging behind the US/Asia for scale-up skills and expertise. Scaling-up of laboratory benchmark experiments is as much as a challenge as initially developing these strains. Laboratory benchmark experiments are poor predictors of successful commercial production. Realistic models of the production process and realistic models of reactor types would greatly aid in translating laboratory results to industrial settings. It was suggested that the extrapolation of lab results to large-scale processes requires the development of computational systems similar to the ones already used in other engineering fields. In addition, strains developed in laboratory benchmark experiments may behave differently in large bioreactors. For example, as microbes are focused on reproduction, there is an active selection for strain mutants that make more product and use less biomass in the bioreactor. As such, strains should be developed that are resistant to mutation and that are focused on biomass production.

In general, there is a lack of capital investments to promote R&D, pilot and demonstration activities. Funding for establishing a plant in Europe is considered to be rather difficult, especially when it is a demonstration plant, given the huge costs. The risk for a demonstration or a first of a kind plant is much higher than for plants with proven technologies. Due to the risks it is hard to find investors for these kinds of plants. The national and EU-authorities are also not willing to support these kind of plants. A lot of SMEs therefore cannot bare the risk for this and wait or even stop. Thus, it was generally agreed that more capital should be made available for piloting and demonstration activities.

Scale-up of Bioconversion: Business Case Specific Hurdles

Biosurfactants

One of the stakeholders did not believe that biosurfactants will be produced via biotechnological approaches, but rather by chemical engineering through the intensification of the processes.

5.4.4 Bioconversion: Economic Viability

Economic Viability Bioconversion: Horizontal Hurdles

The production costs of most biobased chemicals and biofuels is currently not competitive with cost of production of their petrochemical derived equivalents. In addition, development time lines are long. For example, polylactic acid polymers were developed in the 1940s and 1950s, but it took 70 years before production became economically viable. Experts and stakeholder generally agree that one of the causes is that the yield, productivity and robustness of bioconversions are poor and should be greatly improved to allow cost-effective production of chemicals and biofuels. Other non-technological causes are the high feedstock prices, high-energy prices, high prices of enzymes used in biocatalysis and high capital investments. As a result of these hurdles, companies including BioAmber, Myriant and Corbion are building plants in Asia, because of the vicinity of feedstock, lower

energy prices and funding available for plant development. For SMEs specifically, the costs associated with IP protection of technological innovations in bioconversion are a substantial burden. SMEs could be supported in patenting possibilities by simplifying the procedures.

Overall, it was suggested that R&D efforts should be focused on developing bio-based routes for chemical building blocks that are currently difficult or expensive to make from fossil-based feedstock, more specifically developing a method to make complex reactions in one or two steps by microbiological conversion. The first steps would be to develop a map of most expensive and difficult chemical reactions, and start development of new bio-based chemical building blocks based on this list.

The feedstock prices are high, because currently used 1st generation feedstock is also used in food production. The price of 1st generation feedstock has increased because of a growing demand from both the food industry and the industrial biotech industry, mainly for bioethanol production. As discussed previously, stakeholders have suggested that production should be adapted for acceptance of alternative cheap and ubiquitously available feedstock (chapter 4.2). Clearly, this requires aforementioned technology development, as it is currently more economical to burn forestry residue than to use it as a feedstock for biobased products. Stakeholders have suggested reducing production costs by sharing utilities, logistics and feedstock handling.

The European energy prices are high because the gas reserves are decreasing and Europe is becoming increasingly dependent on costly imports. In the USA, there are plenty of reserves of cheap shale gas. In addition, governments in the EU must also use renewable sources to supply 20 percent of Europe's energy. These latter measures have bumped up energy costs for companies to pay for wind farms and solar panels. Stakeholders have suggested reducing energy costs by using low-energy consuming production systems including anaerobic production systems (see also chapter 1.1.1). Such systems consume substantially less energy because oxygen does not have to be actively supplied to the fermentation media.

Prices of enzymes used in biocatalysis are high because of the development costs. In chapter 1.1.1, several actions have been proposed to enable cheaper production of enzymes.

Finally, capital investments are currently high as the present production plants cannot be easily adapted for production of bio-products. Chemical plants take high temperature, pressure, toxic chemicals as a given, while these are not done for bioprocesses. Indeed, in the case of biobased polyesters the conversion of an existing plant failed and the solution was the realisation of a completely new plant. Even the adaptation of plants already producing bio-products is already a problem given that the fermentation conditions are very different between target products. Stakeholders recommended subjecting the entire production process and potential synergies to techno-economical evaluations. Such evaluations will be important to move towards a biorefinery that can use the same feedstock both in chemical and biofuel production whilst maintaining a zero waste process. Companies have to create synergies amongst them to build the biorefinery.

Overall the long development time lines, high capital and operating expenses and modest market uptake of bio-based products greatly hinder capital investments. Fortunately, there is some support from governments, including grants at the national and EU level, for the development of companies in the IB sector. There is also the possibility that these companies are marked by a Special Economic Zone status and granted exception from corporate income tax. This will be further discussed in the

Market and Non Technological Roadmaps. Although there are incentives, bureaucracy and lack of information impaired stakeholders making use of these opportunities. Stakeholders mentioned that improving the visibility of IB would also help raise funds for R&D; pilot and demo activities whilst new business models, in which the return on investment can be 5 years or more, would help support the industry.

Economic Viability: Business Case Specific Hurdles

CO_2 as Feedstock

For the conversion of CO_2 another very specific point for the economic viability is the need of cheap energy as a second feedstock. This topic was selected as one of the most important hurdles at the business case workshop on CO_2 based biotechnology. In this case it should be crucial to integrate the CO_2 conversion in existing energy and chemical infrastructure and to develop "on/off" capabilities for an efficient and low cost "energy peak shaving".

Other possible solutions could be the co-production of high-value products and some more technical developments in CO_2 capture and conversion to make the whole process economically more feasible. With a deeper insight the first concept to produce valuable by-products is not very relevant for the CO_2 utilisation and the objective in this case is to optimise selective conversion routes and avoid co-products that may be difficult and expensive to separate. As a solution the comparative production of high-value products (specialty chemicals) is seen as the best option. Therefore the need for target molecules identification in the field of relatively complex specialties was addressed. The development of appropriate CO_2 conversion routes should include complete IB processes as well as a combination of IB and chemical catalysis processes. The collaboration between experts in IB processes and chemical catalysis as well as with policy makers is needed to ensure a market-uptake for CO_2-based chemicals.

Additional technical optimisation to optimise the process could be the selection of the most appropriate bacterial strain to overall quality of the CO_2 source and the selection of targeted, selective purification technologies (see DSP).

In one interview the need to have modelling tools (especially with regard to the bioconversion step) to support/accelerate development of the bioconversion would be especially useful for the CO_2 fermentation.

Chemical Building Blocks

IB routes for producing biobased chemicals are expensive for several reasons:

1) Low concentrations of final products mean that much water needs to be removed

2) Expensive bioreactors are used

3) Increasing costs for energy and volatile costs for biomass

Consolidated bioprocessing was suggested during the business case workshop as a good way for dealing with lignocellulosic feedstocks, integrating pre-treatment and fermentation steps. But whilst consolidated bioprocessing can reduce CAPEX, it can increase OPEX costs because of the lower yield per unit area. As a result it is currently only suitable for some applications. While *in-situ* product removal was not deemed feasible, other approaches to reducing downstream processing costs were discussed. For some biochemical processes, it was suggested that increasing fermentation selectivity

could help reduce contaminants that need to be reduced in the downstream processing steps. Or downstream processing steps themselves could be developed to be more aligned with the different contaminants produced by microorganisms. Governments could stimulate a reduction in energy costs, but other routes should be explored. For example heat integration by exploiting industrial synergies. Sharing information between different industries on how to overcome energy costs should also be encouraged.

5.4.5 Bioconversion: Quality Assurance

Quality Assurance: Horizontal Hurdles

Experts and stakeholder generally agree that the properties of bio-based products are not adequate for all desired applications, e.g. biopolymers. This limits market uptake. For example, the poor performance of some biopolymers has led some consumers to believe that biobased products have a poor performance in general. Another example is biobased paints. The professional use is mandated, while the quality is yet insufficient. However, this is certainly not always the case. DSM produces biobased polyamides based on sebacic acid, which is being used in parts of the engine compartment of cars, because of its superior resistance to very high temperatures. Avantium is producing polyester polyethylene-furanoate (PEF) bottles, which are superior in performance compared to petrochemically produced polyethylene terephthalate (PET) bottles. Successes in biobased materials should be clearly communicated to consumers to battle this negative perception.

Finally, it is currently difficult to predict potential toxicity of biopolymer components as there are only very few sources of tests and data.

5.4.6 Regional Highlights Regarding Bioconversion

(1) There is the possibility to build additional dedicated facilities in the IB sector e.g. in Łódź covered by the local development plan.

5.4.7 Summary of R&D Hurdles and Actions Regarding Bioconversion

Table 8 provides a summary of the R&D hurdles and actions concerning bioconversion.

Following abbreviations have been used: EA = European Authorities; IO = intermediary organisations; I = investors; LCo = large companies; NA = national authorities, NGO = non-government organisation; RTO = Research and Technology Organisations; SME = small medium enterprise; U = universities. / = no action suggested

Stakeholders mentioned in brackets of the action columns are those involved in overcoming the identified hurdles.

Table 8. Overview of the R&D Hurdles and Actions Regarding Bioconversion

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
High feedstock prices	RTO, U, LCo, SME, EU	• Develop novel microbial production routes through organisms that are able to tolerate and convert cheap feedstocks *[RTO, U, SME, LCo, I, IO, EU, NA]* • Modify cheap feedstocks to allow conversion by current microbial production systems *[RTO, U, SME, LCo]*	• Investigate usage of syngas, methane, lignin, acetate as feedstocks *[RTO, U, EU, NA]*	/
Lack of anaerobic production systems	RTO, U	• Develop genetic transformation tools for anaerobic microbes *[RTO, U, LCo, SME, I, EU]*	/	/
Lack of tools to engineer microbes	RTO, SME, U, LCo,	• Develop bioplatform technologies for improved strain engineering (e.g. improved –omics methods for system understanding, high-throughput	/	/

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
		engineering, high-throughput screening in variable fermentation conditions including non-conventional reaction systems and media. *[RTO, U, SME, LCo, IO, EU, NA]*		
(By) products impair productivity	RTO, U	• Develop microbes resistant to by-products and target products *[RTO, U, SME, Lco]*	/	/
Lack of enzymes for biocatalysis	RTO, SME, U, LCo,	• Identify novel enzymes that improve biocatalysis [*RTO, U, SME, Lco]*	/	/
Poor performance of biocatalysis	RTO, SME, U, LCo MT includes EA, NA	• Identify more active and robust enzymes that improve biocatalysis *[RTO, SME, U, LCo]*	• Align R&D programs of academia and RTOs with industrial needs in enzymology *[RTO, U, SME, LCo, EA, NA]*	/
Lack of overview of enzymes available for biocatalysis	RTO, SME, U, LCo, EA, NA	/	• Develop biocatalyst database *[RTO, SME, U, LCo, EA, NA]*	/
Costly production of enzymes	RTO, U, LCo, SME	• Develop synthetic systems to produce enzymes [*RTO, U, SME, LCo, I, EU, NA, NGO]*	Not mentioned	/
Low yield	RTO, U, LCo, SME	• Develop microbes that have an improved ability to convert feedstocks	• Develop a centre of expertise to help increase the effectiveness	/

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
		in products *[RTO, U, LCo, SME, IO]*	of strain development *[RTO, U, IO, LCo, SME EA, NA]*	
	RTO, U, LCo, SME, EA & NA	/	/	• Improve sharing of information through public databases *[RTO, U, IO, LCo, SME, EU, NA]*
	RTO, U,	/	/	• Use combinations of microbes, in which each microbe has a specific function in bioconversion *[RTO, U]*
Poor fermentation & biocatalysis	RTO, SME, U, LCo, EA, NA	• Develop new water management systems *[RTO, SME, U, LCo, EA, NA]*	/	/
Lack of integration of processes	RTO, SME, U, LCo, EA, NA	• Integrated optimisation and development of pre-treatment, bioconversion, product recovery and downstream processing *[RTO, SME, U, LCo, EA, NA]*	/	/
Lack of integration of processes	RTO, SME, U, LCo, EA, NA	• Tailor pre-treatment and enzymatic hydrolysis to achieve a hydrolysate quality for maximised microbial conversion and improved process yields *[RTO, SME, U, LCo, EA, NA]*	/	/

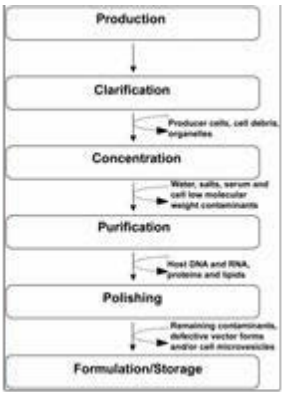
Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
Lack of integration of processes	LCo, EA, NA	• Make more funding available and develop funding models to encourage joint and integrated research between universities, research organisations and industry *[LCo, EA, NA]*	/	/
Lack of skills for process integration and scale-up	EA, NA, NGO, IO	/	• Train more chemical engineers by developing new masters programs, Ph.D programs and apprenticeships focussed upon combining chemistry and chemical engineering disciplines *[EA, NA, NGO, IO]*	/
Lack of continuous fermentation systems	EA, LCo, NA, IO	• Make more funding available *[EA, LCo, NA, IO]*	/	/
Lack of modelling tools for the biocatalysis	RTO	• support/accelerate development of bioconversion	/	/
Lack of integration of processes	RTO, SME, U, LCo	• Integrated optimisation and development of bioconversion, product recovery and downstream processing *[RTO, SME, U, LCo]*	/	/

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
Inadequate performance of processes	SME, LCo, EA	• Development and testing of new industrial physicochemical processes in a variety conditions, for example making use of other solvents and pressure *[SME, LCo, EA]*	/	/
Lack of predictive models for scale-up	RTO, SME, U, LCo	• Develop realistic models of the production process and realistic models of reactor types, such as the computational systems that are already used in other engineering fields *[RTO, SME, U, LCo]*	/	/
Lack of microbes that can sustain productivity in large bioreactors	RTO, U	• Develop strains that are resistant to reverting to mutant strains that are focused on biomass production *[RTO, U]*	/	/
Lack of capital investments to promote R&D, pilot and demonstration activities	EA, IO, LCo, NA	• Provide funding for piloting and demonstration activities *[EA, IO, LCo, NA]*	/	/
Unable to compete with	RTO, SME, U, LCo	/	• Develop a map of the most expensive and difficult chemical	/

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
petrochemicals			reactions, and start development of new bio-based chemical building blocks based on this list *[RTO, SME, U, LCo]*	
High production costs	SME, LCo, IO	/	/	• Stakeholders have suggested to reduce production costs by sharing of utilities, logistics and feedstock handling *[SME, LCo, IO]*
High feedstock prices	RTO, SME, U, LCo	• Production should be adapted for acceptance of alternative cheap and ubiquitously available feedstocks (see actions chapter 1.1.1) *[RTO, SME, U, LCo]*	/	/
High energy prices	RTO, U, LCo, SME	/	• Reduction of energy costs by using low-energy consuming production systems including anaerobic production systems *[RTO, U, LCo, SME]*	/
High prices of enzymes used in biocatalysis	RTO, U	• Develop new enzyme production systems (see actions 1.1.1) *[RTO, U]*	/	/
High capital investments for plant creation	RTO, LCo, SME	• Subject the entire production process and potential synergies to techno-economical evaluations	/	/

Hurdles	Stakeholders involved in hurdles	Short term actions	Mid-term actions	Long term actions
or adaptation		*[RTO, LCo, SME]*		
Lack of capital investments	EA, NA	/	• Provide more transparent information about subsidies, tax exceptions and make application procedures simpler *[EA, NA]*	/
	RTO, SME, U, LCo, EA, NA, IO, NGO	/	• Improve the visibility of industrial biotechnology *[RTO, SME, U, LCo, EA, NA, IO, NGO]*	/
	IO	• Develop new business models, in which the return on investment can be 5 years or more *[IO]*	/	/
Mistrust of consumers in biobased products	NGO, IO, LCo, SME, EA, NA	/	• Clear communication of successes in biobased materials to consumers *[NGO, IO, LCo, SME, EA, NA]*	/
High IP costs	NGO, EA, NA	/	• Simplify patent procedures *[NGO, EA, NA]*	/

5.5 Downstream Processing (DSP)



This paragraph describes the hurdles, enablers and actions concerning downstream processing and R&D. The information for this section was collated using information gathered from a literature review, discussions at the regional and business-case related workshops and interviews with stakeholders and experts.

In most sectors the hurdles associated with DSP have not been identified as the most important factors. Hence, the outcomes of interviews and workshops have largely focused on other technical, non-technical or market factors. Although, within the hurdles and solutions that are discussed for other topics, DSP is likely to become a key component directly or indirectly.

Overview of the Main Hurdles in Terms of DSP

The workshop attendees and interviewed stakeholders have generally validated the findings of the literature study. One major technical hurdle related to DSP consists in the fact that bioconversion systems produce many impurities, which subsequently require several separation steps within the process. This incurs additional costs, amounting up to two thirds of the total process costs. Industrial biotechnology concerns water rich systems, which pose the question of water and energy management for bioconversion in order to facilitate swift and cost effective downstream processing.

Literature review findings highlight the use of aggressive solvents (especially for biopolymer production like PHA) in downstream processing as a hurdle, this was not the case when expert stakeholders were questioned; they did not see solvent use as a major hurdle.

Structure of the Chapter

The following sections will provide a more detailed description of the hurdles related to DSP. More importantly, a series of technological solution pathways to overcome these bottlenecks will be presented. As announced in the beginning of this chapter, the input gathered from the workshops and interviews can be structured along five subject matters:

- Novel (and newly applied) technology;
- Process capability, yield and optimisation;
- R&D / pilot / demo scale;
- Economic viability;
- Quality assurance;
- Water Management
- Regional DSP highlights.

In order to result in a comprehensive analysis, business case specific hurdles and solutions will also be pointed out. The topic section closes with a summary table of all stakeholder suggested actions to overcome DSP issues.

5.5.1 Novel (and Newly Applied) DSP Technology

Novel and (Newly Applied) Technology: Horizontal DSP Hurdles

The main technical challenge for DSP is the level of impurities that need to be removed and a need for enablers to overcome the problem being fairly general. Three different workshops and several stakeholders interviewed identified that the level of impurities produced as a result of the bio-catalytic process, which then require separating in the DSP step, was a hurdle to overcome. Although not every workshop raised impurities as a hurdle; between the interviews and the workshop information this issue was raised in the area of general biotechnology and all business cases except for biosurfactants (see business cases below).

The opinions of technical development requirements for DSP were varied among the participants of the workshops and the experts interviewed. For each interview and workshop the level of development was judged as different, not only for each business case but also for each business! Overall, it is clear that some level of technical development is required in the area of DSP with some businesses requiring breakthrough technology while others state no technical developments are needed. The requirement on downstream processes will depend on the process employed, the product and the required purity. Therefore the technological solution will change and a general biotechnology requirement which will impact DSP is the requirement to develop standardised, energy efficient technology which produces product, by-product and waste streams with consistent and uniform quality when utilising feedstocks with variable and wide ranging specifications.

Incompatibilities between some upstream and DSP technologies also need to be resolved with the potential for alternative methods to be explored, for example, make a gas or solid instead of a liquid to be processed and change the type of technology needed. Novel DSP technologies also needs to be investigated and developed to resolve some of the problems faced with product isolation and contaminant removal with workshops specifically highlighting requirements for improvements in purification technologies and adsorption processes. Furthermore the requirement to move towards continuous processing will require novel or newly applied technology for DSP to be developed.

Three workshops specifically made reference to copious amounts of water being used in the process as a hurdle. It was highlighted that work needs to be done to improve the product recovery from the aqueous reaction medium to make it more economical. An additional challenge is contaminants in the water preventing the water being re-used in the process. Therefore, generic and specific separation technologies need to be developed to aid with the hurdle of product recovery, contaminant removal and water re-use. Alternatively processes and organisms need to be developed that need minimal or even no water!

Novel and (Newly Applied) Technology: Business Case Specific DSP Hurdles

DSP: Advanced Biofuels

Details of DSP challenges for this business case, which will require novel or newly applied technology are below:

- The technical challenge of impurities was raised as an issue during an interview
- Information from interviews and a workshop ranged from no technical development required through to technology required
- In the area of biofuels it is possible to produce bioethanol with a sufficient purity for combustion engines, but a hurdle for DSP is when trying to produce other products from ethanol and the solution to this may come from the development of membrane technologies
- Although not raised under the topic of DSP specifically, the hurdle of having no continuous production capability will inevitably impact on DSP and result in novel technology being required and developed

DSP: Chemical Building Blocks

Details of DSP challenges for this business case that will require novel or newly applied technology are below:

- The technical challenge of impurities was raised as an issue during two stakeholder interviews related to chemical building blocks
- IB routes for producing biobased chemicals are expensive for several reasons. Among them the low concentrations of final products meaning that much water needs to be removed. To overcome this hurdle, DSP technologies should be optimised or new ones should be developed.

DSP: Biopolymers

Details of DSP challenges for this business case, which will require novel or newly applied technology are below:

- The technical challenge of impurities was raised as an issue during two interviews related to biopolymers
- Information from stakeholder interviews ranged from no technical development required through to breakthrough technology required
- An interviewee felt that the reduction of impurities was needed through the development of more efficient bioconversion systems.

DSP: Biosurfactants

The business case of biosurfactants and the requirements of DSP were not covered in detail in the workshops or interviews. The information on DSP for this business case that was available is below.

- Two workshops have reported that some technical development is required for DSP
- The technical challenge of impurities was not raised
-

DSP: CO_2 as a Feedstock

In general in this business case the DSP hurdles are more or less the same as in the BC for chemical building blocks. Details of DSP challenges for this business case that will require novel or newly applied technology can be found below:

- The technical challenge of impurities was raised during a few interviews related to this business case
- Information from interviews and a workshop ranged from no technical development required through to breakthrough technology required. On average some technical development would be required for DSP
- The main need following the business case workshop should be the choice of targeted, selective purification techniques for high-value products or to develop *in-situ* product recovery (ISPR) to separate the product from the bioconversion aqueous medium in an efficient way. The Flemish Institute for Technology (VITO) is working on membrane technologies to maximise the efficiency.
- A next step should be the integration of the CO_2 conversion with further chemical conversion processes in an integrated system to obtain high-value products based on the bioconversion products.

5.5.2 DSP Process Capability, Yield and Optimisation

Process, Yield and Optimisation: Horizontal DSP Hurdles

Some sections of the workshops highlight hurdles, which can indirectly impact DSP. For example; for both biopolymers and chemical building blocks a workshop identified an objective as being able to retrofit petrochemical refineries with biorefining components, another had the vision to have integrated biorefineries which included biofuels. The requirement for biorefineries presents an opportunity to use different feedstocks and to produce different products, but the technological complexity for each step of the operation will increase with each manufacturing change introduced. This will produce a hurdle for DSP due to these changes increasing the required flexibility of the technology and the expected operational window of the downstream processing equipment. Therefore, developing an understanding of the process capability of the downstream processes will be required to ensure optimised operations in the future.

Within the area of industrial biotechnology low process efficiencies are mentioned with the general demand for optimisation. A workshop stated that in the general area of industrial biotechnology a hurdle to overcome is to find more efficient downstream and recovery technologies to optimise production. This includes the use/re-use of by-products and waste streams and increasing the value of these streams. Future hurdles which will impact on the processing capability and outputs of a production plant, will be stricter regulations for waste solvents (see also the Market and Non Technological Roadmap). It is expectant that stricter regulations will require quantities of waste solvents to be minimised while limits for disposal will be tightened resulting in the need for the performance of DSP to be optimised and improved.

Process, Yield and Optimisation: Business Case Specific DSP Hurdles

DSP: Advanced Biofuels

Hurdles raised that were not specifically addressing the topic of DSP but may have a future impact in this area are listed below.

- The issue of low efficiencies for technology in the area of biofuels
- An interviewee stated that biorefineries need to be optimised. By-products from the biorefineries can be used for animal feeds

DSP: Chemical Building Blocks

- Not specifically mentioned for DSP but there is a requirement for efficient biorefineries
- A workshop stated that DSP is not efficient enough and is too costly

DSP: Biopolymers

Not specifically mentioned for DSP but there is a requirement for efficient biorefineries and optimised production processes

DSP: Biosurfactants

The glycolipid biosurfactants, sophorolipid, rhamnolipids and MELs are possible candidates to be used as, at least, partial replacements for the most common surfactant in washing powders and liquids alkyl sulfonates such as linear alkylbenzene sulfonates (LASs). One of the major challenges in the use of these alternative biosurfactants is that each organism produces a mixture of congener molecules with a range of different structures and therefore properties. This makes the downstream processing extremely complicated and costly. Moreover, the current conversion yields remain low for industrial scale production.

DSP: CO_2 as a feedstock

Specifically within the area of DSP, optimisation being needed was mentioned in an interview and also in the workshop for CO_2 based chemicals.

5.5.3 R&D / Pilot / Demo DSP Scale

R&D / Pilot / Demo DSP Scale: Horizontal Hurdles

To allow the required volumes to be manufactured a hurdle is the need to overcome the scale of DSP operations and the difficulties with extrapolating lab scale results to large scale. This was not specifically mentioned for DSP in any workshop but will still be a challenge, for example, during one workshop it was identified that their current status for biofuels was restricted by low scale technology but not necessarily by the capabilities of DSP. An interview also highlighted the difficulty in extrapolating lab scale results to large scale processes due to the fact enzymatic processes are complex and enzymes interact differently which makes scale-up harder than traditional chemical processes. Additionally, producing data and extrapolating for different scales is also a hurdle for developing continuous bioprocesses.

The importance and level of investment in R&D, especially as the requirement for new products increases, has been identified as the solution to issues with the scale of operation and developing continuous bioprocesses. The level of R&D needs to increase with the general need for more facilities at different scales (pilot plant, demonstration scale and flagship) with the companies and research centres working together to improve the quality of products. These facilities should be able to identify and address hurdles with DSP. A long term goal and area of investigation for research centres is that of efficient biorefineries with closed CO_2 cycles. This will require research into fundamental process design to allow the capturing and sequestration of CO_2 and subsequent downstream processing required to recondition the CO_2 to enable its re-use as a feedstock.

A possible action to mitigate DSP challenges was highlighted in the area of biopolymers, where the development of bioconversion systems with better specificity would reduce the level of impurities going into the downstream step; similarly improving an organisms tolerance to impurities and products would enable higher concentrations to be produced without ill-effect. Through increasing the performance of biocatalysts and microorganisms, will allow for the integration or the reduction of the number of DSP steps. An alternative way of solving this is to consider combining bioconversion and DSP as there is a need to integrate both steps in order to improve both bioconversion and DSP efficiencies with *in-situ* product removal (ISPR). To make these advances, modelling and simulation of the entire process will be required to ensure synergy between all process steps which also requires an improvement in process knowledge to ensure the correct identification of key variables for process modelling.

R&D / Pilot / Demo DSP Scale: Business Case Specific DSP Hurdles

DSP Advanced Biofuels

Hurdles raised that were not specifically addressing the topic of DSP but may have a future impact in this area are listed below:

- Participants of one workshop identified that the current status for biofuels was restricted by low scale technology
- The need for R&D into scale-up for aviation fuels was also raised in an stakeholder interview
- There is a need for demonstration scale facilities
- No continuous processes are available

DSP: Chemical Building Blocks

A hurdle raised by one workshop was for more R&D focused on increasing the product concentration and improving downstream separation

Hurdles raised that were not specifically addressing the topic of DSP but may have a future impact in this area are listed below:

- The requirement for efficient biorefineries with closed CO_2 cycles
- The need for pilot plant, demonstration scale and flagship plants that helps to understand the current application of DSP technologies in IB

DSP: Biopolymers

Hurdles raised that were not specifically addressing the topic of DSP but may have a future impact in this area are listed below:

- Participants of one workshop stated that currently there is no provision for biopolymer production on a small scale
- Participants of one workshop stated more involvement for R&D is needed
- The need for pilot plant, demonstration scale and flagship plants that helps to understand the current application of DSP (in relation to biopolymer production) technologies in IB

An action raised which was not specifically addressing the topic of DSP but may have a future impact in the area of DSP is the requirement for R&D into new and fundamentally different production process for the manufacture of products.

DSP CO_2 as a Feedstock

A hurdle raised that is not specifically addressing the topic of DSP but may have a future impact in this is the requirement that more R&D is needed to find innovative applications and high-value chemicals based on the CO_2 conversion.

5.5.4 Economic DSP Viability

Horizontal DSP Hurdles

Generally the costs associated with biotechnology are too high for the considered business cases to be competitive with the already established products thus hindering an increased market share. These high costs apply to both the capital investment and the on-going production costs. The businesses at the workshops and those interviewed mostly agreed that bioconversion systems produce many impurities, which are separated in the DSP step, which represents 50%-66% of the processing costs. Although, one workshop stated that 66% of the process costs for chemical building blocks was in the conversion step. Under the discussion of achieving the required product functionality it was recognised that the raw material, upstream and downstream costs need to be considered. Also, the feedstock and pre-treatment determine the type of bioconversion and DSP possible and thus the corresponding costs. Therefore the whole process should be evaluated to ensure the most cost effective production process is developed. Each business will need to define their own basis for economic viability and apply this to the evaluation of the whole process to ensure the targets for viability are achieved.

In general, the scale of the process determines the cost of the process. For biopolymers and chemical building blocks; technology needs to be cost competitive at different scales. This was a endeavour identified which was not linked specifically to DSP, although to achieve this goal the costs for DSP will also have to be reduced. For CO_2 based chemicals the DSP costs need to be lower to make the technology viable. A workshop did identify that the general costs and environmental footprint for DSP specifically was also a big issue.

An alternative solution to overcome high investment and production costs is to facilitate biotechnology businesses to work in clusters. These companies can share the costs of developing an infrastructure and take advantage of the potential scale and cost efficiencies, for example, by sharing utilities.

Business Case Specific DSP Hurdles

DSP: Advanced Biofuels

- An interview related to this business case agreed that bioconversion systems produce many impurities which are separated in the DSP step representing 50%-66% of the processing costs
- An interview for a company involved with aviation fuels stated that overall cost of production needs to be reduced and that there is a cost impact on achieving the higher quality requirements

DSP: Chemical Building Blocks

- Three stakeholder interviews related to this business case agreed that bioconversion systems produce many impurities which are separated in the DSP step representing 50%-66% of the processing costs
- For one workshop, DSP was identified as a key cost driver with a need to make these costs lower

Hurdles raised, which were not specifically addressing the topic of DSP but may still be relevant are:

- Having cost competitive technologies at different scales

DSP: Biopolymers

Two interviews related to this business case agreed that bioconversion systems produce many impurities that are separated in the DSP step representing 50%-66% of the processing costs.

Hurdles raised that were not specifically addressing the topic of DSP but may still be relevant are:

- Having cost competitive technologies at different scales
- New biopolymers are expensive to make

DSP: CO_2 as a feedstock

Three interviews related to this business case agreed that bioconversion systems produce many impurities that are separated in the DSP step representing 50%-66% of the processing costs. With one interviewee stating that the DSP costs need to be lower to make the technology viable.

5.5.5 DSP Quality Assurance

DSP Quality Assurance: Horizontal Hurdles

Important hurdles not directly mentioned under downstream processing but under other topics that may have a future impact on DSP are the quality of feedstocks, the number of feedstocks, final product quality, product performance properties, by-products and waste stream quality/re-use. Each of these requirements increases the required operational window of the downstream equipment and its ability to operate to the needed efficiencies to ensure the required quality assurance. For example, it was recognised that there are inconsistencies with different feedstocks and each one has different properties that require different processes while at the same time it is important to improve the quality of bio-based products at a lower cost.

DSP Quality Assurance: Business Case Specific DSP Hurdles

DSP: Advanced Biofuels

- A vision from one workshop that was not specifically addressing the topic of DSP but would certainly have an impact is to have plants capable to use multiple feedstocks to make multiple products
- An interviewee stated that current facilities are flexible in terms of the kind of biofuel they can produce (aviation, car, trucks) but there can be a cost impact on achieving the higher quality requirements
- An interviewee stated that by-products from the biorefineries could be used for animal feeds

5.5.6 Regional DSP highlights

Only two hurdles were identified as being important for DSP. For the regions giving a higher importance to DSP, then the main hurdle is the amount of impurities that need to be removed with the requirements to improve technology, knowledge transfer and lower costs to overcome this hurdle. The other DSP related element is the innovative DSP steps that can be transferred from other industry sectors.

The UK, Benelux, Spain, and Germany recognised that the main DSP hurdle was the amount of impurities needing to be removed. It was identified that for DSP, technology transfer from other chemical industry sectors was also a obstacle by all regions except Germany, France and Benelux. For Italy, Poland, Finland; technology transfer was the only element of DSP voted as a hurdle. France identified DSP as a key cost driver with work needed to lower the production costs.

When identifying the most important hurdles for Biotechnology, DSP has featured as a hurdle for all regions; however, it is not the most important priority. DSP was recognised as a bigger hurdle from UK and Benelux. Italy and Spain gave DSP less importance, while for Finland, Germany and Poland; DSP received a very low number of votes.

UK and Benelux raised the topic regarding the levels of water generated in the process and the problems it causes in DSP.

Through the evaluations of workshops and interviews all regions and business cases the hurdle of volatile solvents being used was not significant at this stage for the business involved.

5.5.7 Summary of DSP Hurdles and Actions

Table 9 provides a summary of the R&D hurdles and actions concerning DSP.

Following abbreviations have been used: EA = European Authorities; IO = intermediary organisations; I = investors; LCo = large companies; NA = national authorities, NGO = non-government organisation; RTO = Research and Technology Organisations; SME = small medium enterprise; U = universities. / = no action suggested

Stakeholders mentioned in brackets of the action columns are those involved in overcoming the identified hurdles.

Table 9. Summary of DSP Hurdles and Actions

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
High level of impurities present in the fermentation streams will hamper DSP	LCo, SME	• Some technical development required • Modelling of entire process *[LCo, SME, RTO U, EA, NA]*	• New more efficient bio-catalytic systems • R&D into integrating Bioconversion with DSP *[LCo, SME, RTO, U, EA, NA]*	• Develop organisms to tolerate higher concentrations *[LCo, SME, RTO, U, EA, NA]*
Large amount of water in the process that needs to be removed	LCo, SME	• Improve product recovery from water • Minimising water usage *[LCo, SME, RTO, U, EA, NA]*	/	/
Re-use of process water to minimise the cost	LCo, SME	• Increase the value of the waste and by-product streams through improved DSP yields. *[LCo, SME, RTO, U, EA, NA]*	• Generic and specific separation technologies to improve product recovery, contaminant removal and water re-use *[LCo, SME, RTO, U, EA, NA]*	/
Increasing the number of	LCo, SME	• Determining and improving process capability to allow	/	/

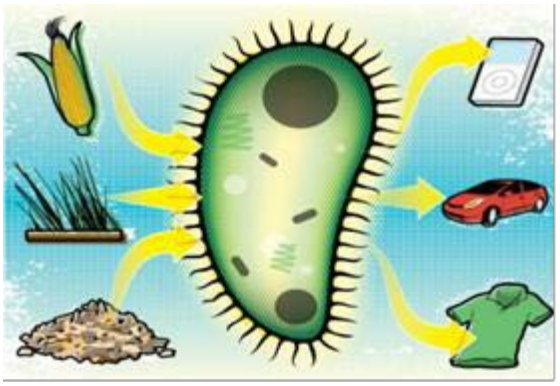
Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
Feedstock that can be processed to give flexibility to DSP		different inputs/outputs of DSP *[LCo, SME, RTO, U, EA, NA]*		
Low process efficiency	LCo, SME	• Process Modelling of the entire process *[LCo, SME, RTO, U, EA, NA]*	• Optimisation of process and/or the provision of novel (and newly applied) technology to provide more efficient downstream and recovery processes to meet product quality • R&D into integrating Bioconversion with DSP *[LCo, SME, RTO, U, EA, NA]*	/
Scale and mode of operation	LCo, SME	• Facilities at different scales required (lab, pilot plant, demonstration and flagship) • Investment in R&D *[LCo, SME, U, RTO, NA, EA]*	• Facilities at different scales required (lab, pilot plant, demonstration and flagship) for the development of continuous bio processes *[LCo, SME, U, RTO, NA, EA]*	/
High capital and operational costs	LCo, SME	• The whole process should be evaluated together (feedstocks, upstream processing, conversion and DSP) to ensure the most cost effective production process is developed *[LCo, SME, U, RTO, NA, EA]*	• DSP processes and equipment needs to be designed and optimised at different scales by multi-disciplined communities to ensure economic viability. *[LCo, SME, U, RTO, NA, EA]*	• Facilitate biotechnology business to work in clusters which can share the costs of developing an infrastructure and take advantage of the potential scale and cost efficiencies.

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
				[LCo, SME, U, RTO, NA, EA]
Required product, by-product specifications and performance	LCo, SME	• Determine quality expectations of feedstocks, final product and byproducts to allow design and optimisation of DSP *[LCo, SME, U, NA, EA,RTO]*	/	/
Quality and number of feedstocks and the impact on the process	LCo, SME	• DSP processes and equipment need to be designed to be capable of operating with flexibility to accommodate various inputs while achieving product specifications *[LCo, SME, U, NA, EA, RTO]*	/	/
Quality of final products to provide the correct product properties	LCo, SME	• DSP processes and equipment need to be designed to be capable of operating with flexibility to accommodate various inputs while achieving product specifications *[LCo, SME, U, NA, EA,RTO]*	/	/
Quality of by-products and waste streams should be improved	LCo, SME	• DSP processes and equipment need to be designed to be capable of operating with flexibility to accommodate various inputs while achieving	/	/

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
		product specifications *[LCo, SME, U, NA, EA,RTO]*		
Variable outputs after Bioconversion	LCo, SME	/	• Technology standardisation for bioconversion and DSP *[LCo, SME, U, NA, EA,RTO]*	/
Incompatibilities between upstream technologies and DSP	LCo, SME	/	• Resolve issues • Potential for alternative methods, novel technology and continuous processing *[LCo, SME, U, NA, EA,RTO]*	/
Product Purity / Quality (refer also to quality assurance section)	LCo, SME	/	• Some technological requirements needed to allow the required product specifications to be achieved • Optimisation of processes to enable the correct product specifications to be achieved *[LCo, SME, U, NA, EA,RTO]*	/
Retrofit Bio refineries	LCo	/	• Determining and improving process capability to allow different inputs/outputs of DSP *[LCo, U, NA, EA]*	/
Increasing different (by)products	LCo, SME	/	• Determining and improving process capability to allow different inputs/outputs of	/

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
from a process			DSP *[LCo, SME, RTO, U, NA, EA]*	
The ability to use by-products and re-use of waste streams	LCo, SME	/	• Optimisation of process and/or the provision of novel (and newly applied) technology to provide more efficient downstream and recovery processes to meet quality and regulatory requirements *[LCo, SME, U, NA, EA,RTO]*	/
Processes need to be energy efficient	LCo, SME	/	• Process optimisation and/or the potential for novel (and newly applied) technology *[LCo, SME, U, NA, EA,RTO]*	/
Integrated Bio refineries	LCo	/	/	• Determining and improving process capability to allow different inputs/outputs of DSP *[LCo, SME, U, NA, EA,RTO]*
Efficiency of bio refineries	LCo, SME	/	/	• R&D into Bio refineries with closed CO_2 cycles *[LCo, SME, U, NA, EA,RTO]*

5.6 Products and Markets



This R&D topic focuses on subjects related to valorisation, commercialisation and the development of products. A first literature exploration identified three main hurdles regarding products and markets:

- Properties of biobased products are not adequate for all desired applications
- Not cost-competitive compared to fossil-based alternatives
- Difficult to go from lab scale to large scale processes because enzyme systems interact

The stakeholder input gathered from the regional and business-case related workshops and the expert interviews has largely validated the hurdles found in the literature. Due to the nature of these hurdles, the suggested approach to tackle them as outlined in the market roadmap. However, the technical aspects regarding the up-scaling process have been covered in the Bioconversion chapter. Table 10 provides a summary of the hurdles and actions related to products and markets and the stakeholders involved in such actions.

Table 10. Summary of Products & Markets Hurdles and Actions

Hurdles on the short/mid-term (1-5 yrs)	Stakeholders involved	Actions
Properties of biobased products are not adequate for all desired applications;	LCo, SME, RTO, U	See market roadmap
Not cost-competitive compared to fossil-based alternatives;	LCo, SME	See market roadmap
Difficult to go from lab scale to large scale processes because enzyme systems interact.	RTO, U	See paragraph 5.3.3.

Properties of Biobased Products: Business Case Hurdles

Chemical Building Blocks

Europe has a number of key disadvantages when it comes to economic production of large-scale commodity chemical building blocks. These are high feedstock and energy costs compared to other regions of the world and the cost-effective production of fossil alternatives and a fragmented biomass industry, which hinders indigenous feedstock supply. This suggests that the EU will struggle to produce chemical building blocks in a cost effective manner and may be better placed to focus on high value-added products.

Routes to developing an industry based on the production of high value-added products in the EU were discussed during the business case workshop. It was suggested that some mechanism was needed to stimulate this sector in the EU. Perhaps this could be a strategic focus on the development of aviation biofuels as a stepping stone for high value added chemicals production, similar to the USA's focus on ethanol production was then able to stimulate the development of other chemical building block products there. The use of lignin for different end uses should be developed further, but needs further R&D actions to make this a reality, and it was suggested that this could be stimulated through Horizon 2020 activities. More widely, actions should be undertaken to improve feedstock availability by educating farmers, foresters and other land owners on the value of their products to the bioeconomy and by stimulating cross-sectorial collaborations, for example between the chemical and forestry industry.

The EU has considerable technological strengths but is disadvantaged by feedstock costs. As such, the sector should focus on high value and high quality applications such as speciality chemicals rather than bulk applications.

5.7 R&D tools

This paragraph describes the hurdles, enablers and actions concerning R&D tools that have been found in literature, and were discussed in the regional and business-case related workshops as well as the interviews with experts. The R&D tools topic focuses on subject matter related to the development of tools supporting R&D, for example the development of models and databases. Most remarks on R&D tools have already been included in previous sections because of the cross-cutting nature of the topic. It can however be added that stakeholder confrontation of the desk study findings has confirmed that a hurdle exists where R&D tools can be of support is the lack of understanding of gene interaction in cells and systems. As a consequence, it was advised to create a microbial R&D database. The need to develop and use early stage modeling tools was stressed, as was the idea to develop tools to find new genes from nature. Regrettably, the exact way to accomplish these actions was not detailed in light of the fact that it was not part of the stakeholders' expertise. The hurdles and actions are summarised in Table 11.

Table 11 Summary of Hurdles and Actions Related to R&D Tool Development

Hurdles on the short to mid-term (1-5 yrs)	Stakeholders involved in hurdle	Actions	Stakeholders involved in action
Lack of understanding of gene interaction in cells and systems	RTO, U, LCo, SME	Develop and use early stage modeling tools	RTO, U, EA, NA
Lack of understanding of gene interaction in cells and systems	RTO, U, LCo, SME	Develop tools to find new genes from nature	RTO, U, LCo, SME, EA, NA
Lack of understanding of gene interaction in cells and systems	RTO, U, LCo, SME	Create a microbial R&D database	RTO, U, LCo, SME, EA, NA

5.8 Knowledge Infrastructure

This paragraph describes the hurdles, enablers and actions concerning knowledge infrastructure, that have been found in literature, and were discussed in the regional and business-case related workshops as well as the interviews with experts.

For knowledge infrastructure in this roadmap a distinction is made between hard and soft knowledge infrastructure. Hard knowledge infrastructure refers to topics related to installation of pilot facilities, connections to existing physical infrastructure. Soft knowledge infrastructure refers to topics related to funding, entrepreneurial climate, presence of knowledge sharing and open innovation models.

The structure of this section is not the same as the paragraphs 5.2 to 5.4 since the knowledge infrastructure issue is not a purely technical one. Drawing up on a more detailed description of the hard and soft knowledge infrastructure related hurdles, several stakeholder recommendations will be outlined. The section concludes with a summary table integrating the suggested actions and solutions for the identified hurdles.

5.8.1 Results from the Literature, Workshops and Interviews Concerning Hard Knowledge Infrastructure

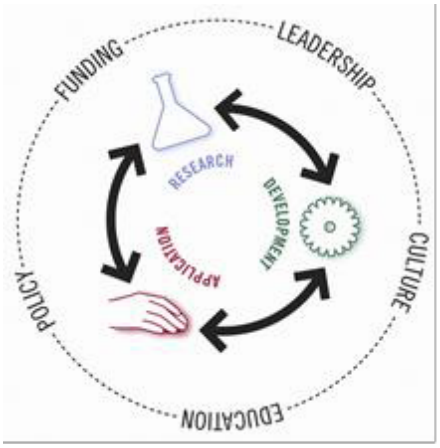
In general, there is a lack of capital investment to promote pilot and demonstration activities. Funding for establishing a plant in Europe is considered to be rather difficult, especially when it is a demonstration plant. The risk for a demonstration or a 'first of a kind' plant is much higher than for plants with proven technologies. Due to the risks it is hard to find investors for these kinds of plants. The national and EU-authorities are also not willing to support these kind of plants and focus their funding more on research and/or pilot plants. A lot of SMEs therefore cannot bare the risk for this and put their activities on hold or have to stop their business. Thus, it was generally agreed that more capital should be made available for piloting and demonstration activities.

The production costs of most biobased chemicals and biofuels is currently not competitive with production of their petrochemical equivalents. The production capacity of current production plants of biobased products can, by no means, compete with that of the petrochemical industry. Most bio-based plants are still in the pilot phase. It will be important to scale up to industrially relevant production. The main bottlenecks are the lack of capital and expertise to either adapt present production plants or build new ones. Building new production plants is very expensive. Conversion of existing plants is cheaper, but technically challenging as the present production plants cannot be easily adapted for production of bio-products. Chemical plants take high temperature, high pressure, toxic chemicals as a given, while these are not encountered with bioprocesses. In addition, biobased technologies have to fit into the formulators existing technology, for example biopolymers have to fit into the processing equipment used by "standard" plastic formulators.

Indeed, in the case of biobased polyesters the conversion of an existing plant failed and the solution was the creation of a completely new plant. Stakeholders recommended subjecting the entire production process and potential synergies to techno-economical evaluations. Such evaluations will be important to move towards a biorefinery, which can use the same feedstock both in chemicals and biofuels production whilst conducting a zero waste process. Companies have to create synergies amongst them to build the biorefinery. Finally, mobile or smaller, decentralised biorefineries could contribute significantly to achieving these growth targets. In that respect, Europe should focus on investing in building production plants in its own backyard for biobased products that only require 1-2 production plants. The production of bio-based acrylic acid for super-absorbents, which is being developed by several companies, could be such an example.

Fortunately, there is some support from governments, including grants at the national and EU level, for the development purposes by companies operating in the IB sector. There is also the possibility that these companies are marked by a Special Economic Zone status and granted exception from corporate income tax. This is further discussed in the Market and Non Technological Roadmaps. Although there are incentives, bureaucracy and lack of information impeding stakeholders making use of these opportunities. Stakeholders mentioned that improving the visibility of IB would also help raise funds for R&D; pilot and demonstration activities whilst new business models, in which the return on investment can be 5 years or more, would help support the industry.

5.8.2 Results Literature, Regional Workshops and Interviews Concerning Soft Knowledge Infrastructure



This paragraph describes hurdles and enablers related to funding, entrepreneurial climate, presence of knowledge sharing and open innovation models. Regional differences in these still have to be highlighted on the basis of the business case workshops.

Actors from industry experience a large discrepancy between research objectives in academia and the needs of industry in Europe. For example, specific areas of enzymology representing real needs for industries are not

covered by research organisations. Funding should be prioritised according to the potential of the technologies to increase the chance that biobased products reach the market.

The issue of knowledge transfer is crucial in this context. Several workshops have stressed that DSP for instance can benefit from improved knowledge transfer from the chemical industry and foster industry's willingness to adopt and implement solutions related to DSP problems. More specifically, the potential future problems with DSP for all the different product groups have not yet been entirely identified and assessed. Workshop participants suggested that a multidisciplinary R&D community could help solve this issue in its comprehensiveness.

Conversely, better knowledge transfer can drive the solutions development in IB issues thanks to better cooperation between academia and industry, as well as the chemical and biotechnology sector. In the biopolymers sector for instance, many producers are not aware of all the available technologies. Identifying the right technologies for lowering the costs for CO_2-based chemicals is also dependent upon effective technology transfer. It was recognised that although education in general is an excellent solution for IB issues, in the CBB case there is a lack of chemical engineering graduates in industrial biotechnology. This limits the transfer of knowledge in separation technologies, subsequently calling for more relevant degree courses with a greater focus on bioprocessing. Indeed, a productive knowledge infrastructure is a crucial requirement in tackling the challenges for IB, and it is especially in the field of DSP as a growing factor that its impact is expected to be most helpful.

As mentioned in the bioconversion chapter, bioconversion, product recovery and downstream processing should be jointly developed and integrated. It was suggested that more funding should be made available and funding models should be developed to encourage joint and integrated research between universities, research organisations and industry. Chemical engineers were mentioned as having the essential skills for integration of biochemical and chemical processes. Unfortunately, there is currently a lack of chemical engineering graduates working in industrial biotechnology. Developing new masters programs, Ph.D programs and apprenticeships focused upon combining chemistry and chemical engineering disciplines with the life sciences were suggested as possible solutions by stakeholders. In the U.K., the lack of skills in industrial biotechnology was successfully addressed by improving basic skills in mathematics and physics at school and university level and introduction of the industrial biotechnology subject.

5.8.3 Summary of R&D Hurdles and Actions Regarding Knowledge Infrastructures

A summary table of the hurdles and actions discussed concerning knowledge infrastructures can be found in Table 12 below.

Following abbreviations have been used: EA = European Authorities; IO = intermediary organisations; I = investors; LCo = large companies; NA = national authorities, NGO = non-government organisation; RTO = Research and Technology Organisations; SME = small medium enterprise; U = universities. / = no action suggested

Table 12. Overview of the R&D Hurdles and Actions Regarding Knowledge Infrastructures

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
Hard Knowledge Infrastructures				
Lack of capital investments to promote pilot and demonstration activities	LCo, SME	• More capital to be made available for piloting and demonstration activities *[LCo, IO, NA, EA]*	/	/
High risk for first of a kind and demonstration plants	LCo	• Support investors in risk-taking (also related to non-technological issues like the lack of knowledge of the benefits of IB) *[LCo, IO, NA, EA]*	/	/
Production capacity of current biobased production	LCo	• Foster scale-up to industrially relevant production *[LCo, IO]*	/	/

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
plants of cannot compete with the petrochemical industry as most of them are still in the pilot phase				
Lack of expertise to adapt present production plants	LCo, SME	/	• Subject the entire production process and potential synergies between (bio)processes to techno-economical evaluations *[NA, EA, U]*	/
Lack of synergies between companies to build the biorefinery	LCo, SMEs	/	• Create plants that can use the same feedstock for chemicals and biofuels production *[LCo, SME]*	/
Lack of infrastructure for biobased production	LCo, SMEs	/	• Consider building mobile or smaller, decentralised biorefineries or opt for specialisation and invest in production plants for biobased products that only require 1 or 2 plants (e.g. biobased acrylic acid) • *[LCo, SME]*	• Consider building mobile or smaller, decentralised biorefineries or opt for specialisation and invest in production plants for biobased products that only require 1 or 2 plants (e.g. biobased acrylic acid) • *[LCo, SME]*

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
Bureaucracy and lack of information on financial opportunities (e.g. EU and national grants)	LCo, SMEs, RTO, U	• Improve visibility of incentives and IB in general *[EA, NA]*	/	/
Soft Knowledge Infrastructures				
Discrepancy between research objectives in academia and industry needs	U, RTO, LCo, SME	• Prioritise funding according to the potential of the technologies to increase the chance that biobased products reach the market [EA, NA]	• Prioritise funding according to the potential of the technologies to increase the chance that biobased products reach the market *[EA, NA]*	/
Lack of integration processes	U, RTO, LCo, SME	/	• Foster funding models that encourage joint and integrated research between industry, universities and research organisations regarding the issues of bioconversion, DSP and product recovery *[EA, NA]*	/
Knowledge transfer	LCo, SME, U, RTO	• Companies and research centres working closer together *[LCo, SME, U, RTO, EA, NA]*	• Improvement of process knowledge *[LCo, SME, U, RTO, EA, NA]*	/

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
Limited engineering knowledge	LCo, SME, U, RTO	• Improve the knowledge infrastructure and knowledge transfer • Multi-disciplinary R&D community • Increase the engagement of chemical engineers *[LCo, SME, U, RTO, EA, NA]*	• Have a greater bio-processing focus in degree courses *[LCo, SME, U, RTO, EA, NA]*	/
Full extent of problems in DSP has not been identified	LCo, SME, U, RTO	• Improve the knowledge infrastructure and knowledge transfer • Multi-disciplinary R&D community • Increase the engagement of chemical engineers *[LCo, SME, U, RTO, EA, NA]*	• Have a greater bio-processing focus in degree courses *[LCo, SME, U, RTO, EA, NA]*	/
Identifying the correct technology	LCo, SME, U, RTO	• Improve the knowledge infrastructure and knowledge transfer • Multi-disciplinary R&D community • Increase the engagement of chemical engineers *[LCo, SME, U, IO, RTO, EA, NA]*	• Have a greater bio-processing focus in degree courses *[LCo, SME, U, IO, RTO, EA, NA]*	/
Producers not knowing all the available technology	LCo, SME, U, RTO	• Improve the knowledge infrastructure and knowledge transfer • Multi-disciplinary R&D community • Increase the engagement of chemical engineers *[LCo, SME, U, IO, RTO, EA, NA]*	• Have a greater bio-processing focus in degree courses *[LCo, SME, U, IO, RTO, EA, NA]*	/

Hurdles	Stakeholders involved	Short term actions	Mid-term actions	Long term actions
Assess where impurities can be accepted (governments, branch associations and NGOs)	LCo, SME, U, RTO	• Improve the knowledge infrastructure and knowledge transfer • Multi-disciplinary R&D community • Increase the engagement of chemical engineers *[LCo, SME, U, IO, RTO, EA, NA]*	• Have a greater bio-processing focus in degree courses *[LCo, SME, U, IO, RTO, EA, NA]*	/

6 Annexes

Annex 1. Additional Literature Sources

European Commission (February 2012), "Innovating for Sustainable Growth: a Bio-economy for Europe.

Technology Development for the Production of Biobased Products from Biorefinery Carbohydrates—the US Department of Energy's "Top 10" revisited Joseph J. Bozell, Gene R. Petersen March 2010

National Bioeconomy Blueprint. The White House, USA Apr 12

Roadmap for the Development of a Knowledge-Based Bio-Economy in North Rhine Westphalia. Capgemini Consulting / Ministry of Innovation, Science and Research of the German State of North Rhine-Westphalia Nov 10

Bio-based Empfehlungen zum Aufbau einer wettbewerbsfähigen und nachhaltigen Bioökonomie -- Beitrag der Industriellen Biotechnologie zum wirtschaftlichen Wandel in Deutschland

Treffenfeldt, W. and Fischer, R. and Heiden, S. and Hirth, T. and Maurer, K.-H. and Patermann, C. and Schäfer, T. and Schmid, A. and Sieden, C. and Weuster-Botz, D. und Zinke, H. 2010

Biotechnologie von morgen DECHEMA Biotechnologie Zukunftsforum 2011

Bio-based Chemicals – Value Added Products from Biorefineries. Ed de Jong and Adrian Higson and Patrick Walsh and Maria Wellisch Feb. 2012

Biorefinery Roadmap Bundesregierung (Wagemann et al.) June, 2012

KET - Industrial Biotechnology Sherpa Group a.o. June, 2011

National Research Strategy BioEconomy 2030 biotechnologie.de for Bundesministerium für Bildung und Forschung (Federal Ministry for Education and Research) 2011

SusChem Vision and SRA SusChem 2005-2006

Technology Roadmap - Biofuels for Transport Anselm Eisentraut and Adam Brown and Lew Fulton and Jana Hanova and Jack Saddler and Paolo Frankl and Didier Houssin and Bo Diczfalusy

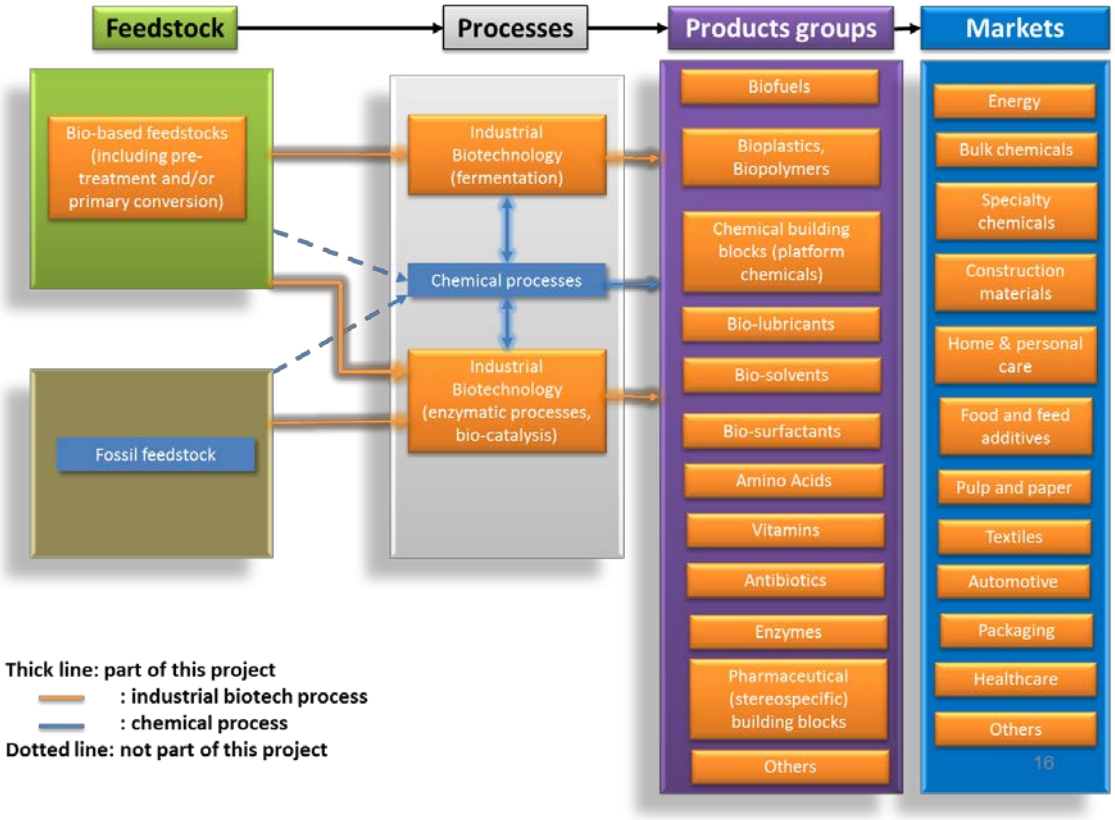
Stakeholder Interviews

Annex 2. Choice of Business Cases

The scope of the BIO-TIC-project is the industrial biotechnology (IB) value chain (Figure 12). While BIO-TIC aims to develop roadmaps with a scope that covers the wider IB market and value chains, it takes a focused approach in analysing the main hurdles, enablers and required actions towards realising IB's potential for Europe. It has been decided to focus the analyses on a limited number of five complementary "business cases for Europe", each of which represent different products and application areas, such that they enable the project partners to discover the widest possible hurdles and enablers that are relevant for the European IB market.

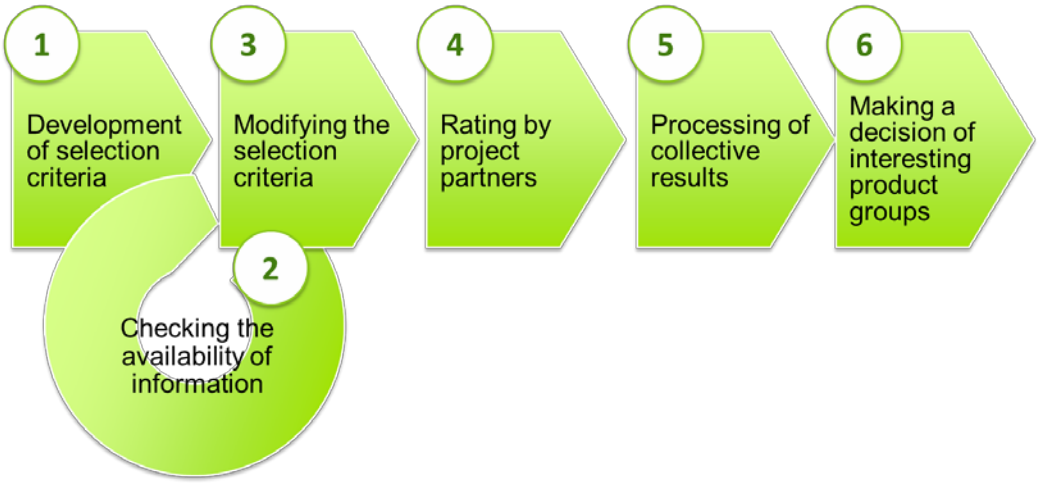
The 5 business cases represent product groups that can make a major contribution to an accelerated take-up of industrial biotechnology into the market place. The selection process and criteria are explained below.

Figure 12. The Industrial Biotechnology Value Chain



The business cases for the roadmaps were selected based on a product group-specific rating carried out by an expert panel comprised of BIO-TIC partners and validated by the Project Coordination Committee and the Advisory Committee of the project. The process included (1) Development of selection criteria, (2) Checking the availability of product group and criteria -specific information with the project partners, (3) Making modifications to the list of criteria on the basis of observed information gaps, (4) Collection of partners' ratings, and (5) Processing of collective results. Finally (6), a decision was made on the most interesting product groups by the Project Coordination Committee and the Advisory Committee of BIO-TIC. The process is summarised in Figure 13.

Figure 13. The Selection Process



In accordance with the aim to identify business sectors that can contribute to the take-up of IB, the selection criteria focused on the potential of IB and on the future market value of the product groups. However, other criteria were considered, too. In fact, the selection criteria represented a continuum from identified societal/consumer needs to market solutions that respond to these needs, to enabling technologies that facilitate these market solutions, and to resources that are needed to support these technologies (Figure 14).

Figure 14. The Selection Criteria

Category	Criterion	Indicator
Societal / Consumer needs	Environmental impacts	• Savings in GHG emissions
		• Improvement in resource efficiency
	Societal impacts	• Value added in the EU
		• Need for incentives
		• Political/ethical disputes
		• Effects on employment
Market solutions	Critical mass	• Predicted IB/bio-based market growth in the EU in 2010-2030
Enabling technologies	Potential for breakthrough	• Potential of IB to change the market through innovation in the next 10 years
Resources needs	Access to biomass	• Availability of biomass in the EU
	EU competitiveness	• EU competitive advantage

Based on the rating of BIO-TIC project partners, the short list of most promising product groups in order of ranking were:

1. Biobased polymers and plastics
2. Chemical building blocks (platform chemicals)
3. Biofuels
4. Enzymes

5. Pharmaceutical (stereospecific) building blocks
6. Biosolvents
7. Biosurfactants

In discussion with the Project Coordination Committee and the Advisory Committee, minor modifications and correctives were made:

- Biofuels were further narrowed down to bioethanol (primarily as a test case to illustrate the effect of subsidies and regulations on markets) and biobased jet fuels (which have great potential future impact)
- Enzymes were determined to be cross cutting, and should be considered as part of all the 5 selected business cases rather than a business case as such
- Pharmaceuticals were disregarded due to the extensive regulatory hurdles in this industry.
- Biosurfactants were chosen instead of biosolvents because the latter would be partly tackled in the context of chemical building blocks
- A new category of CO_2 for biotechnology (CCU = Carbon Capture and Utilisation) was tabled, as it could have a huge impact on the industry, lead to diversification away from biomass as a feedstock, and impact on the society and the environment. The dogma of a need of biomass for non-fossil liquid fuels or chemicals is not any longer true with CCU technologies

The final list of business cases, as agreed and validated by the Advisory Committee, is comprised of 4 business cases that are from biobased origin:

1. Advanced biofuels: bioethanol and biobased jet fuels
2. Chemical building blocks[28]
3. Biobased polymers
4. Biosurfactants

In addition, one business case is based on a fossil raw material (with IB processes):

5. CO_2 as a feedstock: Using IB as tool for reducing CO_2 generated from processes using fossil or biobased raw materials (Carbon Capture and Utilisation)

[28] A decision was made to have a closer look at 5 platform chemicals and these were later defined as Succinic acid; Isoprene; 3-hydroxypropionic acid (3-HPA); 1,3-propanediol (1,3-PDO); and Furfural.

Annex 3. Methodology for R&D Roadmap

Drafting the roadmaps in the BIO-TIC project consists of different steps, each with a different empirical basis. See Figure 15 below.

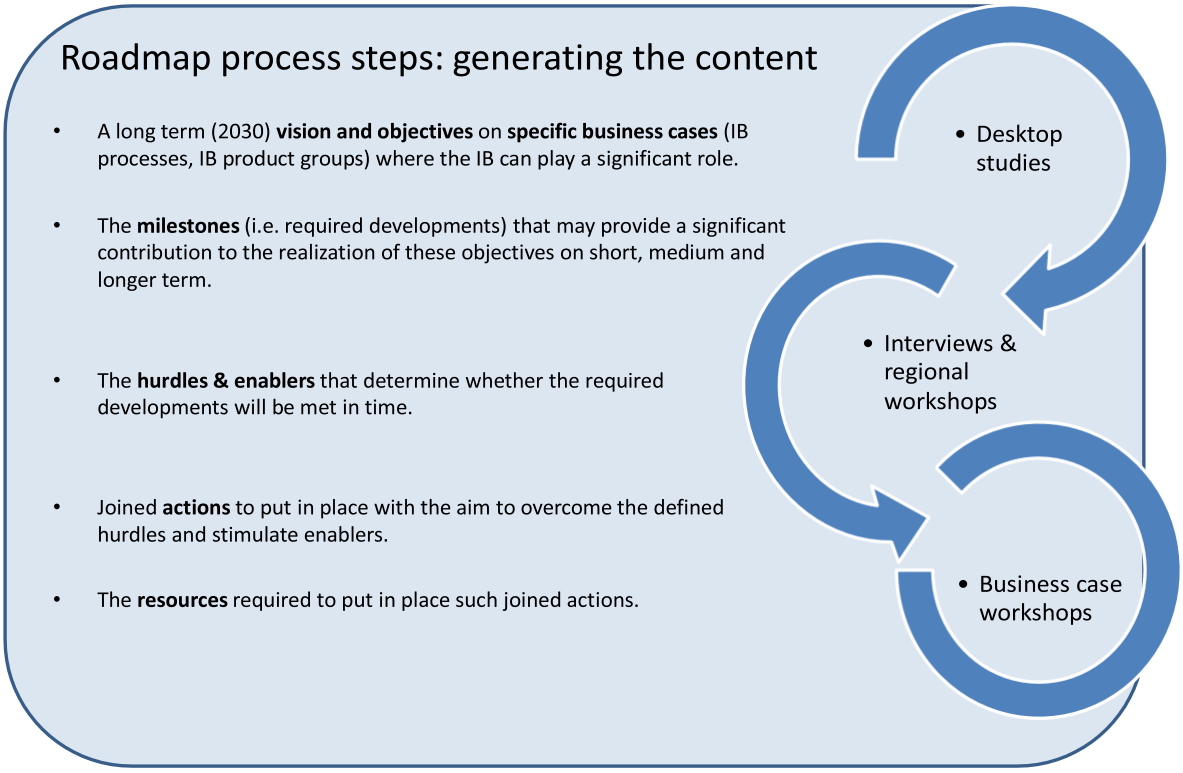


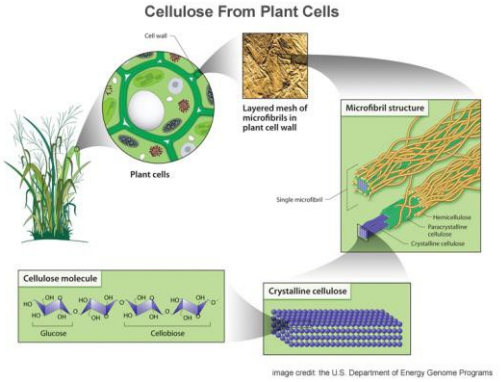
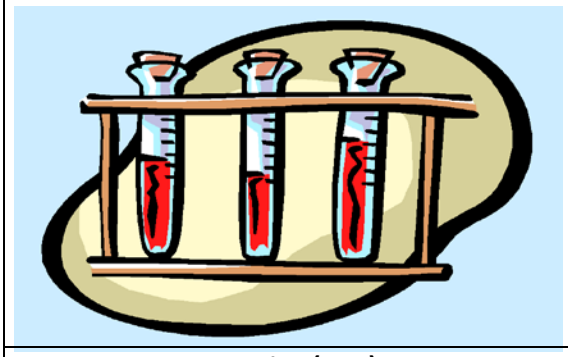
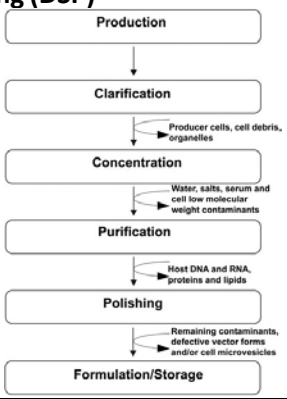
Figure 15 Roadmapping Methodology Summary

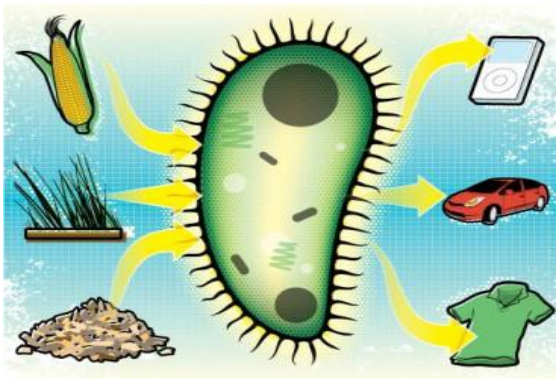
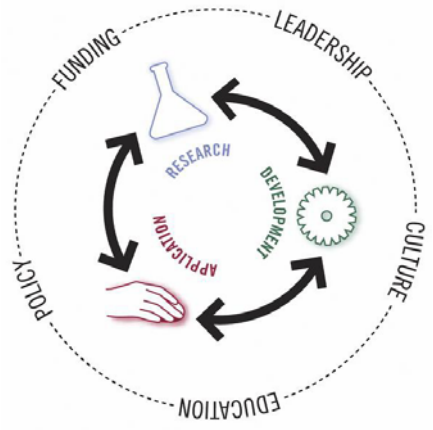
The empirical basis for the 1st draft R&D roadmap consisted of:

- Literature study of vision documents, roadmaps and technical literature (see references)
- Oral communications with various experts from outside the project
- Vision building workshop with several experts from within the project

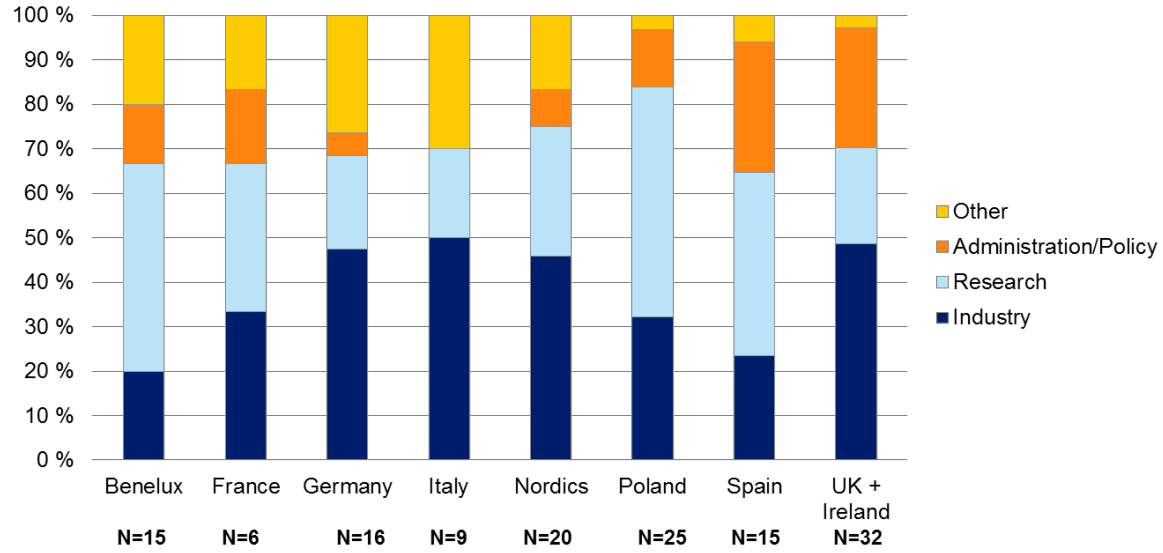
In Table 13 an overview is given of the six R&D topics determined based on the literature study.

Table 13. R&D Topics as Distilled from a Broad Range of Literature Sources

R&D topic	Definition
Feedstock supply 	Topics related to biomass cultivation, logistics, pre-treatment.
Bioconversion 	Topics related to biochemical conversion through biocatalysts, microorganisms.
Downstream Processing (DSP)  	Topics related to biotech process development, e.g. product recovery, water management.

Products & markets 	Topics related to valorisation, commercialisation and development of products.
R&D tools 	Topics related to development of tools supporting R&D, like the development of models and databases.
Knowledge infrastructure – hard 	Topics related to installation of pilot facilities, connections to existing physical infrastructure.
Knowledge infrastructure – soft 	Topics related to funding, entrepreneurial climate, presence of knowledge sharing and open innovation models.

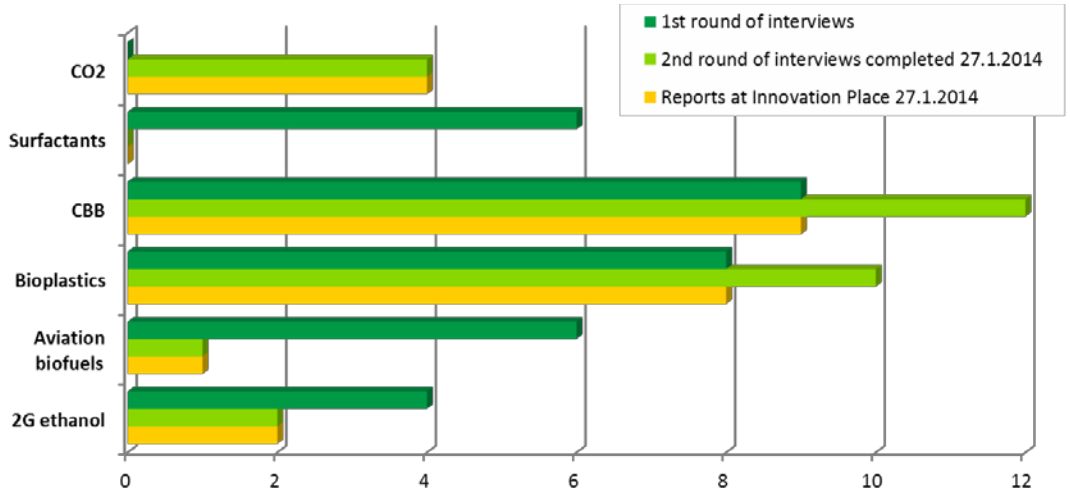
The 2nd draft R&D roadmap is based on the validation of the findings of the 1st roadmap by means of 8 regional workshops and various stakeholder interviews. The BIO-TIC partners have held workshops in eight different countries in order to depict the regional characteristics of France, Germany, UK & Ireland, Italy, Spain, Finland, Benelux and Poland. The agenda of each day generally included a series of presentations explaining the BIO-TIC project and its non-technological, technological and market roadmaps; and a second more interactive part consisting of breakout sessions and exercises to identify hurdles and solutions for IB in Europe. The workshops have brought together more than 140 participants representing industry, academia and policy-makers in the IB sector. Figure 16 below shows the fairly well balanced participant backgrounds throughout the workshops.



* Stakeholder group "Other" mainly includes representatives of regional development agencies, tech transfer offices, networking organisations and consultancies

Figure 16. Overview of Type of Stakeholders Attending the Regional Workshops

The workshops inevitably raised a lot of specific questions but also presented several solutions. So as to further investigate the insights of the workshops, a series of stakeholder interviews were conducted. Up to this stage, nearly 60 interviewees gave their expert opinion and input for the 2nd draft roadmaps. These interviews were, in large part, held anonymously in order to give the respondents enough flexibility to give the most honest and relevant information possible. The Figure 17 shows the business cases and indicative timetable of the completed interviews:



Note: Some companies have been interviewed on several value chains, and are therefore present in more than one column.

Figure 17 Number of Interviews per Business Case

In chapter 5 each above-mentioned R&D topic is further explained as well as the hurdles, enablers and actions for the further development of Industrial Biotechnology in Europe. Each topic covers **both hurdles and enablers**.

Hurdles are defined as characteristics/activities that are currently in place (or will be in very short term) and (potentially) contribute negatively to (R&D) developments/the development of the business case. Hurdles are seen as **the main bottlenecks in the development of the business case within Europe**.

Enablers are defined as characteristics or activities that are currently in place (or will be in very short term) and (potentially) contribute positively to (R&D) developments/the development of the business case. Enablers are seen **as incentives and/or preconditions for potential breakthroughs for the development of the business cases within Europe**.

Insights on the Methodology of the R&D Roadmap

- The state of the art analysis, as currently done, provides a rough overview. For product / technology area's it is hard to find specific information from literature and the regional workshops and interviews focused on the validation of the hurdles. Therefore the business case workshops should be used partly to validate the state of the art descriptions and maybe some additional interviews with experts are needed;
- It turns out to be very hard to find reliable information that can be used to define milestones. We will probably have to rely on expert judgment for this. The business case workshops will be key to provide such knowledge;
- We have observed that the current vision provides insufficient direction to choices to be made on the level of business cases. In the end, the BIO-TIC roadmap should represent a strategy for Europe.
- The question is then primarily what role EU should take, given its current strengths and weaknesses? The following possibilities should be explored:
    - **Leapfrogging:** Will Europe invest in the commercialisation of technology generations not yet developed in the USA or Asia? (skipping 1G and 2G, moving directly to 3G technologies)

- **Follow the leader(s):** Will Europe be a supplier of key technologies (e.g. enzymes) to USA or Asia?
- **New factories or retrofitting existing assets:** Will Europe develop new plants or is it possible to retrofit existing capacity?
- **Feedstock is crucial:** How will Europe deal with the geographical fact that arable land area is limited compared to competitors?

Annex 4. Description of Microbiological Process Development

Microbial process development starts with finding a microorganism that produces the target bio-product with the highest (theoretical) yield. After identification of a suitable production strain, microbial strains have to be optimised to maximise production of the target product, a process called strain development. Strain development involves re-wiring of the microbial metabolism to accommodate maximal production and secretion of single and pure target product while eliminating target product degradation and preventing byproduct formation. The microorganisms are grown in very large vessels called fermenters. Microbial growth and production of the target product is ensured by supplying these fermenters with optimised nutrient media and culturing conditions (temperature, pH, oxygen levels), a process called fermentation. The next step is to separate and purify the target molecule from the nutrient mix. Depending on the nature and future purpose of the extracted compound, additional downstream processing may be required. For example, fungal strains can produce the chemical building block 3-hydroxypropionic acid, which may subsequently be converted to acrylic acid, a commonly used constituent of polymers.

Prepared by:	TNO
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