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TOWARDS BIO-PRODUCTION OF MATERIALS: REPLACING THE OIL BARREL

This report partially fulfils the requirements of Module 3.1 Bio-production, Theme 3.1.3 Replacing the Oil Barrel, of the Programme of Work and Budget (PWB) of the BNCT for Biennium 2015-2016, see Figure 1 of [DSTI/STP(2014)39].

It incorporates changes requested subsequent to the Fourth Session of BNCT in December 2016 and the Fifth Session in May 2017.

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For further information, please contact: James Philp; Email: james.philp@oecd.org

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This revision of report [DSTI/STP/BNCT\(2016\)17](#) partially fulfils the requirements of Module 3.1 Bio-production, Theme 3.1.3 Replacing the Oil Barrel, of the Programme of Work and Budget (PWB) of the BNCT for Biennium 2015-2016 (see Figure 1 of [DSTI/STP\(2014\)39](#)). It incorporates minor changes requested subsequent to the Fourth Session of BNCT in December 2016 and the Fifth Session in May 2017.

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TOWARDS BIO-PRODUCTION OF MATERIALS: REPLACING THE OIL BARREL

EXECUTIVE SUMMARY

1. The entry into force of the Paris Agreement on November 04, 2016¹ shows the desire for the world to move away from fossil-based production and energy. To replace fossil-based production the options are very small. It is not a case of replacing carbon, it cannot be – the vast plethora of products in the market e.g. polythene bags, glues, lubricants, greases, solvents, detergents, cleaners, paints either have to dematerialise or they will be made from an alternative form of carbon. The only possible source of renewable carbon in very large volumes is bio-based. Hence bio-based production of materials with lower carbon footprint will become a major form of production of the future.

2. This paper also looks at the most immediate policy goals of bio-based production. These are (in no particular order): the future growth of OECD chemicals industries; rural development and regeneration as a means of building productivity, and; the circular economy. All of these are policy goals that will require a lot of attention from a wide range of policy makers. That creates the potential for large and expensive overlaps, inconsistency and policy lock-ins. At a more micro-level, bio-production of fuels and energy has clear-cut policy goals. The greater breadth of goals for bio-based materials production could cause an antagonism of policies that needs careful attention and coordination among ministries, departments and regions.

Who should read this?

3. A great deal of public policy has already been dedicated to biofuels and bioenergy, not always with the best outcomes. Bio-based production of materials (e.g. chemicals, plastics, textiles) represents far greater economic opportunities (e.g. job creation and value-added) than biofuels and bioenergy, and yet bio-based materials have all but been ignored in public policy beyond R&D subsidies. Therefore this paper looks into various immediate issues in public policy for bio-production. It looks across different areas of policy; supply and demand-side issues, technology push, market pull.

4. Unlike other papers in this series that deal with the more global issues of biomass sustainability and the regional issues of bio refinery models and policy, this paper has a greater focus on national R&D as R&D subsidies are still at the forefront of issues for public policy makers.

5. Some specific issues, especially those of capacity building, have greater significance for regional governments/local authorities. The distributed manufacturing model has become married to rural regeneration. Building bio refineries in regions is one thing; building the industrial ecosystems of actors from the foresters and farmers through hauliers, logistics, waste management companies, technology SMEs, regulators, standards organisations, investors and several other key intermediaries is best done by regional policy makers, but they may lack the experience required for these kinds of activities.

¹ http://unfccc.int/paris_agreement/items/9444.php

What is meant by “replacing the oil barrel”?

6. The title of this report is “Towards Bio-Production of Materials: Replacing the Oil Barrel.” Liquid fuels such as diesel, petrol and aviation fuels are not the primary concerns of this paper. They have been dealt with by several other organisations over the years. They are not ignored here, but they are not the primary focus.

7. To grasp the goal of this paper, it is important to understand the importance of chemistry in modern life. The chemicals industry produces around 70 000 different products that touch on virtually all manufactured goods. In addition, the petroleum industry produces both fuels and chemicals. Chemistry forms the backbone of virtually all manufacturing.

8. If chemistry is so important, then why speak of replacing the oil barrel? The answer lies in most of the societal grand challenges – at least energy security, food security, resource depletion and climate change. Over the years, the OECD has repeated that climate change is one of the greatest challenges to be faced. The chemicals industry is one of the greatest industrial contributors of greenhouse gases, and is also very energy-intensive. At the same time, the chemicals industry has always been very innovative. Several sources of evidence indicate that bio-production can make significant savings in greenhouse gas (GHG) emissions. At the same time, a view from the chemicals industry now is that the need to reduce emissions and energy use will represent business opportunity in human history (Cayuela, 2013).

9. Green chemistry has its place in reducing the environmental footprint of the chemicals industry but its convergence with industrial biotechnology offers huge potential. Green chemistry refers to chemical production using more environmentally friendly catalysts and conditions, such as lower temperature and pressure, and producing fewer emissions. Industrial biotechnology refers to using renewable materials as feedstocks and biotechnology as the route of production.

10. This is ultimately what is meant by replacing the oil barrel – not seeing grand challenges as insurmountable economic problems, but the chance to rebuild industry and society in a sustainable manner, bringing jobs and value-added through exploitation of biomass rather than fossil resources. The US sees this as a *vision of the future* in the US because “*the core petroleum-based feedstock is a limited resource and diversification of feedstocks will provide even greater opportunity for the chemical manufacturing industry*”.

Bio-based production is becoming more visible

11. Only five years ago there was more talk of ‘molecules’ than ‘products’. There are now many more tangible products which make the life of the policy maker easier as tangibility is important in public acceptance. This report showcases the burgeoning inventory of bio-based products. The real test is in the ability to scale production up to a level that can affect a market. Chemistry leads biotechnology in the production of ‘green chemicals’. A key value of this report is identifying the causes of bottlenecks in bio-production and how these bottlenecks can be overcome.

The level playing field is still a leading policy issue

12. The level playing field operates on more than one level. First of all, massive policy support for biofuels and bioenergy has typically left bio-based materials at a disadvantage: for example, biomass procurement systematically allocates biomass to fuels and energy and not to bio-based materials, which counters the philosophy of the integrated bio refinery where all three are produced in the same production complex. On another level is the lack of a carbon price and massive fossil fuel subsidies that totally distort the markets for fossil products, making the competition of bio-production on price exceedingly difficult.

13. A mechanism to bring bio-based materials into alignment with biofuels policy is suggested. It is constructed in a way that addresses both environmental performance and cost-efficiency for the taxpayer. It is suggested that it would also stimulate R&D in the direction of making the most efficient bio-based chemicals (in terms of GHG emissions reductions) in the most efficient bioprocess (in terms of cost for the manufacturer). It specifically addresses high-volume, low-value chemicals because these have the greatest impact in replacing the oil barrel and in emissions reduction. These are precisely the chemicals that are unattractive to the young bio-based industry as it is extremely difficult to synthesise them efficiently at scale in competition with the petrochemicals industry. Nevertheless, the R&D investment portfolio needs to include both high-volume, low-value and low-volume, high-value products. Companies need both types of products to maintain stability, make a profit and hedge economic and market fluctuations.

Capacity building in industrial biotechnology: a matter for regions as well as national governments

14. The report examines what has been done in some OECD nations to build capacity in industrial biotechnology. They, of course, vary in approaches but with some common themes. Some have dedicated bio economy strategies; others have policy initiatives that clearly aim at creating a bio economy. Centres of excellence have emerged through public funding. In all countries that provided information, the creation of regional clusters has been part of the strategy without exception.

15. The regional cluster concept is simple – bring actors together in regions to help make the supply and value chains in cooperation with the private sector. The members then can expand the clusters by applying for grants and other financial measures to create collaborative projects and new alliances. The real strength in clusters should be the ability to coordinate multiple functions in capacity building, in particular research, demonstration, technology transfer, dissemination and training activities. Ideally the system snowballs to financial self-sufficiency and the regions become joined up. International clusters start to appear by alliance of existing clusters. Regional clusters as a policy mechanism have risks, however. This report also examines what metrics are needed to assess the effectiveness of clusters, and offers more general advice for governments.

Forming and fostering spin-outs

16. In the first instance, governments must fund the relevant R&D in public research institutes and universities. Measures are needed to encourage the creation of spin-out companies, which are faced with years of no or few revenues and high-risk research: a top industrial R&D priority must be to reduce the innovation cycle to a timescale attractive to investors. Industrial biotechnology differs from other biotechnologies in the need for large, expensive and untried production facilities. The IT sector, for example, does not suffer from these long periods of high-risk research.

Market making

17. Markets have long been recognised as important drivers of innovation. The absence of long-term framework support and policy predictability in many OECD countries continues to make the bio economy sectors and bio-based production high-risk investments. Some countries and regions, e.g. Brazil, China, South East Asia have also benefited from more predictable regulatory environments and lower energy costs, sometimes combined with significant incentives and offers of longer term commitments. Public procurement has long been seen as an effective mechanism for market making, but there are complicating issues for bio-based materials.

Roles for Intermediate Research Organisations

18. A study examining alternative financing mechanisms for “exploratory development” consistently point towards the intermediate research organisation (IRO), such as: CSIRO in Australia; the German

Fraunhofer Society; the VTT Technical Research Centre of Finland, and; the Electronics and Telecommunications Research Institute of Korea. They can hold a special place in bio-production due to the need for large, expensive pilot and demonstration facilities that are not needed in other areas of biotechnology. Examples are given where this is already working, including CSIRO, Fraunhofer, the UK Catapult Centres, RIKEN in Japan and the Korea Research Institute of Bioscience & Biotechnology (KRIBB).

Various approaches at the national level

19. Belgium, England and Wales, France, Germany and Italy provided evidence of the ways in which they are building capacity in industrial biotechnology. Differences and similarities exist. A common denominator of these countries is the importance of the chemicals sector to all of them. For example, France has 156 600 direct industrial chemistry jobs, with many more indirect jobs depending on chemistry. By 2017, it is expected that 15% of the raw materials used in the industry's processes will be plant-derived in France. Already France has 23 000 direct jobs in plant-based chemistry, with an expectation of another 19 000 by 2020.

Education and training for industrial biotechnology: a specific issue in capacity building

20. Every country faces the challenge of insufficient people with the skills set required for the challenge ahead. Some of the issues are already old: PhDs are trained in a manner incompatible with industry needs; universities educate by discipline and lack multi-disciplinary approaches; there is a lack of apprenticeships to create a workforce outside of research. However, clearly identifiable gaps exist in the market: there is a lack of automation engineers, biochemical engineers are in shortage and there are very few people who can deal with experimental design when faced with huge amounts of data. Effectively what can be seen is a dislocation between the scientific method and the engineering method. For industrial biotechnology to become a force in production, engineering principles such as standardisation, abstraction, separation of design from manufacture will have to be embraced.

Measuring the impact of the bio economy

21. In these very early days accurate data on the impact of industrial biotechnology on the bio economy and beyond are lacking. There has been an attempt in Europe to quantify the jobs and turnover in the European bio economy. The figures look impressive, but statistical challenges exist. Fundamentally, there are different definitions of the bio economy. Mixed terminologies confuse the situation. There are many different sectors involved, and data are not comparable. The chemicals, plastics and pharmaceuticals sectors include a multitude of fully bio-based (e.g. natural dyes and pigments, enzymes, fatty acids) and partly bio-based products (different chemicals and plastics that are traditionally petro-based but in recent years have become also partly bio-based). For governments to be able to demonstrate growth of the bio economy, these fundamentals need agreement and harmonisation so that verifiable comparisons across nations can be made.

22. The European study concluded that bio-based materials such as chemicals, plastics and textiles offer much greater potential for employment and value added than biofuels and bioenergy. Governments should now prioritise data collection according to agreed definitions and terminology, and identify the national and regional agencies responsible for data collection.

Bio-based production: what are the bottlenecks and what can governments do about them?

23. The commercial successes of technologies such as metabolic engineering remain dwarfed by the research successes. This suggests a serious lack of return on public investment. There are reasons that can be identified that are very specific. Among these progress lacks in: biomass pre-treatment, especially

consolidated bioprocessing (CBP); conversion of C1 compounds to materials; computational enzyme design; minimal cells for bio-contained microbial factories; ‘robustness’ (the ability of microbial catalysts to tolerate the conditions of a bioprocess); titre, yield and productivity; gene and genome editing in production strains. Governments can look to addressing these in specific R&D subsidy programmes for precompetitive research. They might also consider the case for companies in nearer-market research as the typically industrial issues such as productivity are proving to be intractable fundamental issues.

IT/computational convergence: removing the boundary between bioscience and engineering

24. A great deal of accumulating evidence shows that there needs to be greater convergence between industrial biotechnology and IT/computation. In the engineering cycle (the iteration of ‘design-build-test’), the cycle in bio-production lags behind at the test part of the cycle because orders of magnitude more designs can be built (as a result of plummeting DNA synthesis prices) than can be tested. Older issues still abide, e.g. serious problems of reproducibility in biotechnology and synthetic biology. Manufacturing in the modern economy works because design and testing software can talk to manufacturing hardware via multiple layers of application programming interfaces (APIs). This points to the need for biotechnology to have its own high-level programming language(s) and software to transform the engineering design, testing, learning cycle.

25. Integration across technologies remains incomplete. Very few academic groups or companies achieve this today. An integrated technology platform encompassing metabolic modelling, high-throughput pathway and strain construction, quantitative small scale screening, and systems biology, all of which intimately link to fermentation and process engineering, would replace the fractured approach that currently exists. In other words many groups of people can investigate individual components, but very few have all the components linked in a systems approach to manufacturing. There are many places where software, computation and machine learning can help to make this happen. For example, the large number of metabolic engineering studies could provide an invaluable database for capturing information on titre, yield and productivity in response to genetic and fermentation conditions. This could be built into machine learning models, which increasingly remove human involvement in the design-build-test cycle. The day should come when the results of one round of ‘test’ iteration should inform the next round of ‘design’ without human intervention.

26. For policy makers, R&D subsidies alone do not solve the issues as the lack of suitably trained and qualified people remains important. Simply adding new techniques such as CRISPR will not solve the problem. In fact, without attention to removing the barriers and moving towards standardised systems, adding new biological techniques could create further distance from a manufacturing future. As with many issues in this paper, a combination of technologies and a combination of skills sits at the heart of the matter. If one phase were to sum up the situation for the policy maker, it is ‘removing the boundary between bioscience and engineering’.

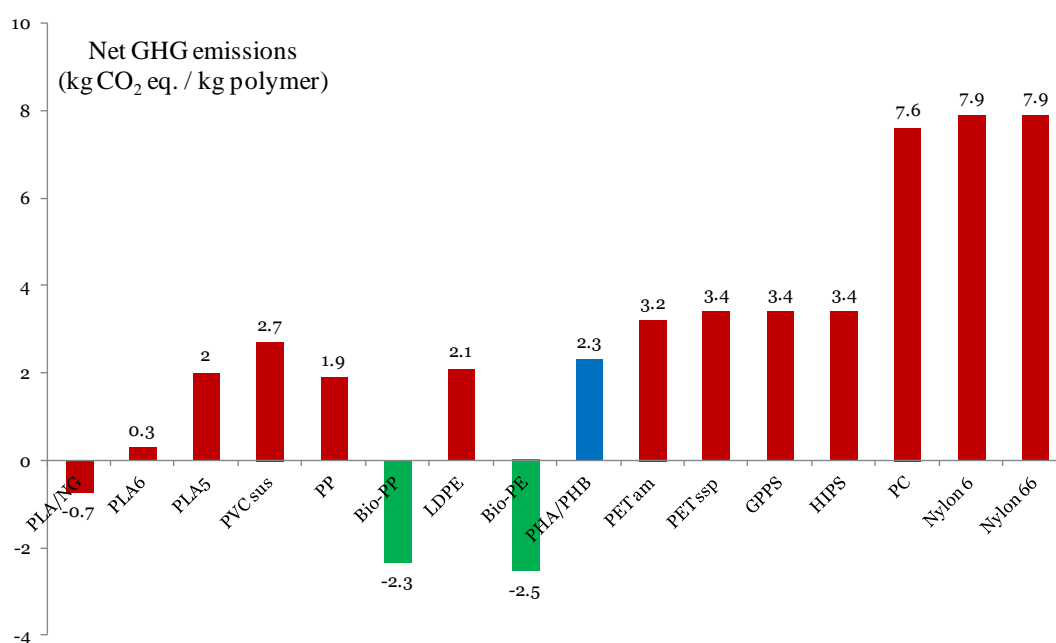
INTRODUCTION

Why replace the oil barrel?

27. This paper pertains mainly to chemicals obtained from the oil barrel rather than fuels. Biofuels are dealt with by several other organisations, including the International Energy Agency. Fuels are not ignored in this paper and the roles of biofuels and bioenergy in meeting national and international emissions reductions are recognised. However, bio-based materials have in past been overlooked in public policy support (OECD, 2014a) and this oversight should be corrected. Chief among these are the environmental credentials (see Box 1) of bio-based materials (e.g. Adom et al., 2014; Hermann et al., 2007; Dornburg et al., 2008; Weiss et al., 2012; Hoefnagels et al., 2013). Resource depletion, principally a remarkable reduction in new conventional crude oil finds (Owen et al., 2010, *Financial Times*, 2016), is another such driver that has been well covered, as is energy security (OECD, 2014a).

Box 1. Environmental performance of bio-based materials

An important aspect of plastics manufacture is GHG generation and its impact on climate change. The projections of the Intergovernmental Panel on Climate Change (IPCC) for stabilisation of atmospheric GHG concentrations at 450 ppm CO₂ by 2050 requires reductions in emissions of 80% compared to the 1990 level (Barker et al., 2007), a huge challenge. Several countries have adopted targets for such large reductions in GHG emissions (Williams et al., 2012), and part of the policy process for many countries is the development of a national strategy for a bio based economy. The wide range of estimates of GHG emissions savings from bioplastics leads to uncertainty about the environmental value of the bioplastics industry as a whole, which could in part be addressed by the measurement and modelling of likely impacts.



Source: various as detailed. Red bars are from Jamshidian et al., 2010; green bars are figures released by Braskem for their bio-equivalents of polyethylene and polypropylene, found in Smith, 2010 and Tullo, 2010; the blue bar is an average taken from three different papers for polyhydroxyalkanoate copolymers or specifically for polyhydroxybutyrate – Gerngross, 1999; Harding et al., 2007; and Kurdikar et al., 2001).

Weiss et al. (2012) compared cradle-to-grave GHG emissions associated with conventional and bio-based

chemicals, based on a total of 44 LCA studies covering approximately 60 individual bio-based materials and 350 different life cycle scenarios. They found that the bio-based materials save, on average, 55 +/- 34 MJ non-renewable energy and 3 +/- 1 kg CO₂ per kg material compared to their fossil-based counterparts.

However, LCA studies on bio-based product GHG savings abound. An observation from the Weiss paper is large variability in the calculations, which results from differences in background assumptions, system boundaries, and methodologies in the LCA calculations. All can differ in different studies, and the results are not easy to compare. Also most such studies deal with ethanol, polylactic acid (PLA) or polyhydroxyalkanoates (PHA). Another limitation is that bioprocess data are often limited.

Hermann et al. (2007) attempted to standardise cradle-to-grave methodology to compare the environmental impacts of various bio-based chemicals with their fossil-based equivalents (below).

Potential worldwide annual production and best case GHG savings of nine bio-based chemicals, with corn starch feedstock and using cradle-to-grave analysis.

Product	Annual GHG savings (kt CO ₂ /year)	
	Today	Future
Acetic acid	N/A	9570
Acrylic acid		4380
Adipic acid	N/A	7880
Butanol	3040	9610
Caprolactam		20 100
Ethyl lactate	1580	2220
Ethylene	191 050	245 710
Lysine	1370	2280
Succinic acid	6070	6780

Note: The analysis did not account for future chemical industry changes.

Source: Hermann et al. (2007).

They showed that the potential GHG savings for current technology and corn starch as feedstock was already 45% compared to the fossil equivalents. The future saving potential is even higher if lignocellulosics or sugar cane are used as feedstocks.

Substantial further savings are possible in the future through improved fermentation and downstream processing, and improvements due to consolidated bioprocessing and synthetic biology are entirely in the future. They concluded that worldwide CO₂ savings in the range of 500-1 000 million tons per year are possible using future technology.

Sophisticated predictive modelling to 2030 in the Netherlands (Hoefnagels et al., 2013) indicates that the production of only three bio-based chemicals (ethylene, caprolactam and hydrogen) and second-generation biofuels can result in large reductions in CO₂ emissions (over 27% compared to 2006 values).

If such predictions become reality, then bio-based chemicals production offers excellent opportunities for mitigating GHG emissions and decreasing dependence on fossil energy sources. However, the variability in calculations is a serious impediment to bio-based production, and international standardisation is required for the credibility of the industry. Serious misgivings concerning the use of LCA as the sole tool in environment impact assessment have been raised (ANEC, 2012). The authors claim that in some cases European policy was based on flawed LCA results (e.g. biofuels). The subject merits further attention by policy makers.

28. But it is worth reiterating here that resource depletion affects many of the grand challenges. It is now necessary to see the opportunities of resource depletion rather than just the threats (Cayuela, 2013). Here lies ultimately what is meant by replacing the oil barrel – not seeing grand challenges as insurmountable economic problems, but the chance to rebuild industry and society in a sustainable manner, bringing jobs and value-added through exploitation of biomass rather than fossil resources. This has been explained as *a vision of the future* in the US because “*the core petroleum-based feedstock is a limited resource and diversification of feedstocks will provide even greater opportunity for the chemical*

manufacturing industry” (National Academy of Sciences, 2015). Even so, some countries such as Canada, with free access to oil-based resources at very low prices, are still accelerating their bio economies.

29. Less often discussed is the need for the OECD countries to keep their chemicals sector competitive. Whilst the environmental drivers, resource depletion and energy security are long-term policy issues, chemicals competitiveness in the OECD countries is often an immediate policy challenge.

30. Chemistry has enjoyed less policy attention and investment in recent years in OECD countries, despite the fact that it is a cornerstone of the economy of several large OECD member states. Of the top ten chemicals producing countries, six of them are OECD nations. World chemicals turnover was valued at over EUR 3 trillion in 2014 (CEFIC, 2016), representing a vast economic enterprise. Central to the modern world economy, the industry converts raw materials into more than 70 000 different products.

31. The importance of chemistry in job creation should also not be overlooked. Germany and France, the fourth and sixth largest industrial chemical manufacturers in the world, have 438 000 and 156 600 direct jobs in industrial chemistry respectively. The industry is well-known for creating many indirect jobs in the value chain, of the order of two to three times the number of direct jobs in Europe, perhaps even more in the US. The US chemicals industry directly employs more than 800 000 workers. The American Chemistry Council claims that chemistry in the US also creates over 5 million jobs in other sectors².

Declining fortunes of OECD country petrochemicals industry: bio-based to stay competitive

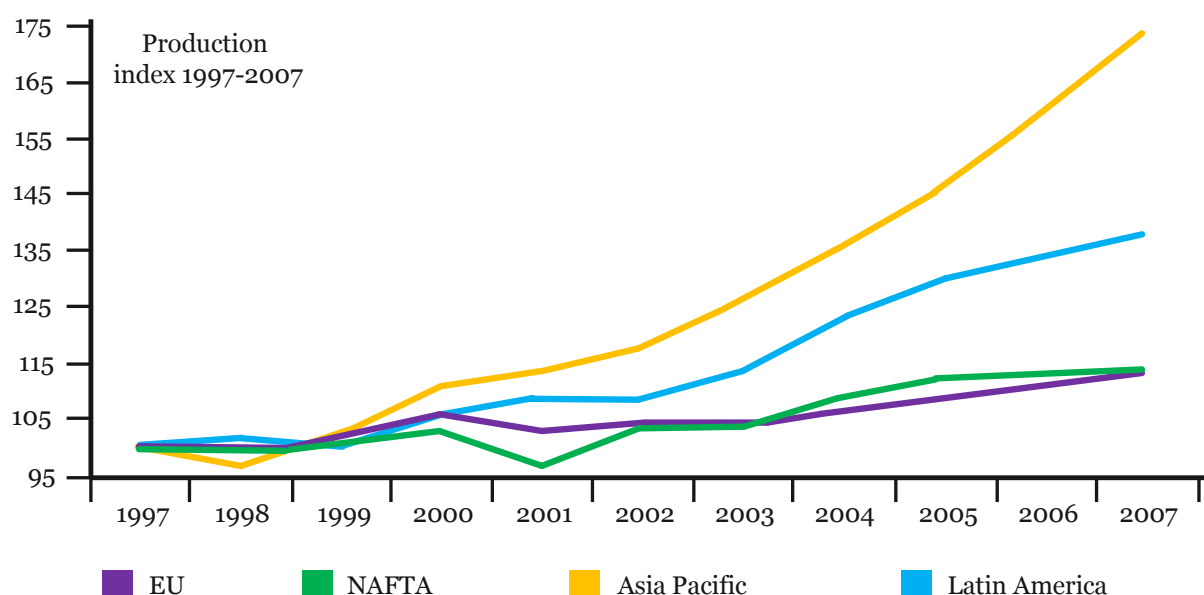
“Over time, the European chemical industry has seen a gradual change in its fortunes, with growing costs and a competitive market with many players. Faced with uncompetitive energy prices and stagnating demand, European chemical companies must adapt quickly or suffer the consequences. They will face continued tough competition from Middle Eastern, Chinese and, increasingly, US producers benefiting from cheap energy and feedstocks.”

Michael Smith, vice president at IHS Chemical, May 2014.³

32. Chemicals production growth pre-financial crisis warrants inspection (Figure 1). Worldwide competition has ratcheted up further in the last ten years. China holds the top ranking in sales, a position once firmly held by Europe. Chemicals sales in Asia have grown to more than double those of the European Union (CEFIC, 2016). Asia and the Middle East benefit from lower energy prices, and especially the Middle East is much closer to the raw materials. For example, the European textile industry has offshored to the Middle East and Asia for proximity to high-growth markets and benefit from lower manufacturing and logistics costs (KPMG, 2010). To stay competitive, the OECD chemicals industry must capitalise on its history of innovation. Coupled with strict emissions reductions objectives, bio-based production represents one way to do this.

² <https://www.americanchemistry.com/Jobs/>

³ <http://www.marketwatch.com/story/german-and-european-chemical-producers-expect-marginal-growth-but-face-headwinds-due-to-increasing-competition-feedstock-cost-disadvantages-and-business-climate-pressures-2014-05-13>.

Figure 1. International comparison of chemical production growth, 1997-2007

Source: Redrawn from KPMG (2010).

33. Europe has seen multiple refinery closures, and crackers are also closing. More will follow in the absence of cheap gas.⁴ The position of Italy is illustrative. Italy entered the global financial crisis with 16 refineries, and as of January 2015 this had been reduced to 11 (ISPI, 2015). According to a Platts analysis⁵, 7-10 new world-scale steam crackers are due to come online in the US over the next few years in the wake of shale gas. Nevertheless, with uncertainties over the lifetime of shale gas and light tight oil, the NAFTA countries must also look to their competitiveness. The loss of competitiveness in chemicals in OECD countries is summarised on Table 1. This should especially worry Japan.

Table 1. The competitiveness of countries in chemicals production.

Country/region	Competitiveness rank in 1992	Competitiveness rank in 2012
Saudi Arabia	4	1
US	1	2
India	6	3
EU	3	4
China	7	5
Japan	2	6
Brazil	5	7

Source: Oxford Economics (2014).

34. The chemicals industry has long been recognised for innovation (Colombo, 1980). One way for OECD chemicals sectors to remain competitive is through industrial biotechnology. With stricter energy

⁴ Financial Times, Feb 10, 2015: "The Grangemouth petrochemicals plant, Scotland's most important industrial complex, is unlikely to survive in the long term without the development of local shale gas resources, its owner Ineos has warned."

⁵ <http://www.platts.com/news-feature/2014/petrochemicals/europe-2014-outlook/index>

and emissions controls, the switch to bio-based chemicals enhances competitiveness. In France, for example, by 2017 there is an expectation that 15% of the raw materials used in industrial chemicals processes will be plant-derived.⁶

Other policy goals

35. Climate change mitigation, energy security and resource depletion are long-term issues for policy makers. The policy goals mentioned require immediate action. Taken altogether, the situation is ripe for policy clashes and contradictions. Coordination and alignment are key considerations.

Reindustrialisation

“Despite its declining share of EU GDP, manufacturing is widely acknowledged as the engine of the modern economy. This is due to its lead contribution to overall productivity; to its input to research and innovation, which is four times higher than its input to GDP; and to its multiplier effects on growth in the rest of the economy”.

European Commission, 2013

36. A policy goal for most OECD countries is for reindustrialisation⁷ to bring manufacturing jobs back,⁸⁹ but in the context of knowledge-driven reindustrialisation. For bio-based production, the decentralised, distributed production model is a central tenet. The distributed manufacturing ‘glocal’ bio-based model means establishing many interconnected local production plants that are integrated with other nearby industries to ensure that residues and wastes are fully utilised in different processes (Luoma et al., 2011). Indeed, Saygin et al. (2014) stated that the location of the plants (i.e. distance to the resource) and their access to biomass supply will be crucial to realising the potential of bio-based production. As well as feedstock production being local, and creating local jobs, the ‘industrial ecosystem’ so created hints at many indirect jobs associated with bio refining.

Rural regeneration

37. Reindustrialisation goes hand-in-hand with a policy goal for rural regeneration. Bio-production, instead of seeing traditional dependence on natural resource-based industries and routine manufacturing in rural areas in a negative manner,¹⁰ would use this as a strength to build high-technology manufacturing.

38. Tackling rural development is regarded as essential for achieving the United Nations Sustainable Development Goals (OECD, 2016). Whilst seen more as a problem of developing countries, there are OECD models to look to. The rapid transformation of Korea from developing status to one of the fastest-growing OECD economies in a generation was possible due to an unprecedented industrialisation process and a multi-sectoral rural development strategy. It invested in agricultural productivity, soft and hard

⁶ <http://www.iar-pole.com/cluster/organisation/state-regions?lang=en>

⁷ <http://www.eurekanetwork.org/content/reindustrialisation-europe-innovation-jobs-growth>

⁸ <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52013IE6859>

⁹ http://www.eulerhermes.us/economic-research/economic-publications/Documents/economic_outlook_1187.pdf

¹⁰ <http://aese.psu.edu/nercrd/about/goals>

infrastructure, and improving the living conditions of the rural population. All this fits with bio-based production as a means to rural regeneration.

Circular Economy

“The bio-based sector has also shown its potential for innovation in new materials, chemicals and processes, which can be an integral part of the circular economy”.

European Commission (2015a)

39. This distributed manufacturing model stresses the proximity both of the sites where raw material is acquired, and where goods and energy are produced and consumed (McCormick and Kautto, 2013), thereby closing loops, a central idea in the circular economy philosophy¹¹. In Italy in 2013, the competitive cluster, Cluster Spring, was created as a national Italian platform to promote a model of circular economy focused on innovative, integrated and multi-sector value-chains and to foster bio economy for regional regeneration.

40. The clearest connection to waste reduction, the circular economy, closed loop production and bio-based materials production is the concept of cascading use of biomass (Odegard et al., 2012) as a means to maximise the efficiency of using biomass (Keegan et al., 2013). Currently in Europe, however, cascading use is not supported by the existing political framework. Incentives only for bioenergy and biofuels hinder a more resource efficient use of biomass in cascades (Carus et al., 2016). Moreover, like the bio economy, circular economy literature displays a lack of precise definitions and criteria for assessing measures to improve the circularity of the economy (Haas et al., 2015), which greatly complicates the integration of bio- and circular economy.

Multiplicity of policy goals and potential policy clashes

41. A glance at the policy goals above will demonstrate how the different goals interact with each other. That, of course, creates the possibilities within any country and government of overlaps of policies, and thereby duplicating effort and expense. There is the distinct danger of creating an expensive lock-in for one policy goal by promoting a policy to support another goal. One example of this is the careful definition of ‘waste’ and ‘by-product’. Designating a material as a waste can make it difficult to use for a bio-based process feedstock in some countries.

42. Bio-production of fuels and energy has clear-cut policy goals. The greater breadth of goals for bio-based materials production could cause an antagonism of policies that needs careful attention and coordination among ministries, departments and regions.

Policy areas for attention: can we make a bio economy policy framework?

43. At least 50 countries have now created either bio economy strategies or policies consistent with a future bio economy. While national bio economy strategies demonstrate intent and commitment, they tend to be short on policy detail. For this reason examining the major policy implications of a bio economy in a single document, whether a framework is feasible or not, is a worthwhile exercise.

¹¹ A circular economy is an alternative to a traditional linear economy (make, use, dispose) in which resources are kept in use for as long as possible, the maximum value is extracted from them whilst in use, then products and/or materials are recovered at the end of each service life.

44. Production of bio-based materials impacts a wide diversity of policy areas, thus making a policy framework more of a theoretical interest than a near-term practicality. This report covers some of the most important areas for action by policy makers and these will be obvious from the titles of the sections. It is appropriate to end this section by identifying the most overarching key policy areas (Table 2) (derived from Carus, 2014).

Table 2. Policy inputs for a bio economy framework

Feedstock/Technology push	Market pull	Push and pull
Local access to feedstocks	Targets and quotas	Standards and norms
International access to feedstocks	Mandates and bans	Certification
R&D subsidy	Public procurement	Skills and education
Pilot and demonstrator support	Labels and raising awareness	Regional clusters
Flagship financial support	Direct financial support for bio-based products	Public acceptance
Tax incentives for industrial R&D	Tax incentives for bio-based products	
Improved investment conditions	Incentives related to GHG emissions (e.g. ETS)	
Technology clusters	Taxes on fossil carbon	
Governance and regulation	Removing fossil fuel subsidies	

Source: Adapted from Carus (2014), OECD (2014e)

Where is biotechnology in bio-based production?

45. This is a focal question of this report. While the portfolio of bio-based products has been growing, the number produced by biotechnology, in particular metabolic engineering and synthetic biology, is very modest. Care is required in definition. For example, in the US BioPreferred program,¹² a bio-based product is described thus: “...is a commercial or industrial product (other than food or feed) that is composed, in whole or in significant part, of biological products, including renewable domestic agricultural materials (including plant, animal, and aquatic materials), forestry materials, intermediate materials, or feedstocks”. The BioPreferred catalogue of bio-based products has burgeoned to over 14 000 products.

46. The research literature (Table 10) shows a great potential for biotechnology to contribute to bio-based materials production across a very wide spectrum of chemical categories: aromatic and aliphatic, commodity and speciality, solvents, lubricants, plastics monomers and intermediates, textiles, even drop-in and hydrocarbon fuels, and others.

47. If accepted that biotechnologically produced bio-based materials are lagging behind chemical production, a function of this report should be to examine the reasons for this. In reality several reasons exist for this. In terms of policy action, this is also described. Unlike other reports in this series that deal with Biomass Sustainability and Bio refineries Models and Policy, there is a distinct focus in this report on R&D subsidy as there are continuing challenges in bringing biotechnologically produced chemicals and materials from the laboratory to the market.

In summary

48. A range of societal grand challenges points to the need to shift to more sustainable energy and production regimes. The energy transition is at least two decades old, but sustainable production is much newer. In a bio economy, a proportion of industrial production is based on renewable feedstocks and

¹²

<https://www.biopreferred.gov/BioPreferred/faces/pages/FAQs.xhtml>

biotechnology. However, that raises many questions for policy makers. In this paper the more technical questions are addressed, particularly about barriers to bio-production and how they might be overcome. This requires not only new R&D, new industrial standards, but also a change in education, skills and training that encompasses multi-disciplinarity.

BEYOND BIOFUELS: DEVELOPMENTS IN BIO-BASED PRODUCTION

Introduction

49. What will be clear since the publication “*Future Prospects for Industrial Biotechnology*” (OECD, 2011b) is that there has indeed been a proliferation of interesting bio-based materials that are now visible (Table 5). Promoting chemistry at a political level poses challenges as chemicals are largely invisible, and yet they play an essential role in virtually all manufactured goods. This is compounded by the challenge of an industry that struggles with a poor public image (Moreau, 2005).

50. This section will examine some of these new bio-based materials spanning a range of different product types. This is bringing a visibility not seen before. It will also illustrate the range of different bio-based chemicals that are coming close to commercialisation.

What would be involved in replacing the oil barrel?

“What I am saying is I don't think it is any different to the chemical industry - there isn't a product that you buy or consume that doesn't require a chemical of one form or another”.

Jim Ratcliffe, INEOS founder and chairman, on the occasion of the arrival of the first shipment of US shale gas into the UK, September 2016, <http://www.bbc.com/news/uk-scotland-37474396>

51. The day could come when light and medium transport can be electrified (Delucchi et al., 2014), thereby eliminating the need for liquid road transport fuels. For example, Scania of Sweden is introducing a hybrid truck for city use that can be driven electric-only or with renewable fuels.¹³ Indeed, it is a Swedish government ambition to have a fossil-independent vehicle fleet by the year 2030 (Hellsmark et al., 2016).

52. For shipping and aviation, alternatives to liquid fuels are hard to envisage. Aviation is responsible for up to 3% of the global man made CO₂ emissions. Unlike other forms of transportation, aviation has less green alternatives to significantly reduce its carbon footprint. To this end, Los Angeles and Oslo are the first airports in the world that have incorporated biofuel into the regular refuelling process (*Bioeconomista*, 2016). Several airlines are now purchasing bio-aviation fuel e.g. KLM and United Airlines. In May 2016, Cathay Pacific commenced a two-year programme of flights from Toulouse to Hong Kong using renewable jet fuel. In September 2016, Gevo announced that it has entered into a heads of agreement with Deutsche Lufthansa AG for the supply of up to 8 million gallons per year of alcohol-to-jet fuel (ATJ). SkyNRG SkyNRG is a market leader for sustainable jet fuel, supplying more than 20 carriers across 5 continents¹⁴.

53. It cannot be ignored, however, that without fuels production, petrochemicals might be much less profitable. Petroleum refiners would have great difficulty producing chemicals at low cost if demand for gasoline or diesel fuel were radically reduced.

54. However, the high standard of living attained in OECD countries is not imaginable without the vast plethora of chemicals in everyday use. As a simple illustrative example, there would be no smart phone without chemistry, or any telephone at all. As 96% of all manufactured goods require at least one

¹³ <https://www.scania.com/group/en/take-control-hybrid-truck-for-city-use/>

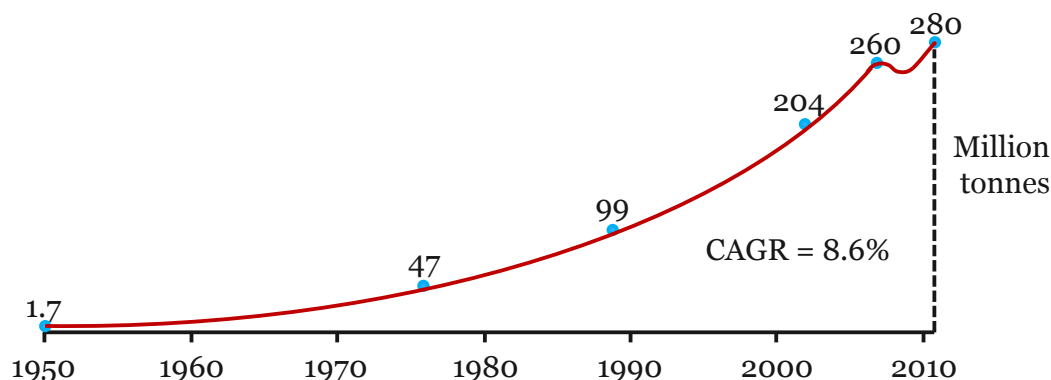
¹⁴ <http://skynrg.com/>

chemical (Milken Institute, 2013), it is clear that petrochemicals will be much harder to replace than fossil fuels. Policy makers could consider that if coal, crude oil and natural gas were conserved by stopping burning them as fuels, then there would be a ready feedstock of fossil resources for many generations to come to make petrochemicals. The likelihood in the medium term of stopping burning fossil fuels is extremely slim, so interim and long term policy solutions need to be pursued.

55. The chemicals sector is the largest industrial energy user, accounting for about 10% of global final energy use (Broeren et al., 2014), and the third largest industrial source of emissions after the iron and steel and cement sectors (IEA, 2012). As some countries struggle to meet their emissions reduction obligations, it is puzzling that the chemical sector has been relatively ignored in this respect compared to fuels and electricity (Philp, 2015).

56. Later this century, a situation may arise where continually increasing demand for chemicals and plastics will cause them to start to compete with fuels for available crude oil. Between 1950 and 2011, plastics consumption rose with a compound annual growth rate (CAGR) of 8.6%, and is currently close to 300 million tonnes per annum (Figure 2). Future growth in plastics consumption is predicted to be about 4% per annum (ANZ Insights, 2012). Since the mid-1980s, the global chemical industry overall has grown by 7% annually. Most of the growth in the past 25 years has been driven by Asia. If current trends continue, global chemical markets could grow on average at 3% per annum in the next 20 years (AT Kearney, 2012).

Figure 2. World plastics consumption, 1950-2011



Source: Redrawn from ANZ Insights (2012).

57. On that basis, plastics consumption could increase some 4-fold by 2050. Approximately 8% of world oil production is used in plastics manufacture: 4% as raw material for plastics and 3-4% as energy for manufacture (Hopewell et al., 2009). Therefore by mid-century, crude oil consumption to make plastics could increase to 28-32% of current levels of production, which would put plastics in competition with fuels for crude oil. Such growth is completely out of step with new oil discoveries, which are at their lowest in 60 years (*Financial Times*, 2016).

58. The most compelling route to drop-in (exact equivalent) or same-function (different molecule that has the same function) sustainable chemicals is through using renewable feedstocks. This would previously have been almost entirely the province of chemistry. For example, there is a whole history of wood chemistry that has been largely forgotten since the petrochemicals era (e.g. USDA, 1956), and a lot more can now be done since this early report. More recently there has been a drive towards 'eco-friendly' chemicals, such as the Ecover brand of washing-up liquids. Biotechnology is a newcomer as a route to

commodity chemicals. Only in 1994, Frost and Lievense (1994) discussed biotechnological routes to aromatics in reference to “*environmental considerations and the scarcity of petroleum*”.

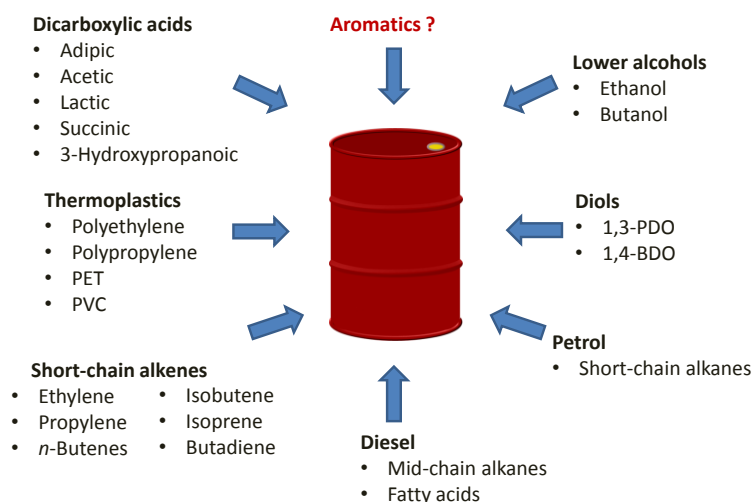
59. The idea of biotechnological routes to entirely unnatural chemicals only took hold with the emergence of metabolic engineering in the 1990s (Wong, 2016). Many of the current inventory of petrochemicals in everyday use have no natural equivalent, are highly reduced in nature compared to carbohydrates, and are often toxic to a microbial catalyst (Yim et al., 2011). This means a daunting task for creating biochemical pathways to a molecule never seen in nature, thus requiring truly synthetic steps. It also requires other features to be built into a microbial catalyst, such as solvent tolerance, that create a ‘robustness’ in the microbe that will allow it to survive the conditions of the bioprocess and the toxicity of the desired product.

60. Despite the challenges, several advantages to a biotechnological route compared to a strictly chemical route exist:

- Microbial metabolism is extremely diverse, and therefore there are very large numbers of biochemical reactions to choose from (one database contains 130 000 hypothetical enzymatic reactions);
- Biology is often very specific and selective, implying that side-reactions that limit productivity could be minimal or minimised;
- Microbial processes occur at low temperatures and mostly at ambient pressures, therefore making the biotechnological route attractive in environmental and economic terms.

61. To date green, renewable chemistry remains far ahead compared to ‘renewable biotechnology’ in the production of commodity chemicals. Figure 3 sums up the challenge.

Figure 3. Chemicals that have been made through metabolic engineering of microorganisms



Source: adapted from Jiménez-Sánchez and Philp (2015)

62. Most of the chemicals in this figure remain as research successes. Many may never reach commercialisation. There are technical and financial reasons for this, and the two are interlinked i.e. more efficient biotechnologies would bring down production price and make bio-based (either drop-in or equivalent function) more cost-competitive with petro chemistry. The technical reasons are dealt with in

another section. Suffice to say at present that engineered strains often display a significant reduction in performance as a result of scale-up (e.g. Takors, 2012). Fundamentally, bio-based production without public policy support faces a mountainous challenge given the economies of scale that have been possible in petro chemistry. For example, IRENA (2012) estimated the worldwide production costs of bio-based ethylene to be on average 50% higher compared to the production of ethylene in the steam cracking process.

63. However, taking a closer look at what constitutes the modern petrochemicals industry, a relatively small number of chemicals represent a large proportion of total organic chemicals production. A US Department of Energy (DOE) report from 2004 (USDOE, 2004) identified twelve building block chemicals that can be produced from sugars via biological or chemical conversions (Table 3). Building block chemicals are considered to be molecules with multiple functional groups that possess the potential to be transformed into new families of useful molecules. They can therefore otherwise be termed platform chemicals.

Table 3. The USDOE top value-added chemicals from biomass feedstocks

Chemicals
1,4 diacids (esp. succinic, fumaric, malic)
3-hydroxypropionic acid
Levulinic acid
Glutamic acid/MSG
Sorbitol
Xylitol/arabinitol
2,5 furan dicarboxylic acid
Aspartic acid
Glucaric acid
Itaconic acid
3-hydroxybutyrolactone
Glycerol

Source: Adapted from USDOE (2004).

64. Saygin et al. (2014) estimated that a total of seven polymers could *technically* replace half of the total common plastics in use of 2007 (Table 4). These polymers were: bio-PE, bio-PET, PHA, PTT, PLA, starch polymers, cellulosic films.

Table 4. Top seven polymers (and ethylene) that could technically replace half of total polymers production in 2007

	CO₂ emissions savings (tonnes CO₂ per tonne)
Bio-ethylene	1.9 – 5.3
Bio-polyethylene (PE)	2.4 – 4.2
Bio-Polyethylene terephthalate (PET)	1.9 – 2.5
Polyhydroxyalkanoates (PHA)	1.4 – 4.0
Polytrimethylene terephthalate (PTT)	1.1 – 1.9
Polylactic acid (PLA)	1.2 – 2.1
Starch polymers	1.7 – 3.6
Cellulosic films	0 – 1.9

Source: Adapted from Saygin et al. (2014).

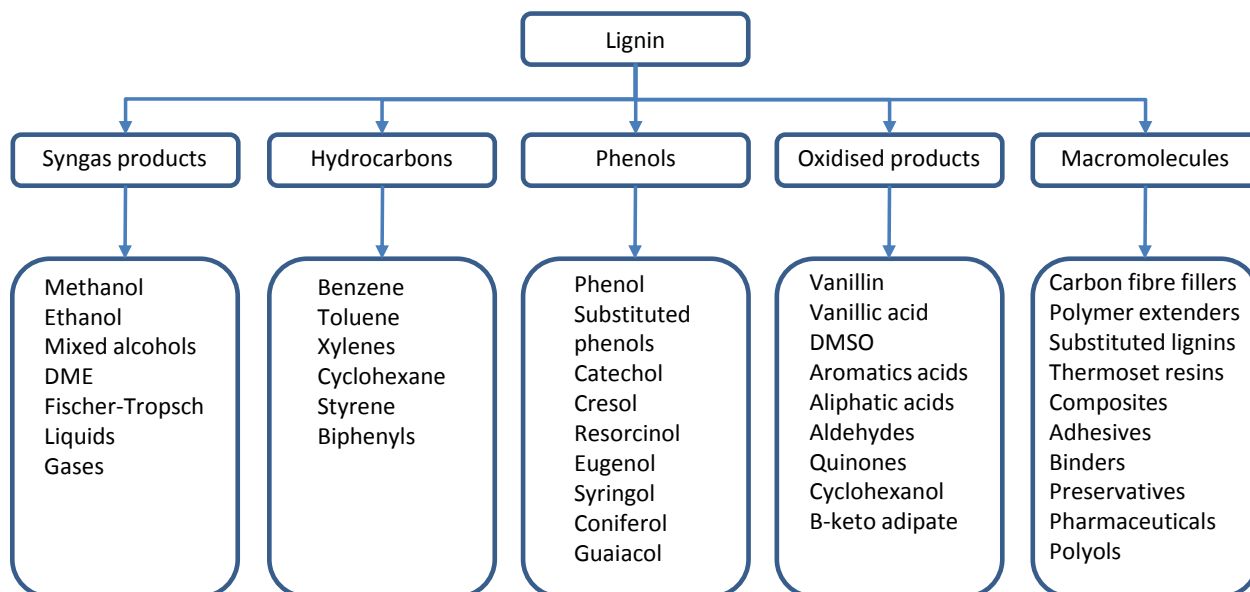
65. One significant development has been the arrival of the bio-based equivalents of the major thermoplastics that dominate the market – polyethylene (PE), polypropylene (PP) and polyethylene terephthalate (PET). Bio-PE and bio-PP are produced chemically from monomers which are produced by fermentation. They have identical performance characteristics to the petro-based equivalents and, importantly, can directly enter existing recycling systems. They can be categorised as bioplastics as their carbon content comes from renewable resources, and they therefore have a potential contribution to make to GHG emissions savings. The global trend in bioplastics production will change significantly to be dominated by durable bio-based thermoplastics (OECD, 2013c), rather than biodegradable plastics. The most dynamic developments are still expected to be in drop-in bio-based polymers (Aeschelmann et al., 2015).

66. A question mark exists for the aromatics. Biotechnological routes to aromatics are particularly challenging. As very high volume chemicals with a large range of functions, they cannot easily be replaced: benzene production alone may exceed 50 million tonnes in 2017.¹⁵ Benzene has specific uses in its own right but has very valuable value chains to other more valuable chemicals. However, commodity aromatics are very toxic to microbial cells. Indeed, most microbiological studies with aromatics are about their biodegradation as pollutants, rather than about their synthesis. Several studies have focussed on microbial aromatics production from biomass (Kawaguchi et al., 2016), but not aimed at commodity aromatics.

67. On the other hand, there clear environmental drivers for replacing aromatics exist. The BTX compounds (benzene, toluene and xylene) are mainly produced by catalytic reforming, typically using hydrogen and catalysts under high temperature (500°C) and high pressure (10-50 Bar) (Eriksson, 2013). The largest renewable reservoirs of aromatic materials are lignin and hemicellulose. Lignin creates the greatest challenges for renewable sources of aromatics, but it is not a resource that can be ignored (Figure 4). Of the order of 50 million tonnes of lignin are available worldwide per annum just from pulping processes.¹⁶ The total lignin availability in the biosphere exceeds 300 billion tonnes and annually increases by around 20 billion tonnes (Frost and Sullivan, 2012).

¹⁵ <https://mcgroup.co.uk/news/20140502/benzene-production-exceed-5095-mln-tonnes.html>

¹⁶ file:///C:/Users/phlip_j/Downloads/NNFCC%20Chemicals%20Factsheet%20Lignin.pdf

Figure 4. The potential for renewable aromatics production from lignin

Source: redrawn from IEA Bioenergy Task Force (2012)

68. Anellotech of the US has renewable chemistry solutions to the aromatic challenge. In their process, non-food biomass such as wood, sawdust, corn stover and sugar cane bagasse are gasified and immediately converted into hydrocarbons by a proprietary, reusable zeolite catalyst. The resulting mixture of benzene, toluene and xylenes (bio-BTX) is identical to the petroleum-derived counterparts.




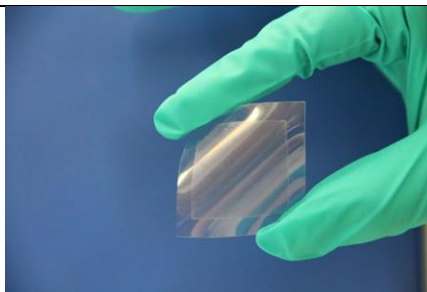

69. The BTX compounds are integral to the production of a wide range of plastics including polyurethane, polycarbonate, polystyrene and nylon. Hence an alliance between Toyota Tsusho and Anellotech (*Biofuels Digest*, 2016): Toyota Tsusho is a multinational strategic equity investor in Anellotech and a corporate partner in the renewable aromatic chemicals supply chain. Aromatics are widely used in the automotive industry, and the Toyota Group has championed the use of renewables in vehicles (OECD, 2011b).

70. In this report emphasis is frequently placed on the alliance of industrial biotechnology with green chemistry. There are already examples where their convergence has solved a challenge that could not be tackled by one or the other. The aromatics challenge is an example of the necessity of support for both. But it also reinforces the issue that biotechnological solutions lag behind chemical solutions.





Bio-based and visibility

71. For the public and policy makers, visibility has been lacking in bio-based production. In Table 5 the selected examples shows that in the last few years this visibility has increased dramatically. Nevertheless, this revolution in production could remain unheralded as a bio-based product looks identical to a fossil-based one e.g. tyre, smart phone screen, drinks bottle. Certification and labelling would help improve this visibility enormously, giving confidence to manufacturers and helping with public perception and acceptance. The increased political impetus from 2015 onwards, especially COP21 and the drive towards a circular economy, could be used as levers to increase this visibility.

Table 5. Bio-based products are becoming more familiar

	<p>Latex from dandelions</p> <p>Prototype tyres containing bio-based latex were showcased in December 2009 at the United Nations Climate Change Conference in Copenhagen. The Fraunhofer society with the tyre company Continental has built a pilot plant for the production of rubber from dandelions. The Russian dandelion thrives in soils unsuitable for agriculture.</p>
	<p>Bottles from sugar</p> <p>Both the Coca Cola and PepsiCo companies have plastic bottles that are at least partly bio-based. The Coca Cola bottle contains mono-ethylene glycol derived from fermentation of sugar. It is mixed with other components to make bio-polyethylene terephthalate (bio-PET). The long-term aim is to replace petro-PET. Avantium (Netherlands) and BASF intend to produce a different bioplastic for bottles (polyethylene furanoate, PEF).</p>
	<p>Straw to fuel</p> <p>In many OECD countries bio-ethanol is moving from first generation to second generation (from cellulosic feedstocks). The first of the second generation bio refineries are open. Clariant of Switzerland's technology breaks down lignocellulose enzymatically, and yeast ferments the sugars to ethanol.</p>
	<p>Soybean to graphene</p> <p>Graphene is more than 200 times stronger than steel and conducts electricity better than copper. About 1% of graphene mixed into plastics could turn them into electrical conductors. Graphene is, however, expensive compared to other materials. Researchers at CSIRO, Australia have created a new method of graphene synthesis from soybean oil (Seo et al., 2017).</p>
	<p>Castor nuts to wall plugs</p> <p>DuPont extracts a chemical building block from castor oil from which is made a 68% bio-based polyamide. It is as strong as the nylon normally used to make wall plugs.</p>

	<p>Bioplastics in cars</p> <p>One of the earliest uses of bioplastics was replacing metal or petro-plastics components in vehicles, saving GHG emissions and/or weight. Among others, Ford and Toyota are investigating and using bioplastics, for uses such as textiles car interiors. Daimler and DSM worked together to create an engine cover that is a 70% bio-based plastic.</p>
	<p>Sugar to carpets</p> <p>Dupont and Mohawk combine bio-based propanediol (PDO) and a petrochemical building block to make a carpet fibre that is soft, durable and easy to clean. The textile is 37% bio-based.</p>
	<p>Yeast to face creams</p> <p>Korres grows yeast cultures which produce hexapeptides when treated with ozone or irradiated with UV light. The compounds are added as anti-aging active ingredients in face creams.</p> <p>Amyris has engineered specialised yeast strains that can produce squalene from sugar. Squalene is used as an emollient in moisturiser lotions (Servick, 2015).</p>
	<p>Ice cream from lupins</p> <p>Prolupin has developed a process to extract protein from the seeds of lupins. The protein is used to make ice cream that contains neither lactose nor gluten. Evolva uses a synthetic biology-derived yeast for fermentation to synthetic vanillin. Other food materials through synthetic biology include stevia (sweetener) and nootkatone (smell of grapefruit).</p>
	<p>Biopharmaceuticals</p> <p>Antibiotics have been traditionally produced from microbes. Synthetic biology has been used to a potent anti-malarial. Sanofi delivered the first large-scale batches of anti-malarial treatments manufactured with a new semi-synthetic artemisinin derivative to malaria endemic countries in Africa in 2014.</p>

	<p>Bacteria in toothpaste</p> <p>Lactobacillus Pro-t-action is a specifically acting probiotic which reduces caries-causing bacteria in the mouth. It can be added to toothpaste. The bacteria are produced by BASF and the toothpaste marketed by Neva Cosmetics.</p>
	<p>Nutrition and food/feed supplements</p> <p>Cargill makes a sweetener using a synthetic biology yeast to convert sugar molecules to mimic the properties of stevia, with no need for the plant itself. It awaits a commercial launch date.</p> <p>Calysta specialises in the production of microbial proteins for the commercial fish feed and livestock markets.</p>
	<p>Enzymes in detergents</p> <p>Biological detergents contain a range of enzymes that allow washing to be done at lower temperatures, such as 30°C, thus saving energy, emissions and money.</p>
	<p>Spider silk to medical implants</p> <p>Spider silk is an exceptionally strong material. Silk material is now also being used for sutures, scaffolds, grafts and some medical implants. Oxford Biomaterials, Orthox Ltd and Neorotex Ltd are investigating a range of biomedical applications of genetically engineered spider silk. The US army is testing protective garments for soldiers made from spider silk. An <i>E. coli</i> variant of spider silk could replace Kevlar in air bags.</p>

Note: The first six examples are truly about replacements for petrochemicals. The others demonstrate the eclectic range of bio-based possibilities.

Sources: Most photographs are courtesy of the German Bio economy Council.¹⁷ More examples are given in Global Bioeconomy Summit (2015).

Brands and recent deals

72. The improvement in visibility is helped now by the interest of brands. Several are named in Table 5. New business alliances ensure that new bio-based products are taking their place in the market (Box 2). Brands can also leverage their marketing and global outreach capacities to open up markets for bio-based products.

¹⁷

<http://biooekonomierat.de/home-en.html>

Box 2. Some recent business developments and alliances in bio-based production

February 2016. B.R.A.I.N. Biotechnology Research and Information Network AG (BRAIN AG) had a stock market launch to become Germany's first listed bio economy company. A particular growth potential is seen in large parts of the chemical industry, where experts foresee a rising share of biotechnology products and procedures. BRAIN AG focuses on the specialty chemicals and the consumer chemicals divisions. The company received gross proceeds of EUR 31.5 million from the IPO. BRAIN was classified by Deutsche Börse as belonging to the specialty chemicals sector.

February 2016. Chinese renewable energy investment company Kaidi announced plans to build a biodiesel refinery in Finland. The value of the investment is EUR 1 billion, making it the biggest Chinese investment in Finland to date. The first of its kind, it will produce biofuels by using wood-based biomass, such as energy wood, harvesting remains and even leftover bark from the forest industry as the main feedstock. The plant will produce 200 000 tonnes of biofuel per year, of which 75% will be renewable diesel and 25% renewable gasoline.

February 2016. Mitsui & Co., BioAmber's partner in the Sarnia (Canada) bio-based succinic acid plant, is investing an additional CAD 25 million in their joint venture. Mitsui will play a stronger role in the commercialisation of bio-succinic acid.

February 2016. Gevo, a renewable products and technology company, announced a license agreement and a joint development agreement with Porta Hnos, a leading alcohols company in Argentina, to construct multiple isobutanol plants in Argentina using corn as a feedstock.

March 2016. Air New Zealand and Virgin Australia announced a partnership to investigate options for locally produced aviation biofuel. The alliance partners are issuing a Request for Information (RFI) to the market to explore the opportunity to procure locally-produced aviation biofuel.

April 2016. A new version of the Tetra Pak (Sweden) Tetra Top package was announced and it will make its global debut in the US. The new generation carton bottle now comes with a cap and top made from high-density polyethylene (HDPE) derived from sugarcane. Combined with the FSC-certified paperboard used in the main sleeve of the carton, this pushes its renewable content up from 53% to 82%, with no impact to its recyclability.

May 2016. Virent of Wisconsin, US announced the world's first 100% plant-based polyester shirts. The development of the Virent technology platform is supported through strategic partners including Cargill, The Coca-Cola Company, Honda, Shell and Tesoro.

May 2016. Aemetis and Edeniq, both headquartered in California, entered into a definitive agreement under which Aemetis will acquire all of Edeniq's outstanding shares in a stock plus cash merger transaction. Aemetis is an advanced fuels and renewable chemicals company. Edeniq is a cellulosic ethanol technology company that has developed innovations that unlock cellulosic and starch sugars through a combination of mechanical and biological processes.

June 2016. PTT (formerly known as Petroleum Authority of Thailand) group joined with Japan's Mitsubishi Chemical Holding Corp to form a USD 100 million joint venture to build Thailand's first polybutylene succinate (PBS) plant with an annual capacity of 20 000 tonnes.

July 2016. Ginkgo Bioworks and Amyris partnered to enable the companies to jointly develop products more efficiently and cost effectively, accelerating time to market. The deal aims to generate USD 300 million in incremental value. Ginkgo is building Bioworks2, a next-generation automated foundry where their organism engineers can develop new designs at massive scale. Amyris has commercialised five products from highly engineered organisms, going into markets from skin care and fragrances to industrial lubricants, tyres and jet fuel.

July 2016. The Ford Motor Company and Jose Cuervo announced an alliance to explore the use of the tequila producer's agave plant by-product to develop more sustainable bioplastics to employ in Ford vehicles.

August 2016. Amyris, in cooperation with Renmatix and Total New Energies USA, will work to develop a manufacturing-ready process utilising wood as the cellulosic feedstock to produce farnesene in a multi-million USD contract with the US DOE.

August 2016. Sacramento County, California, partnered with Neste of Finland for the trial supply of Neste renewable diesel in its fleet of more than 400 trucks and heavy equipment.

September 2016. Toyobo, one of Japan's top fibres and textile manufacturers, and Avantium, a scale-up renewable chemicals company of the Netherlands, partnered on polyethylene furanoate (PEF) polymerisation and PEF films. The two companies have jointly developed thin films made from PEF, a 100% bio-based plastic. Avantium is working in collaboration with brand partners The Coca Cola Company and Danone to bring 100% bio-based PEF bottles to the market.

September 2016. Neste of Finland and IKEA of Sweden announced a partnership to deliver renewable, bio-based plastics. The partnership combines IKEA's commitment to reduce dependence on virgin fossil-based materials and Neste's expertise in renewable solutions.

September 2016. LanzaTech has produced 1 500 gallons of jet fuel, derived from waste industrial gases from steel mills, via a fermentation process. The fuel has passed all its initial performance tests. It is the result of a partnership between Virgin and LanzaTech.

September 2016. Virent established a strategic consortium with Tesoro, Toray, Johnson Matthey and The Coca-Cola Company focused on completing the development and scale up of Virent's BioForming® technology to produce low carbon bio-based fuels and bio-paraxylene (a key raw material for the production of 100% bio-polyester).

September 2016. Global Bioenergies, Preem, Sekab and Sveaskog announced having joined forces to develop a high-performance fuel entirely based on forest resources. The consortium has signed a collaboration agreement to carry out a conceptual scope study for a first plant in Sweden. This work will be carried out as part of the "Bio-Based Gasoline Project" with support from the Swedish Energy Agency.

September 2016. Mater Biotech, a 100% company owned by Novamont, opened its first commercial bio-BDO plant using Genomatica's technology that converts renewable feedstocks into 1,4 butendiol (BDO) in Bottrighe di Adria (Rovigo, Italy). Thanks to an investment of EUR 100 million, Novamont has managed to revive an abandoned manufactory site of Bioitalia. The plant will produce 30 000 tons of renewable BDO per year by 2017.

September 2016. Loblaw of Canada announced the launch of compostable President's Choice (Loblaw's in-house brand) single-serve coffee pods. They are made almost entirely from plant materials and reclaimed coffee bean skins, and are the result of Canadian innovation and collaboration between the University of Guelph's Bioproducts Discovery and Development Centre (BDDC), Club Coffee (a Toronto-based company), and Competitive Green Technologies (Leamington, Ontario, a producer of bio-polymers/plastics and bio-composites).

October 2016. Ginkgo Bioworks and Genomatica announced an alliance to more rapidly deliver biology-based solutions for the world's highest-volume intermediate and specialty chemicals. Mainstream chemical producers can now in-license technology to manufacture their widely-used chemicals with cost-effective and sustainable whole-process solutions that include engineered microorganisms, complete process designs and technology transfer support.

November 2016. The Danish Minister for Environment and Food launched the white paper on Danish circular economy at the conference 'Danish Pioneers of Sustainability' hosted by the Confederation of Danish Industry.

November 2016. Global Bioenergies of France, announced the completion of the construction of its demonstrator plant in Leuna, Germany. This is the only facility in the world dedicated to the direct fermentation of gaseous hydrocarbons.

November 2016. Corbion of the Netherlands is building its new polylactic acid (PLA) bioplastics polymerisation plant at an existing Corbion site in Rayong, Thailand. Upon completion in 2018, it will be able to produce a portfolio of PLA neat resins: from standard PLA to innovative, high heat resistant PLA.

December 2016. Leaf Resources of Australia announced a collaboration with Novozymes to further increase the yields and efficiency associated with Leaf Resources' innovative biomass conversion technology, Glycell, which is a combination of well-established process engineering and innovative chemistry.

December 2016. The South African Department of Agriculture, Forestry and Fisheries has approved four NexSteppe sorghum hybrids for commercial sale in the country. NexSteppe is a US company pioneering the next generation of sustainable feedstock solutions for the biofuels, biopower, biogas and bio-based products industries.

January 2017. LanzaTech of New Zealand and the United States has been selected by the Department of Energy's Bioenergy Technologies Office (BETO) to receive a USD 4 million award to design and plan a demonstration-scale facility using industrial off gases to produce 3 million gallons per year of low carbon jet and diesel fuels. The facility will recycle industrial waste gases from steel manufacturing.

January 2017. In conjunction with the Institute for Materials and Wood Technology at the Bern University of Applied Sciences, AVALON Industries is launching a research project to replace formaldehyde in phenol-formaldehyde (PF) resins with the bio-based, non-toxic platform chemical 5-HMF (5-Hydroxymethylfurfural). Government-sponsored by the Swiss Commission for Technology and Innovation (CTI), the project will build on the positive results in a similar research project to develop non-toxic urea-HMF resins.

February 2017. Clariant of Switzerland, together with Mercedes-Benz and Haltermann Carless, tested the use of sustainable cellulosic ethanol from agricultural residues in a fleet test with Mercedes-Benz series vehicles over a period of 12 months for the first time in Germany. The fuel by Haltermann Carless has a cellulosic ethanol content of 20% by volume (E20) and was produced at Clariant's Sunliquid plant in Straubing, Germany. The cellulosic ethanol allows GHG emission savings of up to 95% across the entire value chain without competing with food production or tying up agricultural land.

February 2017. Global Bioenergies, France, announced the production of ETBE (ethyl-tertiary-butyl ether) purely from renewable resources. It can be used as an additive in vehicle fuel, up to a maximum of 23%, thereby increasing the proportion of biofuels in blends with fossil fuels. It is made by combining renewable ethanol with renewable isobutene. This first production of entirely renewable ETBE was supported by a grant of the German Ministry of Education and Research (BMBF).

March 2017: Danone and Nestlé Waters, the world's two largest bottled water companies, have joined forces with Origin Materials, a Californian start-up, to form the NaturALL Bottle Alliance. Together, the three partners aim to develop and launch at commercial scale a 100% bio-based PET plastic bottle.

March 2017: The initial public offering (IPO) of Avantium raised EUR103 million on Euronext Amsterdam and Euronext Bruxelles. Funds raised will be used to further commercialise Avantium's inventions into viable production processes. This will start with the commercialisation of the YXY technology, in a joint venture with BASF, by building the first commercial scale reference plant for FDCA. On the basis of the share price, Avantium's market capitalisation reached EUR 277 million.

Source : Various

Around 30 key bio-based chemicals are close to full market stability

73. A report for the European Commission (2015b) showed that there are over 90 bio-based chemicals at technology readiness level (TRL) of at least 3 (Table 6). While there are only three at TRL 9, there are, 23 at TRL 8.5, and another eight at TRL 8. In the EARTO classification (EARTO, 2014), this places them at least at the level of: "*Manufacturing fully tested, validated and qualified*", which agrees roughly with other TRL classification systems¹⁸. Therefore it would appear that a reasonable number of important bio-based chemicals are progressing towards TRL 9, effectively stable, competitive manufacturing. However, this says little about their market share or future prospects.

74. It is important to note that many of these chemicals may not be recyclable or non-toxic: they are replacements for petro-based equivalents in many cases. The truly biodegradable, non-toxic ones are usually taking the same or similar function as a petro-based chemical. The over-arching reason for their development is because they have favourable GHG emissions compared to the petro- counterparts.

¹⁸

Technology readiness levels (TRL) are a method of estimating technology maturity, generally ranging from 1 (basic research) to 9 (launch and operations).
https://en.wikipedia.org/wiki/Technology_readiness_level

Table 6. Bio-based chemicals and their TRLs

Chemical	TRL	Chemical	TRL	Chemical	TRL
Ethyl acetate	9	PE	8	Diesel	5
Sorbitol	9	PLA	8	FDCA	5
Ethanol	9	Succinic acid	8	Formic acid	5
1,2-Butanediol	8.5	Isosorbide	7	Gasoline	5
1,3-Propanediol	8.5	PBS	7	Glucaric acid	5
2,3-Butanediol	8.5	1,4-butanediol	7	Isobutene	5
Acetic acid	8.5	Farnesene	7	Methyl methacrylate	5
Acetic anhydride	8.5	PHB	7	<i>p</i> -Xylene	5
Acetone	8.5	Dimethyl isosorbide	6.5	PBS/PLA comp.	5
<i>n</i> -Butanol	8.5	Ethyl lactate	6.5	PBT	5
Epichlorohydrin	8.5	Fatty alcohols	6.5	PET	5
Ethylene glycol	8.5	Furan	6.5	PIA	5
Furfural	8.5	Levulinic acid	6.5	Terephthalic acid	5
Furfuryl alcohol	8.5	Methyl THF	6.5	Furoic acid	5
Glutamic acid	8.5	PHBV	6.5	Caprolactam	4
Itaconic acid	8.5	Poly(isosorbide)	6.5	Dodecanedioic acid	4
Lactic acid	8.5	Butyric acid	5.5	γ -Butyrolactone	4
Lactide	8.5	THF	5.5	Malic acid	4
Lysine	8.5	Isoprene	5.5	Furoate esters	4
PEG	8.5	PHA	5.5	Isopentanol	4
Propylene glycol	8.5	PP	5.5	Fumaric acid	3.5
PTT	8.5	Propylene	5.5	Glycolic acid	3.5
Squalene	8.5	PVC	5.5	Isopropanol	3.5
Terpenes	8.5	3-HPA	5	Methyl levulinate	3.5
Xylitol	8.5	5-HMF	5	Muconic acid	3.5
Acetaldehyde	8.5	Acrylic acid	5	PMMA	3.5
EPDM	8	Adipic acid	5	Heptanone	3
Iso-butanol	8	Jet fuel	5	HMDA	3
ETBE	8	Methacrylic acid	5	Hexane	3
Ethylene	8	Benzene	5	PA 6,6	3
Fatty acids	8	Butadiene	5	Diaminopentane	3

Source: Compiled from European Commission (2015b).

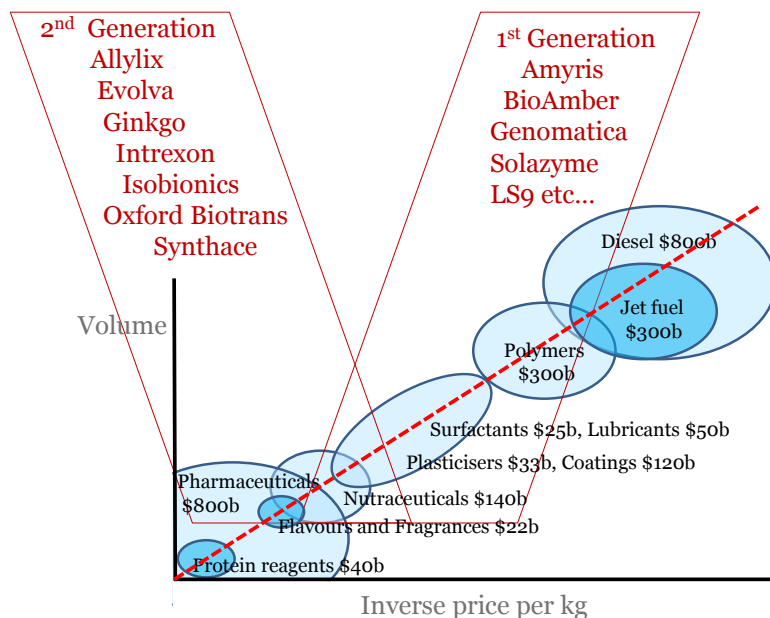
A common denominator: the challenge of scale

75. For the vast majority of these products and chemicals, production at scale is an issue i.e. at a scale that is able to influence a market. For custom and specialty chemicals the challenge is more easily surmounted than for commodity chemicals. Biofuels have proven very difficult to transition from the laboratory to commercial production due to the huge volumes required to affect the market. In some countries, the margins on petrol and diesel production are so low that to make biofuels competitive on price remains a very difficult proposition. The synthetic biology/bio-based production companies involved with fuels can be described as the first generation of synthetic biology, or metabolic engineering, companies (Figure 5).

76. On the other hand, high-value specialty and fine chemicals are mostly produced in more manageable, low volumes (and market sizes) with which a young industry can cope, and they offer larger margins. The successful production of low-volume chemicals via metabolic engineering routes may provide greater market confidence than failure to make high volume fuels. Companies adopting this strategy may be considered as the second generation of synthetic biology, or metabolic engineering, companies (Figure 5).

77. However, large GHG emissions are associated with the large volume, low margin commodity chemicals. In the analysis by Saygin et al. (2014) those seven selected most important bio-based materials had an estimated technical CO₂ emissions reduction potential of 0.3 – 0.7 Giga tonnes (Gt) CO₂ in 2030. Assuming the same potential for the remainder of organic materials production, they estimated a total technical reduction potential of up to 1.3 - 1.4 Gt CO₂ per year by 2030, compared to 3.2-3.7 Gt for fuels.

Figure 5. The evolution of bio-based companies from bulk to low-volume products



Concluding remarks

78. Most of what has been achieved in the nascent bio-based materials industry has been done with very little policy support beyond R&D subsidy (OECD, 2014a). This can be understood as there is a mere handful of liquid fuels, and there are vast numbers of chemicals, complicating the possibilities for mandates, for example. However, not supporting bio-based materials in public policy misses significant

opportunities for GHG savings and other policy goal benefits e.g. a good fit with circular economy ambitions, reindustrialisation, decentralised manufacturing. These policy goals find excellent alignment with the integrated biorefinery concept, the most ambitious but also most complex bio refinery model. Ignoring bio-based chemicals and materials in public policy makes the economics of integrated bio refineries questionable as the margins for many chemicals are usually better than for high-volume fuels. The widespread policy support for biofuels and bioenergy systematically allocate biomass for these purposes, and not for materials.

DECISION SUPPORT TO ENABLE BIO-BASED MATERIALS POLICY

Introduction: improving bio-based materials policy

79. For several years the argument regarding a ‘level playing field’ for bio-based materials (mainly bio-based plastics and chemicals) has been discussed in many publications (e.g. Snyder, 2015) and events (e.g. Friends of Europe, 2012). This refers to the large and widespread support given to biofuels and bioenergy in many countries as part of their obligations to reduce emissions of greenhouse gases (GHG). Public policy support for bio-based materials has been all but absent in most countries that have biofuels and bioenergy policies. Support that has been given has often been limited to R&D subsidy.

80. A main reason this is important is to make the integrated bio refineries of the future economically viable. Much of the profit would come from the lower production volumes of chemicals because their margins are generally superior to those of fuels. Not supporting bio-based materials in policy runs the risk that integrated bio refineries will not be able to function profitably.

81. The purpose of this section is to examine some policy options that will start to address the situation from economic, environmental and social perspectives. The purpose is to help governments implement some policy support for bio-based materials that can be consistent with national biofuels policy support. This would be a cost-efficient mechanism making use of existing support policies and conditions rather than creating a separate support scheme with its own infrastructure and bureaucracy.

82. The starting point used here is the US Renewable Fuel Standard (RFS) which mandates biofuels production targets through to 2022, but also sets GHG emissions targets for each category of biofuel included in the mandate (see Box 3). In order to guarantee improved environmental performance, the RFS mandates steadily increasing production of biofuels with superior GHG emissions reductions, especially cellulosic ethanol, whilst allowing corn-based bioethanol (first generation bioethanol) to reach a plateau (Figure 6).

83. For bio-based materials there is a similar policy goal – to support the development of materials with better environmental performance. The link to volumes is that the greatest reductions in emissions would be gained from the bio-based equivalents of large production volume commodity chemicals. Therefore a policy similar to RFS for materials would provide the same benefits.

Box 3. The Renewable Fuel Standard and mandated targets for biofuels production

The Energy Independence and Security Act (EISA) set minimum volumes of renewable fuels that suppliers must blend into the US supply of transportation fuel each year, irrespective of market prices. This effectively guarantees a market for biofuels. The RFS2 substantially reduces the risk associated with biofuels production, thus providing an indirect subsidy for capital investment in the construction of biofuels plants. As such, the expanding RFS is expected to continue to stimulate growth of the biofuels industry.

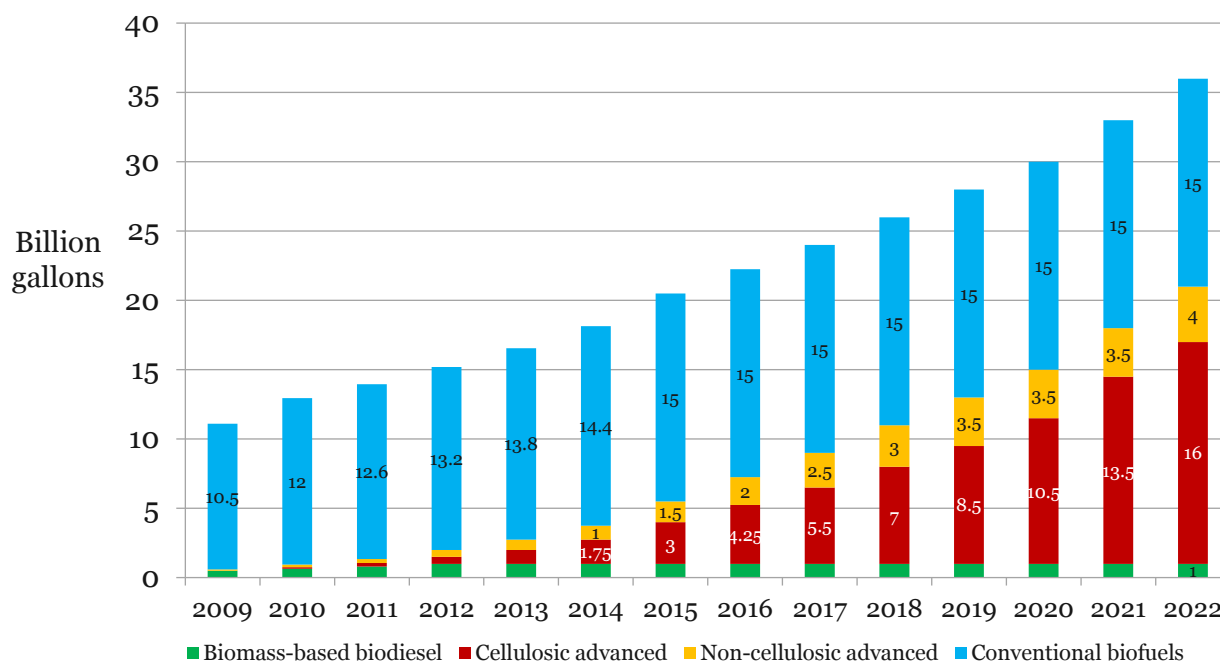
EISA requires that the emissions associated with a renewable fuel be at least a certain percentage lower than the emissions associated with the gasoline or diesel that the renewable fuel replaces (USEPA, 2009). EISA therefore attempts to address energy security, rural regeneration and climate change mitigation, while growing a large number of jobs in the ethanol industry.

The Environmental Protection Agency (EPA) is responsible for establishing and implementing regulations to ensure that the nation's transportation fuel supply contains the mandated biofuels volumes (Congressional Research Service, 2013). The EPA translates the yearly volume requirements in EISA into percentage standards (sometimes called blend requirements) that are based on projections of the total amount of gasoline and diesel that will be used in that year. For example, if the projected amount was 100 billion gallons and the total renewable fuel requirement was 14 billion gallons, EPA would set a 14% blend requirement (Congressional Budget Office, 2014).

To monitor suppliers' compliance with the requirements, EPA assigns a unique 'renewable identification number' (RIN) to each qualifying gallon of renewable fuel. Every RIN includes a code that identifies which of the four RFS categories—total renewable fuels, advanced biofuels, cellulosic biofuels, or biomass-based diesel—the gallon satisfies. Each fuel supplier, regardless of what kind of fuel it produces or imports, must meet all of the blend requirements for a given compliance year.

The supplier can do that by using the required amounts of renewable fuels itself and submitting the corresponding RINs to EPA to demonstrate compliance, by purchasing RINs from other suppliers that have excess RINs to sell, or by submitting RINs that it acquired in the previous year and saved for future use. For the example above, each fuel supplier would have to submit 14 RINs (including 4 for advanced biofuels and 2 for biomass-based diesel) for each 100 gallons of gasoline or diesel that it sold. Suppliers with excess biomass-based diesel RINs could either sell them or apply them toward their advanced biofuel requirement.

84. The obvious difficulty with doing this for bio-based chemicals is the huge variety of chemicals that exists compared to fuels – the chemicals industry is responsible for some 70 000 products. Also making ethanol from yeast is a relatively efficient bioprocess as yeasts can achieve high concentrations of ethanol in solution, and ethanol downstream purification is tried and tested. For many other bio-based chemicals this is certainly not the case. The cascading policy options outlined here is an attempt to address these issues in a manner that also addresses GHG emissions.

Figure 6. RFS mandated production through to 2022¹⁹

Source: Redrawn from US EPA (2010) www.epa.gov/otaq/fuels/renewablefuels/regulations.htm

Policy design

85. Essentially the policy suggestions made here combine elements of industrial and green growth policy as it is about the creation of new manufacturing opportunities that allow economic growth and at the same time avoid the trap of increased emissions (UNEP, 2010). This was at the heart of the 2009 OECD publication: *The bioeconomy to 2030 – designing a policy agenda*.

General points

86. Good policy design should: ensure competitive selection processes; contain costs and; select projects that best serve public policy objectives, without favouring incumbents or providing opportunities for lobbying (OECD, 2013a). This suggests the need for a portfolio of public investment where funding approaches are tailored to the different stages of technology development. Given the range of bio-based chemicals, the technology development currently spans virtually the whole range of 1-9 of technology readiness levels (TRLs) as each is designed on a one-off basis. Therefore this point for policy makers is especially pertinent – policy for bio-based materials has to be flexible enough to cover a wide range of technology readiness.

87. In general, policies for innovation and deployment need to encourage experimentation to develop new options that can help strengthen environmental performance at the lowest cost (OECD, 2013a). Given the early stage development of bio-based materials, policies need to trigger continuous innovation by the

¹⁹

There have been notable set-backs in US biofuels production among some of the ethanol categories that have delayed policy decisions. This is particularly true of cellulosic advanced ethanol.

industry sector to develop improved bio-based alternatives in order to achieve ambitious CO₂ emissions reductions (Saygin et al., 2014).

88. Governments should level the playing field between alternative options, but should in general avoid supporting specific technologies and solutions over others, emphasising competition and technology neutrality. Other sources of organic chemicals in future manufacturing should not be excluded in favour of bio-based. Nevertheless, the sources of carbon for sustainably produced organic chemicals seem limited. Petrochemical manufacturing will continue to be important, but is ultimately unsustainable. The only foreseeable alternative sustainable source to bio-based is waste CO₂ itself, as part of the CO₂ economy.²⁰

89. Against a background that no single technology or policy will drive green innovation, Dutz and Pilat (2014) recommended that countries should use a combination of supply- and demand-side policy instruments to achieve policy goals, which may differ from country to country. This is consistent with the conclusion by Mowery and Rosenberg (1979) that both are necessary for innovation. The relationship between supply and demand-side policies to stimulate innovation is detailed in the OECD publication *Demand-side innovation policies* (OECD, 2011a).

How to tackle thousands of different chemicals

90. Thousands of different chemicals are manufactured from oil. Even the list of ‘significant’ chemicals (in terms of production volume) runs to dozens.²¹ Creating a policy support mechanism akin to the feed-in tariff used successfully for renewable electricity is nigh on impossible for chemicals. Also, the number of types of large volume liquid fuels is a mere handful. This simplifies creating production mandates for biofuels greatly. To try this with individual chemicals would most likely meet with resistance from the industry due to the bureaucratic burden and cost it would create.

91. Carus et al. (2014) described an innovative solution. Their suggested mechanism that would avoid creating and administering individual mandates or quotas for large numbers of different chemicals is to use bioethanol as a reference chemical. Ethanol made using certified sustainable biomass, then used for the manufacture of chemicals and plastics, could be counted in the same way that ethanol is counted for a biofuel. All other bio-based chemicals that are not derived from ethanol, such as lactic acid, could be converted to ethanol “equivalents”, on the basis of, as examples, calorie value or molecular weight or number of carbon atoms in comparison to ethanol. By way of a simple algorithm, dealing with many chemicals individually is avoided.

92. This would imply that greater subsidy would be associated with chemicals ‘larger’ than ethanol, in the sense of molecular weight (higher calorie value, larger number of carbon atoms amount to the same thing). Whilst larger number of carbon atoms may mean greater sequestration of carbon in a chemical, this is not necessarily so: not all bio-based materials are synthesised entirely of bio-based carbon. Therefore more detailed environmental performance data for the chemical are needed for policy making. This requires harmonised LCA procedures to calculate the emissions savings which would become the basis for policy support. If the molecule in question is only partly bio-based, the percentage should be made clear – this could provide the stimulus for improvement in bio-based content.

93. This need not be just a matter of GHG emissions reductions. Sustainability is much more complicated than this, but estimating sustainability will not give immediate policy stimulus as there is a

²⁰ <http://www.greenfireenergy.com/the-co2-economytrade.html>

²¹ A glance at the ‘Petrochemical’ entry in Wikipedia gives an indication of this diversity (<http://en.wikipedia.org/wiki/Petrochemical>)

lack of agreement about how it should be done (see OECD, 2014f). For example, Harding et al. (2007) compared LCA for a bioplastic with two of the most common petrochemical plastics, polypropylene (PP) and polyethylene (PE). In all categories of the LCA, the bioplastic was superior to PP. However, the eutrophication impact of PE production was 500% lower than that of the bioplastic, partially because of the agricultural component of the bioplastic production. Rather than await a comprehensive strategy for sustainability assessment, an alternative that takes into consideration production efficiency that can be calculated readily by the manufacturers is suggested.

Setting target environmental performance threshold levels

94. The Renewable Fuel Standard set GHG emissions reduction thresholds for different categories of biofuels (Table 7). This provides the stimulus for improvements in environmental performance. Thresholds could be set for bio-based materials in a similar manner so that:

- Public R&D funds, and potentially public contributions to scale-up (through, for example, loan guarantees and other PPP mechanisms), are directed to improving environmental performance;
- Projects are selected based on combined merits of environmental and economic attributes;
- Producers are encouraged to continuously strive for improvements through funding R&D.

Table 7. GHG emissions reduction values specified for the Renewable Fuel Standard.

Fuel	GHG threshold (EISA)
Renewable fuel	20%
Advanced biofuel	50%
Biomass-based diesel	50%
Cellulosic biofuel	60%

Note: *Percentage reduction from 2005 baseline.

Source: USEPA (2009).

95. However, a major barrier to setting thresholds exists due to large degrees of error in assessment of the GHG savings for bio-based materials, as highlighted by Weiss et al. (2012). Life cycle analysis (LCA) has created inconsistencies in approach, and its short-comings have been summarised recently (OECD, 2014f).

96. Saygin et al. (2014) selected the seven most important bio-based materials that could technically replace half of petrochemical polymers and fibre consumption worldwide, and estimated a technical CO₂ emissions reduction potential of 0.3 – 0.7 Giga tonnes (Gt) CO₂ in 2030. Assuming the same potential for the remainder of organic materials production, they estimated a total technical reduction potential of up to 1.3 - 1.4 Gt CO₂ per year by 2030. With process improvements, they estimate 1.7-1.9 Gt per year CO₂. These figures are compared to the emissions savings from fuel in Table 8.

Table 8. Technical and economic potentials for CO₂ emissions reductions in 2030 and 2050

Biomass use	Technical potential (with autonomous improvements)		Economic potential (with energy efficiency)	
	2030	2050	2030	2050
Feedstock	1.3 - 1.4	1.7 - 1.9	0.3 - 0.4	0.6 - 0.7
Fuel	3.2 - 3.7	3.4 - 4.1	0.8 - 1.0	1.3 - 1.6
Total	4.5 - 5.1	5.1 - 6.0	1.2 - 1.3	1.9 - 2.2

Note: figures in Gt CO₂ per year.

Source: Extracted from Saygin et al., 2014. (These potentials exclude biomass use in the pulp and paper sector).

97. Overall they conclude that some bio-based materials score better than using biomass to generate steam, while others score worse. Therefore in the near future, policies have to reflect this variability in order to:

- Take account of the fact that biomass supply will be limited, so that decisions can be made based on efficiency of use;
- Make best use of public money, and;
- Provide guidance to business and consumers.

98. For the purposes of creating a first draft skeleton of a decision support tool to allow governments to make specific decisions, the threshold levels of RFS given in Table 7 are suggested. Further research would elucidate if these are appropriate levels. However, in the immediate term, this would allow seamless entry of bio-based materials into biofuels policy. Such a policy should be kept flexible to take account of future innovations to prevent inappropriate lock-in. In other words, future developments are likely to drive improved GHG emissions reductions. Policy should allow for change in threshold values in future to act as a driver for these improvements.

Taking account of production volume

99. The production volume of a chemical becomes relevant when considering its environmental impact through total emissions savings: the greater the production volume, the greater the potential savings. LCA may determine that a chemical has great potential for GHG savings, but if it is a high-value chemical of very low production volume, its overall contribution in terms of tonnes of CO₂ saved per year is limited.

100. However, the nascent bio-based industry has come up against a serious barrier that creates a conundrum for policy making. Trying to make a high-volume bio-based equivalent of a petrochemical suffers two large impediments:

1. Over decades the petrochemical equivalent has had its production process and supply chains perfected and the production plants have been amortised, so that it benefits enormously from economies of scale. A bio-based equivalent would find it very difficult indeed to compete on price, which is confirmed by Saygin et al. (2014). It would be easier to compete on price with a low-volume, high-value chemical;
2. Bioprocesses are notoriously inefficient when it comes to scaling up to a level that can influence a market. Microorganisms have not evolved to work in the severe environment of a bioreactor, and hence serious modification is virtually always required to achieve the titre and yield (see Box

4) necessary to make it economical. This modification is an iterative process that can have long innovation cycles to achieve very high efficiency: it took the industry giants DuPont and Genencor approximately 15 years and 575 person years to develop and produce 1,3-PDO (Hodgman and Jewett, 2012). Currently it takes on average 7.4 years to launch a bio-based product (*Il Bioeconomista*, 2015).

101. Naturally, the small companies trying to make a bio-based chemical commercially opt for high-value chemicals that have low enough production volume for them to be able to influence the market. The conundrum is, though, that replacing the oil barrel for the policy maker requires bio-based alternatives to the major petrochemicals such as ethylene and other short-chain olefins.

102. As a policy option, it is suggested that a stage in the decision making should be based upon making an allowance for total global production volume which triggers a threshold for subsidy support: lower support for lower production volume, greater support for higher volume. This makes sense in the current policy setting as:

- Greater production volume means greater potential GHG emissions saving, therefore higher value in climate change mitigation. This is more attractive for nations using this mechanism to help meet emissions targets;
- It should act as the sought-after R&D stimulus for companies to make process improvements so that the large-volume bio-based equivalents will eventually be competitive at scale.

103. Such a strategy would, of course, differ in different countries. For some countries, a balanced portfolio of investments in high and low production volume products is already high priority. This step, largely dictated by emissions savings, would be entirely optional.

Production efficiency factors

104. By specifically increasing the titre (g per litre of product), yield (g product per g substrate, normally glucose) and productivity (g per litre per hour), obviously the manufacturers and the policy makers benefit, which is the preferred situation to industry and policy being at loggerheads. Lower water and energy requirements are the major outcomes, which mean improved sustainability, with two-way benefits. Here are some examples why.

- Lower volumes of water to recycle and treat can mean lower CO₂ emissions, especially if biological wastewater treatment is involved.
- Lower energy requirements for smaller bioreactors with less water as the final product is more concentrated at the end of fermentation.
- Less water has to be pumped around, less energy is required for reactor heating and/or cooling.
- Less energy is required for cleaning in place (CIP) and sterilisation in place (SIP).
- Down-time between batches would be lower, and maintenance turnaround quicker.
- Higher titre means the product is more concentrated so the process requires less energy input for downstream processing (purification from a very dilute solution can be enormously expensive).

105. What is more, creating a factor that improves production efficiency in this manner stimulates the research that policy makers want – research leading to lower marginal production cost. And, rather than paying through a subsidy, it may be possible for the public cost to be met through R&D tax credits or production tax credits, depending on the eligibility. This in the longer term would be a more palatable mechanism than mandated production.

106. It is not enough that the hardware of the bioprocess is modified to bring about improvement. Biocatalyst genetic engineering and synthetic biology are likely to take improvements much further than can be achieved with reactor design. For example, consolidated bioprocessing (CBP) refers to combining lignocellulosic conversion to fermentable sugars²² within the same microorganism that converts the sugars to bio-based products. The US Department of Energy (US DoE) endorsed the view that CBP technology is widely considered the ultimate low-cost configuration for cellulose hydrolysis and fermentation (US DoE, 2006). Box 4 illustrates the technical issues with lactic acid, a very promising bio-based chemical.

²²

One of the most significant challenges in utilising the vast global lignocellulose resource is the need for large quantities of enzymes to efficiently convert lignocellulose, hemicellulose and cellulose into fermentable sugars. These enzymes represent the second highest contribution to raw material cost after the feedstock itself.

Box 4. Lactic acid bio-production (Adapted from Upadhyaya et al., 2014)

Lactic acid is approved by the US Food and Drug Administration as GRAS (generally regarded as safe), so its applications in food and other chemical industries are diverse. It is used in the cosmetic industry, for example. However, it has recently seen a large increase in demand as a feedstock for the chemical synthesis of poly-lactic acid (PLA), a plastic with some useful engineering properties and a potentially 'green' replacement for petro-plastics in some key sectors, such as automotive (Notta-Cuvier et al., 2014).

Upadhyaya et al. (2014) recently discussed the potential of metabolic engineering as a tool to improve the lactic acid fermentation process in both a cost-efficient and environmentally friendly way. The table below consists of titre and yield data extracted from this paper to illustrate the extraordinary difficulties facing bio-production. Some of these are:

- Lactic acid can be made in various microorganisms, naturally in the lactic acid bacteria, but this synthesis faces chemical and optical purity difficulties;
- Yeasts have been used for their innate acid tolerance but they need require metabolic engineering to introduce and optimise biochemical pathways;
- *Escherichia coli* (*E. coli*) has genes encoding enzymes required for sucrose utilisation, which may allow lactate production from less expensive sugar sources. It can also be considered for fermentation from lignocellulosic hydrolysates, but there are many complications with impurities;
- Microalgae are being considered for lactic acid production, as, among other reasons, the utilisation of light energy to fix carbon could potentially eliminate feedstock costs.

Some organisms for lactic acid production and the productivity challenges.

Organism	Titre (g/l)	Yield (%)	Comments
<i>E. coli</i>	97	90	Sucrose fermentation
	62	97	Xylose fermentation
	75	85	Molasses fermentation
<i>L. rhamnosus</i>	184	>90	Reduced substrate inhibition
<i>L. delbrueckii</i>	135	90	Sucrose fermentation
	54		Starch fermentation
<i>L. pentosus</i>	3.36	95	Improved activity at pH 3.8
<i>S. cerevisiae</i>	122		Beer/bakers' yeast
<i>C. utilis</i>	93.9	91	Xylose
<i>Synechocystis</i> sp.	1.14		CO ₂ fermentation

C. = *Candida*; E. = *Escherichia*; L. = *Lactobacillus*; S. = *Saccharomyces*.

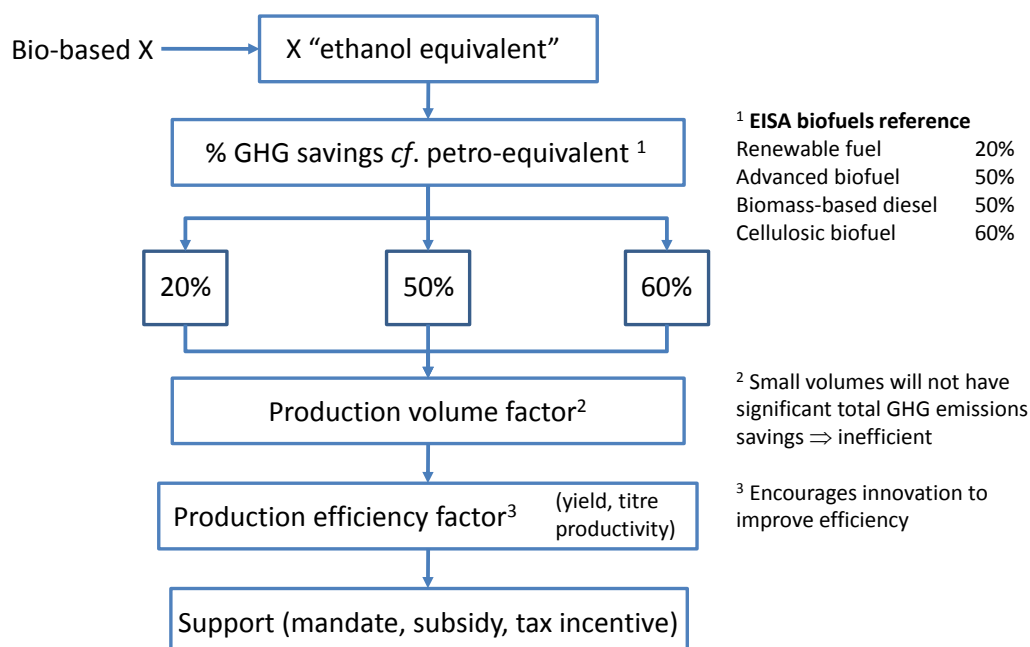
107. The Table in Box 4 shows that productivity can vary enormously with the same microorganism, with similar physico-chemical conditions and different substrates. Laboratory results are often not scalable, or present great difficulties in scaling. The engineering approach of synthetic biology is expected to bring solutions to these problems more quickly than by standard genetic engineering.

Summary

108. A cascading policy support mechanism (Figure 7) would bring bio-based materials under the umbrella of biofuels support. It is constructed in a way that addresses both environmental performance and cost-efficiency for the taxpayer. It could also stimulate R&D in the direction of making the most efficient bio-based chemicals (in terms of GHG emissions reductions) in the most efficient bioprocess (in terms of cost for the manufacturer). It specifically addresses high-volume, low-value chemicals because these have the greatest impact in replacing the oil barrel and in emissions reduction. These are precisely the chemicals

that do not attract the young bio-based industry due to the difficulty to synthesise them efficiently at scale in competition with the petrochemicals industry.

Figure 7. A generic decision support cascade for embedding bio-based materials policy support within biofuels support.



Strengths

1. This rationalises the potentially many chemicals into a single equivalent that is the industry standard (bioethanol) and that already exhibits high bioprocess production efficiency.
2. It includes two measures that are designed to improve environmental performance. The first, in this generic scheme, uses the same GHG emissions standards as in existence in the model biofuel policy (RFS), but is adaptable to any national/regional standards. The second takes account of the potential global GHG savings for any particular chemical that can be easily derived using the global production capacity. Both measures allow flexibility in the event of changes to GHG emissions standards and/or global production tonnages.
3. It should drive innovation to improve the efficiency of bioprocesses for large-volume, low-value chemicals, precisely the ones that are most difficult without policy.
4. It should make best use of public money by removing replication of bureaucracy.
5. Some of the significant issues around ethanol as a biofuel would be avoided or minimised due to, among other things, the much smaller production volumes of chemicals compared to fuels. Examples are: imagined or real food prices impacts²³; blend wall is not an issue; limited impacts

²³

It should be noted that there is a link between “imagined or real food price impacts” and food production. Specifically, one aspect surrounding corn-based ethanol is the diversion of grain for feed (primarily for cattle) to fuel. This avenue, and there could be others, can lead to price impacts.

on transportation infrastructure (e.g. no need for new pipelines) and no fuel stations infrastructure issues; less complex demand-side issues (e.g. no flex-fuel vehicles).

Mitigating the weaknesses

1. *As it stands, the cascade does not include two very important technology categories for renewable chemicals: those produced through waste CO₂, and those that can be produced either entirely by 'green chemistry' or by a combination of bio-based and green chemical technologies.* However, if the GHG emissions reductions for chemicals produced by these technologies are known, they should be rather easily incorporated into the scheme. The best example is bio-based ethylene, the synthesis of which involves fermentation to ethanol followed by chemical conversion to ethylene.
2. *It does not specify eligibility for entry to the scheme.* However, it is intended for production rather than R&D, although eligibility for chemicals that need some near-market R&D is suggested, depending on state-aid rules. Therefore it would seem sensible to make the scheme eligible to chemicals that are at a technology readiness level (TRL) of 7 and above in the US Department of Defense classification,²⁴ or TRL of 8 and above in the EC Horizon 2020 classification.²⁵ Or simply, the policy could specify technologies that are 'beyond demonstration'.
3. *The chemicals being described are identical, drop-in replacements for petrochemicals, and therefore are not 'needed' as such.* In RFS, ethanol is desirable in petrol (gasoline) as a fuel oxygenate. Therefore this would give justification for the petrochemicals industry to accept such a policy.
4. *Such a policy cannot be brought in for many bio-based chemicals as few are produced at volume at present.* This is part of the point for the policy – to stimulate greater production of a greater number of bio-based chemicals. Therefore a phased approach would be needed. Each country would need to make decisions on which chemicals to concentrate on, and slowly add to its inventory by keeping the policy flexible. This could be coordinated with a national bio economy strategy and/or a national bio refinery roadmap. The weakness is that it would be difficult to specify a date when the mandate ends or how the mandate may be phased out, as it must do to remove longer term market distortion.
5. *The position of large polymers is not clear.* Large bio-based equivalents of thermoplastics would sequester a lot of carbon, and this may not be reflected in the current policy. However, it would be reflected in the global production volume of the monomer. For example, ethylene is the largest production volume organic chemical. It is subsequently polymerised to polyethylene. If the manufacturers of ethylene and polyethylene are different, then it may be that one or the other does not qualify in this scheme. But both cannot, as this would amount to double counting as the polymerisation stage does not use any new bio-based carbon; it uses the bio-based carbon in the bio-ethylene.

²⁴ Technology Readiness Assessment (TRA) Guidance. United States Department of Defense. April 2011.

²⁵ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf

Concluding remarks

109. Creating a level playing field between bio-based materials, biofuels and bioenergy has stayed as a defining topic in bio economy arguments. The potential solution laid out here in very basic terms could address the need. Each country would need to develop the idea to suit their own conditions – after all the strengths and weaknesses will differ in different countries. Making integrated bio refineries viable depends on balancing materials, fuels and energy production. Detail work by individual countries could mitigate any weaknesses. The scheme is suggested as a cost-effective way forward as it simplified bureaucracy and infrastructure for policy implementation.

CAPACITY BUILDING IN INDUSTRIAL BIOTECHNOLOGY, SOME SELECTED COUNTRIES

Introduction

110. Any new technology that promises a nation economic growth and job creation faces the challenge of diffusion to that nation. Inevitably at this stage in history a biotechnology must approach that diffusion whilst still in the throes of a long arduous R&D phase. Industrial biotechnology is no exception. Moreover, industrial biotechnology faces a dual market challenge: it makes products that are completely new and therefore must make a market where there is none, but it also makes products to compete with a very large, well-established market (for petrochemicals).

111. For policy makers some of the measures to stimulate uptake of industrial biotechnology are readily identifiable. R&D subsidies and SME support are the most immediately obvious. Public-private partnerships that encourage private sector investments in the big, risky bio refinery investments are not so familiar to policy makers in science research funding.

112. This section examines what has been done in some OECD nations to build capacity in industrial biotechnology. They, of course, vary in approaches but with some common themes. For each country there are some recognisable companies emerging. Some have dedicated bio economy strategies; others have policy initiatives that clearly aim at creating a bio economy (Bioökonomierat, 2015). Centres of excellence have emerged through public funding. In all countries that provided information, the creation of regional clusters has been part of the strategy without exception. It may also be coincidence, but all of the countries here have strong chemical sectors.

113. For industrial biotechnology to thrive, it must start to compete with petrochemicals at the same time as building several industries simultaneously – biomass supply chains, bio-manufacturing, DNA synthesis and high throughput strain design and manufacture. Achieving economies of scale in bio-based production may prove very challenging (Kircher, 2012a). Add to this a particular complex regulatory environment, one which combines both genetic modification and chemicals regulation. Finally, industrial biotechnology has to cope with another major factor that petrochemicals did not – the ever-more urgent need for sustainability.

114. The most prominent policy associated with diffusion of industrial biotechnology has been support for the creation of regional clusters. The concept is simple – bring actors together in regions to help make the supply and value chains in cooperation with the private sector. The members then can expand the clusters by applying for grants and other financial measures to create collaborative projects and new alliances. The real strength in clusters should be the ability to coordinate multiple functions in capacity building, in particular research, demonstration, technology transfer, dissemination and training activities. Ideally the system snowballs to financial self-sufficiency and the regions become joined up. International clusters start to appear by alliance of existing clusters. All these activities are apparent in some OECD countries. Some of these are the nations building success in bio-production and the bio economy. Whether this is by planning or happenstance is difficult to elucidate. Certainly in Europe it is clear enough that investing in clusters has gone hand-in-hand with the diffusion of industrial biotechnology.

115. Regional clusters thus have a special place in this capacity building effort. This section ends by examining what metrics are needed to assess the effectiveness of clusters. This is needed because: among all the capacity building measures seen in different countries, the clusters involve the greatest number of stakeholders; governments have large ambitions for clusters with relatively small investments, and; a set of

risks exist in this strategy (OECD, 2007). That particular publication was more general, and some of the lessons from it are highlighted for the more specific industrial biotechnology clusters.

Forming and fostering spin-outs

116. It should be no surprise that there are commonalities in the way that countries approach capacity building. In the first instance, governments must create R&D incentives in its public research institutes and universities. Measures are needed to encourage the creation of spin-out companies, which then have to be nurtured through years of no or few revenues and high-risk research (Pisano, 2010): a top industrial R&D priority must be to reduce the innovation cycle to timescale attractive to investors.

117. Spin-out creation in biotechnology heavily depends on intellectual property, and Europe is less adept than the US in this regard. Europe is seen to have top class research establishments, infrastructure and capability. It has also been considered less adept at commercialise the results of promising research compared to, say, Japan, Korea and the US. Most European universities have neither funds nor infrastructure to support patenting and licensing activities. Since the late 2000s, however, there has been a general slowdown in IP generation in public research institutions. In 2013 the OECD advised that national policies and strategies for commercialising public research should be strengthened, including traditional patenting and licensing, but especially towards emerging channels such as student entrepreneurship (OECD, 2013b). However, with the seemingly increasing ease of gene editing and the potential torrent of new CRISPR tools (Pennisi, 2015), the potential exists for a similar increase in patent filings in industrial biotechnology.

118. In Germany, North Rhine-Westphalia (NRW) is home to 30% of the German chemicals industry and 50% of European industrial biotechnology start-up companies. CLIB2021 in Germany provides multiple services to spin-outs and SMEs, such as access to infrastructure, investors and production sites as well as business support and legal advice. In France, the competitive bio-based cluster Industries & Agro-Ressources (IAR)²⁶ has responded to the special challenges of fund raising for the transfer from demonstration to commercialisation within SMEs by creating IAR-Invest. It offers an inclusive service for innovative companies to: increase their visibility with private investors, especially the venture capital community; and to arrange interaction with multiple stakeholders to improve the prospects for securing investments e.g. funds, banks, regional councils, incubators and financial institutions.

Market making

119. Many biotechnology spin-out companies find themselves in the unenviable position of not only having to research and develop new products, but they must also try to develop a market. This is one reason why many spin-outs fail – the task is simply too huge with limited resources. Governments will therefore need to play a critical role in market making.

120. Markets have long been recognised as important drivers of innovation. The absence of long-term framework support and policy predictability in many OECD countries continues to make the bio economy sectors and bio-based production high-risk investments.

121. The USDA BiopREFERRED Program is often held up as a successful model for demand-side market creation. It works to increase the purchase and use of designated bio-based products through a preferred procurement initiative for federal agencies. The European Commission (2011) recognises public

²⁶ Industries & Agro-Ressources (IAR). www.iar-pole.com

procurement as a tool for awareness-raising of bio-based products and this needs to be further developed by implementing strong green public procurement programmes for bio-based products.

How to monitor the value for money of PPPs

122. In industrial biotechnology PPPs represent large investments of public money in high-risk ventures. Given that there are various options for delivery of such projects, the value for money of a PPP should be based on input from a prudent ‘public sector comparator’, or an equivalent, to compare value for money across options. How governments could enable such an analysis of PPP efficiency was set out in an OECD Council Recommendation (OECD, 2012).

A role for Intermediate Research Organisations (IROs)

123. A UK study examining alternative financing mechanisms for “exploratory development” consistently pointed towards the intermediate research organisation (IRO) (Mina et al., 2009), such as: CSIRO in Australia; the German Fraunhofer Society; the VTT Technical Research Centre of Finland, and; the Electronics and Telecommunications Research Institute of Korea. One of the policy options set out in this study was for the UK government to establish intermediate research laboratories:

“Government can support the development of some form of ‘Intermediate Research Laboratories’ with a more commercial, mission driven modus operandi through government (and possibly private sector) funding. These can enable work in selected fields to take place without the conflicting pressures of publishing and teaching explicit in academic research and act as attractors for leveraged private sector funding.”

124. What has resulted for the UK is the Centre for Process Innovation (CPI) (Box 5).

Box 5. The Centre for Process Innovation, UK



Fermentation facilities from laboratory through pilot (750 litre) to demonstration (10 000 litre)

A UK parliamentary report stated that insufficient resource were devoted to transforming research into market-ready products, processes and services that create significant value in the United Kingdom economy. The United Kingdom, it was argued, did not have enough innovation centres such as the Fraunhofer Institutes in Germany and VTT in Finland to fill this innovation phase gap. The Centre for Process Innovation (CPI) was thus established with the aim of becoming one of the first elite independent technology innovation centres (TICs).

The preferred CPI model was designed to give the United Kingdom centres greater access to cross-disciplinary skills from a number of universities, thus allowing the centres to develop deep expertise in the technologies, and to be more market driven. This approach, it was hoped, would bring greater focus and market drive than the Fraunhofer approach.

The intention was for the technology innovation centres to be independent of the universities and to be co-ordinated by a central body (the UK Technology Strategy Board). The aim was to create 10 or 12 key technology innovation centres that would play to UK strengths, each with 5 to 6 satellite centres rather than the 59 centres working in the 7 groups of the Fraunhofer.

Initially 100% funded by One NorthEast, the regional development agency of the North-East of England, CPI targeted 50:50 public-private funding (the same as the Fraunhofer model). In its first six years, it diversified its sources of public funding to include the European Union, the Technology Strategy Board, and the Department for Business, Innovation and Skills (BIS) amongst others, and reduced its dependence on One NorthEast to well below 50% of its revenues. During that period, its commercial revenues grew from zero to some 15% of total revenue (GBP 2.5 million).

CPI uses an open innovation model to de-risk process development by providing proof-of-concept testing at scale to accelerate commercialisation. The model is:

- To carry out market analysis with businesses or partners that have technology or a defined market need;
- To set up a team of technology, market and commercial professionals to design assets to develop a range of technologies which meet the market need;
- To find a combination of private and public investment to build and operate the development assets;
- For private companies - both SME and large companies – to use the assets and CPI expertise to prove, develop and scale-up their technology until it is ready for commercialisation;
- For companies then to invest their own funds to take the technology to market and create value; and

- Most importantly, for the development assets to be retained and developed by CPI for use by other companies and projects to build a UK capability in the sector.

It has outgrown its regional beginnings and has created a national and international reputation in two technology areas that are strategically important to the United Kingdom, one of them being Advanced Manufacturing for the Process Industries. Here, CPI develops advanced manufacturing technologies for the energy, high-value chemicals, carbon capture and pharmaceuticals markets amongst others with a combined potential future economic impact for the United Kingdom of between GBP 4 and 12 billion by 2025 (BERR, 2009). This business unit houses the National Industrial Biotechnology Facility (NIBF), the Industrial Biotechnology Demonstrator (IBD) and the Anaerobic Digestion Development Centre (ADDC). All have significant funding from the Department for Business Innovation and Skills (BIS) and the Department for Energy and Climate Change (DECC).

One of the identified growth industries of the future was industrial biotechnology. CPI has an industrial biotechnology team of industry-based scientists, technologists, process operators and engineers who can design and test process flows from the bench to manufacture at scale. Facilities include access to bioprocess assets in the form of development laboratories, an analytical suite, pilot facilities (up to 1 000 litres) and demonstrator facilities (up to 10 000 litres).

The industrial biotechnology services that CPI offers include:

- Product and process development
- Prototyping, demonstration and scale up
- Fabrication and pilot production
- Feedstock and product investigation
- Manufacturability and process assessment
- Process modelling and consultancy
- Technology transfer expertise
- QA/QC/Laboratory support
- ISO 9001

Source : OECD, 2014c.

125. The “Cell factory” of the VTT Technical Research Centre of Finland has facilities in synthetic and systems biology, production research and automation and fermentation facilities ranging from parallel laboratory scale bioreactors to pilot scale units. This unit of VTT is specifically for the production of chemicals and proteins. Finland sees synthetic biology as one of the breakthrough technologies that will have a major impact on future manufacturing. The Living Factories programme aims to create an academia-education-industry environment for this purpose, with funding of EUR 3 955 000 (with two Finnish university partners).

126. CSIRO of Australia is helping build capacity for the nation in a bio refining industry and the production of bio-based materials. For example, the organisation is working on using eucalyptus waste streams at timber or paper mills for manufacturing bio-PET bottles and packaging.²⁷ These bio-based

²⁷

<http://www.csiro.au/en/Research/MF/Areas/Chemicals-and-fibres/Chemistry-and-biotechnology/Biotechnologies>

aromatic chemicals can be further converted to high-value derivatives to replace petroleum-derived additives in packaging materials. Expertise developed in biocatalysis and enzyme engineering is being extended to the development of synthetic biology capability. CSIRO has developed and patented an efficient enzyme nano-factory system, comprising several different nano-machine reactors that can convert glycerol into high-value molecules such as pharmaceuticals.²⁸

127. RIKEN of Japan is the largest research organisation for basic and applied science in the country. It combines basic research with a focus on innovation. The RIKEN Biomass Engineering Program²⁹ combines several research areas, such as bioplastics, synthetic genomics, enzyme research, cellulose research, cell factory research, and also has a business development office that promotes collaboration based on the needs of industry. For example, the cell factory research team has biosynthesised 4-vinyl phenol, the monomer of a plastic with similar properties to polystyrene (Noda et al., 2015).

128. The Korea Research Institute of Bioscience & Biotechnology (KRIBB) has dedicated centres that respond to the needs of bio-based production: the Industrial Bio-materials Research Center; the Biochemicals and Synthetic Biology Research Center; the Cell Factory Research Center; the Biotechnology Process Engineering Center. It also has a SME Support Center that supports capacity building and growth of bio-based SMEs.

Belgium (Flanders)

129. According to a recent patent analysis by the ECOOM institute Flanders has a considerable specialisation in industrial biotechnology compared to other European regions. Further, Flanders has obvious strengths in the fields of industry and logistics with a crucial role for the Flemish chemical industry cluster and the harbours of Ghent and Antwerp. The sector of chemical industry and life sciences is the largest and most R&D intensive sector in Flanders. Over 750 companies employing almost 60 000 people realised a turnover of EUR 43.5 billion in 2013. The R&D expenditures of over EUR 1.6 billion accounts for nearly 50% of total industrial R&D spent in Flanders. The sector is convinced of the need to transform towards a more sustainable industry and is taking discrete steps in that sense. Bio-based technologies constitute an important part of the sector's innovation agenda. A study assigned by the Flemish government further concluded that the impact of the bio-based economy is significant in Flanders, accounting for up to 9% of the gross margin for industry in Flanders and 5.7% for employment.

Flemish Bio economy Strategy

130. In the Flanders region of Belgium, an interdepartmental working group, representing all relevant departments and agencies of the Flemish administration, developed a vision, strategy and action plan for a sustainable Flemish bio economy (published July 2013). The bio economy strategy supports the cascading use of biomass and encourages research, international collaboration, market stimulation and communication.

131. In 2015 the Flemish government assigned a roadmap study on industrial biotechnology. Based on the input of over 100 professionals from industry, academia and government four value chains were identified as being promising for Flanders on the short and medium to long term. These include the production of fine chemicals from bio-based feedstock, the generation and use of second generation sugars,

²⁸ <http://www.csiro.au/en/Research/LWF/Areas/Environmental-contaminants/Environmental-industrial-biotechnology/Biocatalysts/Molecular-machines>

²⁹ http://www.riken.jp/~media/riken/pr/publications/pamphlets/bmep-en_201307.pdf

the use of lignin-rich resources for the production of high added value materials and chemicals and the conversion of carbonaceous (waste)-gases to chemicals.

132. The Flanders region of Belgium supports the innovation hub for sustainable chemistry, FISCH, which has as one of its strategic priorities the production of technology roadmaps for the technological development of sustainable chemistry. It also supports collaboration between industry, public authorities and research organisations.

133. At the more local level, the Province of East Flanders has selected the bio-based economy as one of its focus domains. As a result, a number of initiatives have been supported by the province including the establishment of the Ghent Bio economy cluster organisation (GBEV) and the Bio Base Europe Pilot plant.

Industrial cluster initiatives

134. FlandersBio is the networking organisation for the life sciences and biotechnology sector in Flanders, with currently more than 300 members. FlandersBio supports and facilitates the sector's sustained development to ensure that it remains a strong driver of economic growth in the region. Together with Ghent Bio economy Valley and FISCH they collaborate in the CINBIOS network that was set up in 2008. The CINBIOS network gathers the different actors in the bio-based economy including industry, funding agencies and knowledge centres. Over the past years CINBIOS has organised numerous networking and partnering events, mobilising over 400 organisations in the region. CINBIOS co-authored a number of key reports to the Flemish Government including the KET roadmap on Industrial Biotechnology in 2015.

The Rodenhizedok-Kluizendok bio refinery site and Bio Base Europe pilot Plant

135. The port of Ghent is an important logistical hub in the region specialised in dry bulk. A number of bio-based companies are active in the harbour including Stora Enso, Oleon and Cargill. The port houses one of the largest storage capacities in Europe for agri-bulk. The Ghent Port Company supports the development of the bio-based economy and facilitates the development of synergies between its members. An example of integration is the Rodenhizedok bio refinery cluster which may be Europe's largest integrated bioenergy production complex, with its production of bioethanol (Alco Biofuel), biodiesel (Bioro) and bio-electricity (GDF-Suez) all in one single site. The development of bio-based R&D activities is further supported by GBEV, a not-for-profit organisation established by Ghent University, the City of Ghent, the Port of Ghent and the Development Agency East-Flanders.

136. Since 2010 the Bio Base Europe pilot plant has been operational next to the refinery cluster. The pilot plant is part of Bio Base Europe, one of Europe's first open innovation and education centres for the bio-based economy that received important financial support from Europe, the province of Zeeland and the Flemish region. The pilot plant houses state-of-the-art facilities that operate from a laboratory level to a multi-tonne pilot scale. It operates as a service provider for process development, scale up and custom manufacturing of bio-based products and processes. The Bio Base Europe Pilot Plant is an important step towards realising the growing ambition of the Port of Ghent to not only house a bioenergy production complex, but also move towards the more sophisticated production of bio-based chemicals and other products. For this ambition, the Kluizendok site has been preserved.

LanzaTech - ArcelorMittal - Primetals Technologies waste gas bio refining

137. Europe's first-ever commercial scale production facility to create bioethanol from waste gases produced during the steelmaking process is to be built in Belgium. Construction of the EUR 87 million flagship pilot project, which will be located at ArcelorMittal's steel plant in Ghent, should be ready for operation in mid-2017. A total of EUR 10.2 million has been secured under the EU's 2020 Horizon

programme for research and development and talks are currently taking place with potential equity and debt partners.

138. Steel making is among the most important industrial activities contributing to GHG emissions. Approximately 50% of the carbon used in the chemistry of steelmaking leaves the process as the highly toxic carbon monoxide. LanzaTech technology recycles steel-making waste gases and ferments them with a proprietary microbe to produce bioethanol. Every tonne of bioethanol produced, displaces 5.2 barrels of petrol (gasoline) as well as reducing ArcelorMittal's CO₂ emissions by 2.3 tonnes.

Citrique Belge

139. With a long tradition of citric acid production Citrique Belge in Tienen remains today one of the largest citric acid producers in Europe. The company has developed into a cost-competitive, high quality and service-oriented company to stay ahead in the very competitive world market.

Avantium – BASF Joint Venture³⁰

140. In the port of Antwerp, the creation of a new joint venture of BASF and Avantium will focus on the market introduction of bio-based polyethylene furanoate (PEF), which has a number of advantages over petroleum or even bio-based PET, for which it provides an alternative. PEF is a lighter material with better barrier and thermal properties. Avantium plans to build the world's first commercial plant for the production of furandicarboxylic acid (FDCA), a new chemical building block produced from renewable resources (fructose) in the port of Antwerp. The reference plant is to produce 50 000 tonnes per year. In March 2016 Avantium and BASF launched a joint venture for the production and marketing of FDCA and for the marketing of PEF. The joint venture is supported by a EUR 20 million investment from public and private investors, led by PMV Participatie Maatschappij Vlaanderen, the independent public investment company in Flanders.

Alchemis10

141. In this project, at the Hooge Maey landfill site, Antwerp, algae are mass-produced in photo-bioreactors on a landfill site. Algal growth requires sunlight, water, nutrients and CO₂. Nutrients and CO₂ are provided by the emissions from the anaerobic decomposition of municipal solid waste (MSW) in the landfill. Energy for the automated production process and downstream processing and concentration of the algae is provided by the biogas from the landfill site as well. In addition, the algae result in lower energy consumption in the on-site water treatment unit, as they directly absorb the ammonium contained in the waste water.

142. Bio-based raw materials are extracted from the algae which can be used in the chemical industry. They replace raw materials that are now extracted from fossil fuels. The algae project was developed together with seven partners and received partial financial support from the Flemish Environmental and Energy Technology Innovation Platform (MIP) for three years. Partners are from both the public and private sector.

ILVO

143. ILVO, the Institute for Agricultural and Fisheries Research in Flanders, started GENESYS, a four year coordinated action in 2012 to valorise unused biomass from waste streams and by-products from

³⁰

www.bio-basedpress.eu/2016/05/avantium-investment-climate-europe-has-much-improved/

animal and plant production and fisheries, through the development of innovative valorisation routes and instruments for successful system innovations.

VIB

144. VIB is a life sciences research institute in Flanders, Belgium with more than 1 300 scientists from over 60 countries performing basic research into the molecular foundations of life. VIB is an excellence-based entrepreneurial institute that focuses on translating basic scientific results into pharmaceutical, agricultural and industrial applications. VIB works in close partnership with the five universities of Flanders and is funded by the Flemish government. One of their recent spin-off companies is Global Yeast, a new company that will develop and deliver superior industrial yeast strains for bioethanol and the green chemicals industry. The company raised a total of EUR 6.25 million from an investor consortium composed of a Brazilian VC Fund, two Belgian funds and VIB and will focus on the Brazilian market and large groups worldwide.

VITO

145. VITO is a leading European independent research and technology organisation based in Belgium, with a subsidiary in China. It specialises in the areas of clean technology and sustainable development. VITO is a solutions provider, and advises industry and governments on determining future policy. VITO has 750 employees who work on global projects. The total turnover of VITO amounted to about EUR 140 million in 2014.

146. VITO enhances industrial innovation regarding more efficient (bio)chemical processes, reuse of valuable components from process streams and industrial use of biomass and CO₂. It also specialises in increasing the valorisation of waste and residual biomass streams, and develops and monitors new value chains for a bio economy.

Belgium (Wallonia)

147. To create a new dynamism for the Walloon industry that still was struggling after the decline of heavy industry, the Walloon government in 2004 launched the so-called Marshall Plan defining priority actions until 2009 with a budget of EUR 1.6 billion. After evaluation, in 2009, a follow up strategy was developed with a strong focus on green growth with the Marshall Plan 2.0 Green. This plan mobilised EUR 1.6 billion from the Walloon region and EUR 1 billion from industry in a public private partnership. Additional sources made available a total budget of EUR 2.75 billion until 2014.

Industrial cluster initiative - Greenwin³¹

148. In response to the Marshall Plan 2.0 Green, in 2011, Greenwin, a competitiveness cluster that is focussing on environmental technologies was created. Next to more general objectives to create sustainable economic growth, one of its major objectives set out was to ensure the transition towards a bio-based economy and provide simpler access to recycled resources.

149. In the third Marshall Plan (2022) the transition towards a circular economy is first described as one of the priorities of the Walloon government, next to sustainable use of resources. This is further elaborated in the Marshall 4.0 Plan. The latter governs a budget of EUR 2.9 billion over a period from 2015 to 2019 and has as one of its objectives to set up industrial pilot projects in support of the circular

³¹

www.greenwin.be/en

economy, including the valorisation of waste from agriculture and other sectors and the production of biogas.

Galactic/Futerra

150. With more than 20 years of experience in biotechnology, Galactic has become a leading producer of lactic acid and its derivatives with applications in the food, feed, personal and health care and industrial markets. The company established a 50:50 joint venture with Total Petrochemicals in 2007, named Futerra, to develop technology for polylactic acid (PLA) production from renewable vegetable resources and received support from the Walloon government.

Towards a bio economy strategy in Wallonia

*Valbiom*³²

151. Valbiom was created already in 2002 as a non-profit organisation to valorise non-food biomass to develop the bio economy. ValBiom offers an answer to requests from industry, farmers and administration, a direct support to new projects carriers, a technology watch. Valbiom receives its primary funding through the Walloon Ministry of Agriculture and the Ministry of Energy and works in close collaboration with Gembloux Agro-Bio Tech (University of Liège), the University of Louvain (UCL) and the Walloon Agricultural Centre (CRA-W).

*Coq vert*³³

152. Coq vert is a collaborative initiative between Greenwin, Valbiom, AWEX - a governmental investment body, Essenscia-Wallonie - the regional chemical and life science sector organisation for the development of a competitive bio economy in Wallonia, the Wood Walloon Economic Office and WAGRALIM – the cluster boosting business and employment in the food industry. Coq vert was launched in 2013 as part of the updated Marshall Plan and goals are set up to 2030. In the first phase biomass streams for second generation bio refineries have been identified, as well as relevant companies that will be involved in the bio economy. Coq vert specifically focusses on the use of agricultural by-products and waste, on side streams from paper and food industry and on the use of municipal waste streams. According to these analyses the Walloon bio economy strategy may affect 37 large companies, 15 small and 14 medium size companies. In addition, collaboration with neighbouring regions is sought and 15 synergies were found with neighbouring regions. A strategy document describing how to reach the goals is expected by the end of 2016, at the request of the Minister of Agriculture.

153. According to Essenscia-Wallonie 10% of the turnover in the Walloon chemistry sector is coming from bio-based production. This sector is estimated to account for 2 500 jobs in green chemistry versus 12 000 in the chemical sector excluding the pharmaceutical industry.³⁴ In 2014, five bio-methane production sites were in place, next to eleven heat production sites on wood and three on agricultural biomass.³⁵

³² www.valbiom.be/

³³ www.coqvert.be/en

³⁴ www.coqvert.be/doc/La_chimie_verte_en_Wallonie_chiffres_et_perspectives_2014_2.pdf

³⁵ <http://valbiom.be/files/library/RA-VALBIOM2014-light.pdf>

BIC-Wallonia³⁶

154. A partnership between Valbiom and Greenwin was set up to represent the Walloon bio economy industry in the Bio-based Industries Consortium (BIC) that brings the European bio-based industries together. Nine SMEs³⁷ are represented in this way, in what is called BIC-Wallonie. Many other Belgian companies, universities or institutions are direct members of BIC.

England and Wales

155. Industrial biotechnology is gaining increasing recognition as a vital and emerging part of the UK economy, capable of producing innovative solutions to sustainable and cost-effective manufacture of medicines, chemicals, materials and energy. A report by Capital Economics published in 2015 (Chambers et al., 2015) estimated that British industrial biotechnology and bioenergy activities involved around 225 companies and generated GBP 2.9 billion of sales revenue in 2013/14. When up- and down-stream factors are taken into account, the sector was responsible for GBP 4.5 billion of gross value added and over 63 000 jobs. Importantly this is a high growth sector in the UK with real-terms turnover expected to grow by 40% in five years, 131% in ten and 192% in twenty years.³⁸

Leadership and co-ordination

156. Investments in capacity building for industrial biotechnology are led by the Industrial Biotechnology Leadership Forum (IBLF), which includes key industries in the industrial biotechnology sector, as well as representatives from government, academia and environmental NGOs. The UK Knowledge Transfer Network hosts a team which supports knowledge exchange for industrial biotechnology which includes specialists in bioscience and synthetic biology. The BBIA is a new the UK trade body for companies producing bio-based and biodegradable products and promotes the circular bio economy. Regional initiatives also bring together IB innovation stakeholder: examples include the BioVale Innovation Cluster in Yorkshire and the Humber (see case study) and the North East Bioresources and Renewables (NEBR) cluster.

Innovation support programmes

157. Led by the Biotechnology and Biological Sciences Research Council (BBSRC), the UK Research Councils and Innovate UK have been supporting development of industrial biotechnology capacity through a range of programmes.

BBSRC Sustainable Bioenergy Centre (BSBEC)

158. BSBEC is a GBP 24 million investment which brought together six research groups from twelve universities and institutes with support from fourteen leading industrial associates. Starting in 2009, the programme supported research into cell wall sugars and lignin, lignocellulosic conversion to bioethanol, second generation bacterial biofuels and marine wood borer enzyme discovery.

³⁶ www.coqvert.be/en/bic-bbi

³⁷ Personal communication Valbiom, Jonathan Guévorts, Chef de projet Produits biobasés, biolubrifiants et ACV

³⁸ Biotech Britain: an assessment of the impact of industrial biotechnology and bioenergy on the United Kingdom economy. 10 June 2015 <http://www.bbsrc.ac.uk/documents/capital-economics-biotech-britain-july-2015/>

IB Catalyst

159. The IB Catalyst supports research and development into the processing and production of materials, chemicals (including pharmaceutical precursors and biopharmaceuticals) and bioenergy, as well as the development and commercialisation of innovative industrial biotechnology processes to manufacture a wide range of existing and new products through collaborative and non-collaborative research grants.

160. With joint funding from Innovate UK, the Engineering and Physical Sciences Research Council and BBSRC, the IB Catalyst has already committed over GBP 41 million in projects spanning from production of fine chemicals or proteins through to production of commodity chemicals and fuels. In 2015-16 a further GBP 34 million will be committed.

Networks in Industrial Biotechnology

161. BBSRC, with support from EPSRC, have committed GBP 18 million to fund 13 unique collaborative Networks in Industrial Biotechnology and Bioenergy (BBSRC NIBB). These foster collaborations between academia, industry, policy makers and NGOs in order to find new approaches to tackle research challenges, translate research and deliver key benefits in IBBE. Each network has a particular focus area and provides proof of concept funding and Business Interaction Vouchers.

Department for Transport Advanced Biofuels competition

162. Three companies have been awarded a share of a GBP 25 million fund to develop low emission biofuels and boost local industry.

- Celtic Renewables, based in Edinburgh, has been awarded GBP 11 million to fund a new plant to make biofuels from Scotch whisky by-products with plans to open a further 3 commercial plants across Scotland in the future³⁹.
- Nova Pangaea Technologies Ltd, based in Tees Valley, will receive GBP 3 million to help make biofuels from forestry waste. The process is unique in being continuous and, importantly, it is scalable to oil industry volumes.
- Advanced Plasma Power, in Swindon, will receive GBP 11 million to help develop biofuels from ordinary household waste.

Centre for Process Innovation (CPI): National Industrial Biotechnology Facility and National biologics manufacturing centre

163. CPI, located in the North East of England (see Box 5), bridges the gap between early stage concept and scalable commercial process mitigating scale-associated risk and offering understanding of costs. With state of the art facilities and technical expertise, CPI helps de-risk process development through proof of concept testing to accelerate the commercialisation of new products and process technologies. Their multidisciplinary team has completed feasibility assessments, process development projects and piloting studies for UK, European and international clients. CPI is part of the UK advanced manufacturing catapult centre which helps turn ideas into commercial applications by addressing the gap between technology concept and commercialisation.

³⁹

Now in doubt as the result of the withdrawal of a Chinese investment in the company.

Biorenewables Development Centre (BDC)

164. The BDC combines biology and chemistry to catalyse sustainable business growth across the global bio economy. Spun out of the University of York with investment from the European Regional Development Fund, the Department of Business Innovation and Skills (BIS) and the Higher Education Funding Council for England (HEFCE), the BDC is an open-access RD&D centre that bridges the gap between academia and industry and provides industry with new processes to convert plants, microbes and bio wastes into products. The centre offers pre-processing, process development, genetic analysis, plant science, novel equipment demonstration, analytical services and microbiology. Since its establishment in 2012 it has undertaken over 200 projects all along the bio-based supply chain for clients from SMEs to global multinationals.

Microbiorefinery (MBR)

165. With support from the UK's Regional Growth Fund, the University of Liverpool and Unilever have collaborated to establish an open access microbiorefinery research facility. Now fully operational, the MBR provides state of the art high-throughput bio refining facilities including synthesis, purification and testing as well as expertise to develop novel functional materials from non-petrochemical feedstocks.

Institute of Process Research and Development (IPRD)

166. Established in 2008 at the University of Leeds, the IPRD brings together experts from process chemistry and chemical engineering to develop technologies which delivered cost reductions, quality benefits, increased productivity and reduce waste and energy utilisation in product manufacture. The team works in the fine chemical and pharmaceutical sectors.

BEACON

167. BEACON is led by Aberystwyth University in collaboration with partners at Bangor and Swansea Universities. It aims to build integrated 'Green Supply Chains' with a focus on developing new routes to functional, cost-competitive products using biomass rather than oil. Backed by GBP 10.6 million from the European Regional Development Fund through the Welsh Government, it offers capacity for solutions from bench to demonstration scale for new ways of converting crops such as rye grass, oats and *Miscanthus* into products including pharmaceuticals, chemicals, fuels and cosmetics.

Institute of Food Research

168. The Bio refinery Centre at IFR in Norwich offers tailored solutions to convert waste biomass into added value products using a bespoke approach from laboratory scale through to small pilot, with a focus on second generation biofuels, biomass exploitation, fibre modification, yeast screening and propagation. Expertise includes size reduction and physical separation through pre-treatment options, fermentation and distillation as well as chemical analysis and microscopy.

BioVale, York

169. BioVale is a bio economy innovation cluster in the Yorkshire and Humber region of the UK. BioVale is seen as a gateway to bio economy opportunities across the region, including research and innovation partnerships, bio-based businesses, investment and specialist facilities. Initiated by stakeholders from local government and the knowledge base, the cluster is now steered by a group reflecting regional bio-based industries such as such as AB Agri, Drax, Croda and smaller companies as well as the academic and public sectors.

170. BioVale aims to provide a ‘one-stop-shop’, bringing together business and academia to support the development of innovative, high value products and processes. It brokers a range of support mechanisms that include: open access R&D and demonstration facilities; training and exchange of staff; development of business growth space; inward investment, trade and export, and; advocacy with policy makers.

171. Investments in BioVale are expected to catalyse the creation and safeguarding of 800 new jobs by 2026, as well as generating over GBP 700 million in additional net GVA, contributing to creation of a bio economy of over GBP 12 billion in Yorkshire and the Humber.

172. BioVale signed a memorandum of understanding with the French Industries and Agro-Resources (IAR) cluster in 2014. This has led to a formal agreement with similar clusters based in Holland and Germany, 3Bi, involving joint research, sharing of facilities and cooperation on developing new markets.

France

173. A range of public and private initiatives in France is building capacity in industrial biotechnology, synthetic biology and green chemistry. Other than addressing the grand challenges, France with 156 600 direct industrial chemistry jobs,⁴⁰ has realised the need to keep its chemicals sector competitive while dealing with high energy prices and other factors downgrading the performance of the European chemicals sector more generally. The industrial chemicals sector is the top manufacturing export sector in France, with a turnover of over EUR 80 billion, and is the sixth largest chemicals producer in the world. Therefore a lot is at stake.

French national and regional government initiatives

174. The French State has fostered the development of green chemistry, in line with the government’s *Grenelle* environmental policies. The French chemical industry is shifting towards diversifying feedstocks, and decreasing its dependence on fossil feedstocks: by 2017, it is expected that 15% of the raw materials used in the industry’s processes will be plant-derived. This shift will improve the re-use of green waste and should also provide long-term benefits to the agricultural sector.

175. The French government is also creating Institutes of Excellence for Low-carbon Energy. Other related state-driven initiatives include fostering the green chemistry sector via the FUI Single Inter-ministerial Fund for financing cluster-accredited projects. The French Environment Agency (ADEME) was awarded a 2010 budget of EUR 1.35 billion to foster the deployment of demonstrator projects in the fields of renewable energy and green chemistry.

176. Regarding regional initiatives, both Champagne-Ardenne and Picardie are especially active in fostering green chemistry/industrial biotechnology initiatives with a focus on supporting the agricultural sector. They have strong motivation for doing so: one in every fifteen inhabitants of Champagne-Ardenne is involved in agriculture. In 2004, the Poitou-Charentes regional council started to promote an eco-industrial sector with a view to developing companies active in sustainable development and green growth.

⁴⁰

<http://www.aiche.org/resources/publications/cep/2015/december/frances-chemicals-industry-rooted-tradition>

***Agro-Industrie Recherches et Développements (ARD) and Bioraffinerie Recherches et Innovation (BRI)
- the Biorefinery site at Bazancourt-Pomacle***

177. ARD was created in 1989 by exploiting the notion of value creation through non-food applications to find new opportunities from the produce of its shareholders (around 3 million tonnes per annum of mixed biomass - cereals, sugar beet, alfalfa, and oilseeds). The site employs in total about 1 000 people, and has created a further 600 indirect jobs. The site has received about EUR 1 billion in investments, with annual revenues of the order of EUR 500 million. In terms of demonstrator capability, ARD has previously hosted BioAmber, Amyris and Global Bioenergies.

178. The innovation hub BRI is an open hub in the field of biorefining. BRI brings together various bio refineries at Bazancourt-Pomacle, the R&D centre for ARD, as well as the French engineering schools Ecole Centrale Paris, Agro Paris Tech, and NEOMA Business School. Therefore, it covers the value chain from fundamental research to the pre-industrial prototype. BRI is supported financially by the Ministry of Industry of France, the General Council of the Marne Département, the Region Champagne-Ardenne, and the city of Reims.

179. Perhaps the greatest strength of the Bazancourt-Pomacle complex is the direct involvement of farmers, some 10 000 of them, through co-operatives. As they are at the start of the supply chain, it is extremely important to have farmers as part of the process, a lesson for all stakeholders involved.

Roquette Freres

180. Roquette is a French company with headquarters and main production plant in Lestrem, Northern France. The core business of Roquette is biorefining/ starch production and the company has adopted the concept of integrated bio refining. It transforms in excess of 8 million tonnes of renewable resources such as corn, wheat, potatoes and peas into ingredients for a wide range of food and non-food industries. Roquette has designed more than 700 intermediary products used to modify or improve the manufacture of final products. One of its five major product lines is fermentation process derivatives and fine chemicals. There are now 21 production plants world-wide.

Industry and Agro-resource (IAR) cluster

181. Since its creation more than ten years ago, the IAR Cluster has been committed to plant chemistry and industrial biotechnology. It is now concentrating its efforts on deploying competitive regional bio refineries in the rural setting i.e. in the heart of production areas. In those ten years, around 120 projects have been approved and financed, totalling over EUR 1 billion. If these projects have a common theme it is developing technology and products that replace oil-based raw materials with agricultural, forestry and algal products.

182. IAR-Invest offers partnering services for companies with private investors, mainly those specialising in venture capital. It offers support in fundraising, and facilitates meetings with potential national/regional councils and public/private investors, funds, banks, incubators and financial institutions.

Global Bioenergies

183. Based in Evry, near Paris, Global Bioenergies has specialised in bio-based production of short chain alkenes (olefins), the building blocks of the modern chemicals industry. It recently announced that it is transforming from a microbiology company to a chemical engineering company, heralding the start of the road to commercial production. It was founded in 2008 to develop a process converting renewable resources into isobutene, one of the main petroleum derivatives.

184. It is now entering pilot production of isobutene with help from funding by the French government programme *Investissements d'Avenir*. In May 2015 Global Bioenergies delivered the first batch of renewable gasoline to Audi. The company is replicating its achievement with bio-based isobutene now with bio-based propylene and butadiene, two members of the gaseous olefins family which are key molecules at the heart of petrochemical industry.

Toulouse White Biotechnology (TWB)

185. TWB is a pre-industrial demonstrator for sustainable production based on industrial biotechnology. It is considered a “*future centre of excellence in the field of industrial, or white, biotechnology*”, aimed at being a Joint Service Unit under the auspices of INRA (the National Institute for Agricultural Research), INSA (the National Institute for Applied Sciences) and CNRS (the National Centre for Scientific Research).

186. The philosophy is that, being able to continue the research phase through to pre-industrial pilot testing at the same site, there are various benefits to be had, but especially faster process development. Two key initiatives at TWB are different from those seen in similar organisations. Firstly, time has been spent perfecting a consortium agreement, by which partners are bound, that simplifies contract negotiations, which can often be a source of severe delays. It is considered essential to the TWB consortium, with 23 industrial partners and nine public institutions. Secondly, projects integrate ethics and sustainable development issues to assess future social acceptance.

187. As an example of activities, TWB and Hamilton have collaborated to develop an innovative bioprocessing platform for microbial strain characterisation and optimisation, greatly reducing the time required for strain production.

188. TWB announced the creation of EnobraQ, a company that develops yeast capable of using CO₂ (atmospheric or industrial origins) and transforming it into molecules of interest for the chemical industry. It is based on a breakthrough innovation that involved designing a synthetic *Saccharomyces cerevisiae* which, like plants and microalgae, can use CO₂.

Pôle Eco-Industries de Poitou-Charentes

189. The *Pôle Eco-Industries de Poitou-Charentes* is a competitiveness cluster with a mission oriented to research and innovation in green industrial processes. Since 2008, more than 50 R&D projects have been initiated around industrial ecology and circular economy, renewable energy, energy efficiency and management and recovery of waste and agro-industrial by-products. It brings together farmers, researchers, industries and service providers, with the cooperation of the universities of La Rochelle and Poitiers, CNRS units, INRA research centres and engineering schools.

Sofinnova

190. Sofinnova Partners is a leading European venture capital fund based in Paris investing in start-up and early stage companies across Europe and North America. It has three domains of focus in the life sciences, one being industrial biotechnology. It is often the first institutional investor in Round A financings. Sofinnova take a role on the boards of its portfolio companies and plays an active role from the formation phase.

191. One of the activities of the company is the Sofinnova Partners Renewable Chemistry Start-up Award. In 2015, there were 38 candidates for the award, spanning projects such as: microbial oils; anti-foulants; biorefinery technology to create added value from waste woody material; synthetic biology technology to transform fine and specialty chemical industries using designer cell factories; levulinic acid

directly from biomass; biodegradable plastics from methane gas; cyanobacteria to produce chemicals and fuels from CO₂ and sunlight; algorithms for the rational design of optimised microbial strains for the production of specific target compounds; biomass to high value applications in solvents and plasticisers.

Industrial Biotechnology Innovation of Synthetic Biology Accelerator (IBISBA)

192. The US, Asia and Europe are all investing heavily in industrial biotechnology and synthetic biology. Regarding research infrastructures, Europe needs to overcome the fragmentation of its research effort, and reap better value for public investment. To this end, IBISBA is a proposed pan-European research infrastructure (with the headquarters in Toulouse), dedicated to the acceleration of the development phase of bio-based manufacturing processes. The IBISBA ambition is to create a distributed, highly operational research infrastructure containing world-class facilities that will be available to the European research community and the EU industrial sector alike. The overall aim is to divide the concept-to-market time of bioprocesses (roughly ten years) by two, thus significantly reducing the financial burden and risk associated with industrial biotechnology.

Future initiatives

PIVERT

193. The PIVERT project will focus on the development of third-generation bio refineries for the added-value use of oil seed crops and forest biomass in a range of applications. Public- and private-sector research providers will work together on a technology park and will make PIVERT one of the top institutes in the field of green chemistry. The French government will provide EUR 65 million towards the total project cost of EUR 219 million.

CIMV SA

194. With headquarters in Paris, R&D in Toulouse and pilot plant in Bazancourt, CIMV has been developing its bio refinery technology for over a decade. Now, working with several partners including Dyadic, Rolkem, TWB and Taurus Energy, CIMV intends to build a demonstration plant near Toulouse, which should enter into operation some time in 2017, with the aid of a substantial European Commission grant. According to early announcements the plant will process 24 tons of biomass per day and produce 700 tons of 2G ethanol and 750 tons of BioligninsTM (phenolic substitutes for phenol-formaldehyde resins or polyurethane formulations).

Germany

195. In Germany industrial biotechnology is considered an integral part of the bio economy, which is understood as a vision to secure global nutrition, produce safe and healthy food, shape sustainable agricultural production, develop energy sources based on biomass and support the industrial use of renewable resources. In particular, it comprises the use of biotechnology and the targeted improvement of biological production systems in industry. The realisation of the bio economy, however, should not have adverse effects on global food and nutrition security.

196. By introducing the National Research Strategy Bio Economy 2030, in 2010 the Federal Government laid the foundations for realising a sustainable, bio-based economy by the year 2030 on the base of intensive research, development and innovation. Since 2012, when the Federal Government put forward its cross-departmental policy strategy for co-operation in bio economy, many public strategic efforts were bundled to further strengthen the implementation of the vision of a bio economy. The government is advised by the *Bioökonomierat* a high-level, science-driven policy advice panel. The council

is made up of experts from academic and non-academic research institutes, from the federal government's own departmental research sector and from the private sector.

197. Under the National Research Strategy BioEconomy 2030 research, development and innovation is supported by a series of funding initiatives and programmes set up by Ministries on Federal and State level as well as via institutional funding. To achieve its ambitious goals, the strategy is endowed with financial means of up to EUR 2.4 million for 6 years (until 2016).

198. Funding in the thematic field of bio industry is central among the activities under the bio economy strategy, thus, the Federal Ministry of Research and Education put forward a series of dedicated funding initiatives. The aim of this commitment is primarily to promote research, development and innovation by project funding. Capacity building is also an indispensable issue of public engagement. Thus (public) funding contributed to initiate a number of bio industry clusters and bio refinery plants.

Bioindustry 2021

199. In 2006 the Federal Ministry of Research and Education initiated a cluster competition to strengthen industrial biotechnology in Germany. Five industrial biotechnology clusters were selected and received funding in a total of EUR 60 million:

- *CLIB 2021*: The home region of CLIB2021 is NRW, home to 30% of the German chemical industry and 50% of European start-ups in industrial biotechnology. About 30 % of CLIB's members are non-German;
- *BIOCATALYSIS 2021*: The cluster links the expert knowledge of large concerns, SMEs and academic research groups to translate basic science into innovative products for chemicals, cosmetics, food, pharmaceuticals and detergents;
- *CIB Frankfurt*: CIB is the Cluster for Industrial Biotechnology. The cluster concentrates on industrial biotechnology, with special emphasis on fine and speciality chemistry;
- *The Biopolymers/Biomaterials Cluster*: The cluster supports R&D projects which develop innovative biomaterials and bioplastics to make them accessible for a wide market;
- *IBB Netzwerk GmbH* (formerly *BioM WB GmbH*): The network is focused on the state of Bavaria and became the starting point for numerous start-ups. Clariant's Sunliquid pilot plant in Straubing is part of that regional cluster.

Biotechnology 2020+

200. In 2010 the Federal Ministry of Education and Research launched the strategy process "*Next generation of biotechnological procedures – Biotechnology 2020+*". Carried by the scientific community and supported by funding, the foundations for biotechnological production processes of the future – going beyond current fermentation or bio catalytic processes – are laid.

Industrial Biotechnology Innovation Initiative

201. The Federal Ministry of Education and Research supports strategic alliances of industrial partners for the development and implementation of innovative biotechnological production processes in industry. Five strategic bio-industry alliances were selected for funding so far.

Bio Economy Cluster

202. The vision of the Bio Economy Cluster is to establish the world's first bio economy on a regional scale. The cluster's strategy is to develop the region's economy in the context of a bio economy and to create new impulses for growth. Different sectors, like the timber and forestry industry, the chemical industry, the plastic industry and plant engineering, are working together as part of a regional centre of competency in bio-economics. The Bio Economy Cluster is funded by the Federal Ministry of Education and Research with up to EUR 40 million. In the context of public funding several bio refineries emerged converting a variety of feedstocks to different products, applying dedicated biotechnological and mechanical/thermal approaches.

bioliq®, Karlsruhe

203. Regionally produced biomass is de-centrally pre-treated to obtain an intermediate energy carrier of high energy density (bioliqSyncrude), which can be transported economically over long distances to supply an industrial plant of reasonable size for synthetic fuel production.

Fraunhofer Center for Chemical-Biotechnological Processes (CBP Leuna)

204. Arising from a Fraunhofer pilot facility working on lignocellulose to chemicals, Leuna features a co-localised bio refinery in which biomass, e.g. from regional beech forests, is digested applying the Organosolv process and subsequently biotechnologically converted. The CBP in Leuna closes the gap between the pilot plant and industrial implementation. By making infrastructure and plants/ mini-plants available, the Fraunhofer CBP makes it possible for cooperation partners from research and industry to develop and scale processes for utilising renewable raw materials up to an industrial scale.

205. Further, various facilities on pilot- and lab-scale are located at different research and development centres in German universities and institutions (e.g. Research Center for Industrial Biotechnology, Technische Universität München). Aside from these publicly sponsored plants, there are a number of privately run installations that aim at the optimisation of processes and the development of new processes and products.

Zeitz, Saxony-Anhalt

206. At the bottom-up bio refinery of the CropEnergies Bioethanol GmbH sugar beet and different cereals (wheat, maize, barley and triticale) are treated and converted into sugars and then bioethanol as the main product. Residues are further processed into feed and CO₂ is liquefied to food-grade for use in the food industry, or as cooling liquid anti-freeze agent.

Straubing, Munich

207. The Sunliquid demonstration plant run by Clariant AG is a top-down bio refinery processing wheat and corn straw into cellulose, hemicellulose, lignin and C5-/C6- sugars. Further processing yields bioethanol.

Brensbach, Hesse

208. At the top-down bio refinery run by Biowert GmbH grass and grass silage is converted into different products: AgriCell (insulation, fibre-based), AgriPlast (plastics), AgriFer (fertilizer) and AgriProt (proteins for feed supplements/cosmetics/flavours, proteins/amino acids).

Selbelang, Brandenburg

209. The bottom-up bio refinery jointly operated by BIOPOS e.V., FMS- Futtermittel GmbH, biorefinery.de GmbH, and LINDE AG uses lucerne, clover, and grass as raw materials. Following wet fractionation and pressing, the resulting press juice and cake are further processed (fractionation of liquids, biochemical/ biotechnological/ hydrothermal/ thermo-chemical conversions) into cellulose, hemicellulose, proteins, liquids for fermentation, and sugars.

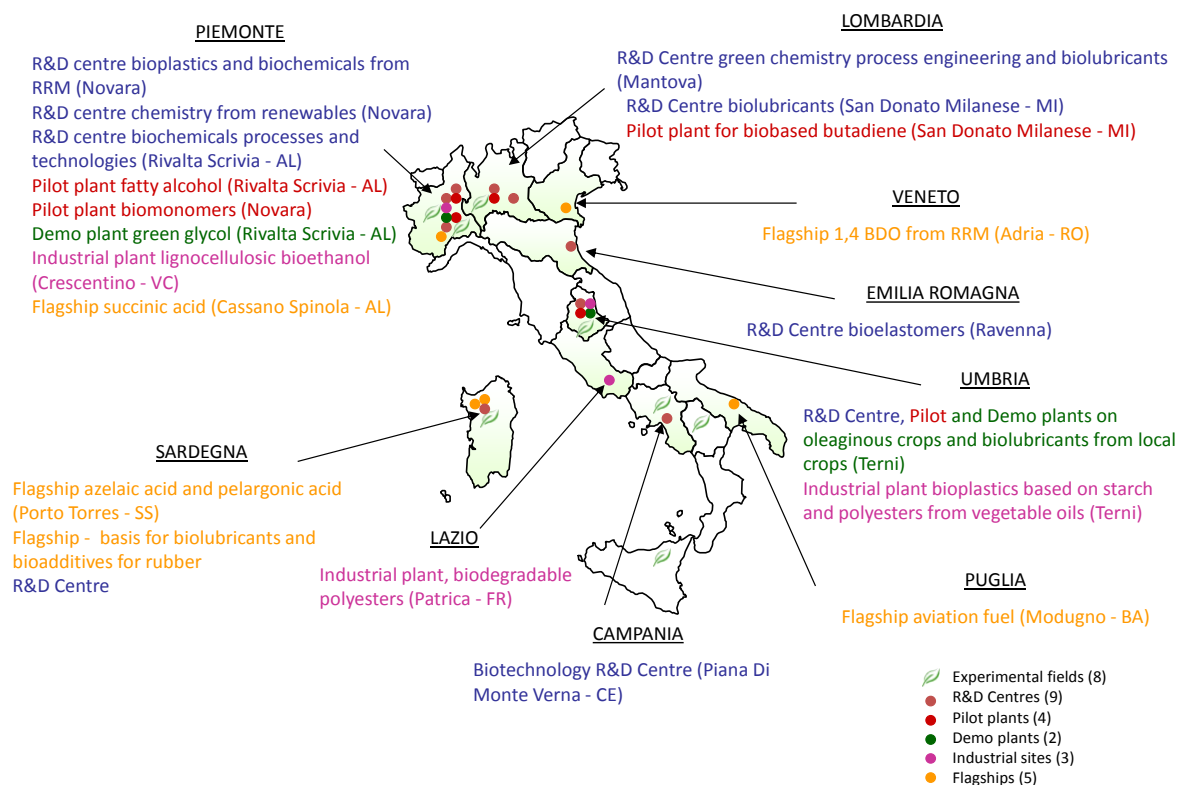
European cooperation

210. On the European level Germany has, until recently, coordinated the collaborative working group “Integrated Biorefineries” under the Standing Committee for Agricultural Research (SCAR), it closely follows the activities of the Private Public Partnership on “Bio-Based Industries” (BBI) as partner in the Member States Representative Group and is active funding partner in the ERA-Net initiative on industrial biotechnology ERA-IB.

Italy

211. Of all of the large chemicals producers in Europe, Italy seems to face some of the biggest challenges. There have been several petrochemicals plant and refinery closures since the financial crisis. However, with its very large agricultural sector, it could take advantage of a wealth of waste materials for bio refining. First-of-kind legislation to ban single-use plastic bags is credited with kick-starting bioplastics production in the country.

212. In the case of Italy the vast majority of the initiatives have come from the private sector (Figure 8), which amounts over EUR 1 billion in private investments, supporting some 1 600 jobs.

Figure 8. R&D and industrial infrastructure in industrial biotechnology in Italy.

Source: Courtesy of Novamont.

Reconversion of no longer competitive industrial sites into integrated bio refineries

213. A significant factor in the Italian capacity building is the conversion of decommissioned or no longer competitive industrial sites into bio refineries dedicated to the production of high added value products, such as biochemical and bioplastics.

214. An example of transformation of traditional industrial processes towards bio-based productions is the Porto Torres plant in Sardinia. Matrìca is the company set up in 2011 from a 50:50 joint venture between Novamont and Versalis (Eni) to reconvert the pre-existing petrochemical site into an integrated bio refinery which makes use of a proprietary technology to produce a range of chemical products (biochemicals, building blocks for bioplastics, bases for lubricants, additives for rubbers and plasticisers for polymers) from agricultural raw materials and vegetable scraps.

215. Matrìca is based on an approach of close collaboration with the local area and represents both a driver for the revitalisation of downstream value chains and a model of integration between industrial and agricultural production, building long-term partnerships with farmers and their associations. In 2015 Novamont and Coldiretti, the largest agricultural organisation in Italy and in Europe, signed a strategic agreement to promote the cultivation of thistle in Sardinia and to enhance its agricultural and environmental value and the further development of innovative agro-industrial chains for bio-products.

216. Another example of industrial reconversion is Mater- Biopolymer. In 2014 Novamont acquired, from Mossi & Ghisolfi Group, the majority of Mater- Biopolymer, the company that controls the plant in

Patrica (FR), originally dedicated to PET production and already partly transformed using proprietary technology for production of bio-polyesters.

217. Another recent industrial development in Italy is the reconversion of a decommissioned site in Veneto into the first plant in the world dedicated to the industrial production of butanediol (BDO) from renewable resources through a fermentation process. The new company, Mater-Biotech, is due to start production in 2016.

218. In Crescentino, the world's first commercial scale cellulosic ethanol facility has been in operation since 2013. Situated in fields in the northern region of Piedmont, it is the first plant in the world to be designed and built to produce bioethanol from agricultural residues and energy crops at commercial scale using enzymatic conversion. Based on second generation technology developed by Biochemtex and on the 2012 strategic partnership between Novozymes and Beta Renewables, the biofuel facility lends proof of the viability cellulosic ethanol plants. More than USD 200 million has been invested in research and development of the technology used to produce cellulosic ethanol at the Crescentino facility in addition to the significant resources in developing the enzymes.

219. The Crescentino facility is a multi-feedstock cellulosic ethanol facility and can handle agricultural waste from a broad variety of crops such as wheat straw and rice straw. Furthermore, the plant uses energy crops like *Arundo donax* (known as giant cane) as feedstock. *Arundo donax* is a high yield energy crop that can grow on marginal lands which provides extra income to the local farmers. The plant can release the value of sugars from cellulose and hemicellulose. In the fermentation, the sugars are converted into ethanol. Lignin is used at an attached power facility, which generates enough power to meet the energy needs of the facility and enables any excess green electricity to be sold to the local grid. The resulting annual output from the plant is up to 40 000 metric ton of cellulosic bioethanol as well as green electricity generated from lignin. The feedstock utilised at the Crescentino plant is readily and sustainably available, and it is estimated that cellulosic ethanol will reduce CO₂ emissions by 90% compared to petroleum-based fuels.

Regulatory initiatives

220. Another factor considered central to the successes developed in Italy is regulatory policy. In January 2011 a law was passed in Italy aimed at reducing the environmental contamination caused by traditional plastic carrier bags. The initiative built on a series of legislative measures introduced in Italy since the late 1990s, in order to address the management of waste in compliance with the Waste Framework Directive and the Landfill Directive. As a consequence of the law, thick, long life and reusable carrier bags and biodegradable, compostable single-use carrier bags (conforming to the harmonised CEN Standard 13432) are now available to consumers and retailers.

221. This strategy has limited the number of single-use carrier bags in circulation, reduced the risk of littering and its consequences on the environment, improved the quality of organic recycling and the conditions for growth of the market for bio-based products, acting as a primer for new investments. It is considered an example of how innovation and growth in the field of bio-based industries can be achieved by legislative measures which encompass environmental benefits and stimulus for investments and job creation. For example, it triggered new investments in bioplastics in Italy, with positive cascade effects, resulting in an installed capacity of biodegradable polymers of more than 200 000 tonnes. It has generated new employment opportunities and fostered innovation along the value chain: agriculture, R&D, downstream sectors (e.g. transformers and end-users) and waste management.

Industrial cluster initiatives

222. In 2012 the Italian Ministry of Education, University and Research promoted the establishment of SPRING, the Italian Technology Cluster in the area of Green Chemistry/ bio-based chemicals, conceived as a national platform in the Bio economy sector. SPRING (Sustainable Processes and Resources for Innovation and National Growth) was formally established in 2014 as a non-profit association by the initiative of four founding partners: Biochemtex, Novamont, Versalis and Federchimica.

223. Fostering the growth and development of the Italian bio-based sector through a holistic approach to innovation, the cluster supports research, demonstration, technological transfer, dissemination and training activities encouraging the creation of bio refineries and multi-sector integrated value chains, thus becoming a reference interlocutor for the bio economy and for the portfolio of EU and national policies concerning bio-based industries.

224. SPRING represents the entire Italian bio-based value chain, from agriculture to research in the field of chemistry from renewable sources and industrial biotechnologies, to the processing of materials and bio-products, to industrial transformation and finally the disposal phase. Counting on the variety of its over 100 members (including big industrial players, SMEs, universities, private and public research centres, associations, foundations, innovation centres and other actors involved in environmental communication and technology transfer), the cluster aims to stimulate research and investments in new technologies with an interdisciplinary approach and the creation of integrated bio refineries, starting by understanding the strengths and specificities of local areas and regions, while being in constant dialogue with local actors. These are represented first and foremost by the Italian regions that from the very beginning have committed to supporting the activities of the cluster through development strategies and planning measures in line with its vision and goals.

225. At the beginning of 2014 SPRING's first four R&D projects, worth a total of EUR 40 million, were launched. Each of them focuses on a specific area within the transformation through highly innovative processes of sustainable biomasses in high-added value chemicals and products. Each is also paired with a specific training project for young researchers with multidisciplinary skills and expertise in order to cover all aspects of the bio refinery development sector.

Biochemtex

226. Biochemtex is a company belonging to the group Mossi & Ghisolfi. It is a leader in the development and engineering of technologies and biochemical processes based on the use of non-food biomass as an alternative to fossil resources such as oil. In collaboration with Beta Renewables, it has developed technologies and plants for the production of bioethanol and other chemicals. Its headquarter is located in Tortona (AL), with dedicated research centres.

Novamont

227. Novamont is an industrial company based in Novara, active since 1989. Born as a research centre with the ambitious goal of integrating chemistry, environment and agriculture, it is today a leader in the field of bioplastics from renewable sources. The Novamont mission is to develop materials and biochemicals by creating bio refineries integrated in the local areas and providing application solutions that could ensure an efficient use of resources all along the life cycle.

Versalis

228. Versalis (Eni) is the largest Italian chemical company, with a leading position in the production of intermediates, polyethylene, styrenics and elastomers. It is engaged in a market-driven turnaround

strategy to reposition the business with a focus on performance-based products, leveraging its technological know-how and R&D expertise in the field of bio-based chemistry.

229. An innovative bio refinery platform is under implementation, currently at engineering level: it will use the guayule crop for the production of both natural rubber and high value products for segments such as consumer and medical specialty markets. Another important project is the production of bio-butadiene for its own use in elastomer and thermoplastic proprietary polymers, as an opportunity to strengthen its competitive position in these businesses.

Federchimica

230. Federchimica is the abbreviated name of the Italian federation of the chemical industry. Currently 1 400 companies with a total of 90 000 employees are part of Federchimica. They are grouped into 17 Associations, articulated into 41 product groups. Federchimica is a member of Confindustria (General Confederation of the Italian Industry) and CEFIC (European Chemical Industry Council). Federchimica, whose primary objectives are the coordination and the protection of the role of the Italian chemical industry as well as the promotion of its development capacity.

Oleochemical industry in Italy

231. The oleochemical industry converts natural renewable raw materials of oleo- or fat origin (mainly tallow and vegetable oils), into chemicals, used later in many advanced technologically products which are on the market. The oleochemical products (glycerol, glycerides, fatty acids, fatty alcohols and their derivatives, mainly esters, amides, soaps) are used both as raw materials for detergents, soaps, lubricants, paints, varnishes, cosmetics and pharmaceuticals, and as additives plastics, rubber and textiles, and as process aids. The Italian oleochemical industry is the second largest producer of oleochemicals in Europe. The oleochemical biorefinery was one of the first industries able to reduce the dependence on fossil resources using waste materials (e.g. animal fats, from slaughter) or by-products from the food industry, or residues from vegetable oils processing, in order to create high-value chemicals.

The Starch industry in Italy

232. The starch industry starts from renewable raw material (cereals and potatoes) and produces many products, of which many are specialty chemicals. In Italy three companies convert over 1 million tonnes of cereals (mainly corn), creating value to 100 000 hectares of farmed land contributing to the income of about 3 000 farmers. The starch produced in Italy is about 10% of European production.

FIRST2RUN

233. FIRST2RUN is the first flagship project funded under the Bio-Based Industries Joint Undertaking (BBI). It is coordinated by Novamont in partnership with four companies: SIP (UK), SoliQz (The Netherlands), Biophil (Slovakia), Matrìca, (Italy - JV 50:50 Novamont/Eni Versalis), with a University partner (The University of Bologna).

234. FIRST2RUN, which has been granted financial assistance of the EU of EUR 17 million, aims to demonstrate the technical, economic and environmental sustainability of an integrated bio refinery. Low input oilseeds such as thistle, cultivated on arid and/or marginal land, are used to extract vegetable oils to be converted into bio-monomers for the formulation of bio-products such as bio-lubricants, cosmetics, plasticisers and bio-plastics. Standardisation, certification and dissemination will be integral aspects of the project, as well as a study into the social impact of products deriving from renewable resources.

China, a major force in industrial biotechnology

235. China has similar motivations for building industrial biotechnology. In particular, the meteoric speed of development has caused the country to suffer a great deal from environmental deterioration and shortages of energy and other resources (Sun and Li, 2015). Part of the solution is the Tianjin Institute of Industrial Biotechnology, a national institute of the Chinese Academy of Sciences. Co-founded with the Tianjin Municipal Government to lead industrial biotechnology development in China, it officially came into being in 2012 with a total investment of more than USD 100 million. Its mission is to establish a national innovation system for industrial biotechnology to promote eco-friendly development of the economy.

236. The institute is effectively a ‘one stop shop’ for industrial biotechnology. Its research is boosted by technology platforms for robotic high-throughput screening, systems biology and industrial enzymes. Facilities move through research to pilot-scale production and scale-up. Domestic and international PPPs have been established with more than 60 companies to help overcome the barriers between scientific discoveries and commercial applications.

237. More generally, it is worth reflecting that China is poised to become the top global R&D performer by the end of this decade if recent trends continue (OECD, 2014d). The rise of China is driven by economic dynamism and its long-term commitment to science, technology and innovation (OECD, 2015). In China’s 13th Five Year Plan, of 33 major targets listed in the document, 16 of them concern the environment and resource use (Seligsohn, 2016).

Clusters in industrial biotechnology: some guidance for governments

238. Among many government measures to grow a bio economy and more specifically bio-production, a common denominator in the example countries is regional clusters. The other measures are described elsewhere, so this section deals specifically with clusters, their relevance and the risks involved. Some general considerations are offered for governments when designing cluster policy.

239. If the regional cluster policy did not exist, it could have been invented for industrial biotechnology, for several reasons:

- Hardly any R&D-intensive technology requires a feedstock that is mainly found in rural environments (food and non-food crops, wood, forest and agricultural residues). In other words, the *preferred* location for industrial biotechnology is regional, not urban;
- R&D centres and public research organisations, however, tend not to be rural, and therefore need some mechanism to connect them to the other actors across the industrial biotechnology value chain;
- The stakeholder groups are so diverse. They include farmers, foresters and their trade associations and cooperatives, buyers, agricultural and forestry machine rings, hauliers and other logistics professionals, chemicals and fuels companies, bio refiners, venture capitalists, food companies, R&D organisations, technology SMEs, waste management companies, regulators, recycling and waste management organisations.

240. Added to this there are policy goals that point industrial biotechnology to a distributed, non-economies-of-scale manufacturing model that repeatedly emphasises rural production and regeneration. The public policy maker is then faced with how to link such diverse stakeholders up: one of the ambitions of industrial biotechnology and the bio economy is to break the silos in which many of these actors dwell.

A clear rationale for the public sector to support clusters concerns the transaction costs and coordination costs to bring the appropriate actors together.

241. Fortunately the regional cluster model is tried and tested for other technologies. That does not imply success, but simply that the model has been used before. A problem is that robust tools for analysing the level of success of a cluster policy do not exist.

242. What follows is some guidance and lessons on designing cluster policy learned more generally from regional cluster policy, derived from earlier OECD work (OECD, 2007) with some specifics added for industrial biotechnology.

What are the objectives of the policy?

243. Cluster policy generally originates from one of three main policy families: regional policy, science and technology policy or industrial/enterprise policy. A few programmes have integrated all three policy streams, in some cases involving considerable resources and registering high on a country's public policy agenda. In industrial biotechnology it will be evident that indeed all three policy families may be involved.

244. Similarly there are three identifiable targets: places (e.g. lagging or leading regions), sectors and specific actors. A key question is whether one programme can address all those objectives simultaneously. There are trade-offs to be made in selecting these different targets. For example, improving opportunities for certain priority sectors helps to focus resources (for some OECD countries the chemicals sector is definitely a target). On the other hand, a catch-all cluster programme for all sectors or regions can dilute available resources and focus.

Be clear about the goals

245. Often the stated goals of cluster-type programmes are broad or vague, seeking generally to enhance competitiveness or innovation capacity. This lack of clarity in turn makes it difficult to select the right targets and establish programme funding levels and duration that are adequate to meet the goals.

Which level of government should do what?

246. For such programmes, there are economic rationales for all levels of government (local, regional, national and in some cases supra-national) to support them. These rationales are based on different perspectives on the value of clusters. For example, does the policy align with a higher supra-national competitiveness policy (such as the EU circular economy) or with a national growth programme, or with a local employment hub for regions? Industrial biotechnology could be all three, but increasingly it is associated with national policy e.g. a national bio economy strategy. In any event, the policy design should identify what is expected of each level of government.

Build in policy coherence at the design stage

247. Because industrial biotechnology cluster policies can be emanating from at least three policy streams, it becomes even more important for policy makers to have a clear understanding of what other policies exist and how they can work together or in a complementary fashion. For example, the environmental policy goals of industrial biotechnology could work together with green growth policy in, say, the provision of green energy for bio-production. And the cascading use of biomass concept is a perfect fit to the concepts of waste reduction and closed loop production inherent to circular economy policy.

Identify sources of risk and mitigate in policy design

248. Risks in regional cluster policy can often relate to a lack of engagement by the private sector. The long-term effectiveness of such policies depends on the private sector continuing to act after a programme ends. There is a strong interaction here with policy coherence. There have been many complaints from the private sector about uncertainty in bio economy policy, especially relating to biofuels policy, where uncertainty beyond 2020 is currently causing under-investment.

249. Equally there is a danger of too heavy-handed involvement of the public sector: the public role can be excessive. For example, there could be a tendency for the public sector to “pick winners”, a function which the private sector is much more adept at. It is important that there is a clear design for a public policy exit strategy, where the timing might be crucial.

250. More specifically there are risks associated with sustainability in industrial biotechnology. Currently the metrics for solid biomass sustainability are not developed and deployed. This could lead to unwanted consequences, such as farmers growing unwanted energy crops. Statistics around agricultural residues are not proven due to a lack of a definition. These are matters best handled by the cluster stakeholders, and therefore they should be built into the policy design explicitly.

Tap into other funding and investment sources

251. Design cluster programmes such that research institutions and companies can exploit other external R&D funding sources and programmes. This leveraging of other funds may draw in other private sector actors and could be used as a metric of success of the programme. By leveraging other private sector investments, this will hasten the day of financial independence and allow a public sector exit.

How is the effectiveness of a cluster or cluster programme to be measured?

252. Again there are common (general clusters and programmes) and specific (industrial biotechnology and bio economy) aspects to the question. Advice is not clear as the tools for quantitative assessment are not developed. However, Kircher (2012b) offered a set of key performance indicators (KPIs) for bio economy clusters (Table 9). Consideration given to how to assess the effectiveness of industrial biotechnology clusters could inform the public sector on its exit strategy, thus maximising the value for money to the taxpayer.

Table 9. Suggested KPIs for bio economy clusters.

Indicator	Units
Saving fossil energy	PJ per year; EUR per GJ
Saving CO ₂ emissions	EUR per tonne CO ₂ equivalent
Extra revenue of the agri sector	EUR million per year
Share of industrial feedstock produced	Percent
Value of industrial feedstock produced	EUR million per year
Share of bio-based energy and chemicals	Percent
Extra revenue in energy and chemicals sectors	EUR million per year
Import of bio-feedstock	EUR million per year
Impact on balance of trade	EUR million per year

Source: Kircher (2012b)

Encourage clusters to become international

253. International agreements can bring several benefits: sharing of technology, mobility of people, tackling of international issues such as biomass sustainability, trade and tapping into international funding programmes. This also helps demonstrate to governments that their national investments are in a valid international context. However, it has to be based on true cooperation, and not end up with the different partners competing with each other. Complementarity of services would be a strong criterion for partnering.

254. Many international initiatives are occurring, often directly involving government departments and the private sector of different countries as the bio economy starts to internationalise. Only a few can be mentioned here, and the examples are chosen for their different characteristics.

255. A notable example in the current context is BIG-C (BioInnovation Growth mega-cluster). It is a cross-border Smart Specialisation initiative aiming at transforming Europe's industrial mega cluster in Flanders, the Netherlands and the German state of North-Rhine Westphalia (NRW) into the global leader of bio-based innovation growth. The German Federal Ministry for Education and Research, as part of its "Internationalisation of Leading-Edge Clusters, Forward-Looking Projects, and Comparable Networks" strategy, will support the project with up to EUR 4 million over the coming years.

256. In March 2015, GBEV and the Malaysian Biotechnology Corporation (BiotechCorp) signed a collaboration agreement in Kuala Lumpur, in support of companies and research institutes in the bio-economy business in Belgium and Malaysia. It aims to facilitate collaboration and the development of commercial applications in both countries. This is consistent with a very ambitious bio economy strategy in Malaysia, the Biotechnology Transformation Programme (BTP) in 2012 as part of the nation's economic transformation strategies (Bioeconomy Malaysia, 2014). Malaysia provides an incentivised platform for the bio-based industries to contribute to its sustainable development agenda, to improve industry competitiveness, to encourage public-private partnerships and bring socio-economic benefits. The initiative is supported by public sector stakeholders such as universities and research centres, economic corridors, financial institutions and inter-ministerial coordination. Already, Malaysia has secured inward investments that demonstrate a shift towards higher value markets instead of simply being a provider of raw materials (D'Hondt et al., 2015).

257. Bio Base NWE is a project funded by the Interreg North-West Europe 2014-2020 Programme.⁴¹ Eight partners from five European countries (Belgium, Germany, Ireland, The Netherlands and the United Kingdom) make up the consortium in this three-year project. The overall aim of Bio Base NWE supports the development of the bio-based economy in NWE by facilitating innovation and business development by small and medium sized enterprises (SMEs) and improving professional training and education for the bio-based economy.

258. Late in October 2015, four clusters - Biobased Delta (The Netherlands), BioEconomy (Germany), BioVale (UK) and IAR (France) - joined forces as the 3BI (Brokering Bio-Based Innovation)⁴² inter-cluster. Their goal is to support European companies to access important new bio economy markets successfully. It builds on complementary strengths of these four leading regional innovation clusters. All four clusters use bio refining to convert biological resources into food, feed, materials, chemicals and fuels. They intend to work together in the research, development and deployment of novel high-tech approaches

⁴¹ <http://www.nweurope.eu/5b/>

⁴² <http://www.3bi-intercluster.org/home/>

to the conversion of biomass, renewable raw materials and waste streams into value-added products and applications.

Concluding remarks

259. One of the toughest decisions for bio economy policy makers is where to locate the production facilities. Ahead of the decision to build the actual bio refineries much needs to be known about the innovation ecosystem of industrial biotechnology, an extremely complex mix of rural and urban actors. Local knowledge is essential. Therefore local governments need to be involved in national decisions. The private sector has essential roles and governments should exploit these sources of knowledge. The bio refinery complex at Bazancourt-Pomacle in northern France is a striking example, with its 10 000 farmers in the ecosystem. Clusters seem central to these plans, especially as a result of the diversity of actors.

260. Given the different policy families involved there is a need for inter-ministerial or inter-agency committees that conceptualise, design or even implement programmes jointly. In a bio economy cluster, it is unlikely that only one of these families of regional or science and technology or industry/enterprise will be involved. Others such as environmental and energy policy makers are quite clearly implicated.

EDUCATION AND TRAINING FOR INDUSTRIAL BIOTECHNOLOGY: A SPECIFIC ISSUE IN CAPACITY BUILDING

“IBioIC has the task of generating GBP 1-1.5 billion of GVA to the Scottish Economy by 2025 from the industrialisation of biology, and it requires a pipeline of talented people to deliver this. As highlighted in the National Plan for Industrial Biotechnology, Scotland faces a series of challenges in maximising its development of IB in Scotland, which includes skills shortages....We have created bespoke educational programmes in direct response to industry need and designed programmes to specifically meet this need across all educational levels from Modern Apprenticeships, Higher National Diploma (HND in Industrial Biotechnology), the UK’s first collaborative MSc in Industrial Biotechnology and PhD studentships with Universities across Scotland and industrial partners across the UK.”

IBioIC, Scotland,⁴³ October 2016

Introduction

261. OECD analysis suggests that innovation thrives in an environment characterised by a few key features. One of them is a skilled workforce (OECD, 2015). Skills will be of central importance to enabling bio-production due to: the newness of the subject, its multi-disciplinary nature, the complexity of biology and bio-production, and the need for many stakeholders with different skills. Jobs for the workforce, not only research jobs, are a major goal of bio-production that will only work well through a focus on rethinking education.

262. Industrial biotechnology calls for education outside of normal disciplinary boundaries. The most obvious combination of skills is synthetic biology or genetic engineering with ‘green’ chemistry, with the reduction-to-practice skills provided by chemical engineering. Other mathematical skills are also important. But for employment in small companies, employees need also to be flexible and willing multi-task and get soft tasks done. This often does not suit a PhD graduate as doctoral training remains very specialist, long-term and driven by publication.

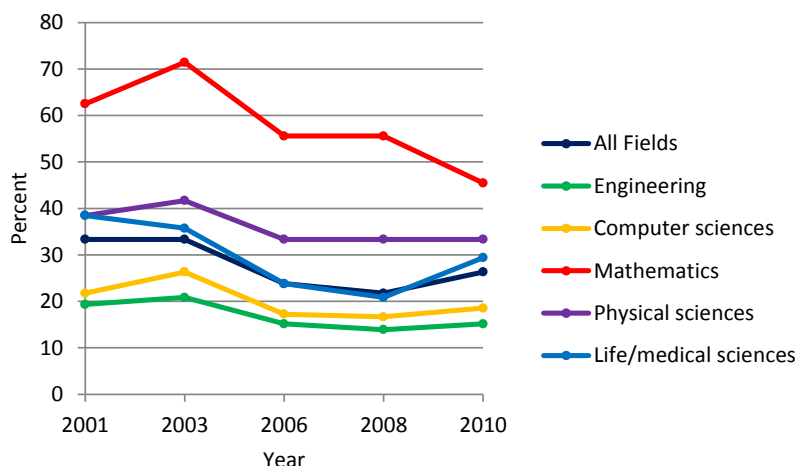
263. A key discipline of industrial biotechnology is microbiology. Current life sciences PhD level education remains focused on training for academic careers (American Society for Microbiology, 2013). However, data published in the National Science Board’s (NSB’s) 2014 Science and Engineering Indicators show that a mere 29% of newly graduated life science PhDs (2010 data) will find a full time faculty position in the US (Figure 9). A recent review also confirmed that growth in the number of US post-doctoral researchers far exceeds the growth in the number of tenure-track job openings (National Academy of Sciences, 2014c). There are simply too many PhD students and too few senior posts (*Nature* Editorial, 2016). On the positive side, then, there should be plenty of choice of post-graduates for entry into industrial biotechnology. However, in microbiology, the field is overwhelmingly dominated by medical microbiology.

⁴³

<https://www.ibioic.com/skills.htm>

Figure 9. Likelihood to work in academia for newly graduated PhDs (percent)

The low figures for engineering and computer sciences reflect the greater likelihood that these PhD graduates will enter industry



Source: Delebecque and Philp, unpublished data.

264. The problems are far from new. As far back as 1995 the United States National Academy of Sciences had expressed the need for change in the education of scientists and engineers (National Academy of Sciences, 1995). This report was concerned that the US was producing too many PhDs and that industry often complained that these graduates were too specialised to accomplish the range of tasks they would be confronted with. Also, when scientists form small biotechnology companies, they are often placed in a managerial role in which they may have no training or know-how (Corolleur et al., 2004). This has all brought about a call for a new type of PhD, one which offered much more breadth and flexibility.

The challenge of multi-disciplinary education

“For generations, classes in science, technology, engineering and mathematics (STEM) have been built around a steady diet of lecture-based learning. Soft skills, such as creative problem solving, critical thinking and collaboration, are often given short shrift. Now educators and education researchers are calling for change. They argue that a slew of ‘twenty-first-century skills’, which include creativity, persistence and motivation, can and should be taught and fostered through well-designed courses”.

From a *Nature* Special, “Building the 21st Century Scientist”, July 15, 2015

265. Traditional scientific education and training has remained divided by disciplines such as microbiology, chemistry and computing. The long-standing conundrum of multi-disciplinary education is the need for both breadth and depth. The challenge to higher education remains on many levels. For example, a central theme in bio economy strategies is sustainability. Training in sustainability itself begs multi-disciplinarity as some of the depth skills needed are systems thinking, strategic planning, and evaluating environmental, social and economic performance. This educational conundrum for sustainability (Mascarelli, 2013) is the same for industrial biotechnology: how to make the inter-disciplinary approach not only substantive, but also practical for early-career scientists.

Life sciences industry-wide issues

266. Some of the life sciences-wide industry issues are clearly crystallised in a report from the US (Coalition of State Bioscience Institutes, 2013). Employer interviews identified several industry-wide gaps in the capabilities and talent of the current workforce pool and proposed reasons:

- The life science industry has a decreased need for deeply trained senior scientists. There is an over-specialisation surplus, whereas employers are looking for a workforce with greater breadth and more soft skills;
- Academic programmes are training students by discipline and not by problem-solving, which typically requires cross-disciplinary skills and capabilities;
- A lack of apprenticeships and long-term training programmes.

267. The UK biopharmaceuticals industry recently highlighted major skills gaps in mathematical and computational areas, which have emerged due to the rapid development of new disciplines such as systems biology and health informatics (ABPI, 2015). For the industrial biotechnology industry, the same holds true. In the following some of the specific and critical training gaps to foster industrial biotechnology and synthetic biology-based manufacturing are addressed. It is an attempt to examine what the workforce and related research base may look like in future if this activity gathers momentum in response to societal grand challenges. This may guide governments in directions that could be taken in higher education.

The critical workforce gaps in bio-based manufacturing

268. The most difficult task is not one of finding biologists. More difficult to find are automation engineers specialising in high throughput strain production critical to synthetic biology-based manufacturing. Managing automated systems will have to be a skill set for graduates in biology and chemistry in the future (Extance, 2016). It has for a long time been difficult to find fermentation staff: this is the province of the biochemical engineer, who combines the mathematics of cell growth with bioreactor and bioprocess design. And yet, bio-manufacturing is the common operation that links together all the different market sectors of the world's biotechnology industry.

269. Perhaps hardest to find of all are employees well versed in experimental design and statistics, especially now that dealing with large data sets is becoming more common. Big data is creating an imperative for more complex design which enables fewer experiments and trials. Scientific irreproducibility - the inability to repeat others' experiments and reach the same conclusion - is a growing concern. Yet few early-career researchers receive formal instruction on topics like experimental design and flaws in statistical analysis (Baker, 2016).

270. This diverse group of employees is essential for a functional synthetic biology-based production plant but remains rare as this business sector currently is a small niche. As sector growth is difficult to forecast, it challenges governments to predict how to invest in and reform higher education to create a workforce that matches the growth dynamics of the sector.

Bioinformatics may be a major roadblock

271. The bottleneck for the growing industrial biotechnology industry is shifting to bioinformatics and data mining. Data mining tools akin to the ones revolutionising social sciences and linguistics will become essential. The Short Read Archive at the US National Center for Biological Information is set to exceed a petabyte (National Academy of Sciences, 2013). As high-throughput sequencing is increasingly deployed

across research organisations, hospitals, biotechnology facilities and companies, the acquisition of genomic information will also burgeon. DNA synthesis cost have tumbled between 2014 and 2016, and combined with the advances in next-generation sequencing, the need and role of advanced software design tools is increasing.

272. ‘Dry lab’ skills have traditionally been isolated from ‘wet lab’ ones. Nevertheless, bioinformatics requires deep knowledge of biology theory and mathematics/computing. These fields are usually not taught in depth in the same programme in higher education, and this is but one more challenge to be overcome.

The scientist as engineer

273. Engineering education depends on several key concepts that have been largely missing in biotechnology (Panke, 2008): comprehensiveness of available relevant knowledge; orthogonality; hierarchy of abstraction; standardisation, and; separation of design from manufacture. Systems modelling and design are well-established in engineering disciplines but until recently have been rare in biology. The sheer complexity of biology has also hindered the development of its formal mathematics. Things are obviously changing, and systems biology has recently started to bridge the gap between biology and engineering. For example:

“Each (biological) network motif can serve as an elementary circuit with a defined function: filters, pulse generators, response accelerators, temporal-pattern-generators and more.”

Uri Alon, <http://www.weizmann.ac.il/mcb/UriAlon/homepage>

274. The education of a biologist still focuses more on the needs of research and has been dominated by a more descriptive tradition. This is in sheer contrast with engineering, dominated by a much more quantitative tradition, and the need to standardise and reduce complexity to practice.

275. However, this comes at a time of widely conflicting attitudes to engineering education. For example, in the US only 4.4% of the undergraduate degrees awarded by US colleges and universities are in engineering, compared with 13% in key European countries and 23% in key Asian countries (National Academy of Sciences, 2014d).

276. Botstein contends that the continuing relationship between technology and discovery requires that cell biologists in the next fifty years will have to be conversant with a broader range of concepts, from physics through chemistry to genetics, but especially with the mathematical and computational methodologies that drive technology development (Botstein, 2010).

277. Whilst the quantitative theoretical and computational component represents a fundamental departure from the tradition of the life sciences, Tadmor and Tidor (2005) stressed that modelling should not be construed as a replacement for experimentation. Indeed, large stores of practical and theoretical knowledge are essential for one to function in a laboratory environment. But creating this depth of laboratory skills is amongst the most expensive and time-consuming elements of higher education and leads back to the dilemma of breadth *versus* depth *versus* adaptability.

The chemical engineer as a role model?

278. Chemical engineers have played a tremendous role in generating and transferring the enormous benefits of the chemicals industry to society. The mathematics and thermodynamics of chemical engineering enabled the transfer of chemistry from the laboratory to full-scale industrial production, using crude oil as the raw material. For industrial biotechnology to fulfil its promise in a bio economy, these

skills will be essential, with the new raw material being biomass. Chemical and biochemical engineers are key elements of the future bio economy because they alone can set the production agenda, knowing the process, energy, materials and cost elements (Woodley et al., 2013).

279. The chemical engineering curriculum is already full. Chemical engineering students may not wish to have industrial biotechnology in the undergraduate curriculum as this could be seen as a diversion from main objective, to get certification to practice in the chemical and petrochemical industries. This may indicate a niche for training chemical engineers at Masters level in industrial biotechnology.

Synthetic biology education: another key ‘inter-discipline’

280. The education system has been responding to the needs of the growing synthetic biology community. The number of courses in synthetic biology has grown at a tremendous rate, with at least 100 institutions involved (Delebecque and Philp, 2015). However, many do not focus on industrial production. Therefore the existing industrial biotechnology courses, and organisations teaching them, are still very much pioneering.

Beyond science and engineering

281. Given the history of the genetic modification (GM) debate, such matters as public perception will also shadow industrial biotechnology and synthetic biology. There is already evidence that political and economic pressures will also guide the development of synthetic biology (e.g. Rai and Boyle, 2007). Kuldell (2007) argued that educational efforts that fail to equip students for these aspects of the emerging discipline are unsound. Public engagement, through fraught, is necessary for the acceptance of synthetic biology and industrial biotechnology more broadly. Public engagement is weakened by a lack of a standard approach (National Academy of Sciences, 2016). Policy makers could include social scientists and ethicists in strategies for developing and encouraging the uptake of bio-based products, and have this embedded in education. On the other hand, care should be taken that public engagement does not become a ‘mode of governance’ of research (Kuntz, 2016).

282. To make employees fit for the workplace, this education also needs to encompass other practices such as regulatory compliance, risk assessment and biosafety, and good manufacturing practice (GMP). These practices are not academic research disciplines. But they can change rapidly, with far-reaching consequences for a small company. In-house training in GMP, for example, takes up considerable time and human resource, and can be burdensome in small companies.

The many faces of regulation

283. Bio-based production creates regulatory challenges across boundaries also. The metabolically engineered microbes (i.e. process) are subject to GMO regulation, while the chemicals and fuels (i.e. products), often being drop-in substitutes for fossil-derived materials, are subject to chemical regulations such as the Toxic Substances Control Act (TSCA) in the US and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) in Europe.

Some approaches to industrial biotechnology education and training

284. A classic example of an approach is the US NSF Center for Biorenewable Chemicals (CBiRC),⁴⁴ a third generation Engineering Research Center (ERC) that was established at Iowa State University in

⁴⁴

<http://www.cbirc.iastate.edu/>

2008. It includes five core partner universities, two affiliated research centres, four international partner institutions, and multiple industrial partners and pre-college entities. The ERC's mission is based on research and education principles that seek to transform the existing petroleum-based chemical industry into an industry based on renewables (Haen et al., 2012). It offers courses for school teachers, through undergraduate and graduate education.

Undergraduate courses: preparing the way

285. It is probably too early to be considering whole undergraduate degrees for this type of biologist i.e. one focused on industrial manufacturing. However, relevant science undergraduate degrees could be re-designed to serve as a platform for post-graduate study. For example, one of the key disciplines, microbiology, has curricula overwhelmingly dominated by medical microbiology. A re-orientation of microbiology undergraduate education could include, apart from the core microbiological skills, quantitative skills that are important for success in industry. Students so equipped with skills in calculus, linear algebra, statistics, large dataset management and programming (American Society for Microbiology, 2013) would be better disposed to future education in, and a career based on, engineering biology. The University of Ottawa, Faculty of Science (biochemistry) and the Faculty of Engineering (chemical engineering) jointly offer an undergraduate Biotechnology programme.

286. The University of Guelph offers an undergraduate program in Biological Engineering which focuses on fundamentals in bio-materials science, bio-systems analysis, bio-mechanics, instrumentation and digital control. The programme can be tailored to explore interests in: the production of renewable fuels such as ethanol and biodiesel; sustainable bioplastics made from plant materials; the extraction and stabilisation of nutraceuticals to provide health benefits, or; the manufacturing of safe food products.

Taught and Research Masters

287. Industrial biotechnology lends itself very well to a research Master degree, emphasising practice-led research combined with relatively few taught modules compared with other Master degrees. This sort of Master degree is designed in most cases to prepare students for doctoral research, but is also useful for those considering a career in the private sector where research is a key focus but a PhD is not specifically required.

288. The University of Georgia Master of Biomanufacturing and Bioprocessing (MBB) degree⁴⁵ is a two-year programme is advertised as unique in its focus on the full bio-manufacturing experience with hands-on training and exposure to industrial grade equipment. Its curriculum includes academic courses in science e.g. biofuels/biochemical, pharmaceuticals manufacture, and business e.g. finance, supply chain issues and manufacturing practices, along with professional training with cutting edge companies through case study projects and internships. Instead of producing a traditional thesis, students complete a research project during the summer of year one and a 400-hour industry internship during the summer of year two.

289. The La Trobe University (Australia) Master of Biotechnology and Bioinformatics focusses on the interface of molecular biology and information technology. It uses the power of computing to tackle biological and medical problems. The need for bioinformatics graduates will increase as computational tools are increasingly incorporated into bio-production.

290. The University of Cagliari (Italy) Master in Chemical and Biotechnological Process Engineering is a course that combines the skills of chemical engineering with the needs of the biotechnology industry.

⁴⁵

<http://biomanufacturing.uga.edu/>

A goal is to teach students how to use the increased knowledge of chemical, physical and biological sciences in order to develop advanced mathematical models for chemical and biotechnological processes.

291. The Grenoble Ecole de Management (France) Master Specialised Management of Biotech Companies is a course that aims to provide specific managerial skills and understanding of issues related to the sector, as well as training in change management and the specific challenges of the biotechnology sector.

292. The University of Guelph, Ontario Master of Biotechnology program brings together the Department of Molecular & Cellular Biology, and the Department of Management to offer courses in business skills (e.g., commercialising innovations) in addition to deeper scientific training.

Massive Open Online Courses (MOOCs)

293. Arguable, MIT pioneered online learning, and the reasoning for offering online versions of established courses was that research consistently showed that students perform better when they take both courses than when they take only one (National Academy of Sciences, 2014d).

294. The traditional on-campus experience could be radically changed by the explosion of Massive Open Online Courses (MOOCs), which will enhance classroom and laboratory work. The evidence for the impact of MOOCs is, however, embryonic, and more analysis is needed as greater experience is acquired with their use. A number of MOOC platforms, such as Coursera⁴⁶ and edX,⁴⁷ now propose a wide array of classes spanning engineering to molecular biology and all the building blocks in between that can now provide the basic toolset to start practicing engineering biology. A specialist MOOC for industrial biotechnology is offered jointly by the Technical University of Delft and the University of Campinas (Box 6).

295. The MIT and Harvard-owned edX MOOC platform differs from other MOOC platforms in that it is non-profit and runs on open-source software. Unlike the traditional lecture, each lesson is a 10-minute lecture segment video on a single concept, followed by self-assessment tools. A most relevant feature of MOOCs is that they are easily scalable and adaptable. As industrial biotechnology is expanding and changing so rapidly, educational materials rapidly lose their freshness, if not also their relevance. When the hard foundational work of creating a MOOC is done, it is feasible that software and screencasts can be used to replace or upgrade course content in a matter of minutes.

Box 6. edX course in Industrial Biotechnology

The course is a joint initiative of TU Delft (Netherlands), the international BE-Basic consortium and University of Campinas (Brazil). It provides the insights and tools for the design of sustainable biotechnology processes. The basics of industrial biotechnology are used by students for the design of fermentation processes for the production of fuels, chemicals and foodstuffs.⁴⁸ Throughout this course, students are challenged to design a biotechnological process and evaluate its performance and sustainability.

Courses such as this can be combined with others that are relevant to build the broader education that bio economy and industrial bio-based manufacturing seems to need. For example, another MOOC offered by TU Delft is on Responsible Innovation. This discipline considers new technologies that are being developed in response to current social challenges (e.g. food safety; smart cities; sustainable energy; and digital security).

⁴⁶ <https://www.coursera.org/>

⁴⁷ <https://www.edx.org/>

⁴⁸ <http://www.be-basic.org/news-center/news/mooc-industrial-biotechnology.html>

The TU Delft MOOCs are offered through the online edX platform, where MIT, Harvard and other universities have been making courses available to anyone with an internet connection since 2012. One of the reasons that TU Delft chose to use edX is that it allows the publication of materials with an open licence, making it possible for others to use the materials as well.

Specialist training facilities

296. For early-career scientists gaining access to bio-based production experience is difficult. Universities do not normally have such facilities. An interesting training model is the National Institutes model in Ireland. One of these is a dedicated facility for training in bioprocessing (the National Institute for Bioprocessing Research and Training, NIBRT).⁴⁹ For a relatively small country, Ireland has a large pharmaceuticals sector. NIBRT provides a ‘one stop shop’ for bioprocessing training requirements. The institute builds tailored training solutions for clients, ranging from operator through to senior management training, and training can be delivered in a realistic GMP-simulated manufacturing environment. This type of environment is not one found typically in universities, and is more appropriate for the training of industry professionals. Equally, such a facility could be used by undergraduate and Master programmes to give students exposure to industry working conditions.

A role for Intermediate Research Organisations (IROs) and laboratories

297. IROs can enable work in selected fields to take place without the conflicting pressures of publishing and teaching explicit in academic research. The concept seems enshrined in the UK Catapult model.⁵⁰ This concept could have been tailor-made for industrial biotechnology. Further, such a model has great potential for application to skills gaps, more so on the apprentice, hands-on model rather than the academic student model.

298. However, such a model can work for PhD students as well. For example, the RIKEN⁵¹ Junior Research Associate (JRA) programme in Japan provides part-time positions at RIKEN for young researchers enrolled in Japanese university PhD programmes. This gives PhD students the opportunity to carry out research alongside RIKEN scientists and it also strengthens the relationships between RIKEN and universities in Japan.

Business management education and training for the industrial biotechnology industry

299. In 2000, a brief article in *The Economist* referred to a burgeoning biotechnology industry in Scotland but noted that “*the whole British industry suffers from a shortage of experienced biotechnology company managers*” (*The Economist*, March 18, 2000).

300. One solution to the problem has been to specify the normally generic MBA programme for the biotechnology industry (OECD, 2005). Theories of business administration have their roots in commerce, which has in past been focussed on non-technological issues (Lambert, 2004). Therefore, the typical MBA programme is not particularly well-suited to industrial biotechnology business management. Given the pressures on small companies active in industrial biotechnology, much shorter courses that focus on specific skills gaps may be more appropriate.

⁴⁹ <http://www.nibrt.ie/>

⁵⁰ <https://www.catapult.org.uk/>

⁵¹ <http://www.riken.jp/en/>

301. Given the potential impact of industrial biotechnology on the chemicals industry, a European 5-day mini-MBA⁵² tailored for mid-level chemical industry managers is pertinent. These managers' roles are being impacted by the rapidly evolving trends of globalisation, REACH, green chemistry, waste reduction, sustainability and operational efficiency. All are also directly relevant to the emerging bio-based industry.

302. An industrial biotechnology 3-day MBA⁵³ has also been developed. It has dealt with: applications and markets; the supply and value chain; research and innovation; business development, and; policies and regulations in the bio-based economy. More specialised to synthetic biology, SynbiCITE developed a 4-day MBA interactive course⁵⁴ that covered the main strategies required to establish, build and manage a biotechnology company built around synthetic biology. It has focused on the early stages of setting up a company, getting funding and understanding the wider reaches of intellectual property (IP).

Training technicians: providing the bio-manufacturing workforce

303. These are workforce employees, not researchers. They will be required in higher numbers than researchers and need a broader range of skills as they will be the day-to-day bio-manufacturing workforce. Industrial biotechnology should be part of their training, not all of it. Some of the foreseeable functions will be:

- Routine maintenance of metabolically engineered strains;
- Embedding synthetic biology with GMP guidance;
- Regulatory and compliance training e.g. bio-banking, transportation of live biologicals and document management;
- Standard operating procedures (SOPs) to deal with accidental spills and releases.

304. They should be also trained in matters such as scale-up, knowledge of packaging and labelling protocols (Wallman et al., 2013). Scale-up is a massive technical barrier in the bio-based industry, especially at the scale of transportation fuels (Westfall and Gardner, 2011), stretching the skills of both strain and fermentation engineers.

305. Manufacturing does not fit well into normal boundaries of university degree programmes and, as a result, is often marginalised (Glaser, 2013). An approach which creates a vocational workforce locally and separately from the universities, for example in technical and community colleges, would take pressure from the universities. It also would create more jobs and investment in the local or community colleges. This aligns well with thinking which envisages bio refineries and bio economy clusters being created in rural environments as a means of rural regeneration.

306. The recently established IBioIC (Industrial Biotechnology Innovation Centre)⁵⁵ in Scotland has developed a range of educational programmes with its collaborative partners to meet the need of the biotechnology industry. Jointly with the Forth Valley College, the Higher National Diploma (HND) is

⁵² These courses do not allow the graduates to use the initials 'MBA' after their names

⁵³ <http://cinbios.be/events/3-day-mba-industrial-biotechnology/>

⁵⁴ <http://synbicite.com/training/three-day-mba/>

⁵⁵ <http://www.ibioic.com/index.php>

specifically designed to create a cadre of technical staff. The newly developed HND involves the study of three crucial disciplines: biology, chemistry and engineering, on either a full-time or part-time basis.

307. Given current plans being developed at national and international levels, ultimately harmonised and standardised qualifications in bio-manufacturing would be desirable, probably even essential. Again, this is not necessarily what universities aim to achieve, and is best done close to the manufacturing to allow efficient cross-fertilisation between the training institutions and industry.

Concluding remarks

308. Industrial biotechnology and synthetic biology training requires a paradigm shift in how education is structured. Programmes are needed that encourage creativity and exploration while harnessing the truly unique inter-disciplinary nature of the field and harvesting the different forms of training highlighted above. In front of the unprecedented pace at which our world is changing, beyond the traditional debate of depth *versus* breadth in education, one of the answers lies in training for adaptability and dynamism. Pioneering universities answering this challenge are and will be training the next generation of creative and cooperative knowledge and venture builders able to update and productively use their knowledge to drive innovation. With the gradual shift to biomass from crude oil and natural gas as the raw material for production, and the plethora of technical difficulties this presents, this ability to use knowledge cooperatively to create the factories and products of the future calls for equally innovative education and bold reforms.

METABOLIC ENGINEERING AND SYNTHETIC BIOLOGY FOR A BIOECONOMY

309. Metabolic engineering and synthetic biology are the core platform technologies relevant to *Replacing the Oil Barrel*. As it stands, both technologies have proven very successful in basic science and in laboratory-scale applications. Their translation into bio economy products to date has been limited, often for technical reasons. This section identifies some of the successes but also highlights the areas where governments could fund pre-competitive and near-market research to increase the rate of success in commercialisation.

310. Biotechnology in food security has been dealt with elsewhere, and bio-based production biotechnology was specifically excluded from those discussions. It is worth the reminder that a bio economy presents a very large conundrum: there will be a competition for biomass between food and industrial production. This section examines the biotechnology of industrial production of bio-based materials. Ethanol, while important, is not a specific target of this examination. It will be evident from this section that a recurring theme is the need for systems integration of computational and experimental approaches, a key message for policy makers that is returned to in the ‘Where next for bio-based production and replacing the oil barrel’ section.

What has been achieved?

311. There has been massive acceptance and uptake of metabolic engineering by the research community involved in bio-based applications. Table 10 highlights a range of research successes across very diverse target chemicals essential to replacing the oil barrel.

Table 10. Selected bio-based products synthesised via metabolic engineering routes

Class	Compound	Reference
Diols	1,3-Propanediol	Nakamura and Whited (2003)
	1,2-Propanediol	Clomburg and Gonzalez (2011)
	1,4-Butanediol	Yim et al. (2011); Burgard et al. (2016)
Bio-based plastics	Polyhydroxyalkanoates	Steinbüchel (2001); Escapa et al. (2011)
	Polylactic acid	Jung and Lee (2011)
Plastics intermediates	Muconic acid	Curran et al. (2013)
	Ethylene	Pirkov et al. (2008); Jindou et al. (2014)
	Styrene	McKenna and Nielsen (2011)
	Adipic acid	US-2013-0157343 (2013)
	Itaconic acid	Chin et al. (2015)
	Succinic acid	Agren et al. (2013); Becker et al. (2013)
	Lactic acid	Singh et al. (2006)
	Terephthalic acid	WO/2013/109865 (2013)
	1,5-Diaminopentane	Kind et al. (2014)
	1,4-Diaminobutane	Lee et al. (2012)
	5-Aminovalerate	Park et al. (2013)
Synthetic rubber	Isoprene	Lindberg et al. (2010)
Short chain olefins		WO2012052427 (2012)
	1,3-Butadiene	EP2607340 (2013)
Spider silk		Xiaa et al. (2010); CEP (2015)
Fatty alcohols		Steen et al. (2010); Fillet et al. (2015); Tang and Chen (2015); Rutter and Rao (2016)
Biofuels	Hydrocarbon fuels	Lee et al. (2015)
	Ethanol	Lee et al. (2010); Kim and Reed (2010); Li et al. (2012); Wargacki et al. (2012)
	Butanol	Bokinsky et al. (2011); Jang et al. (2012a); Lan and Liao (2012)
	Isobutanol	Atsumi et al. (2010)
	Branched chain higher alcohols	Atsumi et al. (2008)
	Alkanes	Choi and Lee (2013), Kageyama et al. (2015); Sheppard et al. (2016)
	Fatty acids and derivatives	Kalscheuer et al. (2006); Steen et al. (2010); Rungtaphan and Keasling (2014)
	Monoterpenes	WO2008-045555 (2008)
	Isopropanol	Inokuma et al. (2010)
	3-Methyl-1-butanol	Connor and Liao (2008)
	Hydrogen	Seol et al. (2011); Srirangan et al. (2011)
	Geraniol, geranyl acetate, limonene, and farnesyl hexanoate	Dunlop et al. (2011); Kiyota et al. (2014);

Note: The list is not exhaustive. Recent reviews list more bio-based fuels (Jang et al., 2012b) and chemicals (Chen et al., 2013). A list of applications using photosynthetic organisms was published by Lai and Lan (2015).

312. Most of these syntheses are not at commercial scale, many may never make it for technical and commercial reasons, and there is a general view of a lack of substantial return on investment in biotechnology (Alberts et al., 2014). This section will briefly review the relevant technologies and the technical barriers to further implementation at commercial scale that are important for future R&D subsidy but also for integration in innovation policy i.e. beyond pre-competitive research.

Bio-based 1,3-propanediol (PDO): a metabolic engineering classic

313. 1,3-PDO has appealing properties for many synthetic reactions and for uses as solvents, adhesives, resins, detergents and cosmetics. It is especially well known as a monomer for the synthesis of polytrimethylene terephthalate (PTT), a polyester with excellent properties for fibres, textiles, carpets and coatings (Zeng and Sabra, 2011). Globally, the 1,3-PDO market will grow from an estimated USD 157 million in 2012 to USD 560 million in 2019 with a compound annual growth rate (CAGR) of 19.9% during the period 2012 to 2019 (OECD, 2014a).

314. One of the considerations for working in *E. coli* is strains based on the *E. coli* K12 strain are eligible for favourable regulatory status in the US. The engineered strain relies on a carbon pathway that diverts carbon from dihydroxyacetone phosphate (DHAP), a major 'pipeline' in central carbon metabolism, to 1,3-propanediol (Box 7).

Box 7. Metabolic engineering for the production of 1,3-propanediol

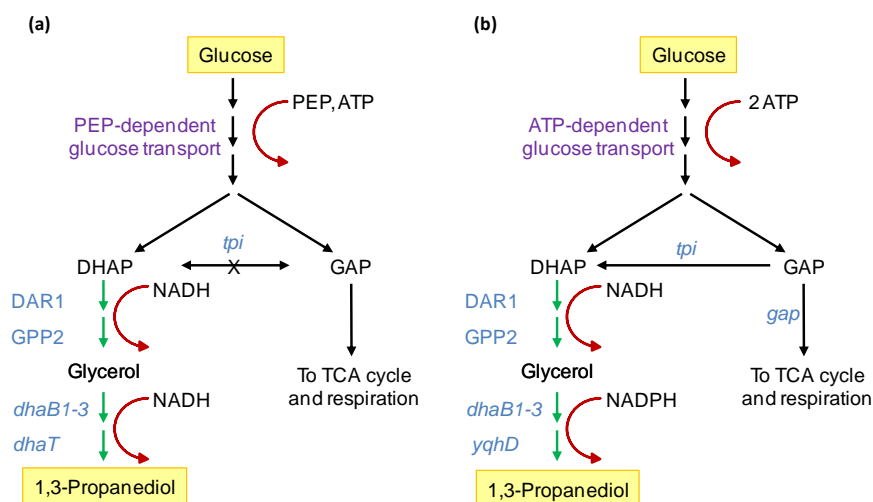
The two most fundamental changes described were:

1. To remove a theoretical yield limitation, the phosphotransferase (PTS) system was replaced with a synthetic system comprising galactose permease (*galP*) and glucokinase (*glk*); both genes are endogenous to *E. coli*.
2. Triosephosphate isomerase (*tpi*) was deleted in an early construct (part (a)). But this also imposed a yield limitation. To overcome this, *gap* (glyceraldehyde 3-phosphate dehydrogenase) was down-regulated, which, along with the reinstatement of *tpi* (part (b)), provided an improved flux control point.

Along with other changes, the end result was a metabolically engineered organism that produced 1,3-propanediol at a titre of 135 g/l, compared to the typical anaerobic titre of 78 g/l.

Metabolic engineering for the production of 1,3-propanediol (a) an early construct; (b) a later construct with improved yield.

Footnote: GAP = glyceraldehyde 3-phosphate, DHAP = dihydroxyacetone phosphate.



Source : Nakamura and Whited (2003)

Bio-based 1,4-butanediol (BDO) production: a unnatural molecule in a bacterium

315. 1,4-Butanediol (BDO) is an important commodity chemical used to manufacture over 2.5 million tonnes of valuable polymers annually. Currently its production is entirely through petro-chemistry. Unlike some other diols, there is no natural 1,4-BDO produced in any organism. Additionally, like many commodity chemicals, it is highly reduced compared to carbohydrates, which makes its biosynthesis even more improbable.

316. As a result, Yim et al. (2011) were required to use metabolic pathway models to identify and rank the potential pathways from *E. coli* central metabolites to BDO. The forced ranking eliminated most of the potential pathways, and those remaining were prioritised according to several criteria, including the number of non-native steps required. On the experimental side, the host *E. coli* strain required to be metabolically engineered to channel carbon and energy resources into the pathway, followed by optimization of the downstream activity. In addition, they examined non-purified feedstocks such as crude, mixed sugars and biomass hydrolysates.

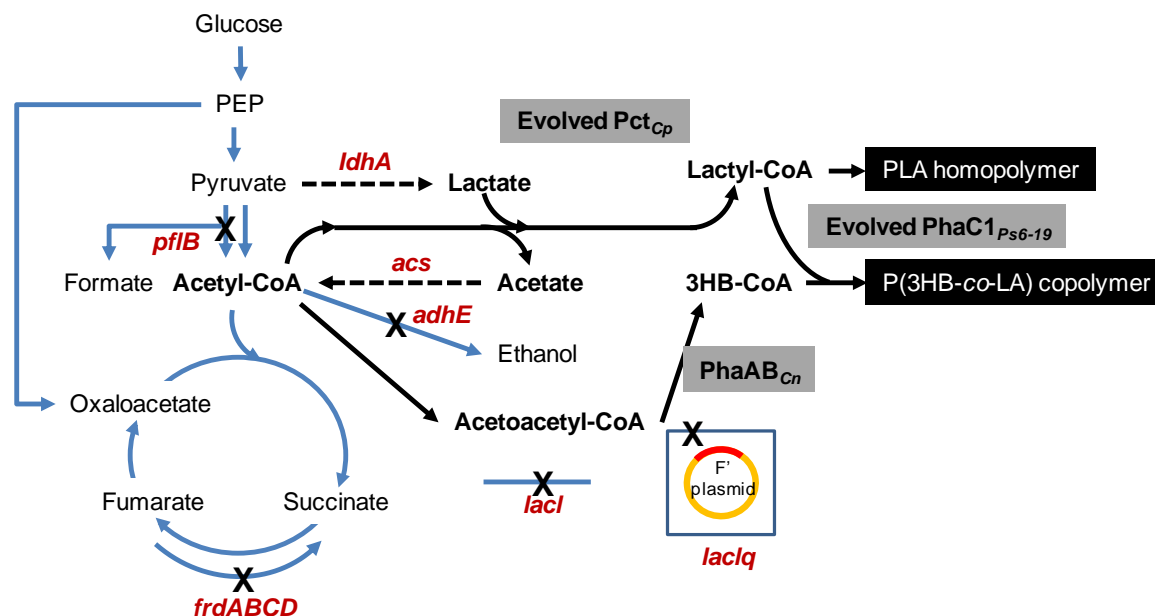
317. These challenges are likely to be similar in the production of any reduced commodity chemical in a biological process. Whilst a commercial process would require at least a 3-5 fold increase in yield of BDO, this work represents a breakthrough as there was no prior example of high TCA flux towards a reduced compound in the literature. It is a strategy that can be applied to the design of other biocatalysts. A commercial production route from sugar to 1,4-butanediol has now been described (Burgard et al., 2016).

Sugar to plastic through metabolic engineering and fermentation

318. Polylactic acid (PLA) has been considered a good alternative to petroleum-based plastic because it possesses several desirable properties such as biodegradability and biocompatibility. The major driver for its production is for large scale use in fibres. For example, it is being used in car interiors, replacing plastics with greater GHG emissions. Current manufacturing consists of fermentation to produce lactic acid followed by one of two major chemical routes to the polymer, both of which are difficult and either use high temperatures and solvents or heavy metal catalysts (Mehta *et al.*, 2005). But there is no existing natural bacterial route to PLA. However, Jung and Lee (2011) described efficient production of PLA by a direct fermentation of glucose without a chemical step (Box 8) in a metabolically engineered *E. coli* chassis strain.

Box 8. Metabolic engineering of *E. coli* for glucose to PLA

Direct fermentation of glucose to PLA in *E. coli*, replacing the chemical polymerisation step.



The overall metabolic network is shown in blue together with the introduced metabolic pathways shown in black for the production of the PLA homopolymer and the P(3HB-co-LA) copolymer in *E. coli*. The genes with cross marks shown in black represent the chromosomal gene inactivation and the elimination of F' plasmid shown in the box, and the genes with dashed arrows shown in black represent the over-expression of the genes by chromosomal promoter replacement.

Source : Jung and Lee (2011), figure redrawn from Jung and Lee.

Technical barriers to bio-based production

319. Major investment in the development and deployment of efficient biomass conversion technologies is necessary (Hellsmark et al., 2016). There exist considerable technical barriers to overcome before a significant bio-based production industry can be achieved. Some relate to the recalcitrance of cellulose and lignocellulose in the preferred feedstocks (essentially waste materials) for second generation ethanol and bio-based materials production. Another relates to the fact that microorganisms did not evolve for the operation in bioreactors at high substrate concentrations and the 'extreme' conditions of industrial operations e.g. pH extremes, solvent tolerance (see Burk and Van Dien, 2016).

Pre-treatment of biomass

320. The pre-treatment of biomass to degrade complex biological polymers to fermentable sugars is probably essential to satisfy an often-cited policy goal of using non-food crops as feedstocks for bio-production. This is specifically to avoid conflict with the policy goal of food security.

321. One of the more significant challenges in utilizing the vast global lignocellulose resource is the need for large quantities of glycoside hydrolase (GH) enzymes to efficiently convert lignocellulose,

hemicellulose and cellulose into fermentable sugars (Table 11) (van Zyl et al., 2007; Chandel et al., 2012). The presence of lignin and hemicellulose reduce the efficiency of the biomass pretreatment (Sun and Cheng, 2002), but much progress has been made in the last decade in modifying enzymes. These enzymes represent the second highest contribution to raw material cost after the feedstock itself (Klein-Marcuschamer et al., 2010).

Table 11. Composition of different lignocellulosic materials.

	Glucose	Xylose	Arabinose	Mannose	Lignin
<i>Hardwood</i>					
Birch	38.2	18.5	-	1.2	22.8
Willow	43.0	24.9	1.2	3.2	24.2
<i>Softwood</i>					
Spruce	43.4	4.9	1.1	12.0	28.1
Pine	46.4	8.8	2.4	11.7	29.4
<i>Grasses</i>					
Wheat straw	38.2	21.2	2.5	0.3	23.4
Rice straw	34.2	24.5	n/d	n/d	11.9
Corn stover	35.6	18.9	2.9	0.3	12.3

Notes: Figures are percentage of total dry weight, Glucose is mainly derived from cellulose; xylose, arabinose and mannose from hemicellulose. Lignin is comprised mainly of phenolics.

n/d = not determined, - = below detection limit.

Source: (Jørgensen et al., 2007)

322. It seems likely that an efficient biomass degradation system requires a large number of enzymes to act in a coordinated fashion, and yet the individual and collective actions of these enzymes are poorly understood. An alternative approach is to combine these enzyme activities with the machinery for making bio-based products within a single bacterial biocatalyst. This is the consolidated bioprocessing (CBP) approach. The complexity of biomass conversion and the rational design approach of synthetic biology makes what has been termed “a match made in heaven” (French, 2009).

323. CBP could potentially improve bioprocess economics (Lynd et al., 2005) by avoiding the costs of a dedicated enzyme generation step. The US Department of Energy endorsed the view that CBP technology is widely considered the ultimate low-cost configuration for cellulose hydrolysis and fermentation (USDOE, 2006). Moreover, in the CBP strategy, cellulosic and hemicellulosic materials should be fermented simultaneously (see review by Hasunuma et al., 2013). In a recent example, an *E. coli* strain was engineered to express recombinant xylanases and polyhydroxyalkanoate (PHA)-producing enzymes for the biosynthesis of the co-polymer poly(lactate-co-3-hydroxybutyrate) [P(LA-co-3HB)] from xylan as a consolidated bioprocess (Salamanca-Cardona et al., 2016). This latter is a research success, not yet a viable commercial process.

324. Another reason this is important is that xylose is the second most abundant carbohydrate in nature and its commercial fermentation to ethanol could provide an alternative fuel source for the future (Jeffries, 2006). The commercial yeast *Saccharomyces cerevisiae* has several advantages over most bacteria as an industrial production strain (see Box 11), but *Saccharomyces cerevisiae* does not naturally use xylose as a substrate (Toivari et al., 2004) and must be engineered to both transport and ferment xylose. There have been several claimed breakthroughs in the metabolic engineering of yeast to unleash this resource (e.g. Wei et al., 2013), but many challenges remain to achieve commercial viability (Moysés et al., 2016).

325. Nevertheless, it has been claimed recently that there is an increasing trend towards CBP as a path to low-cost biorefining from biomass (Agbor et al., 2014). Of the various possible bioprocessing

technologies, CBP may be the most economical in the long run, but productivity is still lacking (Kawaguchi et al., 2016).

Inhibitory compounds in CBP

326. CBP-enabling microorganisms encounter a variety of toxic compounds produced during biomass pre-treatment that inhibit microbial growth and ethanol yield (Hasunuma and Kondo, 2012). However, the harsh conditions used in the pre-treatment of the raw material release fermentation inhibitors including weak organic acids (particularly acetic and formic acids), furan derivatives, and phenolic compounds (there are several reviews, e.g. Almeida *et al.*, 2007). Indeed, ethanol itself is inhibitory to xylose utilization, which is considered to be critical for the production of fuels from biomass hydrolysates (Zhang et al., 2016).

327. To improve fermentation ability of industrial yeast strains for ethanol production, for example, several strategies have been applied to overcome the effect of inhibitors, including: controlling inhibitor concentrations during the fermentation (Martin et al., 2007); a mutagenesis and genome shuffling approach (Zheng et al., 2011); and the overexpression of genes encoding enzymes that confer resistance towards specific inhibitors (Hasunuma and Kondo, 2012). A relatively new approach to engineering tolerance to inhibitors, called global tolerance engineering, is to engineer a phenotype of broad tolerance toward several important inhibitors even when they are structurally dissimilar, while keeping the number of genes being manipulated to a manageable sum (Chen and Dou, 2016).

Growth on C1 compounds

328. Lanzatech has pioneered the conversion of hydrogen and carbon monoxide (CO) into bio-based products at the demonstrator phase. Progress has been slow because bacteria known to use C1 substrates can be difficult to work with in an industrial setting, and many have limited genetic tools. Introduction of carbon utilisation pathways from such strains into a tractable host, such as *E. coli*, also presents significant challenges (Burk and Van Dien, 2016). Nevertheless, many C1 compounds are available in large volumes (e.g. methanol) and others are greenhouse gases that can be harnessed i.e. carbon capture and utilisation (CCU) (e.g. methane, CO₂). The low-cost and ready availability of these molecules makes them attractive feedstocks for bioprocessing. Being able to harness the unique catabolic pathways, either in the native or heterologous (engineered) host could open new possibilities for non-food-based renewable feedstocks whilst helping with the policy goal of climate change mitigation, primary policy goals of a bio economy. Technologies already exist for capturing industrial CO₂: this is used, for example, to carbonate soft drinks. But the volumes of CO₂ are tremendous compared to the volumes used in industrial processes at present.

Computational enzyme design

329. Current approaches for engineering enzymes for improved activity and specificity are semi-rational at best. Although the field is still in its infancy, computational protein design has the potential to facilitate rational protein engineering or even design completely novel functions (Privett et al., 2012). While thousands of naturally occurring enzymes have been identified and characterised, there are still numerous important applications for which there are no biological catalysts capable of performing the desired chemical transformation (Mak and Siegel, 2014). The ability to design specific bespoke enzymes for any given pathway step would greatly accelerate the pace of strain engineering, and expand the opportunities to create entirely new synthetic metabolic pathways (Burk and Van Dien, 2016).

330. A frequently encountered challenge relates to the test component of the engineering cycle in that the computer can generate many more virtual enzymes than can be tested in reality. Obexer et al. (2016) showed that microfluidic-based screening using fluorescence-activated droplet sorting (FADS) is ideally

suited for efficient optimisation of designed enzymes with low starting activity, essentially straight out of the computer.

331. This is a recurring message for policy makers in R&D subsidy – the ability to design and build often exceeds the ability to test, and the answers lie in biology but with system integration and automation. The frontier is in integrated computational/experimental metabolic engineering platforms to design, create, and optimise novel high performance enzymes, but also organisms and bioprocesses (Barton et al., 2015). As the data sets become larger, the systems biology approach will become essential rather than the exception.

Minimal cells for bio-contained microbial factories

332. The start point for designing future production strains will be minimal, or chassis cells, self-replicating minimal machines that can be tailored for the production of specific chemicals or fuels to remove non-essential energy-consuming pathways and carbon sinks and minimise regulatory and toxicity issues (Vickers et al., 2010; Lee et al., 2013). Instead of being restricted by constraints that have shaped the regulatory/metabolic pathways of the production strain, in future it will be less effort to construct functional ‘circuits’ from scratch (Ghim et al., 2010). This is coming closer as the price of DNA synthesis has tumbled.

333. Ostrov et al. (2016) have made a significant advance towards a chassis *E. coli* industrial production strain. The plummeting cost of DNA synthesis has greatly reduced the financial barriers to synthesising entire genomes. They have developed computational and experimental tools to rapidly design and prototype synthetic organisms. As much as synthetic genomes have already been reported, this effort in on a scale that has not yet been previously explored.

334. The ultimate aim of the progression of this work is of producing a virus-resistant, bio-contained bacterium for industrial applications. Once complete, their genetically isolated *rE.coli-57* will offer a unique chassis with expanded synthetic functionality that will be broadly applicable for biotechnology. At current costs, the project could be attained for around USD 1 million.

335. Biocontainment to prevent escape of genetically modified microbes into the environment remains another goal for industrial production strains. Currently there are necessary but insufficient metrics to evaluate biocontainment (Mandell et al., 2015), and therefore the design strategies are as yet incomplete. Progress is continuous, but no existing one mechanism can guarantee biocontainment. The field is well illustrated by Chan et al. (2016), who constructed synthetic ‘kill switches’ that efficiently kill *E. coli* and that can be readily reprogrammed to change their environmental inputs, regulatory architecture and killing mechanism.

Small-scale fermentation models

336. Fermenters are the ultimate arbiters of process optimisation, but they are costly to run and typically require expert supervision. While multiplexing the design and test process should drastically reduce the number of strains to be tested in a fermenter, the fermenter is still necessary to make sure that it is truly the best strains that are chosen for industrial production. Small-scale fermentation is lacking in a number of areas, such as pH and aeration control and the ability to sample frequently, and it is hoped that the solutions will lie in microfluidics (Churski et al., 2015; Burk and Van Dien, 2016).

Robustness

337. Tolerance to inhibitors is part of robustness of microbial production strains. Natural microorganisms were not intended for the conditions of industrial production, and new characteristics to

make them more robust have to be engineered in, a classic function for synthetic biology (Zhu et al., 2012). In an industrial bioreactor, where nutrient levels are often in excess, the environment constantly changes (Wang and Zhong, 2007), toxic metabolites may be produced. High levels of shear stress may be applicable in a bioreactor (Chisti, 1999).

338. There are only few examples as yet where synthetic biology has been deliberately employed to increase robustness in bio-based production. For example, butanol offers some advantages over ethanol as a biofuel (e.g. Abdehagh et al., 2014), but its development is hindered by low yield and titre in the fermentative clostridia (Xue et al., 2013). DARPA has introduced a research programme dedicated to robustness in synthetic biology (Box 9).

Box 9. DARPA (US) and the Biological Robustness in Complex Settings (BRICS) programme

The Biological Robustness in Complex Settings (BRICS) programme seeks to develop the fundamental understanding and component technologies needed to engineer bio-systems that function reliably in changing environments. A long-term goal is to enable the safe transition of synthetic biological systems from well-defined laboratory environments into more complex settings where they can achieve greater biomedical, industrial, and strategic potential.

To date, work in synthetic biology has focused primarily on manipulating individual species of domesticated organisms. These species tend to be fragile—they require precise environmental controls to survive, and they are subject to losing their engineered advantages through genetic attrition or recombination. The costs of maintaining required environmental controls and detecting and compensating for genetic alterations are substantial.

The BRICS portfolio will consist of a set of programmes that aim to elucidate the design principles of engineering robust biological consortia and to apply this fundamental understanding towards specific applications e.g. on-demand bio-production of novel drugs, fuels and coatings.

Source: Adapted from <http://www.darpa.mil/program/biological-robustness-in-complex-settings>

Titre, yield and productivity

339. Most natural microbial processes are incompatible with an industrial process as the product titres (g per litre of product), yields (g product per g substrate, often glucose) and productivity (g per litre per hour) rates are often too low to be scalable (e.g. Lee et al., 2013; Harder et al., 2016). The required economic yield, titre, and productivity of a microbial process depend on whether the product is a bulk or niche chemical. The higher the value of the chemical the more that low titre, yield and productivity can be tolerated. For low-value, bulk chemicals, however, these factors make or break a bioprocess (see Box 10).

Box 10. Glucaric acid

Glucaric acid is an example that highlights central issues. The biggest bulk applications are its potential use as a building block for a number of polymers, including new nylons and polyesters (Moon *et al.*, 2010). For example, it can be converted to adipic acid for nylon production (US Patent Application, 2010). For these and other reasons, D-glucaric acid has been identified as a “*top value-added chemical from biomass*” (Werpy and Petersen, 2004).

As a result, researchers have been exploring metabolic engineering routes to production with a view to maximising product titre. There is a natural biochemical route in mammals but it has too many steps for an industrial production, and therefore most effort has been focused on designing a microbial pathway, typically in *E. coli*.

Metabolic engineering publications often demonstrate huge potential for improvement in titres and yields. Dueber *et al.* (2009) reported a 200-fold increase in glucaric acid titre, but still to only 1.7 g per litre. Raman *et al.* (2014) achieved a 22-fold increase over their *E. coli* parent strain; however, absolute production of glucaric acid remained substantially lower (1.2 mg per litre) than previously reported titres. Despite much elegant metabolic engineering in *E. coli*, available yields through microbial processes are still way too low. Schiue (2014) further improved titres, but a variety of strategies never achieved more than 5 g per litre. This is a long way from the “relatively low conversion” in the glucose chemical oxidation process.

Compare this with what has been achieved with other organic acids. A review indicates that production titres for organic acids range from 29 g per litre to 771 g per litre (Sauer *et al.*, 2008). For comparative purposes, the yeast *Saccharomyces cerevisiae* has an outstanding capacity to produce ethanol and CO₂ from sugars with high productivity, titre and yield: some wine strains can tolerate 15% ethanol or more. Also an oleaginous microorganism is one that can accumulate greater than 20% of its dry body mass as oil in the form of lipids (Ratledge and Wynn, 2002). A recent review of metabolic engineering studies to synthesise lactic acid (Upadhyaya *et al.*, 2014) cited many studies with titres well over 100 g per litre and yields in excess of 90%. Despite its identification as a top value-added biochemical from biomass in 2004, more than a decade later a commercially viable glucaric acid bioprocess is still elusive.

340. A fundamental constraint on host cell productivity is the metabolic burdens that lead to undesirable physiological changes. Engineering cell metabolism for bio production not only consumes building blocks and energy molecules such as ATP, but also triggers energetic inefficiencies in the cell (Wu *et al.*, 2016). The authors stated that the requirements for higher success rates in industrial settings calls are novel genome-scale models, ¹³C-metabolic flux analysis and machine learning for weighting, standardisation and predicting metabolic costs. Certainly the large number of metabolic engineering studies, as demonstrated in Table 10, provides an invaluable database for capturing information on titre, yield and productivity in response to genetic and fermentation conditions. This could be built into machine learning models.

Gene and genome editing in production strains

341. Despite recent advances, the sheer size of even the smallest bacterial genomes renders serial modification of limited utility for truly genome-scale engineering endeavours. Targeted genome editing and engineering have until recently been laborious and costly. Efficient methods enabling multiplex genome editing are urgently needed (Esvelt and Wang, 2013). Here, progress has been rapid even in the last three years. In combination with more sophisticated metabolic modelling tools such new techniques will substantially accelerate metabolic engineering (Sandoval *et al.*, 2012) and could transform the costs involved in making new strains for bio-based production. Chromosomal insertion and gene editing have particular potential in *Saccharomyces cerevisiae*, the ‘original’ industrial microbe used for ethanol production (Box 11).

Box 11. *Saccharomyces cerevisiae* and gene editing: the ultimate bio-based production tools?

Saccharomyces cerevisiae has many advantages as an industrial microorganism. In-depth knowledge of its genetics, genetic engineering, physiology, and biochemistry has been accumulated, and industrial-scale fermentation technologies are readily available (for a review, see Nevoigt, 2008). “Traditional” brewing techniques utilise *Saccharomyces cerevisiae* strains because they have high ethanol yield, high productivity, and their tolerance to high ethanol concentrations keeps distillation costs low (Kasavi *et al.*, 2012). It has the sub-cellular machinery for performing post-translational protein modification. And of course, it plays a central role in modern industrial biotechnology in bioethanol production as a biofuel, both first and second generation. The synthesis of a chromosome in yeast (Annaluru *et al.*, 2014) was a landmark achievement for synthetic biology for various reasons, not least because it is a step towards creating a chassis strain for industrial uses.

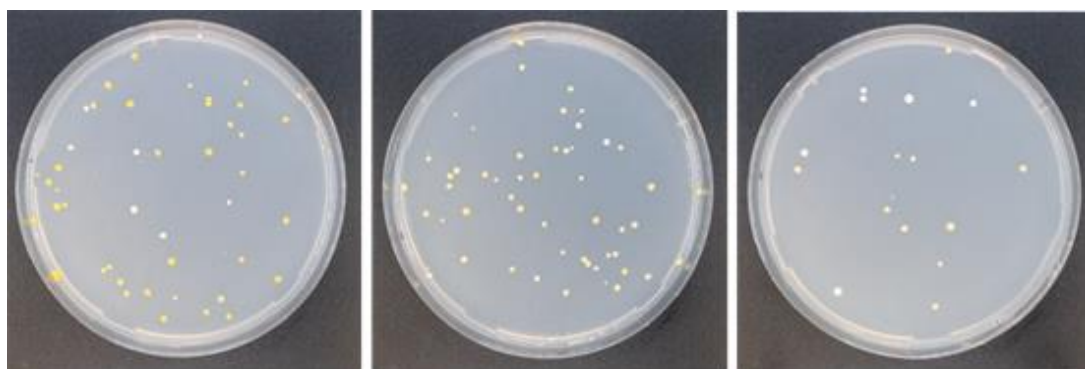
A particular advantage in synthetic biology is its extraordinary efficiency of homologous recombination Kujipers *et al.* (2013). *In vivo* recombination of overlapping DNA fragments for assembly of large DNA constructs in this yeast holds great potential for pathway engineering for automated high-throughput strain construction. Kujipers *et al.* (2013) described a robust method for *in vivo* assembly of plasmids for use in *S. cerevisiae* strain engineering.

But its efficiency of homologous recombination has also facilitated targeted manipulations within chromosomes (Klinner and Schafer, 2004). Amyris, to avoid problems with plasmids, takes advantage of this homologous recombination efficiency to work on chromosomal insertion. Since the adoption of methods using their patented standardised linker system and an automated assembly process, Amyris yeast DNA construction costs have dropped more than 90%, its capacity has increased at least ten-fold, and the fabrication success rates are greater than 95% (Gardner and Hawkins, 2013).

Another extremely important attribute is the fortuitous positive and negative selection system based on *URA3*, a gene on chromosome 5 in *Saccharomyces*. It encodes orotidine-5’phosphate decarboxylase, required for the biosynthesis of uracil. Positive selection is carried out by auxotrophic complementation of *ura3* mutations, whereas highly discriminating negative selection is based on the specific inhibitor 5-fluoro-orotic acid (5-FOA) that prevents growth of the prototrophic strains but allows growth of the *ura3* mutants. This works because 5-FOA appears to be converted to the toxic compound 5-fluorouracil by the action of decarboxylase. In other words, cells transformed with plasmids that contain the wild-type genes and a *ura* marker can be isolated by selecting for growth without uracil, and plasmid-free cells can be recovered by growth with 5-FOA (Forsburg, 2001). Because of this negative selection and its small size, *URA3* is the most widely used yeast marker in yeast vectors, freeing strain engineering from the need for antibiotic resistance markers.

The very recent development of CRISPR/Cas9 genome editing tools may be the ultimate solution for making *S. cerevisiae* production strains (and bacterial strains, for that matter) (Stovicek *et al.*, 2015). DiCarlo *et al.*, 2013) first described the high specificity of CRISPR/Cas9 for *S. cerevisiae* gene editing. The CrEdit (CRISPR/Cas9 mediated genome Editing) (Ronda *et al.*, 2015) combines CRISPR/Cas9 with the convenient genome engineering tool EasyClone (Jensen *et al.*, 2014). They achieved highly efficient and accurate simultaneous genomic integration of multiple pathway gene expression cassettes in different loci in the genome of *S. cerevisiae*. In the same paper they describe integration of three pathway genes involved in the production of β -carotene (see below), a high-value food supplement (Borowitzka, 2013), at three different integration sites located on three different *S. cerevisiae* chromosomes.

Single-step integration of the beta-carotenoid pathway created *S. cerevisiae* colonies that accumulate β - carotene, resulting in an orange pigmentation (from Ronda *et al.*, 2015).



Concluding remarks

342. The story remains the same for bio-based production through metabolic engineering – Herculean research efforts and cash burn, many new ideas from new target molecules to chassis strains to bio-containment strategies. There are large numbers of academic research groups with specific interests in individual areas of research, but relatively few academic groups or companies that can bring together a commercial project from idea to finished product ready for a bioprocess.

343. R&D subsidy decision makers need to rethink R&D programmes in the area. The challenges across the boards are demanding ever-larger data sets to shrink the number of actual physical experiments to reasonably attainable levels. The message to these decision makers is clear: it is now time to fund computational and experimental systems integration. Otherwise standard methodologies and interoperability will become more distant, not less.

THE CONVERGENCE OF INDUSTRIAL BIOTECHNOLOGY WITH GREEN CHEMISTRY

“The scientific opportunities enabled by convergence—the coming together of insights and approaches from originally distinct fields—will make fundamental contributions in our drive to provide creative solutions to the most difficult problems facing us as a society”.

National Academy of Sciences (2014a).

Introduction

344. Convergence can be seen as a natural extension of multi-disciplinary or inter-disciplinary research (and development). And one of the problems associated with multi-disciplinarity is that higher education establishments still teach by discipline, and adapting the training and educational systems proves to be very difficult.

345. The key message of convergence, for the present purpose, is that merging ideas, approaches, and technologies from widely diverse fields of knowledge, when integrated to a high degree, is one crucial strategy for solving complex problems that cannot be addressed by a single discipline or technology. To have a focus, a *working definition* of convergence might be:

“Convergence is the coming together of different technologies to solve problems that cannot be addressed by a single technology”.

346. In this regard, the convergence of industrial biotechnology with green chemistry represents a very powerful example. Both industrial biotechnology and green chemistry have similar policy goals. The drivers for bio-based chemicals production span the classic triple bottom line: economic, environmental and social. In these times of grand challenges, an added dimension in OECD countries is to improve the competitiveness of the chemicals industry. A vision from the US roadmap for the industrialisation of biology is that *“the use of biological and chemical routes must be thought of as equals”* (National Academy of Sciences, 2015).

What is green chemistry?

347. Energy costs on average account for 50–85% of the production costs of bulk chemicals (UNIDO, 2011). This is particularly pertinent to OECD countries as energy costs can be up to seven times higher in fuel importing nations compared to fuel producing nations. Many petrochemical processes require high temperatures and pressures to drive them to completion.

348. Green chemistry is taken to mean designing environmentally ‘benign’ chemical processes that lead to the manufacture of chemicals with lesser environmental footprint i.e. that use less energy in their production (lower temperatures and pressures), that use reduced levels of solvents or none at all, renewable, recyclable catalysts, and the products of green chemistry should have been responsible for lower GHG emissions than chemicals produced from fossil raw materials and supply chains.

349. Anastas and Warner (1998) codified the *12 Principles of Green Chemistry* (Table 12), which provide a roadmap for anticipating, and potentially avoiding, consequences of chemicals and their production process. These authors also stressed that green chemistry innovation can be technically equal or superior to existing chemistry, and financially profitable when commercialised. To date, though, commercial progress has been relatively limited due to competition, especially with petrochemicals.

Table 12. Codification of the 12 principles of green chemistry

1. Prevention: It is better to prevent waste than to treat or clean up waste after it has been created.
2. Atom economy: Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.
3. Less hazardous chemical syntheses: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Designing safer chemicals: Chemical products should be designed to effect their desired function while minimising their toxicity.
5. Safer solvents and auxiliaries: The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Design for energy efficiency: Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. Use of renewable feedstocks: A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Reduce derivatives: Unnecessary derivatisation (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.
9. Catalysis: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Design for degradation: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. Real-time analysis for pollution prevention: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Inherently safer chemistry for accident prevention: Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

Source: Anastas and Warner (1998).

Why convergence of industrial biotechnology with green chemistry?

350. Green chemistry is one of the most important and practically used tools to integrate principles of sustainable development and green economy in the field of chemistry and the chemical industry (Makarova et al., 2017). Industrial biotechnology is largely about using biotechnology to produce chemicals of various hues. The policy objectives of industrial biotechnology and green chemistry are, then, effectively the same. As both are ‘wet’ sciences or technologies, and given that the use of both disciplines can be as tools for the other, there is a natural evolution towards convergence. To speed that evolution requires more than serendipity; if it is regarded as a societal good, then governments would be best placed to use public funding to orchestrate it.

351. One of the greatest challenges for making bio-based equivalents of petrochemicals is that three key metrics of bioprocesses are often poorer than in petro chemistry: titre (g per litre of product), yield (g product per g substrate, often glucose) and productivity (g per litre per hour). Chemistry can be used to improve these metrics. In the case of ethanol, the titres and yields are adequate. For many other chemicals this is not the case. And there will be bio-based chemicals that are best made from biomass using a purely chemical process. In the end, the desired result is the same – the eventual replacement of unsustainable petrochemicals with bio-based equivalents that are sustainable and renewable. This is not a simple case of using chemical tools to aid biology, or biology tools to aid chemistry, but a genuine cooperation to make a better result – the working concept of convergence.

Industrial biotechnology converges with chemistry converges with IT/computing

352. The greatest likelihood is that many successful academic metabolic engineering studies will not make it through to commercialisation. However, the convergence of industrial biotechnology with green chemistry may increase the success rate. For example, Gerbaud et al. (2016) have proposed the computer

aided molecular design (CAMD) approach for designing bio-based commodity molecules. Increasingly there will be examples of how green chemistry and industrial biotechnology converge to solve a particular bio-based chemical synthesis.

WHERE NEXT FOR BIO-BASED PRODUCTION AND REPLACING THE OIL BARREL?: THE CASE FOR TECHNOLOGY CONVERGENCE

353. It still takes 50-300 person years and many millions of dollars to bring a metabolically engineered product to the market (Hong and Nielsen, 2012). Currently it takes on average 7.4 years to launch a bio-based product (*Il Bioeconomista*, 2015).

354. If a deluge of metabolically engineered strains producing bio-based chemicals was subsequently expected, then the deluge has not arrived. Follow-on commercial successes have been few (e.g. Van Dien, 2013), despite the fact that over 30 bio-based chemicals have been identified at technology readiness level (TRL) 8-9 (European Commission, 2015b). Progress has been made: commercial scale runs of 1,4-BDO production were performed less than five years after the first detectable amount of BDO was produced in an engineered *E. coli* strains (Burgard et al., 2016). Even more encouraging is the environmental performance of bio-based BDO: it can be produced from dextrose with up to 83% lower total CO₂-equivalent emissions per kilogram of BDO, and 67% lower fossil energy usage relative to the petrochemical process.

355. In this section the reasons for the widespread failure to commercialise bio-based chemicals though production in metabolically engineered strains is investigated, and policy measures to improve success through R&D are identified. Therefore this section is of most interest to policy makers in public R&D funding, typically: research councils and funding agencies (e.g. RCUK, National Research Foundation, Korea; DARPA, US); innovation agencies (e.g. Tekes, Finland; Vinnova, Sweden); intermediate research organisations (e.g. CSIRO, Australia; Fraunhofer, Germany); organisations that support national research centres (e.g. National Science Foundation, US), national research institutes (e.g. INSA, France; RIKEN, Japan; KIBBR, Korea), and; relevant ministries and departments. It is also of interest to other funding organisations that sponsor collaborative academic/industry R&D, and may be of interest, if closer to market, to other forms of financing with public money e.g. the UK Green Investment Bank. It is of interest to the EU research and innovation programme Horizon 2020.

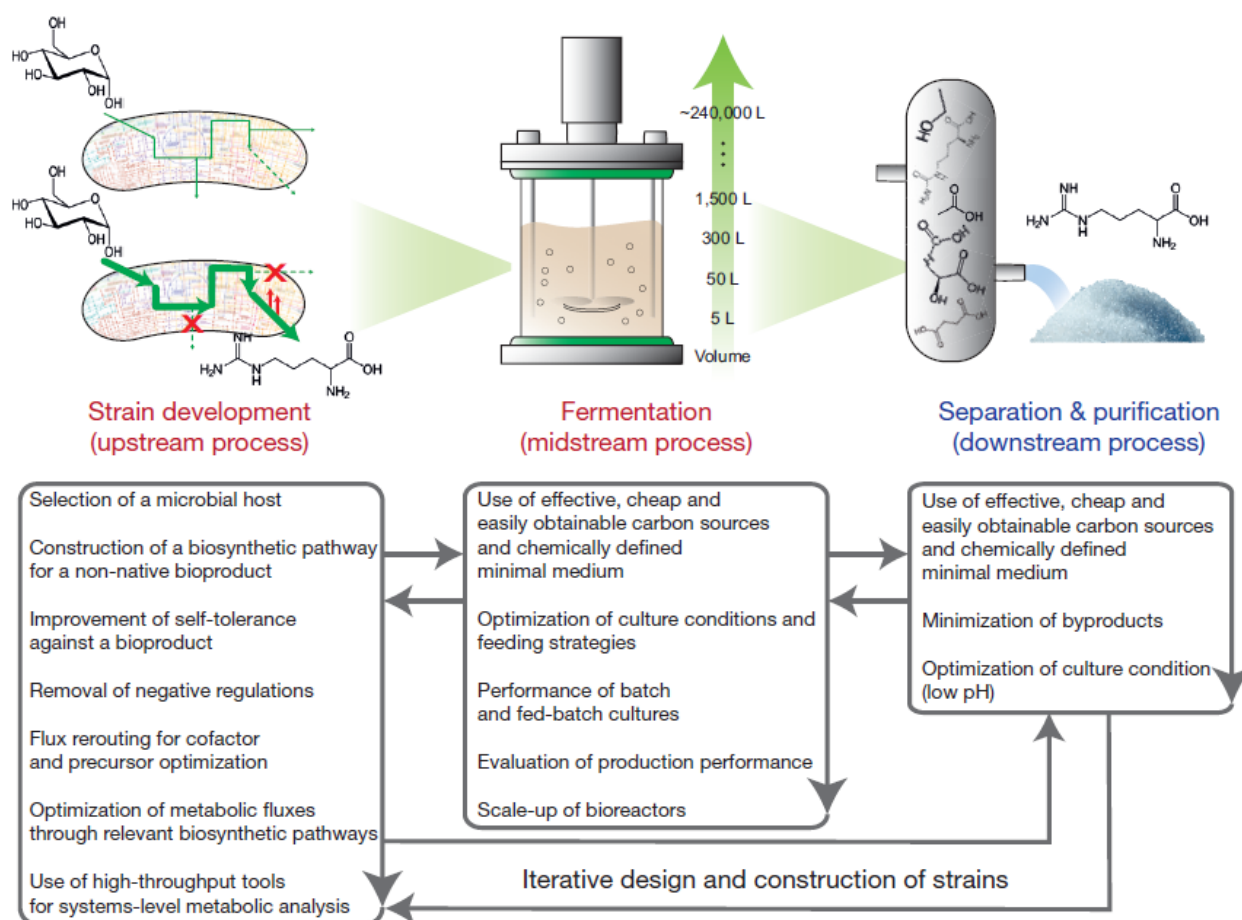
An integrated technology platform to unlock the potential

356. Genomatica of the US is a leader in the field of bio-based chemicals from metabolically engineered strains. For them the key to removing bottlenecks is: “*an integrated technology platform encompassing metabolic modeling, high-throughput (HT) pathway and strain construction, quantitative small scale screening, and systems biology, all of which are intimately linked to fermentation and process engineering*” (Burgard et al., 2016).

357. This agrees with the view of Lee and Kim (2015) of Korea who consider one reason the process is so challenging is “*that researchers often fail to consider a fully integrated industrial bioprocess when developing microbial strains with new activities*”. They refer to this as the “*systems metabolic engineering framework*”.

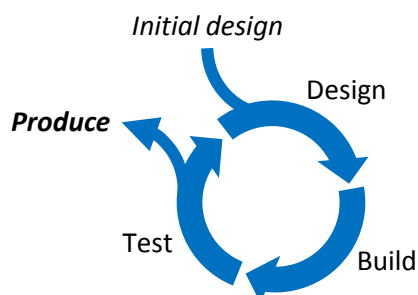
358. In other words, there is no one technology at fault, but it is the failure to integrate several technologies that defeats commercialisation. Different authors give different explanations of the overall process. Figure 10 is one interpretation.

Figure 10. Concept of the systems metabolic engineering framework.



Source: Lee and Kim (2015).

359. At a more fundamental level, most of biotechnology as yet fails to meet some of the specific criteria of engineering. There are essential differences between the scientific method (test a hypothesis through experimentation) and engineering design (design a solution to a problem and test the outcome) that have to be addressed. Concepts such as interoperability, separation of design from manufacture, standardisation of parts and systems, all of which are central to engineering disciplines, have been largely absent from biotechnology (OECD, 2014b). Therefore there can be expected to be weaknesses at the general level of the engineering cycle (Figure 11).

Figure 11. The engineering design cycle.

360. Many variants on the above exist, but this shows the basic elements of engineering design through a phase of initial design, building and testing of a part/system/device. Nobody expects an optimal design at the first attempt. Therefore the process is iterated as often as necessary to meet the engineering specifications.

The test phase is the current bottleneck

361. Phenotype evaluation is a major rate-limiting step in metabolic engineering (Wang et al., 2014). When constructing production strains for biofuels or bio-based chemicals, design success will be measured in the amount of product formed. If this requires the separation of individual strains into, say, 96 well plates and the determination of the concentration of the chemical of interest in each, then the process of multiplexing in design and build has been defeated: in effect, this results in demultiplexing (Rogers and Church, 2016). The throughput is limited to hundreds of thousands of design evaluations per day. Improving this throughput by mechanical or electronic automation is going to be limited as the orders of magnitude of improvement needed are so high. The advances necessary have to come from biology itself (e.g. Rogers et al., 2015; Xiao et al., 2016).

Reproducibility is a continuing problem

362. Early in the history of synthetic biology, reproducibility was highlighted as a challenge (Kwok, 2010) and this remains so (e.g. Hayden, 2015; Beal et al., 2016). This has to be conquered for bio-based manufacturing to take its place as a credible manufacturing platform of the future.

363. Many researchers have called for completely new computational languages for biotechnology. It is argued that variants of natural languages such as English are too imprecise and ambiguous to be useful in tackling the highly complex systems of biology and biotechnology. Antha is perhaps the first *bona fide* attempt to create a programming language for general purpose computation in biology (Sadowski et al., 2016). It is built on Google's Go programming language, but incorporates domain-specific features, such as liquid handling planning. It is claimed to enable experiments of an entirely new level of complexity. It embraces the departure from one-factor-at-a-time (OFAT), enshrined in the scientific method, by enabling detection of interactions between different experimental factors.

364. The creator of Antha, Synthace of London, exemplified the challenge (Box 12). Synthace worked with Merck to create a new microbial manufacturing platform for bio-therapeutics. They examined the interactions between 27 factors in order to integrate strain construction with process development. This is far too large a dimensional space to address with a screening approach. Even screening a billion assays a second would impossible time periods to investigate every permutation of these 27 genetic and process factors. Using multifactorial methods navigated this space, revealing key factor interactions in, of course, a small fraction of the time.

365. Greater convergence of metabolic engineering with IT and computing can be predicted e.g. Hadadi et al. (2016) used computational tools to construct a database of all theoretical biochemical reactions based on known biochemical principles and compounds. It includes more than 130 000 hypothetical enzymatic reactions that connect two or more metabolites through novel enzymatic *reactions that have never been reported to occur in living organisms*. It is organised in a web-based database⁵⁶ that allows the user to search for all possible routes from any substrate compound to any product.

⁵⁶

<http://lcsb-databases.epfl.ch/atlas/>

Box 12. Software approaches to rational design in biotechnology**Synthace, London**

The reason Design for Manufacturing is so important is that as a general rule across industry sectors 70% of the costs of manufacturing a product are determined by design decisions, and only 20% determined by production decisions. That creates a challenge in the life sciences, where research and development are very often totally separated from each other.

Antha is a first-generation high-level programming language for biology from Synthace (<http://www.synthace.com/>). Manufacturing in the modern economy works because design and testing software can talk to manufacturing hardware via multiple layers of application programming interfaces (APIs). By building APIs between design and manufacturing into Antha, the link is made to bioprocess automation. Antha is designed to make simple, reproducible and scalable workflows by stacking smart and reusable elements. An element might be anything from genetic elements to experimental procedures. Antha will automatically track and log all associated data when the element is executed. Essentially this enables not just the standardisation of the genetic parts but standardisation and full tracking of the experimental procedure used to characterise a part. This will inherently allow for greater reproducibility, simplicity and scalability when the elements are wired together to form workflows. It is also a LIM system, data-management system and QA system to enhance traceability and reproducibility.

Synthace has had Innovate UK⁵⁷ grants (GBP 498 000 in 2013; GBP 367 000 in 2014) and a Proof of Concept project grant of GBP 50 000 from SynBiCITE.⁵⁸

Riffyn, California

New products are the lifeblood of life science and chemical companies, but low data quality and data fragmentation in R&D are stalling innovation. Reproducibility has long been an issue in biotechnology and remains so for synthetic biology: errors and false positives translate to failed batches and missed discoveries and opportunities. At the heart of the problem is that design tools for process-based R&D are inadequate. Increasingly life science, chemical and food product development has become a global supply chain of people, instruments, organisations, knowledge and data—a chain that must be orchestrated to deliver an increasingly complex portfolio of products while meeting intensifying cost and regulatory pressures. Integrating software therefore needs to go far beyond integrating in the laboratory: integration across the entire business is the best way to reduce errors.

Riffyn of California (<http://riffyn.com/>) is designing software that combines sharable research/manufacturing process design with integrated experiment design and measurement data analytics, an approach that may currently be unique. The key is in the ability of Riffyn's SaaS software to support a complete engineering design, testing, learning cycle. The main business advantage is that data integration delivers a substantial reduction in time-to-market, a factor that has ended many promising biotechnology projects and start-up companies prematurely. It is cloud-based to remove installation and operating overheads and constitutes a real-time collaboration with just a browser. The process designs are self-contained descriptions of both process specifications and process performance. They can be shared with collaborators, access controlled, version controlled, and transferred between R&D, manufacturing and laboratories.

From the founder of Riffyn, Tim Gardner:

"The scientific method remains as relevant to R&D today as it was 300 years ago. But the means of communication of 300 years ago are not so relevant or adequate. Yet we have confined ourselves to a centuries-old method of communication - written Materials and Methods sections in papers - that cannot express the complexity of modern science. Moreover, such paper artifacts are artificially static - and go against the fundamental learning cycle where ideas are tested, iterated and re-tested till the best process or product or state of knowledge is achieved. Riffyn technology is an attempt to transform the status quo with collaborative computer-aided design and statistical data analytics for the scientific method itself".

⁵⁷ <https://www.gov.uk/government/organisations/innovate-uk>

⁵⁸ <http://www.synbicite.com/>

Conquering these challenges will move the bottleneck to data analysis and storage

366. A fully multiplexed design-build-test cycle that links phenotype to DNA sequence will enable the evaluation of millions of designs per cycle. However, this will create an unprecedented amount of data, which may move the bottleneck to data storage. It will also necessitate a new data analysis pipeline that simplifies the interrogation of phenotype-sequence relationships. In the age of machine learning, ultimately the data should inform the next iteration of design without lumpen human intervention (Rogers and Church, 2016). For example, AutoBioCAD promises to design genetic circuits for *E. coli* with virtually no human user input (Rodrigo and Jaramillo, 2013). Thus algorithms are needed that incorporate machine learning to correlate data from different data sets for the purpose of linking genes, proteins, and pathways without *a priori* knowledge (Wurtzel and Kutchan, 2016).

367. A rapid drop in the cost of DNA synthesis has rendered the costs trivial for many laboratories. There now remains a large bottleneck – magnitude orders of constructs fewer can be tested than designed and built. Mechanical or electronic automation cannot bridge the gap – the answers will have to come from biology itself with the aid of computational models (Rogers and Church, 2016). The time seems right for dedicated programming languages for the life sciences. Sadowski et al. (2016) argue that the most crucial need now is the development and adoption of high-level machine languages for executable bioprocesses.

368. Most natural microbial processes are incompatible with an industrial process as the product titres, yields and productivity rates are often too low to be scalable (e.g. Harder et al., 2016; Maiti et al., 2016). Titre, yield and productivity may be perceived as issues for near-market R&D, but the challenges have been so pervasive and intractable that there is probably a need for more funding in basic research. Lee and Kim (2015) described ten general strategies behind the successful development of industrial microbial strains through systems metabolic engineering. Putting such practices into action points to the need for R&D subsidy in programmes that give grants to companies. Funding agencies that subsidise public research as well as SMEs could be well placed to run such programmes e.g. Tekes in Finland. Alternatively the research could be conducted in IROs.

Gene editing: a new paradigm, or new hype?

369. Gene editing techniques promised both ease of application and precision. Therefore it would seem suited to the iterative nature of metabolic engineering, where multiple pathways may interact to create unwanted side reactions. Political will is growing for more bio-based production, and it may be that gene editing solves technical challenges that have inhibited the deployment of more bio-based production routes, especially to the plethora of useful chemicals that have no natural occurrence, and require pathways to be created in standard production models *de novo*.

370. Another aspect that gene editing may benefit is creating robustness in production strains. There are many issues e.g. an environment in constant flux, tolerance to pH changes, nutrient levels way in excess of those found in nature, toxic metabolites, shear stress, mixing and oxygen transfer. This seems to call for many precise genetic interventions, and would therefore seem suited to the qualities that gene editing is purported to bring.

Applications to existing production strains

371. While metabolic engineering is widely applied to modify *Escherichia coli*, it still needs efficient genome-scale editing tools to make industrial strains. Jiang et al. (2015) claim to have created a CRISPR-based gene modification system that “*offers unprecedented convenience and efficiency in design and manipulation*”. Similarly CRISPR/Cas9 genome editing tools have been developed for making *S. cerevisiae* production strains (Stovicek et al., 2015). Although *Streptomyces* species remain invaluable

hosts for the discovery and engineering of natural products, the genetic manipulation of these bacteria is often labour- and time-intensive. Cobb et al. (2015) have introduced CRISPR/Cas9-based gene editing tools to simplify the manipulation of *Streptomyces*.

Application to new potential biocatalysts

372. Industrial scale bio-based production is limited to a very small number of production strain models that have favourable regulatory status e.g. *E. coli* and *Saccharomyces cerevisiae*. However, it may be easier to gene edit a promising non-standard organism than bring a host of traits into a standard strain. Examples are as yet rare. For example, for decades the potential of marine microalgae in industrial production has been discussed but with few commercial successes. Diatoms are unicellular photosynthetic algae with promise for green production of fuels and other chemicals (Weyman et al., 2014).

373. Daboussi et al. (2014) have done what is probably the first gene editing on diatoms, indeed one of the first gene editing efforts in any marine organism. The authors report highly efficient gene editing using sequence-specific nucleases, with high frequencies of TALEN-mediated genome modification in this species. They generated an enhanced lipid-producing strain with a 45-fold increase in triacylglycerol content when compared with the parental strain. So here is the potential for future biofuel manufacture from a diatom. And the ability to manipulate metabolic pathways using sequence-specific nucleases, they said, “*will pave the way for synthetic biology in diatoms*”. Nymark et al. (2016) developed a very efficient CRISPR/Cas9 genome editing and selection method for the model diatom *Phaeodactylum tricornutum*, which can be potentially adapted for use in other microalgae.

CRISPR could be easily over-hyped

374. Hying the promise early, if followed by stagnation in actual commercial and societal benefits, have then inhibit further public and private investments, and this may occur at critical moments of the ‘valley of death’. Equally, an exciting new technology is always accompanied by forecasts of the market size, turnover, and job creation. Certainly the markets addressed in bio-based production and food security are very large, but it is very difficult to ascertain what the actual contribution of gene editing would be.

375. There is plenty of discussion in the open literature of breakthroughs, powerful new tools, a new era in bio-production, but what is lacking is standardisation. This is understandable as the technique is so new and applicable in so many organisms and to so many genes. For it to become part of the “systems metabolic engineering framework”, companies will be required to standardise their own systems. However, that does not lend itself to interoperability.

376. Here lies an opportunity for public policy: collaboration with the private sector to create the necessary standards to diffuse the technology widely. This would make the technology cheaper, and in the end would bring customer satisfaction and confidence. However, the opposite might happen – gene editing could face the same kind of public backlash that bedevilled the previous generation of genetically modified plants and animals, and to avoid it, scientists need to communicate the advantages of their work (Reardon, 2016).

377. Another issue facing gene editing is the protracted patent wrangle over CRISPR. A legal verdict on the CRISPR patents could still be months, or even years, away, with an expected appeal by the losing party expected further drag the process out (Ledford, 2016).

Concluding remarks

378. New hope and new techniques are appearing in bio-production regularly, but this may only serve to bewilder public policy makers further. If a common theme is discernible, it is the need for greater

integration of techniques to improve the rate of commercialisation success as there is a clear gulf between academic success and commercial reality. It is also clear that there is an increasing need for convergence with IT/computation to achieve this higher level of integration. Furthermore, to drive the industry will require standardisation, both of biotechnologies themselves and the computational tools to bring the science closer to engineering criteria required of modern manufacturing.

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