Using biological systems to develop high value products and processes

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Summary

- High value biorenewables are bio-based products, typically valued at greater than £10/kg and produced at low volumes using industrial biotechnology methods (i.e., produced using biological systems). They range from small bio-derived molecules to complex molecules (e.g., polymers, proteins, and enzymes) and cells.
- High value biorenewables have a wide variety of applications across industrial sectors that underpin the UK economy. For example, they can be used as ingredients in pharmaceuticals, cosmetics, agrochemicals, home and personal care products, and foods.
- There are opportunities for new and improved products using high value biorenewables, and they can also provide sustainability benefits such as decreased greenhouse gas emissions or reduced reliance on fossil feedstocks or unsustainable natural resources. Deploying high value biorenewables at scale could also offer broader environmental, economic, and social benefits.
- The UK is well placed to reap the potential benefits of high value biorenewables due to its wealth of research and industrial expertise. However, there are barriers to developing and deploying these products at commercial scales, and action across industry, academia, and government will be required to overcome them.
- Government intervention will be required to create an enabling environment for this sector to continue to grow. This includes appropriate funding at all stages of research and innovation, a supportive regulatory environment, investment in skills, and policies that encourage the use of sustainable products.

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1. Introduction

Modern society relies on chemical products to meet our day-to-day needs: they are in medicines, clothes, cleaning products, and the agricultural chemicals that enable us to produce enough food. However, the sustainability of many of these products is subject to increasing scrutiny. They are often made from fossil feedstocks, and there can be detrimental impacts to the environment and people's health along the value chain [1-4]. We need to address these impacts whilst also making products to meet the needs of our growing population.

One solution is to turn to biology: biological systems and bio-based feedstocks can be used to produce a variety of chemical products. As well as bulk products such as bio-based plastics, this includes a range of high-value, low-volume products (>£10 per kg, and <1000 metric tonnes per year), such as pharmaceuticals, dyes, fragrances, and speciality chemicals.

This report focuses on the generation of high value products made using industrial biotechnology methods, which are referred to throughout as high value biorenewables. Specifically, the report details how high value biorenewables are made, the opportunities they provide, and the potential risks and challenges associated with their deployment. Information was collated through a review of the scientific literature, engagement with members and the Management Board of the High Value Biorenewables Network, and a series of stakeholder workshops that gathered input from academic and industry experts from various sectors and disciplines.

2. Making high value biorenewables using industrial biotechnology

The production of high value biorenewables by biological production platforms is summarised in Figure 1. This briefing focuses on high value biorenewables produced in microbes, plants, algae, and enzymes, but it is also possible to use fungi, or animal or insect cells. The inputs required vary by the platform used: plants and algae utilise light, carbon dioxide, water, and nutrients, whereas microbes and enzymes convert biomass feedstocks (e.g., crops, forestry biomass, wastes and residues) or bio-derived compounds (e.g., sugar or polymers from biomass feedstocks) into desired products[1].

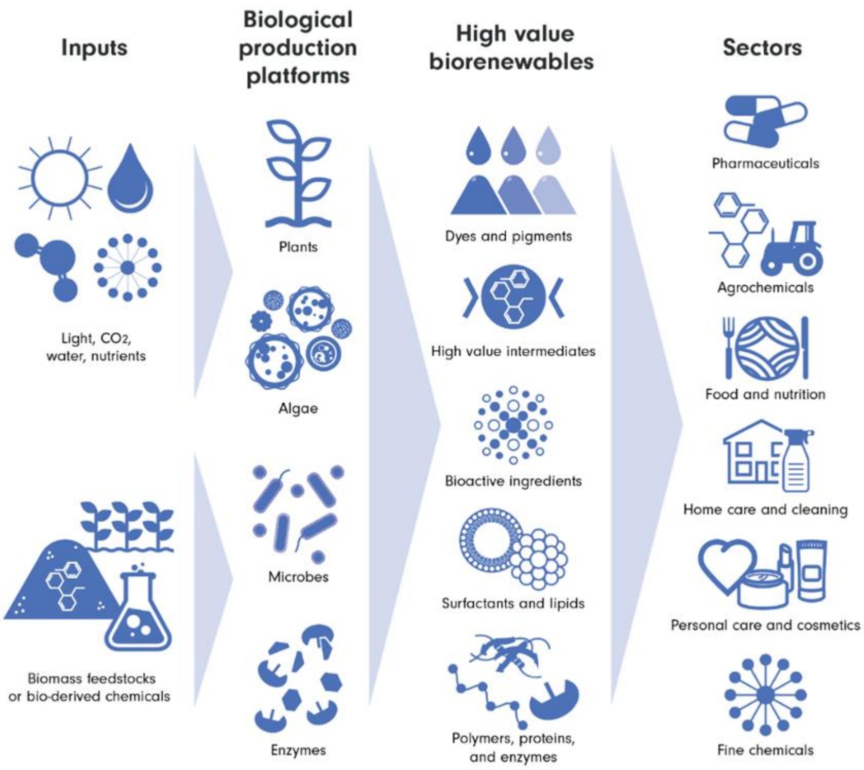

Figure 1. Production of high value biorenewables using biological systems

[1] Microbial and enzymatic systems can be used to convert fossil derived chemicals into products, but these products would not fall under the definition of biorenewables and are not considered here.

High value biorenewables range from small bio-derived molecules to large and complex biological molecules (e.g., polymers, proteins, and enzymes) and cells. Some examples of high value biorenewables are detailed in Table 1.

Table 1. Examples of high value biorenewable products

High value biorenewable	Biological production platform	Description
Nootkatone	Enzyme or microbe	Nootkatone is a **fragrance/ flavouring** used in foods, perfumes, cosmetics, and pharmaceuticals which also has applications as an insecticide. It was traditionally sourced from grapefruit using a process that was expensive and unsustainable due to the large volumes of plant material required. University of Oxford spinout Oxford Biotrans developed a process using an engineered enzyme to convert a cheaper substrate to nootkatone [5]. Fermentation derived nootkatone is also commercially available [6].
Squalene	Microbe or plant	Squalene is an oil used primarily in **personal care products** as well as pharmaceuticals. It is sourced from the livers of deep-sea sharks or at low concentrations from plants like olives. However, squalene can now be produced through microbial fermentation and chemical synthesis [7] and researchers at Royal Holloway University are developing a method that uses modified tobacco plants [8].
Spinosad and spinetoram	Microbe	Spinosad and spinetoram are fermentation derived i**nsecticides** developed by Corteva Agriscience and traded as Qalcova™ and Jemvelva™ [9]. They can replace some fossil-derived synthetic insecticides such as organophosphates and have been shown to have reduced impacts on non-target species and benefits to human health compared to alternatives [10].
Paclitaxel	Plant cell culture	Paclitaxel is an important **chemotherapy medication**. Until the 1990s it was sourced from the bark of the endangered Pacific Yew tree, using a method that killed the tree. Attempts to create an entirely synthetic paclitaxel failed due to the complexity of its structure but it is now principally produced through plant cell culture, avoiding reliance on an endangered tree species [11].
Sitagliptin	Enzyme	Sitagliptin is a type II **diabetes drug**. Previous synthetic chemistry approaches either required multiple steps with relatively low yields and generation of a lot of waste or required a heavy-metal catalyst and high pressures. Merck developed an enzymatic method for commercial production which increased productivity and yield, reduced waste, and eliminated the need for a heavy-metal catalyst [12, 13].
Astaxanthin	Algae	Astaxanthin is one of the most potent **antioxidants**, reportedly 65 times more effective than vitamin C and 100 times more than alpha-tocopherol. It is primarily produced through a petrochemical process due to cost. However human trials using astaxanthin derived from the freshwater microalgae *Haematococcus pluvalis* has demonstrated this source to have superior bioavailability, safety and health benefits in human clinical trials [14, 15].
Vitamin A	Microbe	Like many other vitamins, **vitamin A** was initially produced by extraction from natural sources. Currently, all vitamin A is derived from petrochemical intermediates via chemical synthesis [16]. Recently, DSM-Firmenich demonstrated the pilot-scale production of bio-based vitamin A using an engineered yeast strain [16, 17] which has lower energy consumption and improved environmental performance when compared to the synthetic route.
Nitrogen fixing bacteria	Microbe	Azotic Technologies produce liquid formulations containing bacteria that can be directly applied to crops [18]. Bacteria fix nitrogen from the atmosphere and thus reduces the need for synthetic **fertiliser**.

Industrial biotechnology can employ naturally occurring biological systems but there is also the potential to modify systems to improve performance in industrial conditions or make different products, including through the application of engineering biology [19-35].

Each biological production platform has its advantages and limitations, but there are some common themes. For example, biological systems can use feedstocks and carry out chemical transformations that would be difficult, expensive, or impossible via synthetic chemistry routes, and they can be good at making complex chemical structures. There are also common technical challenges to be overcome, mainly because many bio-based systems give low yields or rates of production or require extensive downstream processing to recover the desired product which can negatively affect economic and environmental performance. Overcoming these challenges and progressing new technologies towards commercialisation will require multidisciplinary research and scale up activity. This will demand input from disciplines such as synthetic biology, genetics, biochemistry, molecular biology, agronomy, plant breeding, and chemical engineering, as well as support from bioinformatics, AI, regulatory science, lifecycle assessment and techno-economic analysis.

Plants as production platforms

Plants are an essential source of valuable, diverse products with desirable properties, such as bioactive molecules with therapeutic effects [36, 37]. Whilst synthetic routes for some of these compounds have been developed, this is often challenging due to the product's complex molecular structures [19]. This means that plants remain an important source for extraction of many high-value products. Wild plants are used in some cases, but more often the desired species are cultivated in fields or controlled environments such as glasshouses (vertical farming technologies).

Plants can be modified to increase product yields, which are often low in natural systems, or make non-native products, such as therapeutic proteins and vaccines in tobacco plants [19, 20]. However, engineering biology in plants is more challenging and less well developed than for other platforms such as microbes, and the research process is often slower. Some genetically modified plants also face regulatory restrictions on where or how they can be grown. The recent High Value Biorenewables Network (HVB) publication 'UK Grown: how biotechnology can unlock higher value from UK grown crops' highlights examples of plants that could be grown in the UK and through the application of industrial biotechnology could deliver high value biorenewable products [36].

Plant cells can also be grown in suspension in bioreactors [11, 25, 38-40]. Plant cell culture overcomes issues around generation time, seasonality, weather impacts, land use and agrichemical inputs. In addition, it can be useful for some plants that cannot be cultivated and/or processed economically. However, commercial deployment is still limited with ongoing technical challenges to be overcome [38].

Benefits	Challenges
• Diverse range of high value natural products [37] • Suitable for complex chemical structures [38] • Engineered crops can increase yields or new products. • Potential for integration with carbon dioxide capture and environmental land management.	• Impacted by seasons and weather fluctuations except in controlled growth environments • Often low product concentrations and yields, and significant downstream processing required to recover and purify products • Engineering biology is more challenging and R&D is slower than for other platforms • Genetically Modified Organisms (GMOs) subject to regulatory restrictions except in controlled environments

Using algae to make high value products

Algae includes macroalgae (seaweeds) and microalgae [41]. Like higher plants, algae obtain energy through photosynthesis, and they also make many useful natural products. Seaweeds contain natural polymers such as alginates, carrageenan and agars, which are now used in the personal care and food processing industries [42]. However, it is the production of high value biorenewables in microalgae where industrial biotechnology tends to play a more important role. Microalgae are grown in open ponds, fermenters, runways, or closed photo bioreactors, and are supplied with nutrients, light, and carbon dioxide [43]. Some algae are grown in bioreactor systems and provided with a carbon source instead of depending on photosynthesis.

Microalgal biotechnology has grown significantly in recent years, and currently over 200 microalgae species are cultured worldwide for different sectors [44]. The species used have diverse capabilities and are well suited to the biosynthesis of complex chemical structures. Naturally produced high value biorenewables from microalgae include omega-3 oils, polymers, pigments, antioxidants, and compounds with antimicrobial and anti-inflammatory effects, and they can also be modified to produce new compounds or improve product yields [26-32].

Benefits	Challenges
• Diverse range of high value natural products • Suitable for production of complex chemical structures • Strain improvement is possible	• Often low product concentrations and yields • Significant downstream processing to recover and purify products • Open cultivation is weather dependant and less efficient • Photobioreactors face technical challenges, such as costly artificial light • Engineering biology is challenging

Microbial production platforms for biorenewables

Microbes are mainly single cell microorganisms such as bacteria and microscopic fungi (i.e., yeasts) which are important biological platforms for industrial chemical production. Though the most well-known product of microbial fermentation is bioethanol for transportation fuel applications, microbes can also be used to make a range of high value products [33, 45-48]. Microbes are grown in bioreactors on biomass feedstocks or biomass derived molecules like sugar and starch. Different microbes make different products and may also utilise different feedstocks.

As with the other platforms discussed in this briefing, microbes can also be engineered to increase yields or suitability for industrial processes or to make novel products. Engineering biology approaches have been developed for many microbial systems, and this tends to be faster and simpler than for other biological platforms like plants.

The benefits of microbes for industrial production and the relative ease of engineering means there are many examples of microbes being used to make non-native high value biorenewables [22-25].

Benefits	Challenges
• Rapid growth and production • Wide range of biomass feedstocks including wastes and residues • Engineering biology is more versatile, faster, simpler, and better studied than for other platforms	• Often low product concentrations and yields, and significant downstream processing required to recover and purify products • Challenges around some complex chemical production • Translation from other organisms requires gene discovery and engineering work

Making high value products using enzymes

Enzymes are biological catalysts that speed up chemical reactions in nature and they are now being adopted as tools for industrial chemistry [49, 50]. The enzymes in plants, algae, and microbes can be extracted from living cells and used in isolation [51]. Nature produces a vast array of unique enzymes capable of catalysing different reactions, many of which are yet to be discovered and understood [34].

Industrial applications of enzymes use their ability to convert chemical substrates into products to replace traditional chemical catalysts whilst often providing higher product selectivity and enabling milder conditions (less energy and toxic solvents). In some cases, they carry out reactions that would not be possible using traditional chemical synthesis or that would be costly due to the need for multiple synthetic steps [12]. As a result, they are well suited to producing high value biorenewables and are already used in industries such as fine chemicals, fragrance and flavourings production, and pharmaceuticals [5, 33, 34, 52]. Enzymes can also be deployed in other ways in industrial processes or products, for example in the extraction of high value biorenewables from plant materials [36] or directly in laundry detergents to help clean clothes.

The use of enzymatic biocatalysis has become more widespread as the range of chemical transformations that are possible has expanded. The full potential of enzymes for industrial applications is expanding with the development of new tools for understanding their structure and approaches for modification to catalyse reactions more efficiently or rapidly or be more tolerant to industrial conditions [33-35].

Benefits	Challenges
• Engineering biology is straightforward and R&D faster than for other platforms • Product recovery is often easier than for other system, especially if enzymes are immobilised	• Enzymes need to be engineered for stability and speed, or immobilised • Dependency on expensive cofactors

3. Applications of high value biorenewables

High value biorenewables can have many applications including but not limited to: dyes or pigments in inks, paints, textiles, food; bioactive ingredients in pharmaceutical, cosmetic, nutraceutical or agrochemical products; fragrances or flavourings in home and personal care products and foods; functional food ingredients and nutraceuticals; surfactants for cleaning products and cosmetics; and high value biopolymers with specialised properties such as gelling, thickening, moisturising, with applications in a wide range of products [5, 10, 22, 27-30, 33, 46, 53-57]. In addition, high value biorenewables can be intermediates used to make other downstream products. They can be drop-in (chemically and functionally identical) replacements for existing products or novel products with unique functionalities.

Industry stakeholders highlighted that the major drivers for interest in high value biorenewables are the potential for performance and environmental benefits, examples of which have been given in Table 1. Performance benefits arise where high value biorenewables with new functionalities that enable new or improved products, such as better cosmetics or novel therapeutics. Environmental benefits can include greenhouse gas (GHG) emission reductions due to the displacement of fossil feedstocks and energy-intense processes as well as non-carbon benefits (see Box 1).

Industry interest is also influenced by the need to meet sustainability targets, but in some sectors it is also driven by increased consumer demand for sustainable products or expected changes in policy and regulation. It should be noted that not all high value biorenewables come with performance and sustainability benefits. Some may not have reduced environmental impacts compared to existing products, be more costly to manufacture, or perform less well than those they are intended to replace, and this is a significant barrier to uptake.

Box 1 - Sustainability of high value biorenewables

Industrial biotechnology tends to require milder conditions (e.g., lower temperatures, fewer hazardous reagents or rare metal catalysts) than traditional manufacturing routes [58]. The reduced energy consumption associated with many industrial biotechnology processes, coupled with the use of renewable resources instead of fossil feedstocks, leads to the potential for high value biorenewables with reduced lifecycle GHG emissions.

Some novel high value biorenewables can also offer additional environmental benefits through new functionalities. For example, there are novel high value biorenewables that can offer safer alternatives to traditional chemical products which are hazardous to health or the environment, and there are biodegradable ingredients to help tackle pollution.

Industrial biotechnology can also offer new routes to natural products that have previously relied upon unsustainable sources such as rare wild plants [11].

However, none of these benefits are guaranteed [4, 58] and evidence on the environmental performance of products, processes, and feedstocks will be essential to support decision making and enable the deployment of sustainable high value biorenewables.

Whilst many high value biorenewables have been demonstrated at lab scale, fewer have been commercialised even when performance or sustainability benefits have been proven. Often there are technical challenges to be overcome which impact the feasibility and economic viability at scale. Successfully deploying a new product or technology also requires significant time, money, and potential IP and regulatory approvals, which can be challenging. Furthermore, high value biorenewables must compete economically with the components they would displace, and they can cost more and require more investment. This means that unless there is policy or regulatory intervention that drives the uptake of more sustainable products, many high value biorenewables will not be developed and deployed by industry even if they are more sustainable than the alternatives.

The main drivers and challenges associated with the uptake of high value biorenewables also vary according to the industrial sector. Sustainability and consumer demand play more of a role in some sectors, and others have stringent regulatory requirements that impact on alternative components being explored. This is detailed in the following sections which review the applications of high value biorenewables in three different industrial sectors.

Sector Profile: home and personal care products

Home and personal care products include shampoos, soaps, perfumes, cosmetics, skincare, sun cream, toothpaste, cleaning products, polishes, and detergents. They often comprise ingredients that are derived from fossil feedstocks. This includes compounds that are necessary for the function of the product (e.g., surfactants in cleaning products or antioxidants in anti-ageing skin creams), to give the product a desirable fragrance, texture, appearance, or increase product shelf life. This is a consumer facing industry, and there is always an interest in new ingredients that offer performance benefits and improved products. However, home and personal care manufacturers are also increasingly looking for new options for safe and sustainable ingredients and processes, driven by industrial sustainability targets, consumer demand for natural or sustainable products, and in some cases regulatory changes. This includes replacing ingredients that rely on unsustainable feedstocks (e.g., fossil feedstocks or some bio-based feedstocks like palm oil), or with those that can reduce environmental impacts and avoid ecological or health risks.

In the search for better, safer, or more sustainable ingredients, many in the sector are looking to high value biorenewables to replace different speciality chemicals such as flavours and fragrances, antioxidants, pigments, and surfactants [5, 7, 33, 46, 54, 59]. Large and complex biological molecules also provide useful functions such as biological polymers used as thickeners or stabilisers [28, 33], and enzymes used in products for desired activities (e.g., in toothpaste or detergent) [60].

Though consumer demand for natural or sustainable products is an important driver, it also poses a challenge because there is no agreed definition of “natural” or “sustainable” and so there is a risk of greenwashing and misleading claims. Another particularly relevant challenge to this sector is the lack of cost competitiveness with existing products and processes. Industrial stakeholders also highlighted that they would only be interested in novel ingredients if they perform as well or better than those they replace, regardless of their sustainability.

Sector Profile: pharmaceuticals

The active pharmaceutical ingredient in most therapeutics is a small molecule derived from fossil-based fine chemicals via chemical synthesis [2, 61]. Sustainability has, to date, been less of a focus for this sector but the sector is under increasing pressure to become more sustainable [61-63]. Several large pharmaceutical companies have set their own sustainability targets, and high value biorenewables could help meet these targets by decreasing GHG emissions and enabling more sustainable manufacturing processes. Novel high value biorenewables could also lead to new pharmaceuticals that address unmet medical needs, and this is a strong driver in the pharmaceutical sector.

In recent decades, biocatalysis has been deployed by the pharmaceutical industry to make small molecule pharmaceuticals (usually between 0.1 and 1.0 kDa). Biocatalysis is suited to the production of complex molecules and can simplify otherwise challenging synthetic processes, and in some cases avoid the use of rare metal catalysts [12, 13, 34, 64, 65]. High value biorenewables could also be used as fine chemical intermediates or, as in the case of some bioactive natural products, directly as pharmaceutical ingredients [19, 23, 61, 64].

Biological systems can also yield complex bio-derived pharmaceuticals known as biologics, which are increasingly used in treating diseases including diabetes and cancer [66]. Biologics are large biological molecules such as proteins [66]. They are often produced in mammalian, bacterial, yeast, or insect cell cultures but there is growing interest in using plants for biologics production [20, 67].

Although there may be interest in more sustainable feedstocks and technologies, this is a heavily regulated sector. Altering the production of an existing pharmaceutical to use a biological process or bio-based intermediates would require costly and time-consuming trials to gain regulatory approval. As a result, high value biorenewables are likely to be used in developing new drugs rather than improving the sustainability of existing ones.

Sector Profile: agrochemicals

The agricultural sector relies on synthetic pesticides and fertilisers to increase productivity and maximise food production. However, the sector is facing increasing pressure to reduce the use of synthetic agrochemicals due to negative climate and environmental impacts. In addition, agrochemicals are made from fossil feedstocks that leads to GHG emissions in their manufacture and breakdown products. Synthetic fertilisers also cause air and water quality issues, and increasing numbers of pesticides are now subject to regulatory bans or restrictions due to risks to the environment, ecosystems (including non-target species) and human health [68]. New ways to control pests and diseases are needed to reduce reliance on synthetic agrochemicals. One approach is to find novel bio-based agrochemicals.

Industrial biotechnology can yield bioactive products that can be used as biopesticides or plant biostimulants[2] [10, 24, 36, 68-71]. Biopesticides can have reduced environmental, or ecosystem impacts compared to synthetic pesticides, with many being less toxic and more specific [72-74]. Although not always as effective, biopesticides can reduce the use of synthetic pesticides as part of an integrated pest management approach. In addition, plant biostimulants enhance how efficiently crops take up and use nutrients and tolerate stressful conditions, increasing yields and potentially reducing the need for fertilisers [36, 69, 71]. Many of the bioactive molecules that can be used as bio-agrochemicals are natural products that could be directly extracted from plants or seaweed, but this is not always sustainable or commercially viable and industrial biotechnology provides an opportunity to produce the desired compounds from plant cell culture, microbial systems or microalgae instead [10, 24, 69]. Additionally, some microbes can be directly applied to crops as biopesticides or biostimulants or for nitrogen fixation [18, 29, 36, 69-71].

Regulatory changes around the use of some synthetic agrichemicals as well as the development of a better process for assessing biopesticides are a significant driver for change in this sector. There may however be issues relating to the uptake of novel products and new approaches by farmers and potential issues of poor performance – and concomitant impact on profitability - compared to synthetic products. More evidence is needed regarding the efficacy of novel bio-agrichemicals and their environmental impacts or risks.

4. High value biorenewables in the UK: opportunities and challenges

High value biorenewables and the applied research activity related to them could afford a range of environmental, economic, and social benefits for the UK, supporting several UK Government objectives. However, there are barriers to developing and deploying these products and technologies in the UK that must be addressed if the potential benefits are to be delivered. The main opportunities and challenges identified through stakeholder discussion and review of published material are detailed below. Many of the opportunities and challenges described here extend to other applications of industrial biotechnology and the bioeconomy.

Opportunities

Reducing GHG emissions and supporting the transition to net zero

High value biorenewables and industrial biotechnology offer opportunities to develop manufacturing processes and products with lower lifecycle GHG emissions and support the decarbonisation of industry, the transition to net zero, and the reduction of consumption related emissions. As high value biorenewables are produced in low volumes, the total emissions potential is not as impactful as for larger volume, lower value products such as fuels or plastic. However, cuts to emissions across the economy will be needed to achieve ambitious climate targets.

Waste valorisation and circular economy

The use of wastes and residues potentially offer economic and environmental benefits by creating additional value therefore supporting improved resource efficiency and the transition to a circular economy.

Sustainable farming and benefits to rural economies

Plants can be used as production platforms for high value biorenewables in addition to being feedstocks for other production platforms. High value biorenewables represent an opportunity to valorise agricultural residues, plant non-food crops, and access new markets, therefore supporting more diverse and resilient income streams for farmers and developing rural economies [36, 75].

[2] Industrial biotechnology and engineering biology approaches can also be used develop crops with characteristics that reduce the need for added agrochemicals, such as increased pest resistance, but this is not the focus of this briefing.

Non-food crops offer opportunities to use less productive agricultural land or can be used as a cover or catch crop and may provide ecosystem benefits (e.g. improved soil carbon or biodiversity benefits). The HVB commissioned review 'UK Grown: how biotechnology can unlock higher value from UK grown crops' contains information on opportunities for agriculture in the production of high value biorenewables [36].

Reducing pollution and exposure to harmful chemicals

There are opportunities to displace hazardous or polluting ingredients with high value biorenewables that perform the same function but with new chemistries. This includes bio-based crop protection products that can reduce the need for synthetic agrochemicals or biodegradable ingredients for personal care products. Industrial biotechnology processes can also reduce the need for hazardous reagents during manufacturing processes.

Novel products for societal benefits

Novel high value biorenewables offer opportunities for wider benefits to people and society, from new pharmaceuticals that can help address medical needs to food ingredients that can support improved health and nutrition.

Global leadership and green growth in science and technology

The UK is a world leader in biosciences and industrial biotechnology, with significant research expertise in high value biorenewables throughout the innovation pipeline from academic to industrial environments [76]. The UK has an opportunity to capitalise on its world leading research in high value biorenewables for green growth. Increased UK-based scale up and commercialisation could bring economic benefits and create new skilled jobs and is an opportunity for existing industries to thrive and become more sustainable [75, 76]. Continued support and investment will allow the UK to maintain global leadership.

Challenges

Cost

Many high value biorenewables are currently not cost competitive with the products they are designed to replace, and they often require significant investment to develop and deploy at scale. Technoeconomic analysis is increasingly being applied during early-stage research and innovation process to support the development of more economically viable processes and products, but there are often challenges when competing with well-established products derived from cheap feedstocks and efficient processes. Policy or regulatory mechanisms that incentivise or place value on sustainability of products (e.g., mandates for renewable carbon in chemical products, sustainable public procurement, or high carbon tax), could make high value biorenewables more competitive [77]. Additionally, regulatory measures that restrict the specified products due to health or environmental concerns can create opportunities for novel products that can replace them [76].

Feedstock availability

A secure supply of appropriate feedstocks is essential for commercial viability of industrial biotechnology systems [77]. The policy landscape will affect what feedstocks are available for the sector. For example, non-food crops that could be used for high value biorenewables can be a less profitable option for farmers than existing options, but interventions could support and de-risk uptake. In addition the ability to redirect feedstocks from the waste sector is currently limited by end-of-waste regulations [36, 77]. It is important to note that the definition of high value products means that they are generally produced in much lower volumes than products like commodity chemicals or plastics, meaning that feedstock availability may be less of an issue and smaller volumes of localised resource could be deployed. There may also be opportunities to improve resource efficiency by combining the production of high value biorenewables and bulk chemicals or fuels in integrated biorefineries.

Sustainability

High value biorenewables and industrial biotechnology can have environmental benefits compared to existing products and processes, but this assumption needs to be validated on a case-by-case basis to avoid overstating the benefits, greenwashing and/or unintended consequences. This includes evaluating the sustainability of feedstocks. Policies aimed at encouraging uptake of novel products or feedstocks should be underpinned by appropriate evidence and rigorous sustainability governance to build trust and support the delivery of products that truly deliver environmental benefits. For example, lifecycle assessment (LCA) is important for determining the environmental impacts (e.g., GHG emissions or water consumption) of processes. If LCA is considered during technology development and revisited regularly, it can help steer improvement in the environmental performance of new systems.

Regulation

High value biorenewables are subject to various forms of regulation in sourcing feedstock, process development, and within the sectors they are used. As such, it is incredibly challenging to focus on one set of regulations or standards in isolation. Stakeholders indicated three key areas of regulation for high value biorenewables: regulation relating to products in particular applications; regulation of genetically engineered organisms, and the Nagoya protocol, all of which are explored in more detail in Box 2.

Regulation is an important tool for managing the risks associated with new technologies and products and can be a driver for innovation [76]. Stakeholders highlighted that the regulatory environment can be complex and hard to navigate, particularly for academics, spin outs and SMEs because they are less likely to have access to relevant expertise and support [75, 76]. Stakeholders also felt that regulation is often not reactive enough to new technologies and science. Adaptive, science-based regulation will be important to encourage the development of high value biorenewables and other industrial biotechnology products and processes [77].

Box 2 – Key areas of regulation for high value biorenewables

Feedstock regulations including the current 'end of waste' regulations (which impacts on a waste being reused) sustainability criteria that apply to biomass feedstocks.

The **Nagoya Protocol,** a supplementary agreement to the Convention on Biological Diversity, which is enforced in the UK through Access and Benefit Sharing regulations [78]. It aims to ensure the fair and equitable sharing of the benefits of using genetic resources and associated traditional knowledge which are obtained from outside of the UK [78]. The Nagoya Protocol relates to both research (including in academic settings) and commercial activity, and the burden of demonstrating compliance is on the user (e.g. the researcher) [79]. Stakeholders indicated that the major challenge associated with Nagoya is in navigating the regulation and ensuring compliance, and that there is capacity and expertise to support people in the UK.

Product regulations which relate to the intended application of the compound [77]. Many high value biorenewables have multiple potential applications, which require different types of regulatory approval, making this particularly complex to navigate. For example, chemical substances are subject to UK REACH regulation [80], food ingredients may require Novel Food authorisation [81], pesticides (including biopesticides) are subject to the Plant Protection Product Regulations, cosmetics are bound by Cosmetic Regulations. The process is very demanding for pharmaceuticals, and stakeholders indicated that this means some choose other markets despite pharmaceutical potential.

Regulation of modified organisms such as GMOs. Regulation of GMOs is very different between organisms grown in contained environments (e.g., bacteria, plant cells, or algae grown in reactors) and those not contained (e.g., plants grown in a field). Currently, GMOs can be used in the UK for commercial applications in contained use but not otherwise [82]. However, there have been some recent changes relating to crops in the form of the Genetic Technology (Precision Breeding) Act, passed into law in England in March 2023. This law states that crops or animals produced by gene editing that does not result in foreign DNA being introduced should not be regulated as GMOs, instead defining them as precision-bred organisms [83]. This will open the door to research and commercial applications of gene editing in the UK. Stakeholders felt that this would likely be a positive step for the development of high value biorenewables due to the potential for precision bred crops with improved performance as feedstocks or production platforms. However, the process of putting secondary legislation in place to enforce the act is ongoing, so it is not yet clear what this will look like in practice. A more detailed discussion of the Precision Breeding Act and the science of gene-edited organisms can be found in the literature [21, 77, 84-86].

Scale up and commercialisation

Although the UK has an excellent research base in industrial biotechnology and strong collaborations between academia and industry, it lags behind other nations in moving opportunities along the Technology Readiness Level (TRL) and translating excellent research into commercial applications [75, 76]. Scaling up industrial biotechnology processes from lab to commercial scale is often technically challenging, costly, and time-consuming. Stakeholders identified difficulties accessing finance and appropriate scale up facilities as key barriers to commercialisation in the UK [75, 76]. Pilot and demonstration scale trials of technologies are important for testing, optimising and de-risking investment in the technology by providing evidence of success. Open access scale up facilities are important in enabling this and are particularly important for the industrial biotechnology sector which involves university spin outs. Spin outs and academics are also likely to face challenges with navigating the IP landscape, identifying routes to market, or understanding regulatory requirements, and some stakeholders felt that the UK lacks the enabling environment that encourages transfer of university research seen in other countries.

Although the UK may benefit from the deployment of UK technologies elsewhere in the world, there would likely be more economic benefit and jobs from the translation of UK technologies into UK manufacturing. This will be influenced by more than the support for scale up, also depending on the policy and regulatory landscape and how attractive the UK is a place to build manufacturing facilities.

Skills

Industrial biotechnology research, development, and manufacturing demands a skilled, multidisciplinary workforce. Previous work from the UK's Industrial Biotechnology Leadership Forum has highlighted several skills essential for industrial biotechnology that are lacking in the UK workforce [75].

Public profile

Social acceptability can be a challenge, particularly for GMO products based on synthetic biology technologies [77, 87]. This often stems from concerns about the risks such technologies pose to people and the environment and, in some cases, ethical concerns [87]. There is a need for clear communication of scientific evidence to support public conversations on these topics, and incorporation of Responsible Research and Innovation (RRI) approaches including principles of co-creation into research. Stakeholders felt that there is a lack of awareness of the benefits that the bioeconomy and industrial biotechnology can bring, which the sector can help to address through clear communication of the benefits and the risks [77].

5. Conclusion

The UK is well positioned to reap the potential environmental, economic, and societal benefits of high value biorenewables due to its wealth of research and industrial expertise and key unpinning disciplines. However, action will likely be required across industry, academia, and government to unlock this potential.

Developing new products will require further multidisciplinary research and innovation, which must include collaboration and engagement with industry, government, and society to support the creation of scalable and sustainable high value biorenewables that meet people's needs and fit social values.

The policy and regulatory environment will be a deciding factor in the successful deployment of many of these products and in the scale up and commercialisation of UK developed technologies, as well as playing an essential role in ensuring products and feedstocks are genuinely sustainable. The UK Government needs to decide what its ambitions are in this space and consider the actions required to overcome the barriers.

This briefing has introduced high value biorenewables, the key technologies involved, and the opportunities and challenges associated with their deployment. It is intended to inform and act as a starting point for further engagement on specific areas of interest to inform policy and future research.

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The High Value Biorenewables Network

The High Value Biorenewables Network (HVB) is one of six Phase II Networks in Industrial Biotechnology and Bioenergy funded by the Biotechnology and Biological Science Research Council to encourage the growth of Industrial Biotechnology in the UK. HVB actively promotes and facilitates collaboration between academia and industry in the biorenewables sector, and works to promote discovery, development and application of bio-based chemicals, tools and platform technologies, facilitate partnership and knowledge transfer between UK academia and industry, and provide inspirational leadership to the Industrial biotechnology community in the UK.

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Briefing Note: A two-page briefing note, summarising this report, is available from the HVB website (www.highvaluebiorenewables.net/policy/).

7. Key definitions

Bioactive substances are those which cause an effect in a living system.

Biorefineries are dedicated facilities or systems that turn biomass feedstocks into multiple valuable product streams that exploit the whole input resource and results in increased resource efficiency and potential benefits for the economics and environmental performance of a system. For example, in a biorefinery, a plant could be used to produce a high value product remaining biomass could be utilised to produce another product or feed into energy production [88-90]. A biorefinery approach is attractive because it supports resource efficiency and can potentially improve the economics and environmental performance of a system [88, 89].

Drop-in refers to a product that is chemically identical to an existing product that is currently derived from other sources (e.g., a fossil-based chemical) and can be used as a direct replacement. In this briefing, the term **novel** identifies those high value biorenewables that are not chemically identical, drop-in replacements.

Engineering biology is the application of engineering principles to the design of biological systems. Engineering biology encompasses the academic discipline **synthetic biology**, which is the rational design and construction of new biological systems for new or improved functions [91].

Genetic engineering uses molecular biology to modify the DNA (genetic material) of organisms [86].

Gene editing is a genetic engineering approach that alters the characteristics of organisms without introducing foreign DNA, mimicking changes that occur more slowly through traditional breeding routes [21, 77, 84]. **Genetic modification** is a more general term that can include modifying an organism by introducing DNA from another organism. Genetic modification results in genetically modified organisms (GMOs).

High value biorenewables are high value, low volume (typically > £10 per kg, and less than 1000 metric tonnes per annum) bio-based chemicals and products made using industrial biotechnology. They range from small bio-derived molecules to complex molecules (e.g., polymers, proteins, and enzymes) and cells.

Industrial biotechnology is the use of natural or engineered biological systems to turn biological resources into products with industrial and/or societal value such as chemicals, materials, or energy. It uses biological systems such as bacteria, yeast, fungi, plants, algae, enzymes (i.e., proteins that act as biological catalysts), animal or insect cells.

Life cycle assessment (LCA) is a method for assessing the environmental impacts associated with the stages of life cycle of a product, process or service. This can span from raw material extraction and processing, through manufacture and distribution, to use and subsequent disposal. An LCA is based on the system's energy and mass inputs and outputs and is often used to assess life cycle greenhouse gas (GHG) emissions.

Techno-economic assessment (TEA) is a method for evaluating the economic performance of technology and assesses the overall value of a technology to permit accost-benefit analysis of a product of process.

Technology Readiness level (TRL) is a type of measurement system commonly used to assess the maturity level of a particular technology during its progress from a research idea to commercialisation. There are nine TRLS: TRL 1 is the lowest (basic principles explored) and TRL 9 is the highest (full operational deployment at scale of a technology or process).

Responsible Research and Innovation focusses on engaging the public in the research process to better align the goals and outcomes with the needs of society and to address societal challenges. It aims to deliver socially acceptable, ethical, and sustainable outputs by making the research process more transparent [92]. For example, RRI includes public engagement, which allows researchers to talk to the public about new technologies, but also helps them understand societal views and potentially inform future research activities [87].

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