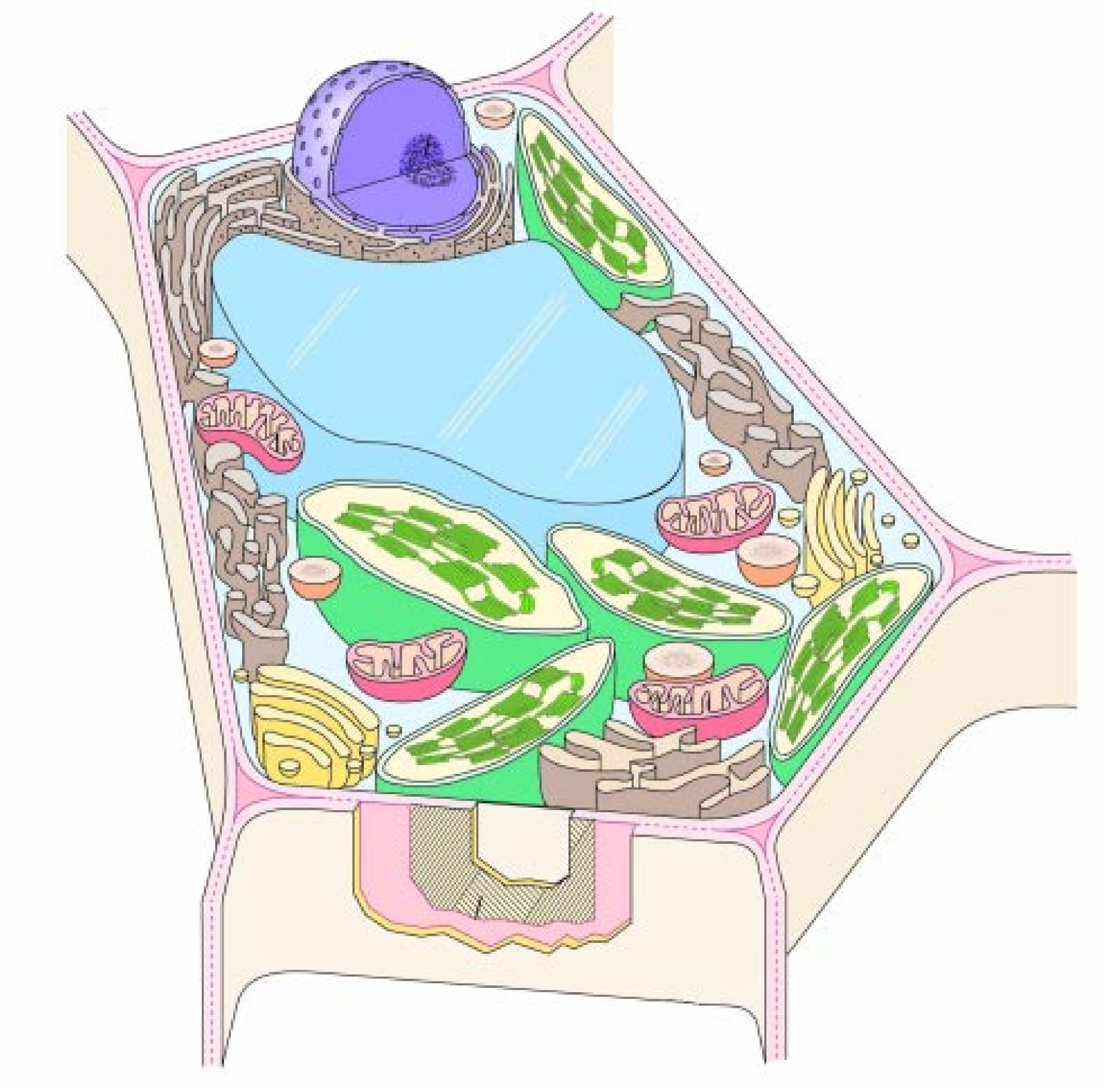
CR 7656

CATALYSIS IN RENEWABLE FEEDSTOCKS



A Technology Roadmap V1a

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SUMMARY

Depleting reserves and rising prices of oil, coupled with the need for sustainable production and a reduction in greenhouse gases, lead to an emerging need to produce chemicals from renewable feedstocks. This implies a corresponding requirement to consider catalysis in such processes, and the purpose of this roadmap is to plan and stimulate collaboration among four communities:

- Agricultural Industries
- Manufacturing Industries
- The Science Base, including:
  - Plant and Crop Science
  - Catalysis
- Government, including DEFRA, DTI and RDAs

The long-term vision is one of five business opportunities for the UK:

- Produce chemicals from commodity crops the UK can grow well
- Produce specialist chemicals from specialist crops grown in the UK
- Produce low-volume, high value chemicals, especially pharmaceuticals
- Add value to imported platform chemicals
- Develop and exploit IPR worldwide, along with consulting, legal and financial services,

supported by three areas of Government and Research Council policy:

- Government procurement to stimulate demand in selected areas
- Co-ordinated national and regional policies to integrate regional priorities within a national framework
- Co-ordinated Government and Research Council Funding of research. Relatively few, large programmes are envisaged on selected UK priorities, encompassing basic research, development and demonstration projects to form robust supply chains. A risk-taking culture needs to be fostered at the basic research stage.

The roadmap describes the state of the art in processing four types of feedstock: waste, lignocellulose, commodity crops and specialist crops. It then considers how this can be developed into the long-term vision through seven inter-related themes

Developments in the Energy Economy: Non-specialist renewable chemicals will depend on the energy economy in terms of their competitiveness against fossil rivals. They will also be influenced by the renewable fuels that emerge and either become available as or give rise to platform chemicals. It is therefore necessary to consider candidate renewable fuels, including methanol, ethanol, hydrogen and biodiesel. European growth in such fuels is likely, as the EU Biofuels Directive requires Member States to set indicative targets for their use. Developments in the field require monitoring and their impact evaluating.

Waste Processing: The continuing European pressure to process rather than dispose of waste means this is a likely growth area. More stringent European legislation provides an opportunity to establish a lead in the field, as already achieved in anaerobic digestion of municipal solid waste.

Biorefineries and Platform Chemicals: Biorefineries produce a multitude of products from a biomass feedstock and the platforms recognised by the US Biomass Program are Sugars, Thermochemical, Biogas, Oils and Plants. Each will produce "platform chemicals"

having the potential to be converted into new families of useful molecules. The US priorities are Sugars and Thermochemical, and a recent report considers platform chemicals they could produce. In the short term, a workshop is proposed to identify areas in which UK industry and academia could profitably develop IPR in the field. Hand-picked specialists will be invited, including the two US authors.

In the medium to long term, however, the US prioritisation of platforms raises key issues:

- The extent to which limited UK resources should be channelled towards competition with, collaboration with or the supply of niche technologies to US priorities
- Whether UK efforts would be more profitably directed at one or more of the other platforms: Biogas, Oils and Plants
- Whether it is commercially feasible for platform chemicals to be imported and value added to them, or whether this activity will be undertaken abroad

Oleochemicals Industry: The UK is perceived to have particular strengths in oil seed crops and oleochemicals might therefore represent a priority for development. Oils can be transformed into medium-value products such as surfactants, polymers, lubricants and solvents, or into high-value healthcare products. The roadmap describes necessary developments in Chemistry.

Specialist Crops: Specialist crops might produce oil seeds, secondary metabolites or recombinant proteins, by open-field or contained cultivation, or in plant tissue cultures. The production of high-value chemicals, especially pharmaceuticals, is most relevant.

Marine Biotechnology: The Foresight Marine Panel has recently highlighted UK prospects for marine biotechnology. The sea yields three of the four types of feedstock found on land, including waste from fishing, commodity crops in the form of seaweed and shells, and specialist crops in the form of cultures of organisms or their genes. In addition, it might provide catalysts to transform feedstocks into products, renewable or otherwise.

Infrastructure: A Knowledge Transfer Network (KTN) on Catalysis in Renewable Feedstocks is seen as a vehicle to deliver the following infrastructure components:

- Evaluating international developments in a UK context and disseminating findings. Disruptive science and technology and changing legislation are key factors to assess
- Evaluating developments in the energy economy, for reasons discussed above
- Providing suggestions to the NNFCC Strategy Group on Non-Food Crops, Research Councils and other public funders of research
- Implementing the resulting Strategy within the Catalysis field. Industrial supply chains need to be forged while fostering collaboration between catalysis and plant scientists. The subject lies between current networks and centres of excellence, and collaboration is needed to coordinate activities. Relevant bodies include, non-exhaustively, NNFCC, Pro-Bio Faraday, Crystal Faraday, the Green Chemistry Network, CoEBiO3, CNAP and any NERC KTN on Marine Biotechnology. Links with BBSRC and EPSRC are also desirable, as they develop strategies in Crop Science and Catalysis
- Collaborating with any KTN emerging in Design, Simulation and Modelling, to ensure that modellers and design engineers have information on renewable feedstocks
- Updating the roadmap to reflect changing circumstances and deepening its coverage of each of the preceding six themes
- Fostering education and training in the field
- Embedding academic networks within the KTN, to link basic science with industrial priorities

CONTENTS

Page

Anaerobic digestion

Biohydrogen production

1. BACKGROUND

The emerging need to produce chemicals from renewable feedstocks implies a corresponding requirement to consider the role of catalysis in this venture. The purpose of this roadmap is to plan and stimulate collaboration among plant and catalysis scientists and between agricultural and manufacturing industries. It is a specialist development of two earlier roadmaps:

- The U.S. Technology Roadmap for Plant/Crop-Based Renewable Resources (1)
- The Dutch Technology Roadmap "Catalysis, Key to Sustainability" (2)

The U.S. roadmap sees four areas of opportunity to increase the use of renewables:

1. Basic plant science
2. Production of the crop
3. Processing the crop into useable materials
4. Utilising the derived materials more effectively

This UK roadmap focuses on the third of these areas and in particular on one of the report's six priority research topics: advanced (bio)catalysts for monomeric & polymeric conversions.

The Dutch roadmap identifies three clusters:

Cluster I	Refining, Energy and Transport
Cluster II	Bulk Chemicals, Polymers & Materials and Detergents & Textiles
Cluster III	Fine Chemicals, Pharma and Food & Feed

and notes that the historic dependency of clusters II and III for feedstocks from cluster I is not sustainable. It sees alternative feedstocks as one of three high-priority goals for Bulk Chemicals and the conversion of biological materials and bio-mass cracking as two routes to attain that goal. In both cases, catalyst discovery is listed as a key technology.

Catalysis in renewable feedstocks is, however, a relatively new research topic in the UK. Moreover, the UK industrial and academic landscape differs form other countries and this roadmap adopts a national perspective on the subject. It is seen as a working document requiring continuous improvement, and seeks the future, continuing involvement of four communities:

- Agricultural Industries
- Manufacturing Industries
- The Science Base, including:
    - Plant and Crop Science
    - Catalysis
- Government, including DEFRA, DTI and RDAs

The report begins with a two-page summary, before describing the current state-of-the-art in section 2 and the long-term vision in section 3. Section 4 then discusses the intervening, future timeframe in terms of seven thematic areas. These are highlighted in bold on the roadmap, which also uses the symbol ¢ to indicate a catalytic process.

The roadmap has been produced by a consortium including BHR Group, NNFCC, Innovation Management and the Universities of York and Liverpool. It uses information derived from a workshop of industrial and academic participants, together with published material. Acknowledgements are provided in section 5 and references in section 6.

The roadmap presents all four feedstock types, waste, lignocellulose, commodity and specialist crops in a single layer, rather than the common practice of distinguishing between product, technology and science layers. This aids concise presentation at the expense of an imprecise distinction between current and future timeframes.

2. CURRENT STATE OF THE ART

The current state of the art can most conveniently be described in terms of four principal types of renewable feedstock:

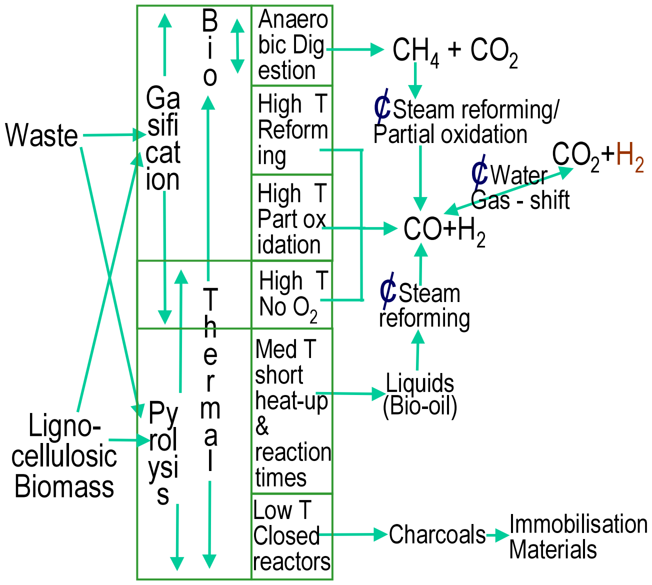
- Waste biomass
- Ligno-cellulosic biomass
- Commodity crops
- Specialist crops

There are, however, overlaps in these feedstocks and these are considered below.

2.1 Waste biomass

The main sources of waste biomass are:

- Municipal wastes, including:
  - sewage sludge
  - municipal solid wastes (refuse)
- Agricultural solid wastes, including:
  - manure
  - crop residues
- Forestry residues, including:
  - waste from logging operations in the forest
  - sawdust and bark residues from timber manufacture
- Industrial wastes, of which the most important sources are:
  - the pulp and paper industry
  - the food industry



The main alternatives for waste processing are biological gasification, thermal gasification and pyrolysis and these are discussed in sections 2.2.1 and 2.2.2. It should be noted that both crop and forestry residues are generally lignocellulosic in nature, and that the lignin currently prevents such waste from biological degradation in acceptable timescales, so only the other two methods are available.

It should also be noted that there is considerable scope for downstream inter-conversion of the gases produced either biologically or thermally. For example, the methane produced by anaerobic digestion or any trace carbohydrate produced in thermal gasification can be

$$CH_4 + H_2O \longrightarrow CO + 3H_2$$

$$CH_4 + O_2 \longrightarrow CO + 2H_2$$

converted to carbon monoxide and hydrogen by steam reforming or partial oxidation. Currently, nickel catalysts are used for the former reaction, at 30 bar pressure and 750°C.

Similarly, if the balance between CO and H_2 produced by thermal gasification is unsuitable, it can be shifted by the water gas shift reaction.

$$H_2 + CO + H_2O \rightleftharpoons CO_2 + 2H_2$$

The carbon dioxide and water are separated out from the desired blend.

2.1.1 Biological Gasification

The two main biological gasification methods are anaerobic digestion and biohydrogen production. Although inter-related, they are introduced separately as the former is in widespread commercial use while the latter is under research or development.

Anaerobic digestion produces a mixture of methane and carbon dioxide, along with small amounts of hydrogen, hydrogen sulphide and ammonia. After pre-treatment to remove unwanted materials and achieve an appropriate particle size, two or more sources of waste may be mixed to achieve an acceptable carbon: nitrogen ratio in the feedstock. The digestion process itself requires a mixed culture of at least three types of organism, each performing a separate stage:

- Hydrolysis of complex polymers into carbon dioxide, hydrogen and monomers that include fatty acids, monosaccharides, amino acids, purines and pyrimidines.

- Acetogenesis of the monomers into acetate, carbon dioxide and hydrogen. Intermediate products such as propionate, butyrate or ethanol are fermented further into acetate

- Methanogenesis of the acetate, carbon dioxide and hydrogen into methane. Aceticlastic methanogens convert acetate into methane, and account for about 70% of its production, while hydrogenotrophic methanogens operate on carbon dioxide and hydrogen.

The process can operate under either mesophilic (20-45°C) or thermophilic (50-65°C) temperature conditions. The latter are more efficient in terms of loading rate, gas production and the retention time required for degradation, this being 12-14 days compared with 15-30 days for mesophiles. They are, however, more sensitive to variation in operating conditions.

A wide variety of reactor types is in use, including continuous stirred tank, plug-flow, multi-stage, packed or fluidised bed. Continuous stirred tanks have been in use for many years and are simple to operate. Their disadvantages, however, include relatively low solids concentration and hence large equipment size, along with the possibility of short-circuiting of influent to the exit pipe, with the consequent need to pasteurise effluent. Short-circuiting is avoided in plug-flow reactors, which are also capable of handling high solids concentrations, with their higher viscosities. Multi-stage digesters have been developed in recent years, to gain additional control over the hydrolysis, acetogenesis and methanogenesis stages. A two-stage process, for example, would typically undertake hydrolysis and acetogenesis in a vessel separate from methanogenesis. The methanogenesis vessel may use organisms suspended in the medium or supported on an inert material. Supported catalysts are also employed in the packed and fluidised bed type of reactors. Among other future developments (3), membrane separation may be used to produce a high-quality effluent.

Europe is reported (4) to hold a lead in anaerobic digestion of municipal solid waste, owing to more stringent environmental legislation and higher energy costs. Germany and Denmark are the leading countries, followed by Sweden, Switzerland and Austria.

Biohydrogen production is possible via

- **Single-stage anaerobic digestion** to produce methane, followed by steam reforming or partial oxidation to carbon monoxide and hydrogen and the water gas shift reaction to maximum hydrogen

- **Multi-stage anaerobic digestion**, in which the hydrogen and carbon dioxide formed at the acetogenesis stage is separated from the organic acids, which are then converted into methane and carbon dioxide by aceticlastic methanogens. Steam reforming of the methane to hydrogen then follows.

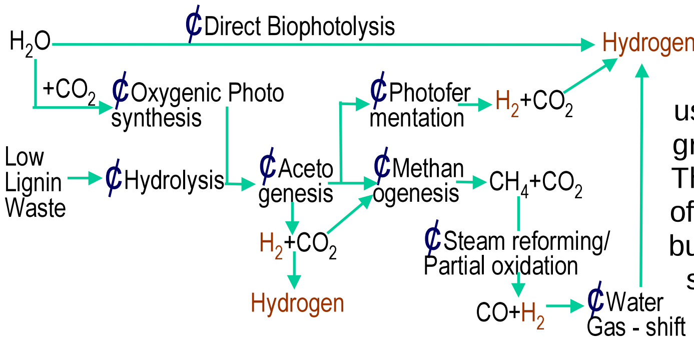
Other techniques use photosynthetic organisms in a variety of modes. Photosynthesis occurs as a result of the “light reactions” that convert photons into a short-term store of electrochemical energy, followed by the “dark reactions” that normally reduce carbon dioxide into carbohydrate. Oxygenic photosynthetic organisms use water as a hydrogen donor, and include higher plants, green algae and cyanobacteria, along with red and brown algae, brown diatoms, cryptophytes and prochlorophytes, all of which contain chlorophyll a. Anoxygenic photosynthetic organisms use a variety of compounds as hydrogen donors, ranging from H_2S to organic acids. They comprise purple and green bacteria and contain either bacteriochlorophyll a or b.

As well as being able to reduce CO_2 into carbohydrate, however, a few groups of oxygenic microalgae and cyanobacteria can use the stored electrochemical energy to produce hydrogen from water. This is mediated by either hydrogenase or nitrogenase enzymes, although both are rapidly deactivated by oxygen. While cyanobacteria compartmentalise nitrogenase to protect it from oxygen, hydrogenase remains vulnerable. Basic research has revealed that hydrogenase can derive reducing power from intracellular carbohydrates such as starch, as well as water. Green algae such as *Scenedesmus* and cyanobacteria such as *Spirulina* can also employ hydrogenase under dark anaerobic conditions, using intracellular carbohydrate as the reducing source. Some anoxygenic photosynthetic organisms are also powerful hydrogen producers, using lactic, succinic and butyric acids as substrates and nitrogenase as catalyst.

Possible processes to produce hydrogen biologically are as follows.

- **Direct biophotolysis** uses sunlight and organisms containing either hydrogenase or nitrogenase in a closed photobioreactor. As hydrogenase is not compartmentalised within the cell, however, a low partial pressure of oxygen must be maintained, either by *in situ* removal or a sweeping gas, and separation of the gases adds to costs. While nitrogenase is compartmentalised, it requires a large amount of metabolic energy, with a consequently low overall efficiency.

- **Indirect biophotolysis** uses the normal oxygenic photosynthetic processes of microalgae to produce carbohydrate as an intermediate, before producing hydrogen from this by employing their dark anaerobic and photosynthetic anaerobic mechanisms. The use of an intermediate separates the production of oxygen and hydrogen, so avoiding a drawback of direct photolysis.



The microalgae can either be cultivated within the same reactor used for hydrogen production, or grown in open ponds and transferred. The former uses temporal separation of oxygen and hydrogen production, but is costly. The latter provides spatial separation and, although the algae require concentration before transfer, lowers costs.

The second, dark anaerobic stage is essentially the same as the acetogenic stage of anaerobic digestion, as the carbohydrate is converted into hydrogen, carbon dioxide and organic acids. The third stage differs from the methanogenesis stage of anaerobic digestion however, as anoxygenic photosynthetic mechanisms are used to produce hydrogen instead of methane.

- **Combined anaerobic digestion and photofermentation.**

  As noted earlier, the first two stages of anaerobic digesters use hydrolytic and acetogenic bacteria to break down organic polymers into hydrogen, carbon dioxide and organic acids. By decoupling these from the third stage, it is possible to treat the acids with anoxygenic photosynthetic organisms to produce hydrogen, rather than with methanogenic organisms to produce methane.

  A Dutch consortium (5) is developing such a process, although preliminary investigations suggested that volumetric productivity need to be increased by an order of magnitude to achieve acceptable costs of production.

2.1.2 Thermal Gasification and Pyrolysis

Thermal gasification and pyrolysis also break down biomass, with pyrolysis defined as thermal decomposition in the absence of oxygen. While three main methods of each can be identified, one of the gasification methods is also a type of pyrolysis, leaving five distinct thermal methods in all.

Thermal Gasification methods, performed with or without catalysts, include:

- “Reforming”, in which biomass is gasified in the presence of another reactant such as steam, steam-oxygen or steam-air
- Partial oxidation, using less than the stoichiometric amount of oxygen required for complete combustion and yielding partially oxidised products
- High-temperature pyrolysis, in which charcoal and liquids are either minor product components or absent

Under idealised condition, the products of the 3 processes are essentially the same: mainly carbon monoxide and hydrogen, with some carbon dioxide, methane and other light hydrocarbons. Using cellulose as a model feedstock, examples of stoichiometries are:

Steam reforming: $C_6H_{10}O_5 + H_2O \longrightarrow 5CO + 5H_2 + CO_2$

Partial oxidation: $C_6H_{10}O_5 + O_2 \longrightarrow 5CO + 5H_2 + CO_2$

Pyrolysis: $C_6H_{10}O_5 \longrightarrow 5CO + 3H_2 + CH_4$

Gases with low calorific value are generally formed when there is direct contact with air, as this results in dilution with nitrogen. Medium energy gases result when oxygen is used or when air is used but the gasifier is heated indirectly. High-energy gases result at lower temperatures and high pressures which favour the production of methane and other light hydrocarbons.

Pyrolysis process conditions vary widely and the product composition depends on the residence time, heating rate and temperature. Typical examples are as follows (35).

Technology	Residence Time	Heating rate	Temp (°C)	Major Products
Conventional carbonisation	Hours-days	Very low	300-500	Charcoal
Pressurised carbonisation	15-120 min	Medium	450	Charcoal
Conventional pyrolysis	Hours	Low	400-600	Charcoal, liquids, gases
Conventional pyrolysis	5-30 min	Medium	700-900	Charcoal, gases
Flash pyrolysis	0.1-2s	High	400-650	Liquids
Flash pyrolysis	<1s	High	650-900	Liquids, gases
Flash pyrolysis	<1s	Very high	1000-3000	Gases
Vacuum pyrolysis	2-30s	Medium	350-450	Liquids
Pressurised hydropyrolysis	<10s	High	<500	Liquids

These can be summarised in terms of the conditions required to produce either gas, liquid or solid:

- Gasification dominates at temperatures above 600°C
- Volatile liquids are the main products at temperatures of 450-600°C, with some chars, tars and gases. The yield of liquid products is maximised by short heat-up and reaction times and by rapid removal and quenching of the volatiles before they are carbonised.
- Chars, tars and dehydration products are formed at temperatures below 250-300°C and at low heating rates. The proportion of char can be increased by running at low temperatures and with closed reactors to keep the volatiles in the pyrolysis zone and hence promote their carbonisation. Modern charcoal processes are faster than the conventional, slow techniques.

In the case of the cellulose component, two pathways for pyrolysis are generally recognised:

- at low temperatures: dehydration to char, tar, CO, CO_2 & H_2O
- at high temperatures: depolymerisation via a levoglucosan intermediate to chars and combustible volatiles

Meanwhile hemicelluloses will be converted to furanoses and furans, lignins to aromatic and phenolic compounds and proteins to a wide range of aliphatic and heterocyclic compounds containing nitrogen.

2.2 Ligno-cellulosic biomass

Lignocellulose is derived from the cell wall, whose main components are:

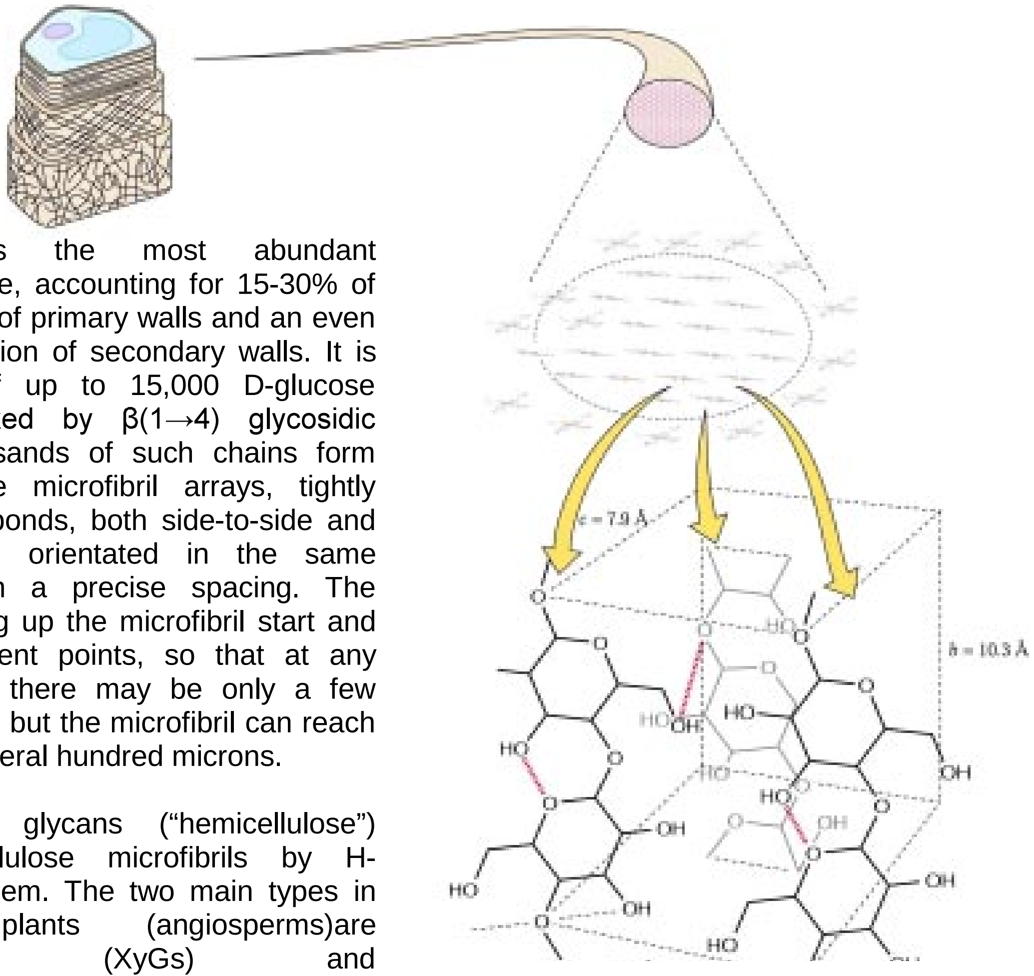
- cellulose
- cross-linked glycans, usually referred to as “hemicellulose”,
- structural phenylpropanoids (lignin),

and, as more minor components:

- aromatics, proteins and, in some walls, pectic polysaccharides

Each of these described below, followed by the hydrolysis of the three main components into their monomeric components. The processing of monomers into platform chemicals is then considered.

2.2.1 Cell Wall Components



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Cellulose is the most abundant polysaccharide, accounting for 15-30% of the dry mass of primary walls and an even larger proportion of secondary walls. It is composed of up to 15,000 D-glucose residues linked by β(1→4) glycosidic bonds. Thousands of such chains form paracrystalline microfibril arrays, tightly linked by H bonds, both side-to-side and top-to-bottom, orientated in the same direction with a precise spacing. The chains making up the microfibril start and end at different points, so that at any cross-section there may be only a few dozen chains, but the microfibril can reach lengths of several hundred microns.

Cross-linking glycans (“hemicellulose”) interlock cellulose microfibrils by H-bonding to them. The two main types in flowering plants (angiosperms)are xyloglucans (XyGs) and glucuronoarabinoxylans (GAXs). The former are the major cross-linkers for the walls of dicots and about half the monocots, which thereby display a “Type I” architecture. GAXs are the main cross-linkers for the “commelinoid” monocots, with a Type II structure. These include the order poales that contain cereals and grasses, which also have a third cross-linking glycan, the “mixed-linkage” (1→3)(1→4)β-D-glucans. Other, less abundant cross-linking glycans based on mannose are (galacto)glucomannans, galactomannans and mannans.

Pectins are a mixture of heterogeneous, branched and highly hydrated polysaccharides rich in D-galacturonic acid. Among a wide variety of functions, they are thought to determine wall porosity, thereby affecting cell growth by regulating the access of wall-loosening enzymes to their glycan substrates. Pectin occurs in low concentrations, and mainly in Type I rather than Type II walls. Structural proteins such as extensin also form networks, although their precise function has yet to be elucidated.

Lignins are a class of phenylpropanoid that evolved in the transfer of plants from an aquatic to a terrestrial environment, reinforcing cell walls to enable them to support massive weights and transport water and minerals from root to leaves. After cellulose, they are the most abundant organic material, accounting for 20-30% of all vascular plant tissue. They are polymers containing bonds such as 8-O-4’, 5-5’-O-4’, 8-5’ and 8-8’, between monomers that include coniferyl, sinapyl and p-coumaryl alcohol. They biodegrade only slowly, and their conversion to CO_2 is the rate-limiting step in recycling biological carbon.

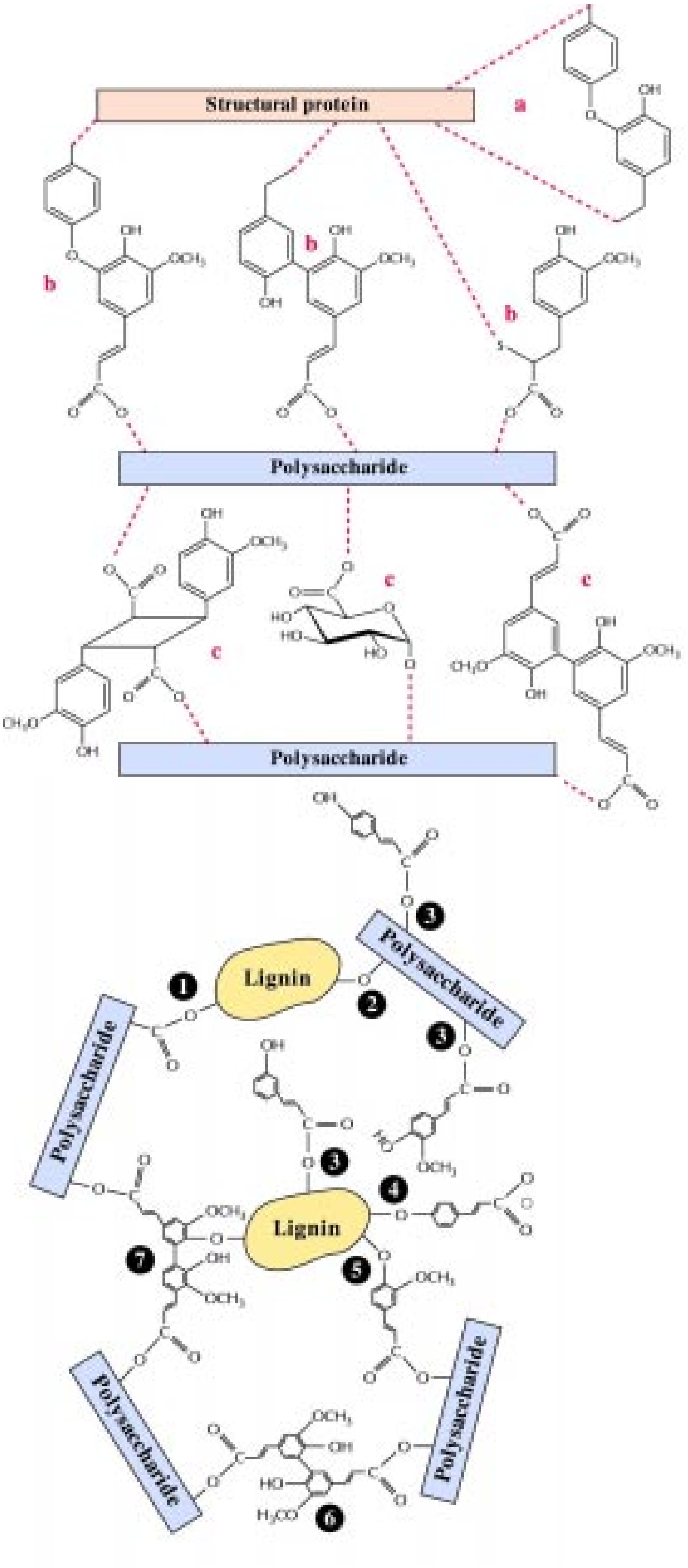
Some nonlignified primary cell walls contain significant amounts of aromatic substances, and many of these are hydroxycinnamic acids such as ferulic and *p*-coumaric acids, which are precursors of lignin monomers. Examples inlcude the commelinoid orders of monocots and the Chenopodiiaceae, such as sugar beet and spinach.

In grasses, these hydroxycinnamates are attached to the O5 positions of a few of the Ara units of GAXs. Some of the ferulic acid units of neighbouring GAXs may cross-link by phenyl-phenyl or phenyl-ether linkages to interconnect the GAX into a large network

Several types of polysaccharide-polysaccharide and polysaccharide-protein cross-bridges are possible, many involving aromatics. Isodityrosine forms as an intrapeptide linkage to stabilise extensin rods (**a**). Tyrosine, lysine (not shown) and sulphur-containing amino acids can form ether and aryl linkages with hydroxycinnamic acids esterified to polysaccharides (**b**). Neighbouring polysaccharides may contain cross-bridges esterified directly to sugars (**c**).

The kinds of aromatic ester and ether cross-links between carbohydrate and lignin can be summarised as follows:

1. Direct ester linkage
2. Direct ether linkage
3. Hydroxycinnamic acid ester
4. Hydroxycinnamic acid ether
5. Ferulic acid bridge
6. Dehydrodiferulic acid diester bridge.
7. Dehydrodiferulic acid diester-ether bridge



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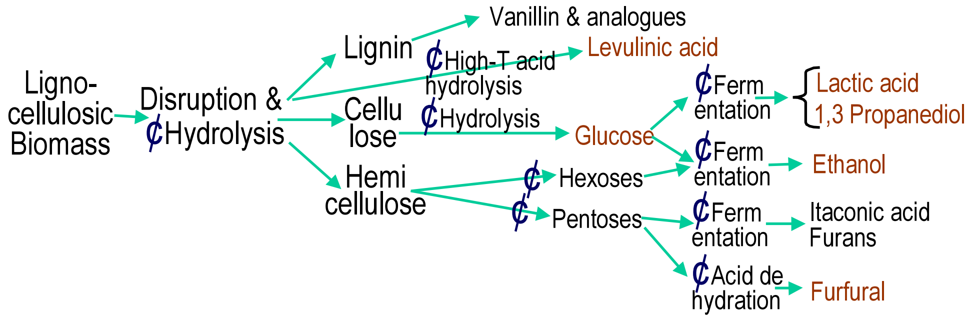
2.2.2 Hydrolysis to Monomers

Before either of the three polymers, cellulose, hemicellulose or lignin are hydrolysed, their interlinking may be disrupted by explosive decompression, using either steam, hydrogen peroxide or ammonia as the decompressive medium. The hydrolysis itself can be undertaken by concentrated or dilute acids or by enzymes. The three polymers display differing resistances to hydrolysis, offering a feature to be exploited in the process design. Hemicellulose is the most easily hydrolysable and mild acid hydrolysis will suffice. Lignin is the most resistant and treatment with concentrated acid dissolves the cellulose and hemicellulose, leaving lignin virtually intact.

The **Concentrated Acid Hydrolysis** process generally uses a dilute acid pre-treatment stage to hydrolyse the hemicellulose, which is separated off. The main, concentrated acid stage then disrupts the hydrogen bonding between cellulose chains and converts it from a paracrystalline to an amorphous, gel state. Dilution with water and modest heating is then sufficient for rapid and complete hydrolysis of the cellulose to glucose. The acid/sugar solution is decanted off for separation while the remaining lignin is processed separately. Recent improvements in acid/sugar separation and recovery have improved the economics of the process, and both Arkenol and Masada Resources Group in the US are commercialising processes (41). Both companies target the conversion of lignocellulose to ethanol, the former from rice straw and the latter from Municipal Solid Waste.

Dilute Acid Hydrolysis processes also hydrolyse hemicellulose in a mild pre-treatment stage, before more severe conditions are used to hydrolyse cellulose. One of the drawbacks, however, is the dilute process streams that result. Both acid hydrolysis processes also produce furfural as an inhibitory degradation product.

Enzymatic hydrolysis avoids the expense of the acid and its neutralisation, but is generally slower. Hemicellulose is again the most straightforward material to process, as suitable enzymes are already used in the paper and pulp industries (6). The tightly-bonded, paracrystalline structure of cellulose, however, means that it is more resistant to hydrolysis. In addition, cellulase enzymes are expensive, although research is being undertaken by both Genencor and Novozymes to achieve a ten- to fifty-fold decrease in effective costs, either by reducing production costs or increasing enzyme activity (6). Cellulase may be inhibited by any lignin not removed during pre-treatment and by the glucose it produces. Product inhibition may, however, be avoided by simultaneous saccharification and fermentation (7), in which sugars are fermented in the same reactor to a product such as ethanol.



The Biofine process (8) is a commercial example of a two-step dilute acid hydrolysis technology. Wastes including paper mill sludge, municipal solid waste, paper and wood wastes and agricultural residues are mixed with dilute acid before being fed into a high temperature tubular steam reactor and then into a mixed reactor. The acid catalyst is recycled, levulinic acid and furfural recovered and a solid char formed from lignin gasified to produce hydrogen. A pilot plant has been operating since 1998 and a commercial plant for the past few years at Caserta, Italy. The process produces levulinic acid at prices between £0.55 and £0.11/kg compared with costs of (£6.00/kg) in processes using fossil feedstocks (6).

Derivatives of levulinic acid include methyl tetrahydrofuran (MTHF), δ-amino levulinic acid (DALA) and diphenolic acid (DPA). MTHF is used to produce the antimalarial primaquine and may be used as an extender for petrol in blends up to 70% by volume. DALA is an active chemical in a new group of herbicides and pesticides and in cancer treatment. DPA is an alternative to bisphenol A in polycarbonates and phenolic resins.

An example of enzymatic hydrolysis is Iogen's EcoEthanol™ process to convert agriculture residues into sugars, which are then fermented and distilled into ethanol (54). A demonstration facility is currently operational in Ottawa.

2.2.3 Monomers to Platform Chemicals

While glucose is the sole monomer arising from cellulose hydrolysis, those produced from hemicellulose are mainly a mixture of pentoses such as xylose and arabinose. These can be processed into platform chemicals either biochemically, with enzymatic or whole cell biocatalysts, or thermochemically, with chemical catalysis and/or high pressure and temperature. Future platform chemicals are discussed in section 4.4, while examples of current products are given here.

Biochemical processes can ferment both hexoses and pentoses, although current bacteria have a higher activity for the former. Research currently funded by the US DoE (9) to produce bacteria able to ferment C5 sugars, alone or with C6 sugars, will if successful have a significant impact on the economics of renewable feedstocks. The most common pentose being fermented is xylose, whose principal derivatives are itaconic acid and furans. The former could, if produced at a competitive price, compete with methyl methacrylate and other methacrylates, and in the pressure-sensitive adhesives market. Furans such as furfural, furfuryl alcohol and 2-hydroxymethyl tetrahydrofuran are mainly produced in China by the fermentation of corn cobs. Hexose fermentation, using glucose as the substrate, currently produces 1,3-propanediol and lactic acid.

- **1,3 Propanediol** is used with terepthalic acid to make polytrimethylene terepthalate (PTT), with uses in clothing, upholstery and speciality resins. It is currently produced from fossil resources, but a lower-cost route based on glucose fermentation by *E.coli* has been developed by Genencor and DuPont and will enter production in 2006.

- **Lactic acid** is in large-scale production using C6 sugars derived from grain. While improved fermentation and separation have reduced production costs from £1.20 to £0.60/kg, it is considered practical (6) to reduce this further to £0.30/kg and a realistic longer-term target is thought to be £0.15/kg. In addition to its own uses, lactic acid can be converted to polylactic acid (PLA), by condensation to lactide, which is subjected to a ring-opening polymerisation. PLA is cost-competitive with and offers performance properties equal or greater to those of conventional polymers. It requires 30-50% less fossil fuel than conventional polymers and can be composted at the end of its life, or melted down and re-used. PLA can be used as packaging, where it has high stiffness, grease resistance and barrier properties for flavour and aroma. When used for food service, it enables composting without the need for separating food from the packaging. It may also be used as a textile, where it has high dyeability and better wickability than polyester. Other potential derivatives of lactic acid at the research stage include:

- Ethyl lactate, a solvent that can be customised by blending with methyl soyate. Current work to reduce costs includes membrane separation of lactic acid and reactive membrane conversion of lactic acid salts directly to ethyl lactate.

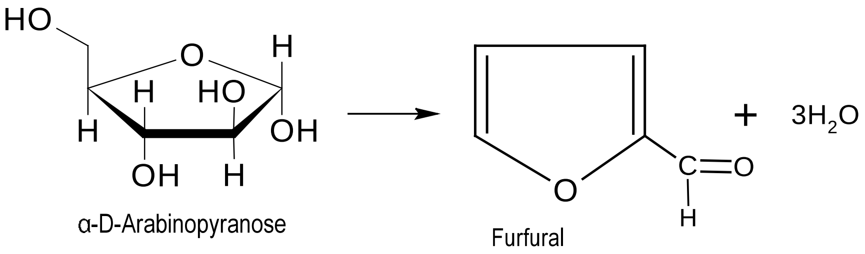
- Acrylic acid, currently produced by the gas-phase catalytic oxidation of propylene via acrolein. Research is underway on the enzymatic or thermochemical dehydration of lactic acid, with a target competitive price of £0.60/kg

- Propylene glycol, currently produced by the hydration of propylene oxide. While it is possible to convert sugars to propylene glycol thermochemically, it may also be possible to produce it cost-competitively from lactic acid

- Pyruvic acid, with specialist uses including pharmaceuticals and emulsifiers. It has, recently been discovered (48) that pyruvate decarboxylase can be driven in reverse at pH 11 to produce pyruvic acid and work is continuing on this process.

Example of current products from thermochemical processes are:

- **Furfural**, produced by dehydrating pentoses with dilute sulphuric acid.



As noted earlier, it is a troublesome by-product of the acid hydrolysis of lignocellulose. It is used in the manufacture of dyes, plastics and fumaric acid.

- **Vanillin** can be produced from the lignin found in the waste from the sulphite process of the paper industry (10). After fermenting the sugars also found in the waste, the remainder is treated with alkali and oxidising agent to produce vanillin. The process is nevertheless wasteful, and manufacturing vanillin from petrochemical benzene via phenol, catechol and guaiacol has a higher atom efficiency. The petrochemical process, however, operates at 40 atmospheres pressure and 260°C, whereas an alternative route to catechol via the bacterial biotransformation of D-Glucose occurs at 37°C and atmospheric pressure. An alternative biotransformation uses bacteria or fungi acting on the ferulic acid found in sugar beet pulp or the bran in wheat or maize.

  Lignin can be converted by acid catalysis or biocatalysis to a complex mixture of substituted quinones, phenols and catechols. Examples of selective chemistry that can isolate and functionalise molecules from this mixture may now be emerging (11).

2.3 Commodity Crops

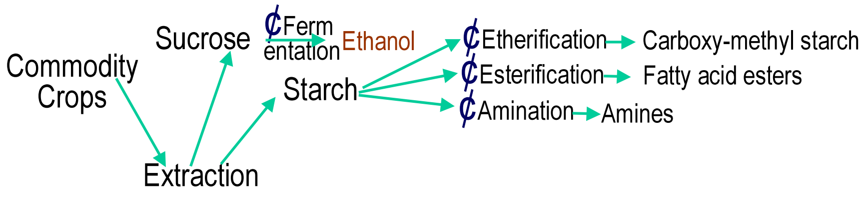
Commodity crops include sugar beet, wheat, barley and oil seed rape. While the sucrose from sugar beet, like its sugar cane cousin, could be used to produce ethanol by fermentation, its main current use is in food. Ethanol as a fuel or platform chemical is considered in section 4.3

Crops such as wheat and barley contain two main components of interest: starches and proteins, although these materials can also be derived from crops such as potato and pea, or from animal sources. Oil seed rape is grown mainly for its oil, but there is now interest in adding value to it by making better use of its residual protein. It might be noted, however, that there are also a number of other oils seed crops such as Linseed and Crambe, which because of their small production volume may currently be regarded as specialist crops. Similarly, transgenic plants used to produce proteins such as vaccines and antibodies also fall into the specialist crop category and are considered in section 2.4. Starch, oil and protein are considered in the sub-sections that follow.

2.3.1 Starch

Starch has long been used as a chemicals feedstock. Including food and non-food uses, about 30% of vegetable starch is unmodified, 17% chemically modified and 53% hydrolysed (49). Hydrolysis can be either partial, to modify properties such as viscosity and adhesion, or complete, to produce glucose. While the glucose can be used to produce any of the platform chemicals or their derivatives described in section 4.4, its main current use is for fermentation to ethanol, particularly in the US and Brazil. As discussed more fully in section 4.3, the main use of bioethanol is currently as an additive for petrol, replacing methyl tertiary butyl ether.

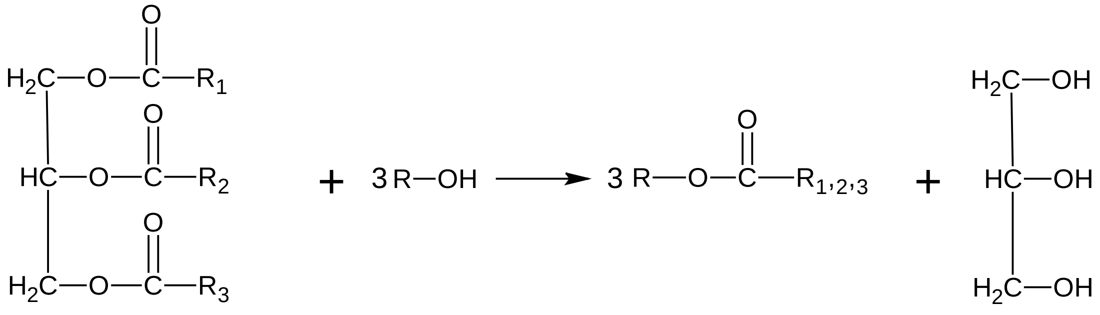
Starch chemical modification includes etherification, esterification and amination. While some starch esters and ethers are used as food additives, the main application is non-food, particularly as sizing or coatings for the paper industry.



As high amylose maize starch was found to be resistant to gastric juices, it has been used as an encapsulating material to deliver probiotic bacteria to the colon, whose flora are able to degrade it (12). For the same reason, amylose has been used to encapsulate colon-specific drugs. In this case, however, it was necessary to combine the amylose with ethyl cellulose, to prevent swelling and the premature release of the drug through pores. Another pharmaceutical application is starch cross-linked with epichlorhydrine to form microspheres for nasal drug delivery.

2.3.2 Oil

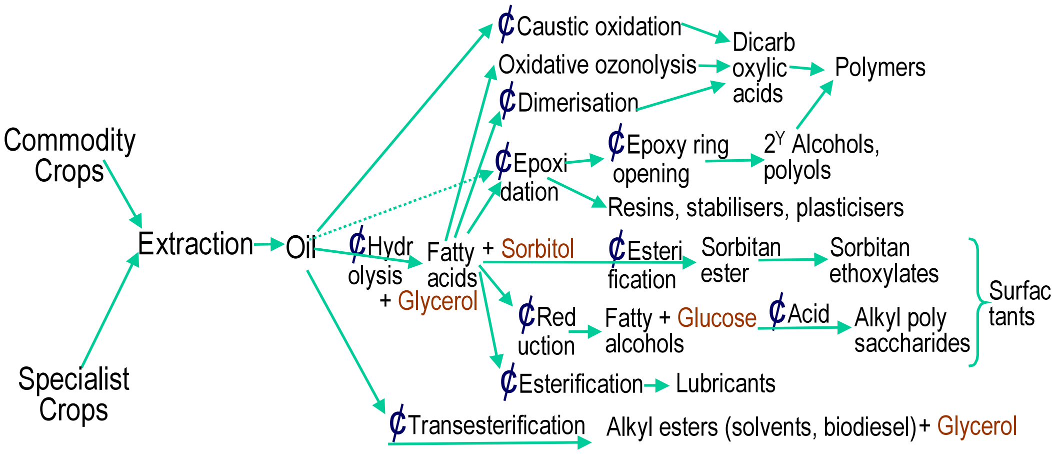
The two most common processes for triglyceride vegetable oils are hydrolysis to the component fatty acids or transesterification to fatty acid alkyl esters. In both cases, glycerol is a by-product.



R = H, hydrolysis; R = CH_3 , C_2H_5, ... transesterification

Hydrolysis occurs in pressurised water at 220°C, while transesterification is a catalysed reaction. Methanol or ethanol are the alcohols commonly used, usually to excess so that yields of the esters is increased. Methanol is often preferred, as it allows the simultaneous separation of glycerol.

If Brönsted acid catalysts such as sulphonic or sulphuric acids are used, the yields are high, but the reactions slow. As base catalysts are faster and less corrosive, they are usually preferred in industrial processes, and alkaline metal alkoxides, hydroxides and sodium or potassium carbonates are used. Alkaline metal alkoxides give very high yields (> 98%) in short reaction times (30 min) even if they are applied at low molar concentrations (0.5 mol%). They must, however, operate in the absence of water, making them inappropriate for many processes. Alkaline metal hydroxides are less active but cheaper, and the same yields can be achieved by increasing the catalyst concentration to 1 or 2 mol%. Nevertheless, However, some water is produced by the reaction of the hydroxide with the alcohol, giving rise to hydrolysis of some of the produced ester and soap formation. Potassium carbonate at concentrations of 2 or 3 mol% gives high yields and reduces soap formation, as bicarbonate is formed instead of water and the esters are not hydrolysed. Hydrolytic enzymes can also be used, although yields and reaction times are lower compared to base catalysts (13). The fatty acids and fatty acid alkyl esters produced from vegetable oils have several current applications and derivatives noted below.



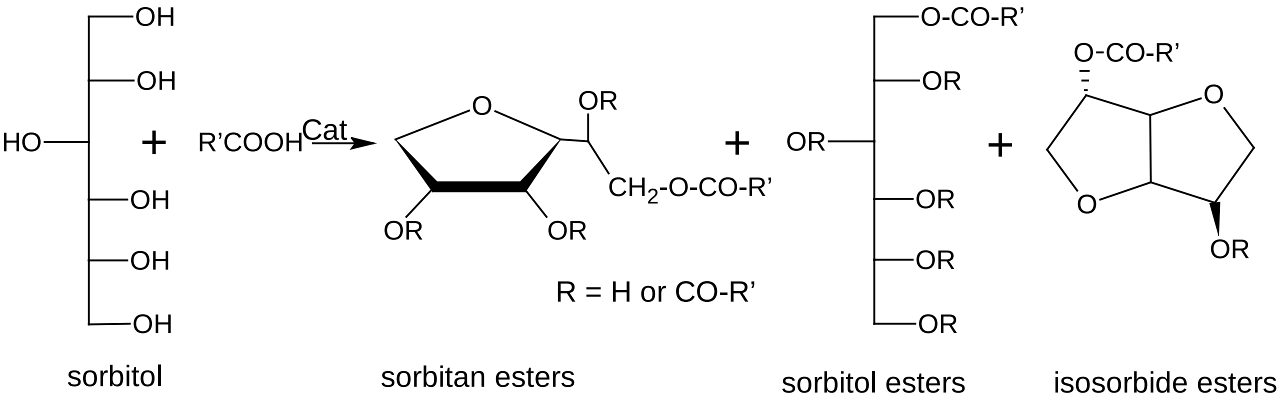
Biodiesel as a term usually refers to fatty acid alkyl esters produced by the transesterification of vegetable oils. It is sometimes used, however, to describe bioethanol-blended diesel. Vegetable oils themselves are unsuitable as engine fuels because of their high viscosity and low volatility, and because the toxin acrolein is formed by the thermal decomposition of glycerol. Alternatives to transesterification of oils have been investigated, including

- dilution of diesel fuel in the ratio 3:1
- microemulsions with short chain alcohols such as ethanol or methanol
- thermal decomposition, to produce alkanes, alkenes, carboxylic acids and aromatics
- catalytic cracking, producing alkanes, cycloalkanes and alkylbenzenes

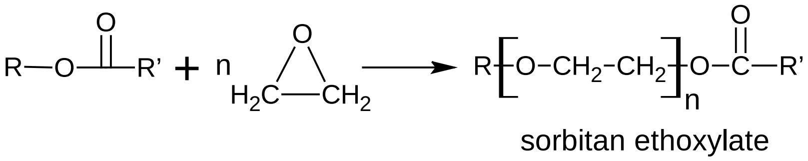
Transesterification is the preferred choice, as the physical properties of fatty acid methyl or ethyl esters are very close to those of diesel fuel and can be burned directly in unmodified diesel engines, with very low deposit formation. Fatty acid alkyl esters also act as effective **solvents.**

Surfactants are an important environmental target for biodegradable renewable alternatives, as their widespread use but low concentrations mean they are inevitably released into the environment. Fatty acids provide a ready source of hydrophobes and C8-C20 chain lengths are usually used, while saccharides provide an equally plentiful supply of nonionic hydrophiles. Anionic surfactants can meanwhile be prepared by, for example, adding a sulphate groups to a fatty alcohol.

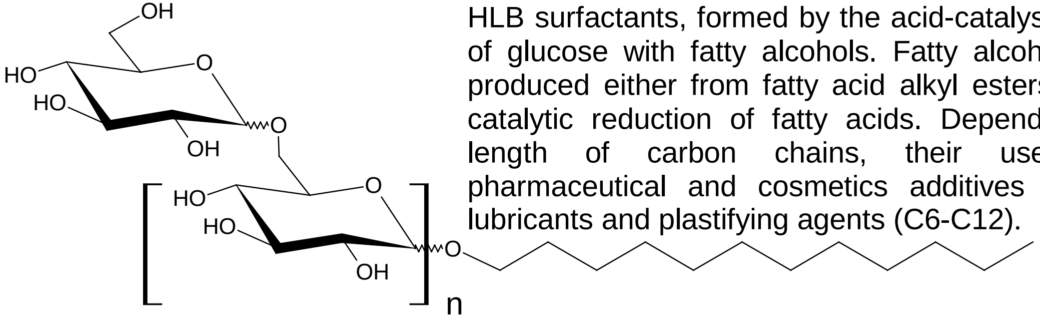
Sorbitan esters are a group of surfactants with relatively low Hydrophile-Lipophile Balance (HLB) ratios, and are therefore suitable to stabilise water-in-oil emulsions. They result from esterifying fatty acids with sorbitol, a reaction that also produces sorbitol and isosorbide esters as byproducts. The esterification conditions currently used are unselective, so a mixture of mono- di- and oligo-substituted sorbitan esters are produced. As a mixture of fatty acids is usually used, a complex mixture of esters results, with the composition dependent on the catalyst type and concentration, along with temperature (14).



Sorbitan ethoxylates are surfactants with higher HLB ratios and are produced by reacting sorbitan esters with ethylene oxide.



Alkyl polyglycosides are an alternative group of high HLB surfactants, formed by the acid-catalysed reaction of glucose with fatty alcohols. Fatty alcohols can be produced either from fatty acid alkyl esters or by the catalytic reduction of fatty acids. Depending on the length of carbon chains, their uses include pharmaceutical and cosmetics additives (C16-C18), lubricants and plastifying agents (C6-C12).



Polymers are another potentially large area for renewable oleochemicals. The oils themselves can be polymerised into useful materials, for example drying oils produced from cottonseed, tung or linseed oil. These form an elastic film when exposed to air, and are used in paints, inks, varnishes and laquers. Another example is the polymerisation of linseed oil to produce linoleum. Epoxidised vegetable oils have also been combined with acrylate, isocyanates and polycarboxylic acid anhydrides to produce thermosetting resins (15).

Derivatives of vegetable oils, such as secondary alcohols, polyols and dimer alcohols can also act as monomers for polyesters, polyamides and polyurethanes (16). The chemistry centres on the double bonds of unsaturated fatty acids, with dimerisation, ozonolysis, caustic oxidation and epoxidation with subsequent epoxy ring opening being some of the methods used.

Secondary alcohols and polyols are produced by epoxidation and ring opening of the oils or the fatty acids at the double bonds. Dimer alcohols can be produced either by the dimerisation of oleyl alcohols or by the hydrogenation of dicarboxylic acids. Dicarboxylic acids can be produced by the dimerisation of fatty acids at their double bonds. Alternatively, oxidative ozonolysis of a fatty acid leads to a mixture of a dicarboxylic and moncarboxylic acids that can be separated (17).

Lubricants and **hydraulic oils** can also be produced from esters of either fatty acids or alcohols. The appropriate blend of esters can be chosen to meet a specified combination of viscosity and anti-wear properties. While the non-toxic, biodegradable and renewable nature of these oils are prime benefits, their high costs currently limits them to specialist applications. **Cleaning fluids** for industrial printers can also be derived from such esters.

2.3.3 Proteins

Uses for proteins are currently few (6), but include ingredients in polymers, coatings, composites, inks, cosmetics and personal care products. Two specialist applications are as encapsulation materials, including the encapsulation of whole-cell biocatalysts (12), and the production of vaccines and antibodies by genetically-engineered plants. The former is discussed here and the latter in section 2.4.1.

To encapsulate, proteins must form a film over the core material and this means they need to be unfolded. The modification of surface groups may be required to produce desired properties and this may be achieved by physical, chemical or enzymatic means. It may, for example, be desirable to hydrophilise the protein by replacing amide groups with carboxylate, and hence improve its film-forming properties. Or improved water resistance may be provided by introducing hydrophobic alkyl or aromatic groups.

Cross-linking is a further example of surface modification. Physical cross-linking methods include treatment with heat or radiation, while enzymatic modifications include:

- Transglutaminase catalysis of an acyl-transfer reaction between the γ-carboxyamide group of glutamic acid residues and primary amines, leading to glutamyl-lysine cross-links
- Peroxidase- or catalase-mediated reaction between tyrosine groups
- Disulphide isomerase catalysis of breakage and reformation of disulphide bonds
- Polyphenol oxidase-mediated hydrolysis of tyrosine followed by reaction with amine or thiol groups

Chemical crosslinking can be performed by homobifunctional reagents with two identical functional groups, of which the best-known example is glutaraldehyde. Heterobifunctional reagents may however provide more control over the process, for example by cross-linking in two steps.

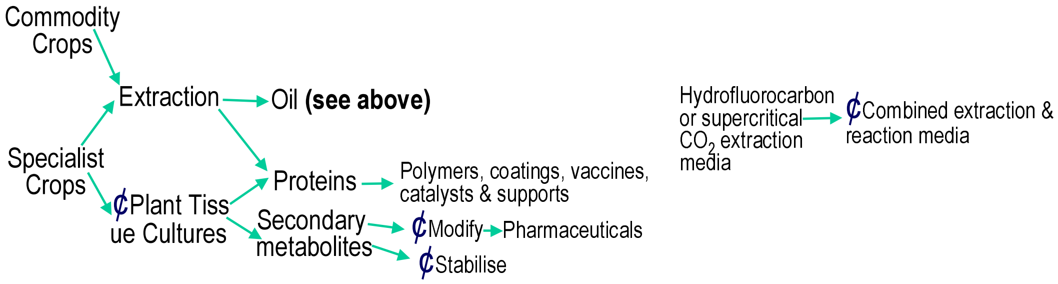
Proteins of potential use in encapsulation include collagen, gelatin, casein, whey, albumin, gluten, zein, soy and pea protein. Collagen is the most abundant protein of higher vertebrates and easily isolated from many biological sources. Its amino acid sequence is typically triplets, repeated many hundreds of times, of [glycine-X-Y] where X is often proline and Y 4,hydroxyproline. This sequence forms a left-handed helix with about three residues per turn and three such helices form a right-handed superhelix with the aid of hydrogen bonds between glycine and proline residues of parallel sequences. The counter-rotating helices provide tensional strength, while low solubility in water is achieved by cross-linking of lysine and histidine side chains. Gelatin is obtained from collagen by partial hydrolysis and therefore has a similar amino acid composition. Upon dissolution in water and cooling, a gel is formed.

Caseins are predominately phosphoproteins with low levels of cysteine and hence few disulphide cross-links and an open, random coil structure. Caseinates are derived from them by treatment with sodium or calcium hydroxide. A large proportion of caseins in milk exist as colloidal dispersed micelles in the 10 to 250nm size range, whereas caseinates remain as monomers. Both are amphiphilic and form flexible films from aqueous solution.

Whey contains five main protein types: β-lactoglobulin, α-lactalbumin, bovine serum albumin, immunoglobulins and proteose-peptones. The first two of these are the most important for encapsulation but, due to their globular nature, require heat treatment to form films. In addition to bovine serum albumin, egg albumin has been used to produce porous microspheres.

Gluten is a mixture of the polymeric and elastic glutenins with the monomeric and viscous gliadins. Both are rich in glutamine and proline and are insoluble in water. This is currently limiting the range of applications, but can be overcome by the chemical or enzymatic deamidation of glutamine to glutamic acid.

Zein is another plant protein that is insoluble in water owing to the large proportion of non-polar amino acids it contains. In addition to protective film applications, however, it has been used in systems for the controlled release of pesticides and medications. Soy protein contains four main sedimentation fractions, of which the largest consists of glycinin. In addition to uses in coatings and adhesives, soy protein has been used to microencapsulate insecticides, food ingredients and pharmaceuticals, with a recent possible use in hydrogel delivery of drugs. The main components of pea protein are vicillin and legumin and, as there are many reactive amino groups, chemical modification is possible. Little work has yet been done, however, on using the protein in microencapsulation.



2.4 Specialist Crops

Specialist non-food crops may be grown for oil, secondary metabolities or recombinant proteins. They may be grown in traditional, open-field cultivation, contained cultivation in protected environments or as plant tissue cultures within bioreactors. The following sections consider product types, cultivation methods, and extraction methods of interest.

2.4.1 Product Types

The main product types considered below are specialist oil seeds, secondary metabolites and recombinant proteins

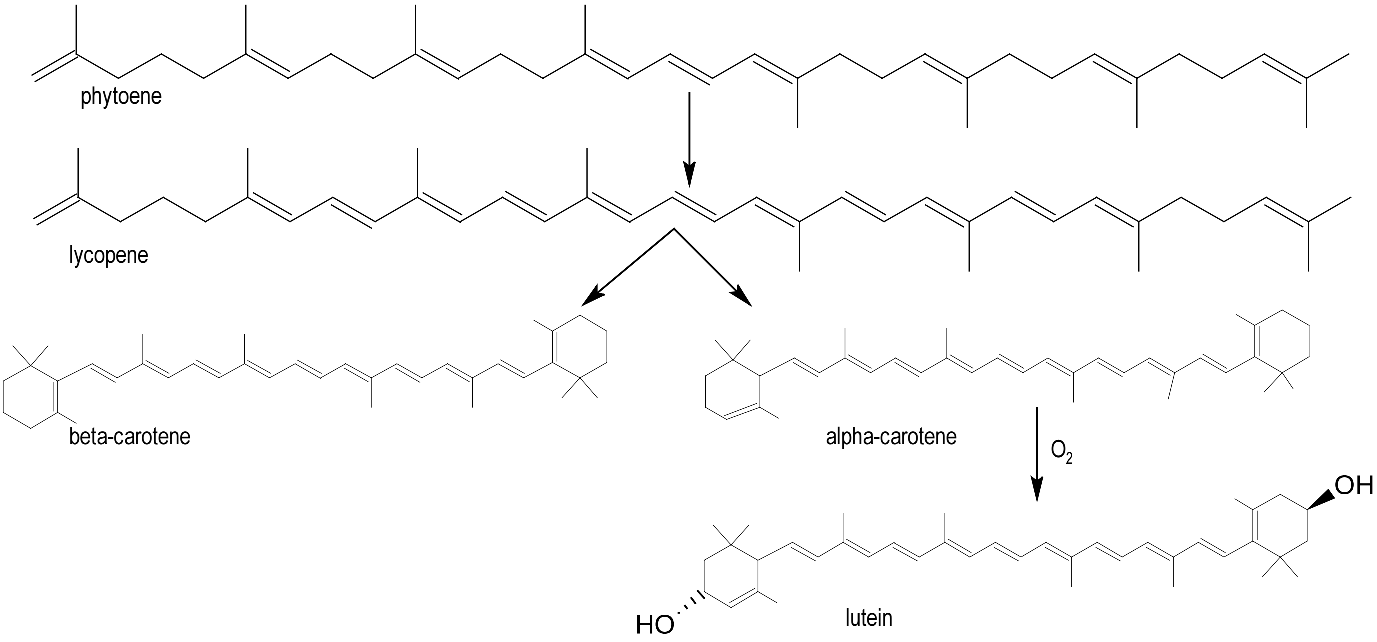
2.4.1.1 Specialist Oil Seeds

Some oil seed crops currently have such low areas under cultivation that they can be classified as specialist. Examples, with UK hectare coverage in brackets, include echium (~200), borage (1800) and crambe (4000). The uses for crambe are mainly industrial, of the sort discussed in section 2.3.2 (18,19). Those for echium (20), by contrast, are mainly for healthcare, based on its unique ratio of omega-3 and omega-6 fatty acids, appreciable amounts of g-linolenic acid (GLA) and the rare stearidonic acid (cis 6,9,12,15 – 18:4).

2.4.1.2 Secondary Metabolites

While primary metabolites participate in nutrition and essential metabolic processes, secondary metabolites influence ecological interactions between the plant and its environment, such as protection against herbivory and microbial infection, attractants for pollinators and seed-dispersing animals and competition among plant species. They have long been exploited in the form of medicinal herbs, commercial examples of which include echinacea and St John's Wort. Secondary metabolites can be divided into terpenoids, alkaloids and phenols.

Terpenoids are derived by repeated fusion of branched 5-carbon units based on the 2-methyl butane skeleton and are compartmentalised in plants. For example, the glandular trichomes and secretory cavities of leaves and the glandular epiderms of flower petals generate and store or emit terpenoid essential oils that encourage insect polination. These specialised structures sequester secondary metabolites away from sensitive metabolic processes, so preventing autotoxicity. Some of the best-known examples are the antioxidants lycopene, β-carotene and lutein, all of which are derived *in vivo* from the tetraterpene phytoene and are available as dietary supplements.



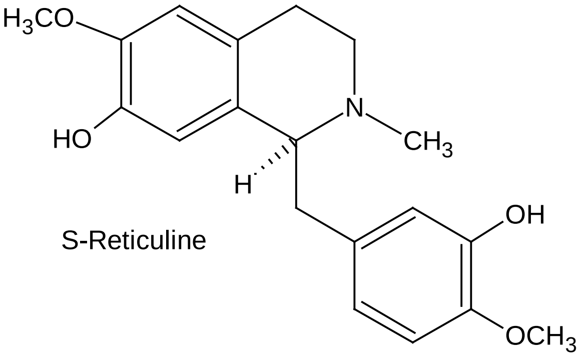
Other commercially important examples are artemisinin, an antimalarial and precursor for other semisynthetic derivatives, and the anticarcinogen 10-deacetyl baccatin III (for paclitaxel).

Alkaloids contain nitrogen, and more than12,000 have so far been isolated. About 20% of flowering plants produce them, each in a unique pattern. Most are pharmacologically active and basic, and those in use in today include the following (21).

Alkaloid	**Plant Source**	**Use**
Ajmaline	*Rauwolfa serpentina*	Antiarrythmic: inhibits glucose uptake by heart tissue mitochondria
Atropine	*Hyoscyamus niger*	Anticholinergenic, antidote to nerve gas poisoning
Caffeine	*Coffea arabica*	Stimulant of central nervous system
Camptothecin	*Camptotheca acuminata*	Potent anticancer agent
Cocaine	*Erythoxylon coca*	Topical anaesthetic; stimulant of central nervous system; adrenergic blocker; drug of abuse
Codeine	*Papaver somniferum*	Relatively nonaddictive analgesic and antitussive
Coniine	*Conium maculatum*	Extremely toxic; paralyses motor nerve endings; used in homeopathy in small doses
Emetine	*Uragoga ipecacuanha*	Orally active emetic; amoebicide
Morphine	*Papaver somniferum*	Powerful narcotic analgesic, addictive drug of abuse
Nicotine	*Nicotiana tabacum*	Highly toxic, causes respiratory paralysis, horticultural insecticide, drug of abuse
Pilocarpine	*Pilocarpus jaborandi*	Peripheral stimulant of parasympathetic system, used to treat glaucoma
Quinine	*Cinchona officinalis*	Antimalarial, treating *Plasmodium falciparum* strains resistant to other antimalarials
Sanguinarine	*Eschscholzia californica*	Antibacterial with antiplaque activity, used in toothpaste and oral rinses
Scopalamine	*Hyoscyamus niger*	Powerful narcotic, sedative for motion sickness
Strychnine	*Strychnos nux-vomica*	Violent tetanic poison, rat poison, used in homeopathy
Tubocuranine	*Chondodendron tomentosm*	Nondepolarising muscle relaxant producing paralysis, used as adjuvant to anaesthesia
Vinblastine	*Catharanthus roseus*	Antineoplastic used to treat Hodgkin's disease and other lymphomas

Of topical interest are thebaine and oripavine, the opiate precursors found in the top1 mutant of the opium poppy *papaver somniferum.* This is being exploited in Tasmania, which now produces 40% of legally-traded opiates, although some is now grown in the UK. Plant scientists at the Australian National University are working to produce a mutant that produces only thebaine as a precursor, as it is more valuable than oripavine (22).

It is notable that plants appear to use the concept of "platform chemicals" to synthesise alkaloids. The intermediate strictosidine, for example, is converted into a multitude of alkaloids, including vincamine, vinblastine, vincristine, yohimbine, quinine, strychnine, ajmalicine and ajmaline. Another example is (s)-reticuline which, depending on the way in which it is twisted, can be converted into a huge array of alkaloids of vastly differing structure, including codeine, morphine, protopine, noscapine, sanguinarine, papaverine, berberine and corydaline.



S-Reticuline

Phenolics are metabolites whose aromatic rings have or had attached 1 or more acidic hydroxyl groups. Their classes include the following:

- lignans, which can defend against pathogens or act as antioxidants and are generally taken to mean all products of phenylpropanoid (C_6C_3) coupling, although originally the term meant only those formed through 8-8' bonds. An example is pinoresinol, the precursor of the antioxidant sesamin in sesame seeds, and lariciresinol and secoisolariciresinol, whose dehydrogenation yields matairesinol. These last two are found in green beans and rye and are respectively converted by human digestive bacteria into enterodiol and enterolactone, which are believed to protect against prostate and breast cancer. Matairesinol is thought to be the precursors of plicatic acid and podophyllotoxin, the latter being used to treat venereal warts and be derivatised synthetically into teniposide, which is widely used in cancer treatment.

- lignins, discussed in section 2.2.1

- those found in suberised tissue, which contain alternating hydrophobic (aliphatic) and hydrophilic (phenolic) structural substances. Present in cork, bark, roots and certain periderm tissues (e.g. potato skin) suberised tissue provides a protective barrier against pathogen attack and atmospheric dessication

- flavonoids, an extremely diverse class of more than 4500 compounds divided into the groups anthocyanins, proanthocyanins, leucoanthocyanins, flavones, flavonones, isoflavonoids, flavonols, chalcones, aurones and catechins. They perform a wide range of functions, influencing in particular the interactions between plants and animals, such as colouring, protection against UV-B radiation, feeding attractants, antifeedents, signal molecules and defence against fungal attack.

  Some flavonoids have also been investigated as health aids and pharmaceuticals, including the modulation of immune and inflammatory responses, their impact on smooth muscle function and anticancer, antiviral, antitoxic and hepatoprotective agents. The isoflavonoids daidzein and genistein, which are present in soybeans, are thought to reduce substantially the incidence of breast and prostate cancer.

- coumarins, furacoumarins and stilbenes, which protect against bacterial and fungal pathogens, discourage herbivory and inhibit seed germination

  Ingesting coumarins from plants such as clover can cause massive internal bleeding in mammals, a discovery that led to the development of warfarin as a rodenticide and related compounds to treat and prevent stroke. The stilbene combretastatin is an antineoplastic while resveratrol in red grapes and wine suppresses tumor formation.

- miscellaneous phenols that are not products of phenylpropanoid metabolism, most notably the cannabinoids tetrahydrocannabinol and cannabidiol. Along with certain terpenes and flavonoids, these form the main components of GW Pharma's Sativex® medicine for the symptomatic relief of multiple sclerosis and neuropathic and rheumatoid arthritic pain.

2.4.1.3 Recombinant Proteins

Plants offer a platform to produce recombinant proteins and the discussion below is taken from a recent review paper (23), to which the reader is referred for more detail.

The extraction of proteins from natural sources can be difficult and expensive and also pose health risks, for example from contaminated blood products or hormones. In some cases, such as single-chain variable fragments, the proteins do not occur naturally. As shown in the table below, production systems using microbial or mammalian cell cultures or transgenic animals have disadvantages in terms of cost, scalability, contamination risks or quality. Plant production systems, or "molecular farming" may address some of these drawbacks.

	Cost	Production timescale	Scalability	Product Quality	Glycosylation	Contamination risks	Storage costs
Bacteria	Low	Short	High	Low	None	Endotoxins	Moderate
Yeast	Medium	Medium	High	Medium	Incorrect	Low risk	Moderate
Mammalian cells	High	Long	Very low	Very high	Correct	Viruses, prions, oncogenic DNA	Expensive
Transgenic animals	High	Very long	Low	Very high	Correct	Viruses, prions, oncogenic DNA	Expensive
Plant cell cultures	Medium	Medium	Medium	High	Minor differences	Low risk	Moderate
Transgenic plants	Very low	Long	Very high	High	Minor differences	Low risk	Inexpensive

Recombinant proteins that have already been produced in plants include:

- **Biopharmaceuticals** such as human serum albumin, growth hormone and α-interferon

- **Monoclonal antibodies**, including many examples of the most common immunoglobulin in the bloodstream, IgG, the more complex secretory antibody SIgA/G, as well as engineered single-chain variable fragments (scFv). Whereas scFv fragments are single proteins, and relatively easy to produce in all recombinant expression systems, full length antibodies (IgG and SIgA) are complex multimeric proteins that require protein folding and assembly mechanisms that are only found in eukaryotic cells such as plants and animals

- **Recombinant subunit vaccines**, such as the hepatitis B virus envelope protein, the *E.coli* heat labile toxin and the capsid protein of the Norwalk virus.

- **Other proteins**, including human collagen and a synthetic spider silk

The most common method to generate transgenic plants is to use the natural mechanism of *Agrobacterium tumefaciens* to transfer foreign genes into the nuclei of plants. Another is particle bombardment, in which DNA is coated onto microprojectiles, and which is suitable for gene transfer into either the nucleus or the chloroplasts. Transplastomic plants are a relatively recent development, in which the foreign genes are located in plastids rather than the nucleus. An advantage of this technique is an increase in yield, due to the larger number of gene copies present per cell. A drawback is that plastids do not have all the assembly mechanisms required for many proteins, nor do they perform post-translational modifications such as glycosylation.

To achieve controllable and high yields, all stages of expression must be optimised, from transcription to protein stability. To help achieve this, the transgene is typically bracketed by regulatory genes such as a promoter and a polyadenylation site, to form an "gene construct". Promoters allowing expression of the recombinant protein in a particular plant tissue, at a specific developmental time, or under specific environmental conditions can also be used. Restricting expression to seeds or tubers, for example, might be a measure that enhances environmental biosafety. Inducible promoters have also been used to restrict expression of the foreign gene to particular physical or chemical environments. Examples include expression under the mechanical stress brought about by processing harvested leaves, or when the crop is brought into contact with chemicals such as ethanol, dexamethasone or other specific chemicals such as the insecticide methoxyfenozide.

The design of the gene constructs also determines how plant cells make the foreign protein, for example whether it enters the cytosol or the secretory pathway. The latter is generally preferable for high yields, owing to the presence of molecular chaperones, the relative absence of proteases and the ability to glycosylate proteins. A signal peptide attached to the protein will ensure its entry to the secretory pathway. Yield increases have been reported for some proteins if an appropriate tag for retention in the endoplasmic reticulum is included, rather than allowing secretion to the apoplast. Proteins can be targeted for secretion through the leaves or roots. The latter is particularly attractive as it lends itself to hydroponic culture, and proteins are easier to purify from culture medium than leaves.

Although plant derived proteins are functionally authentic, their glycosylation differs from those produced in mammalian cells. For some clinical applications, this might be problematic, as the carbohydrates associated with a protein can affect its activity, distribution and longevity. Concern has also been raised about human allergic responses to plant-specific glycans, although others point to the presence of these plant glycans in the human diet, the natural variability of glycan structures, the observation that carbohydrate epitopes are rarely allergenic and the absence of any clinical evidence in trials, to cast doubt on these fears. The main differences between glycosylation in plants and animals is that the former have β(1,2)xylose and α(1,3)fucose groups, while the latter usually have terminal galactose and sialic acid residues. Techniques to “humanise” the glycosylation of plants have been reviewed in ref (24). They include using purified human galactosyltransferase and sialyltransferase enzymes to modify proteins *in vitro* and expressing human galactosyltransferase in transgenic plants.

The main plant hosts used so far for recombinant proteins include tobacco, potato, tomato, lettuce, maize, rice and alfalfa. There is no single ideal crop and decisions need to be made on a case-by-case basis, assessing the protein target, local regulatory issues, and local agriculture.

As a non-food crop, tobacco enjoys a well-developed genetic technology, a high biomass yield, rapid scale-up because of its high seed production and an existing infrastructure for processing. A disadvantage is the presence of alkaloids in the leaves, which are also unstable and must either be processed locally, or dried or frozen for transport.

Where food crops are used as hosts, a key issue is the potential for inadvertent mixing with food streams. The advantages of crops such as maize or rice, however, include the ability to target the protein to the seeds, which are their natural, stable storage compartment. Seeds enable stable protein storage for extended periods of time at ambient temperatures, while their dry nature reduces protease activity and non-enzymatic hydrolysis. Fruits, vegetables and salad crops meanwhile offer the possibility of direct oral delivery of vaccines. Potatoes, tomatoes and lettuce have been investigated as candidate hosts, while bananas have the advantage of being grown most widely in parts of the world where the need for such medicines is greatest.

2.4.1.4 Other transgenic products

While the main focus of attention for transgenic plants are proteins, other targets include astaxanthin and PUFAs that occur naturally in marine algae, along with polyhydroxyalkanoates normally found in bacteria.

2.4.2 Cultivation Methods

The two main alternatives to open-field cultivation are contained cultivation and plant tissue cultures. Each is considered below.

2.4.2.1. Contained cultivation

This offers a means both to control the growing environment of the crops and, in the case of transgenic plants, to avoid the escape of foreign genes into the environment. The cannabis plants used to produce Sativex® provide an example of the former benefit, as they are cultivated in UK greenhouses providing a tightly-controlled environment. This includes high levels of supplementary lighting that largely smooths out seasonal variation in crop yields. Given the existing UK strengths in horticulture, this example may provide a model for other specialist crops grown in contained environments, either for climatic reasons or to ensure the control of quality or supply. If genetically modified plants are used to produce either secondary metabolites or proteins, contained cultivation may offer a viable alternative to either open-field cultivation or plant tissue cultures.

2.4.2.2 Plant Tissue Cultures

Plant tissues or cells may be cultured in fermenters to produce recombinant proteins or to produce secondary metabolites, either by de novo synthesis or by biotransformation. Compared to open-field or greenhouse cultivation, the potential advantages include avoiding variability in supply and quality, the ability to match production to demand and a reduced requirement for land.

Ref (25) reports the use of a tobacco cell culture to express several recombinant proteins. Ref (26) lists more than 90 cell cultures capable of producing secondary metabolites for medicinal use, of which some of the more important are:

- Taxol, the anticancer agent
- Morphine and Codeine, the well-known analgesics
- Ginsenosides, the bioactive agents of the *Panax ginseng* herbal medicine
- L-DOPA, a powerful drug for Parkinson’s disease
- Berberine, an antibacterial
- Diosgenin, a precursor for the chemical synthesis of steroidal drugs
- Camptothecin, an antitumor alkaloid
- Vinblastine and Vincristine, also antitumor alkaloids
- Tanshinones, a group of terpenoids believed to be active in the Chinese medicine Danshen
- Podophyllotoxin, an antitumor lignan

The technique has so far been employed commercially by Mitsui to produce shikonin, by Nitto Denko to produce ginseng and by Samyang Genex for Taxol.

2.4.3 Extraction Methods

Liquid or supercritical carbon dioxide has been used to extract natural products for 25 years (27), including both secondary metabolites and oils. Molecules can be extracted selectively and sequentially in such solvents by exploiting the temperature and pressure dependency of their solubility. The extracted product is relatively pure and suffers little degradation compared with conventional solvents, while the starting material is untainted by solvent residues.

Recent developments have extended the operational range of the solvents up to 1000 bar and 90°C. Future developments are likely to include systems that use supercritical carbon dioxide as both an extraction and reaction medium, combining these two processing steps into one. Pressuirised liquid hydrofluorocarbons are an alternative “tunable” solvent system that may also be developed for commercial use (28).

3. LONG-TERM VISION

This section describes the long-term vision in terms of potential business opportunities and the market and infrastructure requirements to support them.

3.1 Potential Business Opportunities

Roadmap contributors identified several components of the long-term vision, with one of the distinguishing factors being whether or not the crops are grown in the UK. This may determine the potential coupling between rural and urban economies and between the UK agricultural and manufacturing industries. They are:

- Produce chemicals from commodity crops the UK can grow well
- Produce specialist chemicals from specialist crops grown in the UK
- Produce low-volume, high value chemicals, especially pharmaceuticals
- Add value to imported platform chemicals
- Develop and exploit IPR worldwide, along with consulting, legal and financial services

They represent a spectrum of what the UK may be able to grow, make or create knowledge in well. They are seen not as mutually exclusive, but in some cases as inter-related. Each is now dealt with in turn.

- **Manufacture chemicals from commodity crops with high UK yields**

In this scenario, open-field commodity crops are grown in the UK and transformed into marketable chemicals. The crops identified as suitable for the UK climate include wheat, oil seeds and sugar beet. Commodity crops are seen as desirable as they can be replaced by imports in the event of crop failure, avoiding disruption to supply. Some question the reality of this threat, however, pointing out the rarity of crop failures in practice. If the commodity status is relaxed, economics nevertheless dictate that the requirement of high-yield be maintained.

This vision arguably represents the highest degree of inter-relationship between the agricultural and industrial sectors, with potential social and economic benefits. It has been suggested that the UK may have an advantage over much larger countries in that its centres of agriculture and industry are relatively close together, keeping transportation costs low.

- **Manufacture specialist chemicals from specialist crops grown in the UK**

Low-volume, specialist crops could be grown to produce specialist, high-value chemicals including pharmaceuticals or their precursors. The crops in this vision would be chosen less on the basis of what may be grown in the UK, than what is required for a specified product. Open-field cultivation would be possible if the crop suited the UK climate, while contained cultivation or plant tissue cultures are alternatives if they are financially viable. The latter two options may be preferred if genetic modification is required to produce the chemical in acceptable yields.

A high degree of integration between urban and rural economies would develop in this scenario, but possibly with the horticultural rather than the agricultural sector. The workshop suggested that the UK may have a competitive advantage in higher standards of crop traceability than others. This may be particularly valuable where genetic modification of crops is employed.

- **Produce low-volume, high value chemicals, especially pharmaceuticals**

This component of the vision recognises that the UK cannot compete in the bulk chemicals sector, where economies with either a plentiful supply of renewable feedstock or low labour costs are likely to dominate. Instead, the UK must focus on specialist, high value chemicals derived from renewable resources. A non-exhaustive list would include surfactants, cosmetics components, immobilisation materials and pharmaceuticals or their precursors, the latter building on an area of particular importance to the UK economy. All the workshop attendees shared this view. High-value chemicals could be produced either from commodity or specialist crops grown in the UK, or by the derivatisation of imported platform chemicals (see below).

- **Add value to imported platform chemicals**

While the UK may be unable to compete in the manufacture of platform chemicals, it may be able to import and add value to them. The final products may be medium-volume, such as detergents, coatings, plastics and fibres, or lower-volume specialist chemicals.

Some roadmap contributors voiced doubts, however, whether this scenario was viable. In their view, globalisation will mean that not only will the platform chemicals be produced in countries with low wage costs, but their derivatised products, too.

- **Develop and exploit IPR worldwide, along with consulting, legal and financial services**

This scenario is the most general, free of climatic constraints on UK crops, the economics of UK chemicals production, or even of UK strengths in pharmaceuticals. It envisages the UK supplying or licensing products, processes or services to the global renewable feedstocks industry, wherever its centres of operation may emerge. Examples include catalysts, reactors, separation systems or other process technologies, along with legal and financial services.

The scenario is an example of what is referred to as “the knowledge-based economy”. In addition to the UK strengths in catalysis and process engineering, those in the legal and financial industries are also likely to be exploitable, as IPR protection and venture capital will play a key role in the development of emerging science and technology.

3.2 Market and Infrastructure

Three areas of Government and Research Council policy were identified that could support these business opportunities. The first two already form part of the Action Plan in The Government’s Strategy for Non-food Crops and Uses (29).

- **Government procurement policy**

In addition to considering opportunities for biomass heating in offices, Government envisages two new actions:

- Consulting on adding materials derived from non-food crops to the Market Transformation Programme / Quick Wins list. This provides Government buyers with current and future minimum standards.

- The preparation of product datasheets for public procurement nationally and regionally

It is likely that these can be supplemented with further actions to stimulate markets for chemicals derived from non-food crops.

- **Co-ordinated national and regional policies**

While some areas of policy may best be implemented at a national level, and Regional Development Agencies may define policies to suit the idiosyncrasies of their regions, it was suggested that a co-ordinated approach to these two levels of policy-making would lead to best results. Government's Action Plan already contains four relevant actions:

- Commissioning sectoral analyses for 3-5 products with the potential for early development

- Aligning these analyses with Regional Economic Strategies to differentiate the competitive advantages of geographical regions

- The production of report by the Agricultural and Environment Biotechnology Commission (AEBC) on the role of biotechnology in non-food agriculture. Biofuels, biopharmaceuticals and biomaterials will be included as case studies

- Following this AEBC report, Defra and DTI will define a strategy to develop high-value products such as pharmaceuticals from crops

- **Co-ordinated Government and Research Council Funding**

The workshop also envisaged relatively few, large research programmes on UK priorities, combined with demonstration projects to develop robust supply chains. This implies co-ordination between Government and Research Council funding and is timely in view of the recent review of BBSRC research on crop science (30). It also resonates with the review, which perceived a lack of a coherent strategy for crop research, weakened by fragmentation of funding. While the £65m annual expenditure covers food and non-food use, the main elements relevant to this roadmap are as follows:

- A recommendation that BBSRC should develop a research strategy for non-food uses of crops that fosters a flexible science base for current and future needs

- Likely changes in demands, including more non-food use of crops and a need for flexibility in exploiting genomics, proteomics and metabolomics for both transgenic and non-transgenic approaches, depending on societal acceptability

- The proposed development of accelerated breeding strategies informed by genetic and genomic information

- A target of broadening the range and number of crops, including novel crops and products for bioenergy, biopharmaceuticals and biopolymers

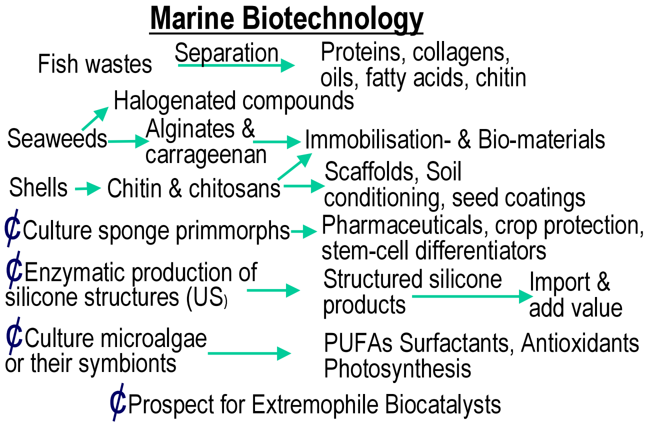
- The creation of a high-level steering group to oversee the implementation and co-ordination of targets and priorities for crop science research

- The appointment of 3 crop co-ordinators, including one for non-food uses of crops

4. FUTURE

This section considers how the state of the art described in section 2 might be developed into the long-term vision proposed in section 3. It does so in 6 technical sub-sections, each devoted to a future theme as depicted on the roadmap, followed by a section concerned with the infrastructure requirements needed to support them. As depicted on the roadmap and described in the text that follows, these sections are strongly inter-related.

4.1 Marine Biotechnology



The terrestrial and marine environments have so far been investigated and exploited by different communities and the latter is sometimes overlooked as a source of feedstocks, novel catalysts and bioactives. Yet the deep sea may account for more than 60% of bacterial biomass on earth and 10% of global biomass. The Marine Biotechnology Group of the Foresight Marine Panel has recently published a report on the prospects for marine biotechnology in the UK (31). A future theme will be to exploit marine biotechnology more fully and, as a contribution to this process, observations are offered below on how some of this may be undertaken within the framework of terrestrial renewables.

The marine environment can be viewed as yielding 3 of the 4 types of feedstock identified at the beginning of section 2, with only ligno-cellulosic feedstocks being absent. The main feedstocks and their products are as follows.

Waste	Fish Waste	Proteins, oils, fatty acids, chitin
Commodity Crops	Seaweed and Shells	Immobilisation and bio-materials, scaffolds and soil conditioners
Specialist Crops	Cultures of marine organisms or their genes	Polyunsaturated fatty acids, surfactants and antioxidants

In addition, the sea might provide some of the catalysts to transform feedstocks into products, renewable or not. Each area is considered below.

4.1.1 Fish Wastes

Fish wastes are relatively well-separated and high-value, with proteins, oils, fatty acids and chitin among its components. While these could be broken down by anaerobic digestion into low-value syngas, the recent development of multi-stage digesters may make it feasible to derive higher-value components. In particular, as the first stage is hydrolysis into monomers, carbon dioxide and hydrogen, it may be possible to recover the monomers, rather than convert them into acetate and subsequently methane.

As noted in sections 2.1.1 and 3 respectively, Europe has a lead in anaerobic digestion of municipal waste, while the US NREL does not see this as current priority. The topic may therefore represent a niche opportunity for the UK to exploit.

4.1.2 Commodity Crops: Seaweeds and Shells

Seaweeds are a source of alginates, agarose and carrageenan used as immobilisation materials for catalysts or active molecules, and as biomaterials.

Alginate is a polysaccharide composed of D-mannuronate (M) and L-guluronate (G). The G and M residues occur in homopolymeric blocks such as GGG or MMMM, or in heteropolymeric blocks GMGMGM, but without regular repeating units. The sequential arrangement and G:M ratio vary widely and determine functional properties. Alginates can be gelled by divalent cations such as Ca^{2+}, although the loss of the cation into the surrounding fluid causes unpredictable dissolution and represents a limitation on use. It can, however, be covalently cross-linked using bifunctional molecules such as methyl ester L-lysine and polyethylene glycol. Alginate may be modified with lectin or arginine-glycine-aspartic acid sequences to promote cell adhesion and, when used in capsules, may be coated with a polyamino acid such as poly-L-lysine or poly-L-ornithine to produce selective permeability.

Agarose gels are relatively porous and stable mechanically and form thermally reversible gels. They are also resistant to microbial attack as the agarase enzymes that attack them are found only in microorganisms on seaweed. While agarose can be used to entrap catalysts or active compounds, cross-linking with agents such as epichlorohydrin is required to allow heat-sterilisation and to avoid dissolution in alkaline and organic solvents. Mainly used for capsules, it can also form scaffolds for chondrocytes in cartilage repair.

Chitin and chitosan have structures similar to cellulose, but with each C2 OH group replaced by acetamide or amine functions respectively. Chitin is the primary structural component of many invertebrate exoskeletons and chitosan is obtained from it by deacylation in concentrated NaOH solution. Carbonyl derivatives on either are obtainable by treatment with glutaraldehyde and enable covalent bonding to enzymes. Chitosan forms hydrogels by ionic interactions (50) or chemical cross-linking with glutaraldehyde (51). It has been combined with collagen to produce capsules, while its degradation by surface enzymatic action means it can be used as a scaffold, after mechanical strengthening by calcium phosphate.

While the UK is unlikely to be able to compete with warmer climates for culturing and drying seaweed, catalyst immobilisation, controlled release of active agents and biomaterials are all growth areas of importance to the economy. The UK should therefore focus on importing and adding value to marine crops for these purposes.

4.1.3 Specialist Crops: Cultures of Marine Organisms or Genes

Like their terrestrial cousins, microalgal plants are sources of polyunsaturated fatty acids (PUFAs), surfactants and antioxidants such as astaxanthin. Microalgae can either be cultured in a fermenter or the responsible genes transferred to other organisms, including bacteria or terrestrial plant cells. Sponges can also be cultured to produce bioactive compounds. While complete sponges are being grown in the warm waters of the Mediterranean, the Dutch University of Wageningen is culturing clusters of cells - sponge primmorphs – for this purpose. These products are low-volume and high value, mirroring their terrestrial counterparts identified as priorities for the UK. Terrestrial PUFAs and surfactants are derived from oil seeds, while antioxidants and bioactives are plant secondary metabolites (see sections 2.4.1.1, 2.4.1.2 and 4.2). The priority status should apply to marine molecules, too.

As noted in section 2.1.1, photosynthetic microalgae and cyanobacteria can be induced to reduce water to hydrogen rather than carbon dioxide to carbohydrate. Significant scientific and technological barriers exist, however, and the subject is likely to remain at the research stage for some time. Commercial exploitation also depends on how the energy economy develops, and whether molecular hydrogen will be used as a fuel or whether hydrogen carriers such as ethanol or methanol will be preferred.

Marine organisms producing silicon structures are being exploited by a US joint venture between Dow Corning and Genencor. In the short term, potential uses include products for personal care, cleaning and fabric care. Longer term, the returns on the investment may be substantial, with possible applications for nano-structured silica including biosensors, electronics, diagnostics and controlled delivery of active agents. For the UK, the commercial opportunity may be to import these products and add value to them.

4.1.4 Marine Biocatalysts

Many of the biocatalysts found in the marine environment are extremophile, operating at unusual temperatures, pressures or salinity. Very high pressures are encountered at deep-sea vents, for example, where temperature gradients can be 2°C to more than 360°C over a few metres. Yet it is estimated that between 500,000 to 5 million species of marine organism remain to be discovered. Prospecting the marine environment for industrially useful biocatalysts is part of the remit of the NERC Marine & Freshwater Microbial Biodiversity (M&FMB) programme (32). Their use falls within the scope of the FIRST Faraday Partnership on bioremediation (33) and the Pro-Bio Faraday Partnership on industrial biocatalysis (34). The latter now has two members with libraries of marine biocatalysts and will continue to promote their use in industry.

The prospects report (31) identifies the development of novel bioreactors for extremophile microorganisms as an area that could be exploited in the UK. An alternative approach is to incorporate the genes of interest in organisms operating under more ambient conditions.

4.2 Waste Processing

The continuing pressure in Europe to process waste rather than dispose of it through landfill or other routes means this is likely to be a future growth area. It could be argued that the more stringent European environmental legislation compared with the US provides an opportunity for its industry to create a lead in the field, and that seems to be the case for anaerobic digestion of municipal solid waste.

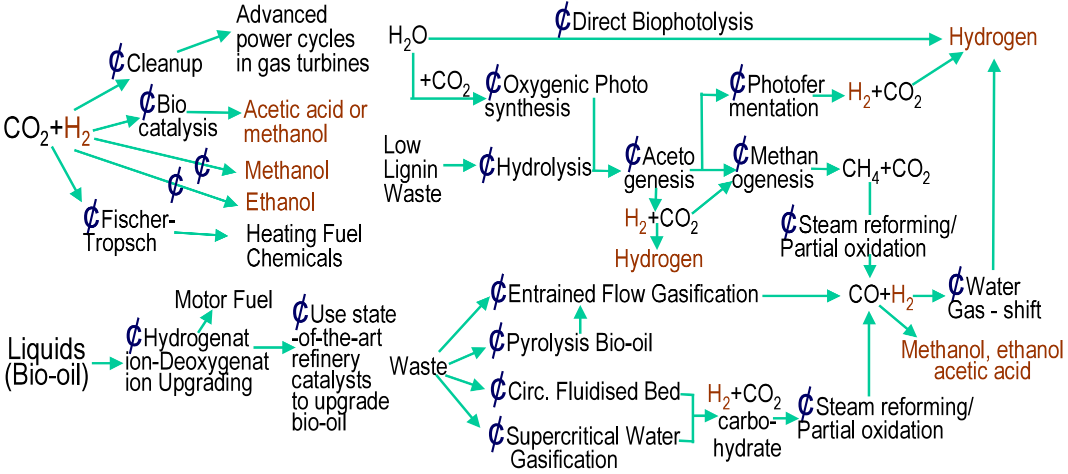
Before use as a fuel, gas from anaerobic digesters must have unwanted or corrosive gaseous components removed, including hydrogen sulphide, carbon dioxide, halogenated hydrocarbons and siloxanes. Gasification also produces undesirable emissions and by-products such as particulates, alkali and heavy metals, oils, tars and aqueous condensates. Hot gas cleanup with specialised filtration and catalytic systems is a US research priority (35), as this enables use in advanced gas turbine power cycles without cooling, yielding higher thermodynamic efficiencies. Other research needs include determining the effect of additives, including catalysts, to minimise tar production; and the use of materials to capture contaminants.

Pyrolysis reactions exhibit, with few exceptions, poor product selectivities and the liquids are a complex mixture of compounds that are highly oxygenated, acidic and unstable. While the charcoals can be separated off easily, the gases are a low-energy mixture. In most cases, complex separations and further product refining is required to produce pure chemicals. The high oxygen content and acidity of liquids also limits their use as fuels to heating oils. Recent work has focussed on catalytic hydrogenation and deoxygenation to “upgrade” the liquids into hydrocarbons for use as motor fuels (35). The catalytic effects in pyrolysis that may require further study include:

- the use of state-of-the-art refinery catalysts to upgrade liquids for use as motor fuels. Zeolites such as ZMS-5, for example, reduce the amount of oxygenated compounds and increase the amount of aromatics and polycyclics
- the catalytic effects of metals contained in the biomass
- the increase in methanol yield brought about by acidic and basic catalysts
- the reduction in tar formation by nickel catalysts
- catalytic steam reforming of syn gas or liquid bio-oil by nickel catalysts (36)

Gas derived from waste could also be used, however, as a source of renewable chemicals. Methanol is currently produced from syn gas derived from natural gas, naptha or refinery light gas. While some is used directly, most is converted into higher value chemicals such as formaldehyde, methyl tertiary butyl ester and acetic acid (37). A sustained rise in natural gas prices may lead to methanol production from biologically-derived gas. Ethanol can also be produced from syn gas, making this route an alternative to that of sugars fermentation and US research is underway (6)

Waste Processing & Energy Economy



Another approach to producing chemicals and fuel from syn gas is Fischer-Tropsch chemistry. This uses either cobalt catalysts in fixed beds or iron in fixed or fluidised beds at high temperature and pressure to produce paraffins, monoolefins, aromatics, alcohols, aldehydes, ketones and fatty acids. Yield, selectivity and product composition depend on the catalyst and the reactor type and conditions. The main problem is heat removal from a highly exothermic reaction. Molecules containing between 1 and 35 carbons are produced and the lighter hydrocarbons can be used to produce hydrogen that is later used to refine the heavier ones. An alternative future use for the hydrogen is as a transportation fuel.

Syngas can also be converted biocatalytically to acetic acid or methanol. US research work is underway (38), the latter route involving enzymes supported in sol-gel (39).

4.3 Developments in the Energy Economy

As noted in a previous roadmap (2), petrochemicals are an adjunct to the Refining, Energy and Transport cluster. Non-specialist renewable chemicals will also depend on the energy economy, in terms of their competitiveness against fossil rivals. They will also be influenced by the renewable fuels that emerge and either become available as or give rise to platform chemicals. While chemicals are the focus of this roadmap, it is therefore necessary to consider candidate renewable fuels, including methanol, ethanol, hydrogen and biodiesel. European growth in such fuels is likely, as the EU Biofuels Directive requires Member States to set indicative targets for their use. As discussed in section 4.7, developments in the field require constant monitoring and their impact evaluating.

4.3.1 Methanol and Ethanol

Methanol is produced by passing syngas at 200 bar over a catalyst of copper, zinc and chromium oxides at 300°C, or by passing a methane:oxygen mixture at 100 bar through a copper tube at 200°C. Currently, the syngas is derived from natural gas by steam reforming, and the methane also sourced petrochemically. Biological syngas from thermal gasification could be used, however, as could methane from anaerobic digestion, while pyrolysing wood is the direct and original renewable method of production. As a vehicle fuel, methanol enjoys lower emissions, higher performance and lower flammability than petrol, but produces high concentrations of formaldehyde. It may, however, have an automotive future through use as a hydrogen carrier for fuel cells.

As noted above, ethanol can be produced from renewable feedstocks either by the fermentation of sugars or by the catalytic conversion of syngas. For fuel use it can be blended with petrol, where it is a safe replacement for toxic octane enhancers such as benzene, toluene, xylene and methyl tertiary butyl ether (MTBE). It is in widespread use in Brazil, while a blend of 10% ethanol to 90% petrol is mandatory in some parts of the US, as individual states ban MTBE. Higher blend ratios, such as 85% ethanol or above, are being promoted under the 1992 US Energy Policy Act (40). In the UK, a 20p/litre reduction in excise duty has been introduced for bioethanol since 1st January 2005, matching a similar reduction for biodiesel. Ethanol is also a potential hydrogen carrier for fuel cells.

It therefore seems likely that methanol and ethanol will emerge as renewable platform chemicals. The useful derivatives of methanol include acetic acid, produced by reaction with CO using a cobalt octacarbonyl catalyst at 210°C, alkanes, using HZSM-5 catalysts, higher alcohols (through reaction with syngas), acrylic acid and formaldehyde. Those of ethanol include ethene, acetaldehyde and acetic acid, each with a plethora of derivatives (35). Likely future catalytic developments related to ethanol include:

- Combined hydrolysis and fermentation of polysaccharides in a single yeast
- The use of thermophilic yeasts to enable reaction at a higher temperature
- On-board reforming catalysts to produce hydrogen for fuel cells, such as Ni/La_2O_3 and Ru/Al_2O_3 at > 750°C

While both alcohols are likely to witness

- The continuing developments of catalysts to derivatise them as platform chemicals

4.3.2 Hydrogen

Future biological methods of hydrogen production were described in section 2.1.1. In addition to these, ref (5) considers the potential of 4 innovative thermal gasification methods to Dutch energy requirements for the 2020-2050 timeframe:

- **Entrained Flow Gasification of Biomass**

High superficial velocities and hence short residence times are combined with high temperatures and small particle sizes to eliminate hydrocarbon production. Hydrogen results from use of the water gas shift reaction and carbon dioxide removal. The technology is already mature for use with petroleum residues and has been demonstrated with coal. The only technical drawbacks are the initial size reduction of the feedstock to below 1mm and the residual ash that remains as an impurity to be removed.

- **Entrained Flow Gasification of Pyrolysis Oil**

The drawbacks of size reduction and ash removal inherent in the above technique can be avoided by first pyrolysing the biomass at 450-550°C to oil. The main drawbacks are the lower efficiency that results and the need to avoid polymerisation of the oil at high temperatures.

- **Circulating Fluidised Bed Gasification**

A variety of circulating fluidised bed systems are under development, all using lower temperatures than entrained flow gasification. The result is less complete production of syn gas, with tars and some C_1-C_4 hydrocarbons produced. Steam reforming or partial oxidation is therefore required before the water gas shift reaction is deployed.

- **Supercritical Water Gasification**

Supercritical water at 500-700°C and 200-400bar is capable of gasifying biomass at high efficiency, even if wet or toxic. Significant quantities of CO_2 and CH_4 are, however, produced, the latter requiring steam reforming or partial oxidation for conversion to CO_2 and H_2. Water gas shift is once again used to convert CO to CO_2 and H_2. The technology is relatively new, and thought likely to be available commercially by 2020.

The report considered 5 applications and, while all would use fossil hydrogen sources, renewable methods are also envisaged:

Micro Combined Heat and Power: The local production of hydrogen for Proton Exchange Membrane Fuel Cells is envisaged by 2020 for combined heat and power to about 1000 houses. Single- and multi-stage anaerobic digestion are seen as viable technologies in this timeframe, coupled to steam reforming of the resulting methane.

Blending Hydrogen with Natural Gas: A blend of natural gas and hydrogen in the national distribution network would reduce carbon dioxide emissions significantly. It, too, would be viable by 2020 and served by single- and multi-stage anaerobic digestion.

Pipeline Distribution: The large-scale production of hydrogen for distribution to micro combined heat and power systems is more efficient than local production, but is unlikely to be viable until after 2020. Supercritical water gasification is the preferred renewable technology, exploiting its ability to process wet feedstocks at high thermal efficiency.

Locally-supplied Refuelling Stations: Hydrogen as an automotive fuel might be produced local to the refuelling station by 2020, using supercritical water gasification.

Nationally-supplied Refuelling Stations: As the locally-supplied refuelling stations become interconnected, large-scale hydrogen production becomes possible. The higher efficiencies of entrained flow gasification would then be exploited, probably in the 2020 to 2050 timeframe.

4.3.3 Biodiesel

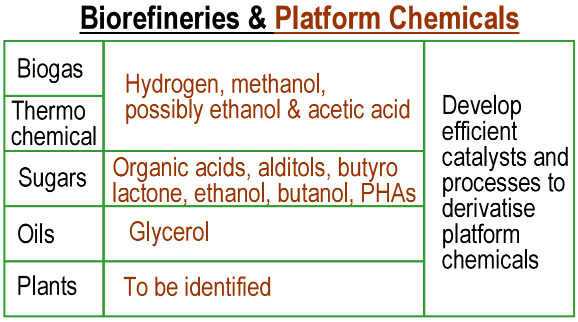
The 20p/litre reduction in excise duty on biodiesel introduced in 2002 has stimulated annual sales of about 24 million litres (29). While most is currently either the result of imports, or produced from waste cooking oil, more may in future be produced from oil seed crops (section 4.5). The transesterification of oils produces glycerol as a by-product, which seems set to become a major renewable platform chemical.

4.4 Biorefineries and Platform Chemicals

A biorefinery may be defined as a system that produces a multitude of products from a biomass feedstock. By analogy with an oil refinery, it is generally envisaged that one of the products would be transportation fuel, in addition to chemicals. It is conceivable, however, that a low-volume, specialist biorefinery, such as one based on specialist crops, would focus exclusively on high-value chemicals. The technology required depends on the type of feedstock used and the US Biomass Program (41) recognises five such technology "platforms":

- Sugar Platform
- Thermochemical Platform
- Biogas Platform
- Carbon-rich Chains Platform (i.e. Oils Platform), and
- Plant Products Platform

In terms of the roadmap presented here, the first of these maps into cellulose, hemicellulose and starch, while the second and third relate to waste feedstocks. The "Carbon-rich chains" platform refers to vegetable oils, while the Plants products platform maps into the specialist crops feedstock.

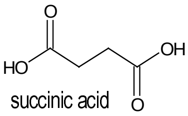
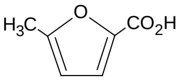
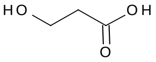
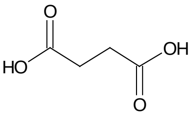
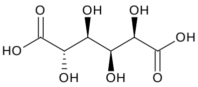


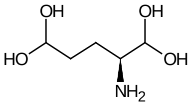
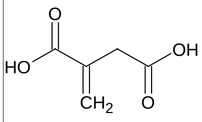
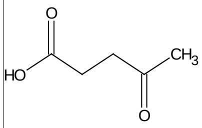
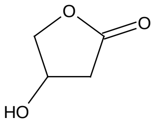
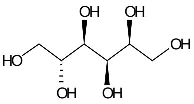
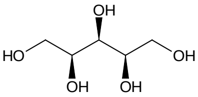
Biorefineries & Platform Chemicals

Biogas	Hydrogen, methanol, possibly ethanol & acetic acid	Develop efficient catalysts and processes to derivatise platform chemicals
Thermo chemical		
Sugars	Organic acids, alditols, butyro lactone, ethanol, butanol, PHAs	
Oils	Glycerol	
Plants	To be identified	

The biorefinery concept envisages these technology platforms producing a small number of "platform chemicals" defined as those having multiple functional groups and the potential to be transformed into new families of useful molecules. This, too, is analogous with petrochemicals, in which all products are derived from the commodity chemicals benzene, xylene, toluene, butane, ethane, ethene, propene, chlorine, carbon monoxide, hydrogen and sulphuric acid. As with petrochemicals, a considerable amount of science and engineering will be required to convert platform chemicals into intermediate chemicals and finished products.

The stated priorities of the US Programme are the first two platforms listed, sugar and thermochemical, and the recent report (42) considers the platform chemicals that could be derived from them. The report envisages sister versions being produced in due course to consider candidate platform chemicals derived from lignin and oils. The report identified just 2 platform chemicals from syngas, hydrogen and methanol, reasoning that other alcohols, aldehydes and Fischer-Tropsch liquids from biomass were uneconomic at present. It meanwhile identified 11 platform chemicals from sugars and the barriers to their production and derivatisation are summarised below:

Platform Chemical	Pathway	Barriers
Four-carbon 1,4-Diacids (Succinic, Fumaric, Maleic)  succinic acid	**Production by:** fermentation using Krebs cycle pathways	• Microbial biocatalysts to - reduce acetic acid coproducts - increase yields and productivities • Inexpensive recovery process to reduce unwanted salts • Improved scale-up and system integration
	Reduction to: butanediol, tetrahydrofuran, γ-butyrolactone	• Selective reductions to alcohols, lactones and furans • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Reductive Amination to: pyrrolidinone family	• Selective reductions of acid salts • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Direct Polymerisation to: straight-chain polymers branched polymers	• Commercial polymer processes • Selective esterifications to control branching • Control of molecular weight & properties
2,5-Furan dicarboxylic acid 	**Production by:** oxidative dehydration of C6 sugars enzymatic conversions? →	• Selective dehydration without side reaction • Dehydration steps to anhydrides or lactones • Solid acid catalysts to replace liquid catalysts • Oxidation of alcohols to acids • Avoiding exotic oxidants in favour of air, oxygen & hydrogen peroxide • Tolerance to inhibitory components of biomass processing • Oxidation of aldehydes to acids and alcohols to aldehydes • unknown
	Reduction to: diols and aminations; levulinic and succinic acids	• Selective reduction of acids in presence of alkenes • Direct reduction of carboxylic acids to alcohols • Knowledge of properties of polymer derivatives • Selective catalytic tools
	Direct Polymerisation to: polyethylene terepthalate analogues & furanoic polyamines	• Reactivity of monomer • Controlling polymerisation rates • Selective esterification to control branching • Control of molecular weight and properties
3-Hydroxy propionic acid 	**Production by:** unknown industrial fermentation	• Microbial biocatalysts to - reduce other acid coproducts - increase yields and productivities • Inexpensive recovery process to reduce unwanted salts • Improved scale-up and system integration
	Reduction to: 1,3 propane diol	• Selective direct reduction of carboxylic acids • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Dehydration to: acrylate family	• Selective dehydration without side reactions • Solid acid catalyst with high selectivity to replace liquid catalyst
Aspartic acid 	**Production by:** - Lyase amination of fumaric acid Direct fermentation of sugars	• Cost of fumaric acid • Metabolic engineering without compromising viability of organism
	Reduction to: amine butanediol, amine tetra hydrofuran, amine γ-butyrolactone	Analogous to reduction of 4-carbon 1,4 diacids: • Selective reductions to alcohols, lactones and furans • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Dehydration to: aspartic anhydride	• Selective dehydration without side reactions • Solid acid catalyst to replace liquid catalyst
	Direct Polymerisation to: polyaspartic	• Selective esterification to control branching • Control of molecular weight and properties
Glucaric acid 	**Production by:** - oxidation of glucose	• Avoiding exotic oxidants in favour of air, oxygen & hydrogen peroxide • Tolerance to inhibitory components of biomass processing • Lowering oxidant concentration • Development of heterogeneous catalyst
	Dehydration to: Lactones	• Selective dehydration without side reactions • Solid acid catalyst to replace liquid catalyst
	Direct Polymerisation to: polyglucaric esters & amides	• Controlling polymerisation rates • Selective esterification to control branching • Control of molecular weight and properties

Glutamic acid 	**Production by:** - fermentation of sugars	• Microbial biocatalysts to - reduce other acid coproducts - increase yields and productivities • Inexpensive recovery process to reduce unwanted salts • Improved scale-up and system integration
	Reduction to: glutaminol, glutaric acid, 1,5 pentane diol, 5-amino-1-butanol	• Selective deamination, reduction and reductive deamination • Development of catalysts unaffected by fermentation impurities
Itaconic acid 	**Production by:** - multistep chemical synthesis fungal fermentation of sugars	• Costly chemical synthesis; fewer steps required • Biocatalysts to - reduce other acid coproducts - increase yields and productivities • Inexpensive recovery process • Improved scale-up and system integration
	Reduction to: methyl butanediol, butyrolactone, tetrahydrofurans, pyrollidinones	• Selective reductions of specific functionalities • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Direct Polymerisation to: polyitaconic	• Controlling polymerisation rates • Selective esterification to control branching • Control of molecular weight and properties
Levulinic acid 	**Production by:** - one step acid decomposition and catalysed dehydration of lignocellulosic biomass	• Selective dehydration without side reactions • Solid acid catalysts to replace liquid catalysts
	Reduction to: methyl tetrahydrofuran, γ-butyrolactone	• Selective reductions • Operation at mild temperature and pressure • Catalyst tolerance to inhibitory compounds and catalyst lifetime
	Oxidation to: β-acetylacrylic acid, derived to δ-amino levulinic acid	• Selective oxidation • Avoiding exotic oxidants in favour of air, oxygen & hydrogen peroxide • Tolerance to inhibitory components of biomass processing • Lowering oxidant concentration • Enzymatic oxidation requires cofactors
	Condensation to: diphenolic acid & subsequent polymerisation	• Controlling polymerisation rates • Control of molecular weight and properties
3-hydroxy butyrolactone 	**Production by:** possible fermentation to malic acid and thence to 3HB	• Low cost fermentation routes
	Reduction to: furans	• Selective reduction at low temperature and pressure
	Dehydration to: γ-butenyl lactone	•
	Esterfication to: acrylate lactone	•
Sorbitol 	**Production by:** hydrogenation of glucose	• Few problems – 99.7% yield
	Dehydration to: isosorbide, anhydrosugars	• Selective dehydrations without side reactions • Solid acid catalysts to replace liquid catalysts
	Bond cleavage to: propylene glycol, lactic acid	• Specificity for C-C C-O bonds • Increasing rates • Tolerance to catalyst poisons form biomass sugar streams
	Direct Polymerisation to: branched polysaccharides	• Selective esterification to control branching • Control of molecular weight and properties
Xylitol/arabinotol  arabinotol	**Production by:** hydrogenation of pentoses	• Few problems
	Oxidation to: xylaric acid	• Selective oxidation at high yield • Use of oxygen rather than nitric or peracetic acid
	Bond cleavage to: propylene glycol, lactic acid	• Specificity for C-C C-O bonds • Increasing rates • Tolerance to catalyst poisons form biomass sugar streams
	Direct Polymerisation to: polyesters	• Controlling polymerisation rates • Selective esterification to control branching • Control of molecular weight and properties

The earlier report (6) also identified 2 other platform chemicals

- **Butanol**, a high volume chemical with uses as a solvent, plasticiser and precursor to amino resins and butylamines. It can also be used as a transportation fuel that is more efficient than ethanol on a volume basis. While glucose fermentation was used in its production a century ago, this was superseded by the lower-cost hydrogenation of fossil-derived n-butyraldehyde. Research is underway to re-introduce the glucose fermentation route by developing improved bacteria and reactor technology.

- **Polyhydroxyalkanoates** (PHAs) are a family of natural polymers produced by many bacteria for carbon and energy storage. Their versatility and performance means they could capture a large share of the plastics market if produced at a competitive price. This approach was followed by ICI, Zeneca and Monsanto under the trade name Biopol in the 1990s, but the then fermentation and separation technology could not produce a competitive product. Metabolix later developed a lower-cost fermentation method for PHAs and launched its first product in 2002. An alternative route via the genetic modification of plants is also being developed by Metabolix and Monsanto.

For the UK, the US prioritisation of biorefinery platforms and identification of likely platform chemicals raises several issues:

- The extent to which limited UK resources should be channelled towards competition with, collaboration with or the supply of niche technologies to US priorities

- Whether UK efforts would be more profitably directed at one or more of the other platforms: biogas, oils and plants

- Whether it is commercially feasible for platform chemicals to be imported into the UK and value added to them by derivatisation, or whether this activity will be undertaken in the country of their production, or in countries with low wage costs

Whatever the answers to these questions, it seems likely that the UK could produce and exploit IPR related to the derivatisation of platform chemicals. It is therefore worthwhile evaluating which chemicals are likely to emerge as platform and which catalytic processes are required to derivatise them. So far as the sugar platform chemicals identified by the US report are concerned, it is recommended that:

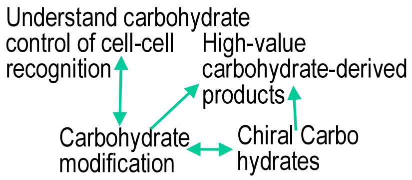
- The UK should hold a workshop to review the report and identify those areas in which UK industry and academia could profitably contribute. It is recommended that hand-picked specialists in the field be invited, including the 2 main US authors.

In addition to these platform chemicals, sugars might also be derivatised into high-value carbohydrate products. The importance of glycosylating recombinant proteins has already been noted in section 2.4.1.3, while the biochemical importance of glycoproteins, glycolipids and oligosaccharides is described in ref 52. These include:

- the modulation of growth factors
- the peptidoglycans in bacterial cell walls, whose synthesis is inhibited by antibiotics
- the polysaccharide O-antigens on the outer walls of gram-negative bacteria
- the glycoprotein mucins that form part of protective and lubricative mucus
- the glycoproteins and glycolipids that form the protective glycocalyx coating around eukaryotic cells

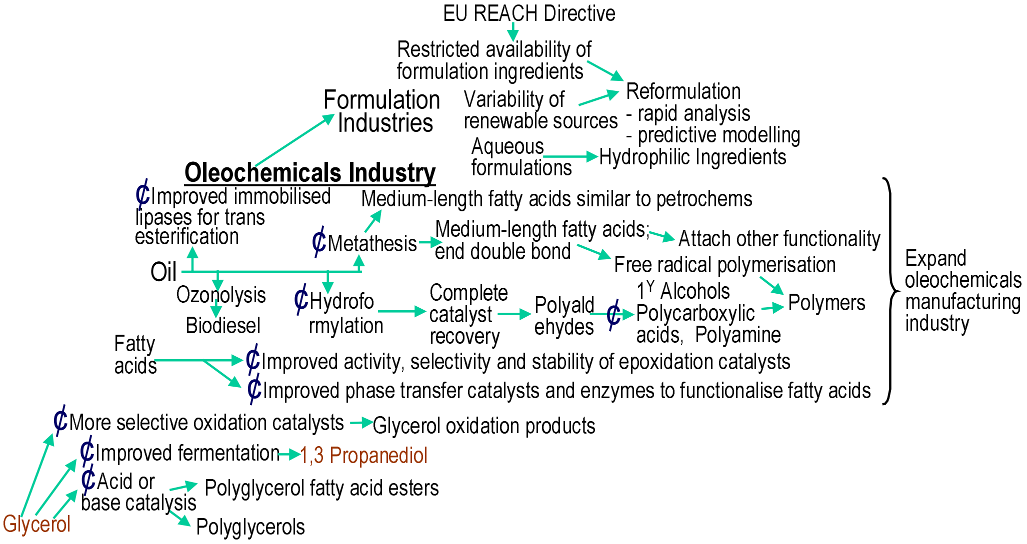
- roles in a range of cell-cell interactions including contact inhibition of non-cancerous cells, fertilisation, cellular differentiation and aggregation to form organs and bacterial or viral infection mechanisms

A workshop suggestion was that as these cell-cell interactions are understood further, a market will develop in high-value carbohydrates to mediate them. Pharmaceuticals are one example of chiral products that might be derived from sugars, the others including their delivery systems, membranes, liquid crystals and biosensors (53). The UK strengths in pharmaceuticals and chiral chemistry suggest that these possibilities should be examined further.



4.5 Oleochemicals Industry

The workshop suggested that the UK has particular strengths in oil seed crops and that oleochemicals might therefore represent a priority for development. As noted in sections 2.3.2 and 2.4.1.1, oils can be transformed into medium-value products such as surfactants, polymers, lubricants and solvents, or into high-value healthcare products. Section 4.2 noted that marine organisms are also a potential source of polyunsaturated fatty acids and surfactants. It was also suggested in section 4.3 that the area might be linked with another UK strength, pharmaceuticals, by acting as a source of O- and N-heterocycles. Some of the development tasks in Chemistry required to implement this vision are as follows.

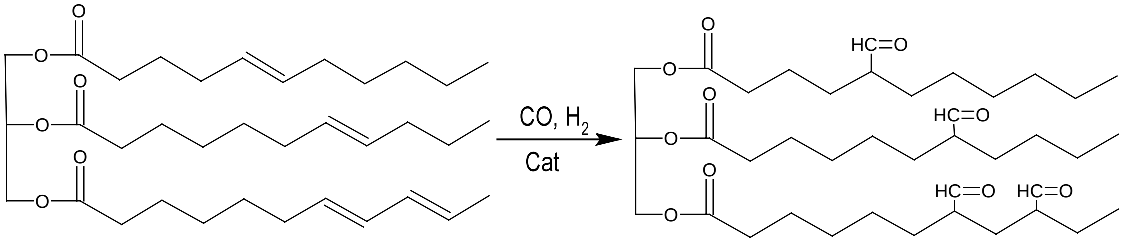


- **Improved Immobilised Lipases for Transesterification**

As hydrolysis of oils to fatty acids or transesterification to fatty acid alkyl esters is often the first step in oleochemistry, improved catalysts for this step would clearly be desirable. As reported in a review paper (13), lipases are under development for this purpose, but their activities and yields are uncompetitive with base-catalysed systems. Immobilised enzymes are desirable to enable their recovery and re-use, along with use of continuous-flow reactors.

- **Recoverable Hydroformylation Catalysts**

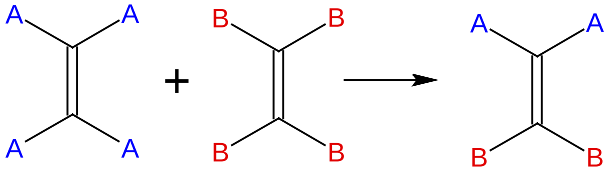
Hydroformylation adds the CHO formyl group to an alkene double bond, generally as a preliminary to further derivatisation steps. These include a reduction to primary alcohols, which are more reactive than the secondary alcohols produced via epoxidation and so allow new chemistry to produce new polymers. Alternatively, oxidation to polycarboxylic acids or amination to polyamines might also lead to new polymers.



When applied to petrochemical alkenes, hydroformylation yields volatile products that can be separated from the catalyst by distillation. The non-volatile nature of vegetable oils, however, precludes distillation and an alternative separation method is required to recover the expensive Rhodium or Cobalt catalysts used. As reported in (6), the US Department of Energy has commissioned research to achieve this objective (43).

- **Metathesis Catalysts**

Metathesis reactions re-arrange the groups on either side of an alkene double bond and so could be applied to unsaturated fatty acids. Of those depicted, if either the A or B group is long and the other short, the product will be a medium-length one of the sort required in lubricants. If either A or B is Hydrogen, the product has a terminal double bond and could participate in free-radical polymerisation reactions or be derivatised with other functional groups.



- **Improved Epoxidation and Phase Transfer Catalysts**

As epoxidation of oils or fatty acids is often the first step in more complex elaboration, there is a continuing need for more active, selective and stable catalysts to mediate the reaction. Improved catalysts to functionalise fatty acids are also a continuing need, and phase transfer catalysts are attractive where they mediate a reaction between a hydrophilic reagent and the hydrophobic fatty acid.

- **Glycerol Catalysis**

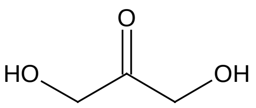
Glycerol is a by-product of the hydrolysis or transesterification of plant oils and a glut may result from the growth of these processes. Increased biodiesel production is thought to be the likeliest example. Fortunately, the presence of a hydroxyl group on each of the 3 carbons means that the molecule can be derivatised to more than 1500 useful known derivatives, making glycerol a prime example of a likely platform chemical (see section 4.4). Improved catalysts to mediate these reactions are therefore likely to be a continuing need. Some of the more important products and their catalysis needs are as follows:

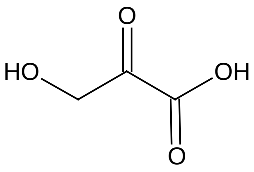
    - Polyglycerols: used in personal care products or drilling or cutting fluids, these can be produced by sulphuric acid or base catalysed oligomerisation

- Polyglycerol fatty acid esters: acid or base catalysis leads to products with a wide variety of uses

- 1,3 Propanediol (see section 2.2.3.1), produced by a fermentation process requiring improvements

- Glycerol oxidation products such as dihydroxyacetone or hydroxypyruvic acid, requiring improved oxidation catalysts





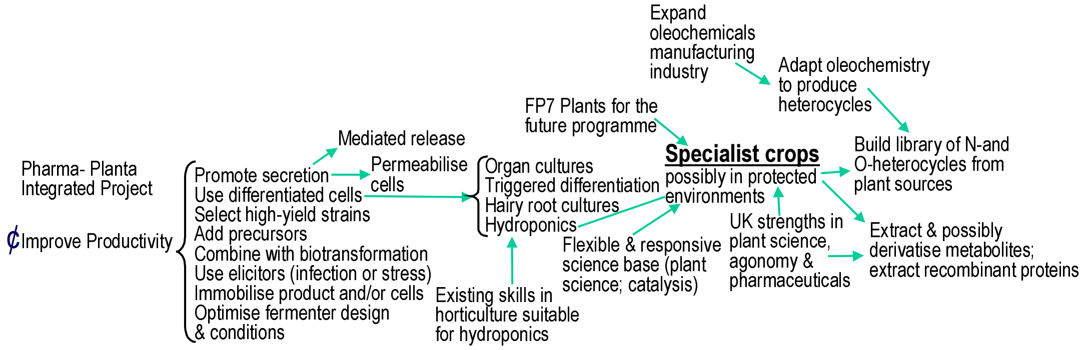
- **Reformulation Tools**

One of the main customers for surfactants are the “formulation industries” who produce colloidal products such as detergents, coatings and personal care products. The EU REACH directive may restrict the availability of formulation ingredients as their registration under the legislation will be uneconomic. This, coupled with the emergence of renewable alternatives, may lead to a significant amount of reformulation being required. Predictive modelling tools and rapid analysis techniques may need to be developed for this purpose.

4.6 Specialist Crops

As noted in section 2.4, specialist crops might produce oil seeds, secondary metabolites or recombinant proteins. Three cultivation methods are available: open-field, contained cultivation and plant tissue cultures. Of the business opportunities discussed in section 3.1, the production of high-value chemicals, especially pharmaceuticals, is most relevant. A workshop suggestion was that effort should focus on the production of low-volume, pharmaceutical platform chemicals and, as noted in section 2.4.1.2, this would mimic the practice of plants in their production of secondary metabolites.

One of the workshop suggestions was that attention should be given to the production of O- and N-heterocycles from plants, owing to the importance of such molecules in medicinal chemistry. One of the feedstocks that might be used is specialist oil seeds.



While some plant oils or fatty acids are already used in healthcare applications, it was suggested that oleochemistry might be developed to produce heterocycles from such molecules, for example by epoxidation and ring opening. It may be possible to use existing or new, traditionally-bred varieties for this purpose, or genetic modification may be desirable to achieve a suitable fatty acid starting point.

Genetic modification may also be desirable for the production of plant secondary metabolites, which suffers from low plant productivity and the limited number of tissues or cell types in which metabolites are formed. Genetic engineering offers a solution to the first of these problems, by modifying the metabolic pathway leading to the chemical of interest

(44). It could also address the second factor, either by increasing the range of tissues producing the metabolite or by inducing a proliferation of the cells that are active. An example of the former is “golden rice” with high levels of provitamin A. An example of the latter is increased production of flavonoids in tomatoes, while glandular trichomes are also an attractive target for terpenoids in essential oils.

Recombinant protein production by its very nature also requires genetic modification. The EU Integrated Project Pharma-Planta was launched in 2004, with the aims of:

- building a plant based production platform for pharmaceuticals in Europe
- entering the first candidates of this pipeline into Phase I clinical trials
- developing robust risk-assessment and risk-management practices based on health and environmental impact, working with EU regulatory authorities to ensure safety and acceptance

While GM pharmaceuticals such as human insulin and hepatitis B vaccine have already been developed, plant derived proteins for human use have not been addressed in the EU. A major outcome will be to define the regulatory requirements through engagement and consultation with relevant regulatory bodies. Monoclonal antibodies will be the first to be developed for Phase I trials, including neutralising antibodies for HIV and rabies. The project also includes targets representing second generation molecules, to feed the development pipeline for European SMEs beyond the lifetime of the project. Intellectual property management is also included, to facilitate the availability of plant derived recombinant pharmaceuticals to the poor in developing countries. The consortium comprises 31 partner organisations from 11 European countries, including 9 from the UK.

The issue of genetic modification to crops will be considered in the forthcoming report of the Agricultural and Environment Biotechnology Commission. As noted in section 3.2, this will be followed by Defra and DTI defining a strategy to develop high-value products such as pharmaceuticals from crops.

4.6.1 Contained Cultivation

The development of contained cultivation was one of the recommendations of the IOIR report (45), as it would build on a UK expertise tradition in greenhouse cultivation, and would produce high yields of quality products. The use of hydroponics was suggested during the roadmap workshop, as it offers a means of carefully controlling plant nutrition and of extracting products secreted through the roots. Like other greenhouse systems, it was suggested that hydroponics could be served by existing agricultural skills. Contained cultivation may therefore bring socio-economic benefits, over and above its technical merits, in terms of revitalising the rural economy and integrating it with the urban chemicals industry. Specialist UK manufacturers of contained environments such as Unigro already exist and, as noted in section 2.4.2.1, Sativex® is produced from cannabis plants in a contained environment.

4.6.2 Plant Tissue Cultures

Ref (46) considers the problems sometimes encountered with plant tissue cultures used for secondary metabolite production

- the sensitivity of the cells to shear
- high doubling times and hence extended fermentation times and high costs
- metabolites are often stored in the vacuole instead of being secreted, so product inhibition can reduce yields

- the instability of cell lines
- cultured plant cells often produce reduced quantities and different profiles of secondary metabolites compared with the intact plant. Sometimes, however, metabolites are over–produced compared with the whole plant. These differences are ascribed to a lack of cell differentiation.

An obvious means of improving productivity is to select high-yielding strains. The production of a secondary metabolites can also be stimulated by adding its precursor, or by biotransforming a substrate molecule. As secondary metabolites are often the response to infection or stress, elicitor treatment involving these stimuli can also be used. Product secretion might be encouraged by permeabilising the cells or by (electro)chemically mediated release and this would reduce any effect of product inhibition on yields.

It may be possible improve cell permeabilisation by extending recent work on fungal and bacterial glycoside hydrolases (47). The catalytic domains of such hydrolases are tethered to non-catalytic carbohydrate binding modules (CBMs) that bind to plant glycosides, thereby enhancing their action. Fungal hydrolases are almost exclusively tethered to one family of surface-acting CBMs that bind to crystalline cellulose. The less active bacterial enzymes, by contrast, use at least 37 different CBM families to bind to a range of plant polysaccharides, including non-crystalline cellulose, xylans, mannans and glucomannan. Studies with members of fungal CBMs and xylan-binding examples of bacterial CBMs both reveal significant differences in their specificity when presented to the cell wall. It may be possible to combine the enhanced activity of fungal catalytic domains with the wider range of bacterial CBMs. By a careful selection of these CBMs, it might also be possible to permeabilise plant cell walls in a controlled and predictable fashion.

Differentiated cells would also improve yields, and might be provided by the use of organ cultures, or by biochemically triggering the cells into differentiation, for example the creation of hairy-root cultures. These result from the ability of *Agrobacterium rhizogenes* to insert the Ri plasmid into wounded tissue and cause the growth of fine adventitious roots. The roots can be grown in a hormone-free medium and enjoy enhanced accumulation of metabolite.

Engineering improvements to productivity include optimising the culture conditions, such as the medium, pH, temperature, oxygen concentration or light, or improving the fermenter design and using high cell density cultures. They also include immobilising the product or the cells, the latter with potential benefits that include:

- an extended viability of cells in the stationary, producing stage
- simplified downstream processing
- the possible promotion of differentiation, linked to enhanced secondary metabolism
- a higher cell density and hence lower reactor size and costs
- reduced shear sensitivity
- the promotion of metabolite secretion
- the possible use of flow-through reactors
- a lower increase in viscosity that might otherwise cause mixing and aeration problems

and difficulties that include:

- immobilisation is normally limited to production decoupled from cell growth
- the initial biomass must be grown in suspension
- the secretion of the product into the extracellular medium is a pre-requisite

If the identification of plant tissue cultures as a UK priority is confirmed, these avenues to improve productivity may warrant development.

4.7 Infrastructure

While the themes identified in the previous sections are largely scientific and engineering in nature, there are also infrastructure requirements to ensure that they convert the current state-of-the-art into the long-term vision. The main components of this infrastructure are seen as follows.

- **Evaluate and Report International Developments**

As mentioned in the Introduction, this roadmap is a specialist development of a US roadmap on renewable feedstocks (1) and a Dutch roadmap on catalysis (2). It has subsequently drawn on several other overseas reviews, reports and evaluations in other sections. There is a clear advantage in monitoring other countries' work, evaluating it in a UK context and disseminating findings. This is likely to be a significant task, as governments and industry around the world increase expenditure in the field. Disruptive science and technology and changing legislation are among the key factors to monitor and assess. It is suggested that a prime audience for such information is the new NNFCC Strategy Group on Non-Food Crops.

One example referred to in section 4.4 is the recent US report on platform chemicals from the sugars platform, identified as a US priority. To re-iterate the recommendation made there, a workshop is envisaged to identify areas in which UK industry and academia could profitably contribute.

- **Monitor and Evaluate Developments in the Energy Economy**

Developments in the energy economy will have a profound effect on most sectors of renewable feedstocks. With the possible exception of specialist crops, the economic viability of renewable chemicals will depend strongly on the price of energy and fossil-derived counterparts. In addition, renewable fuels such as methanol and ethanol may emerge as platform chemicals in their own right, and their price will influence the viability of alternatives. In addition to monitoring developments, it may be desirable to construct a quantitative economic model of the supply chain, to assist companies make informed decisions about the development of their markets.

- **National and Regional Strategies**

Developments in both international plans and the energy economy are seen as key inputs to the work of the NNFCC Strategy Group on Non-Food Crops. This roadmap, too, is offered for discussion by the Board and by the wider community. As noted in the Introduction, it is seen as a working document requiring continuous improvement and seeks the future, continuing involvement of four communities:

- Agricultural Industries
- Manufacturing Industries
- The Science Base, including:
    - Plant and Crop Science
    - Catalysis
- Government, including DEFRA, DTI and RDAs

A structural problem with most public-domain roadmaps is that they are seldom revised, but appear in a single, original edition. This contrasts strongly with private roadmaps, which are usually updated regularly to reflect changing circumstances, as a matter of corporate policy. In addition to accommodating change, this practice can achieve a degree of buy-in to the corporate vision and a medium through which to express it.

It is suggested that this roadmap, too, should be updated regularly. The long-term vision expressed in section 3 should, in particular, be revised to reflect that of the Strategy Group, along with any implications such a revision might have on the Future developments described in section 4. The benefits of a shared vision and a dissemination medium would then be transferred from the private to the public sector. Its publication might also influence the deliberations of overseas counterparts to the Group, and foster international collaboration.

While being updated, the roadmap might also be deepened, with more detail being provided on activities and timings. Each of the themes discussed in sections 4.1 to 4.6, for example, might be the subject of a subsidiary roadmap. At this level of detail, individual projects and supporting activities would appear.

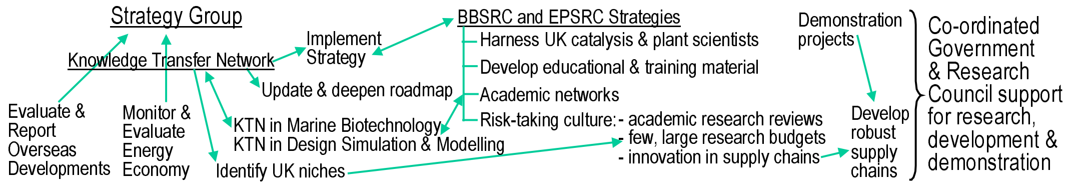
One of the strategic factors identified by the workshop was the need to combine the skills of UK catalysis and plant scientists. Also suggested was that a risk-taking research culture should be fostered through the academic research reviews, in which failure to achieve ambitious objectives is not punished, but seen as an inevitable counterpart of taking risk. Such risks nevertheless need to be taken in identified niche areas in which the UK can realistically compete. It was suggested that relatively few, large research programmes should be supported in these fields, and combined with demonstration projects to develop robust supply chains. This implies a co-ordinated approach from Research Councils, DTI, DEFRA and the RDAs to focus R&D funding on UK priorities.

A key issue in a UK strategy will therefore be identifying those areas in which it should take a lead and those priorities of other countries in which it might develop and exploit IPR. As noted in section 4.4, the stated US priorities are the sugar and thermochemical platforms. Oleochemicals and specialist crops were proposed as UK priorities by the workshop, while this report also notes a perceived European lead in anaerobic digestion.

- **Knowledge Transfer Network to Implement Strategy**

A Knowledge Transfer Network (KTN) as envisaged by DTI is a potential vehicle to deliver the vision determined by the Strategy Group. This is perceived as an effective means to harness the skills of catalysis and plant scientists while forging robust supply chains between agricultural and chemicals industries. The subject-matter falls between existing networks and centres of excellence, and collaboration with them is required to complement their activities. Relevant bodies include, non-exhaustively, NNFCC, Pro-Bio Faraday, Crystal Faraday, the Green Chemistry Network, CoEBiO3 and CNAP. The relevance of Marine Biotechnology as described in section 4.1 means that collaborative links should be fostered with any NERC KTN emerging in that field, too.

Collaboration should also be sought with any KTN emerging in Design, Simulation and Modelling (DSM). A plethora of DSM tools are employed in the design and operation of chemical plants, ranging from fundamental models of physical, chemical or biological phenomena, through fluid mechanical and structural simulation tools, to design packages enabling processes and plant to be installed and run. At present, however, such tools are provided almost exclusively with information related to petrochemical feedstocks and intermediates. To give the Design Engineer the option of choosing renewable feedstocks or intermediates, the equivalent information must also be embedded in the software.



The KTN might also be a vehicle to deliver the other 2 elements of infrastructure noted above: evaluating and reporting both international work and developments in the energy economy. It should also collaborate with BBSRC and EPSRC, as they develop their strategies in Crop Science and Catalysis. Links between basic science and industrial priorities would also be strengthened by embedding academic networks within the KTN. A further role for academia would be to develop educational and training material for this emerging subject.

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The roadmap would not have been possible without the Advisory Panel drawn from the consortium members. This consisted of Warren Smith, Bruce Knight, Jeff Hardy and Stan Roberts, each of whom prepared a presentation for the workshop and much of this material lies embedded in the report unreferenced. Also a pre-requisite for the roadmap were workshop attendees, who were Steve Bowra, David Parker, Paul Fowler, Ann Thompson, Steve Wade, Philip John, Roger Lawrence, Gary Punter and Dianne Carter. Their advice and comments, too, form an integral part of the report. Opinions expressed in the report, however, do not necessarily reflect those of individual contributors. Special thanks are due to Richard Jackson for many consultations and his help with the workshop.

Contributions to the roadmap also derive from those not present at the workshop, including the many authors of review papers and reference material it uses. Amongst others, these include Mark Paster, Joan Pellegrino, Tracy Carole (6), Julian Ma and Paul Christou (23), D.L.Klass (35) and T.Werpy, G.Peterson *et al* (42). Marine Biotechnology was included with the help of the members of the Marine Biotechnology Group of the UK Fore*sight* Marine Panel, Tony Guttierez of SAMS and Andrew Mearns Spragg of Aquapharm. Much of the background material on plant biochemistry, together with several figures, were derived from the book (21).

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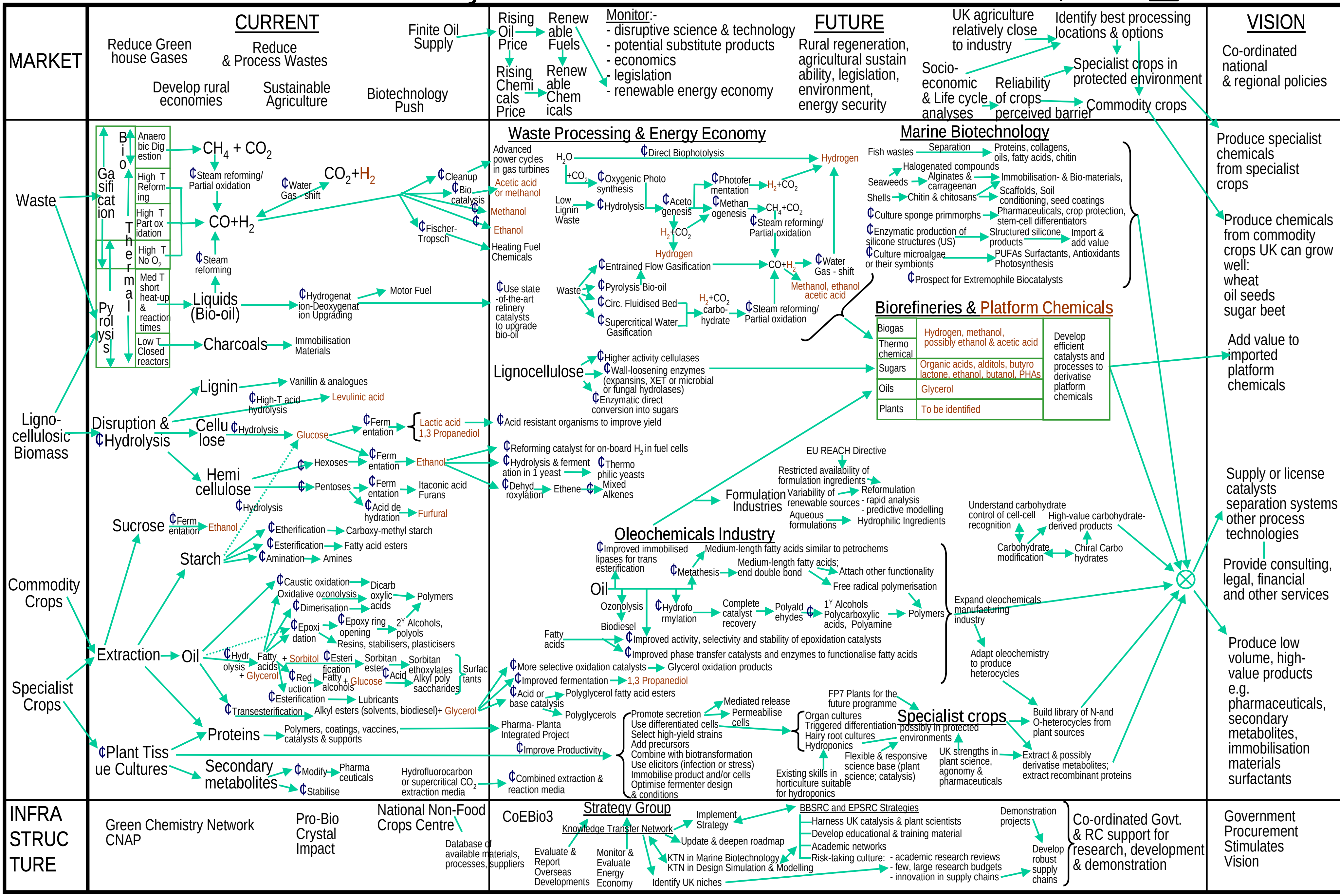
Catalysis in Renewable Feedstocks

KEY: ₵ Catalytic Process 🟫 Platform Chemical



MARKET

CURRENT

Reduce Green house Gases

Reduce & Process Wastes

Finite Oil Supply

Develop rural economies

Sustainable Agriculture

Biotechnology Push

Rising Oil Price

Renew able Fuels

Rising Chemi cals Price

Renew able Chem icals

Monitor:-
- disruptive science & technology
- potential substitute products
- economics
- legislation
- renewable energy economy

FUTURE

Rural regeneration, agricultural sustain ability, legislation, environment, energy security

UK agriculture relatively close to industry

Socio-economic & Life cycle analyses

Reliability of crops perceived barrier

Identify best processing locations & options

Specialist crops in protected environment

Commodity crops

VISION

Co-ordinated national & regional policies

Waste

Ligno-cellulosic Biomass

Commodity Crops

Specialist Crops

Gasification

Pyrolysis

Bio

Thermal

Anaerobic Digestion

High T Reforming

High T Part oxidation

High T No O_2

Med T short heat-up & reaction times

Low T Closed reactors

$CH_4 + CO_2$

₵Steam reforming/ Partial oxidation

$CO+H_2$

₵Steam reforming

₵Water Gas - shift

CO_2+H_2

₵Cleanup

₵Bio catalysis

₵

₵

₵Fischer-Tropsch

Liquids (Bio-oil)

₵Hydrogenation-Deoxygenation Upgrading

Motor Fuel

Charcoals

Immobilisation Materials

Advanced power cycles in gas turbines

Acetic acid or methanol

Methanol

Ethanol

Heating Fuel Chemicals

₵Use state-of-the-art refinery catalysts to upgrade bio-oil

Lignin

Vanillin & analogues

₵High-T acid hydrolysis

Levulinic acid

Disruption & ₵Hydrolysis

Cellulose

₵Hydrolysis

Glucose

₵Fermentation

Lactic acid
1,3 Propanediol

₵Acid resistant organisms to improve yield

Hemi cellulose

₵ Hexoses

₵Fermentation

Ethanol

₵ Pentoses

₵Fermentation

Itaconic acid Furans

₵Acid dehydration

Furfural

₵Hydrolysis

₵Reforming catalyst for on-board H_2 in fuel cells

₵Hydrolysis & fermentation in 1 yeast

₵Thermo philic yeasts

₵Dehydroxylation

Ethene

₵

Mixed Alkenes

Sucrose

₵Fermentation

Ethanol

Starch

₵Etherification

Carboxy-methyl starch

₵Esterification

Fatty acid esters

₵Amination

Amines

Extraction

Oil

₵Caustic oxidation

Oxidative ozonolysis

Dicarboxylic acids

Polymers

₵Dimerisation

₵Epoxidation

₵Epoxy ring opening

2^{Y} Alcohols, polyols

Resins, stabilisers, plasticisers

₵Hydrolysis

Fatty acids + Glycerol

+ Sorbitol

₵Esterification

Sorbitan ester

Sorbitan ethoxylates

₵Acid

₵Reduction

Fatty alcohols

+ Glucose

Alkyl poly saccharides

Surfactants

₵Esterification

Lubricants

₵Transesterification

Alkyl esters (solvents, biodiesel)+ Glycerol

₵More selective oxidation catalysts

Glycerol oxidation products

₵Improved fermentation

1,3 Propanediol

₵Acid or base catalysis

Polyglycerol fatty acid esters

Polyglycerols

Proteins

Polymers, coatings, vaccines, catalysts & supports

Pharma- Planta Integrated Project

₵Plant Tissue Cultures

₵Improve Productivity

Secondary metabolites

₵Modify

Pharmaceuticals

₵Stabilise

Hydrofluorocarbon or supercritical CO_2 extraction media

₵Combined extraction & reaction media

Waste Processing & Energy Economy

H_2O

₵Direct Biophotolysis

Hydrogen

$+CO_2$

₵Oxygenic Photo synthesis

Low Lignin Waste

₵Hydrolysis

₵Acetogenesis

H_2+CO_2

Hydrogen

₵Photofermentation

H_2+CO_2

₵Methanogenesis

CH_4+CO_2

₵Steam reforming/ Partial oxidation

Waste

₵Entrained Flow Gasification

₵Pyrolysis Bio-oil

₵Circ. Fluidised Bed

₵Supercritical Water Gasification

H_2+CO_2 carbo-hydrate

₵Steam reforming/ Partial oxidation

$CO+H_2$

₵Water Gas - shift

Methanol, ethanol acetic acid

Lignocellulose

₵Higher activity cellulases

₵Wall-loosening enzymes (expansins, XET or microbial or fungal hydrolases)

₵Enzymatic direct conversion into sugars

Marine Biotechnology

Fish wastes

Separation

Proteins, collagens, oils, fatty acids, chitin

Halogenated compounds

Seaweeds

Alginates & carrageenan

Immobilisation- & Bio-materials,

Shells

Chitin & chitosans

Scaffolds, Soil conditioning, seed coatings

₵Culture sponge primmorphs

Pharmaceuticals, crop protection, stem-cell differentiators

₵Enzymatic production of silicone structures (US)

Structured silicone products

Import & add value

₵Culture microalgae or their symbionts

PUFAs Surfactants, Antioxidants Photosynthesis

₵Prospect for Extremophile Biocatalysts

Biorefineries & Platform Chemicals

Biogas Thermo chemical	Hydrogen, methanol, possibly ethanol & acetic acid	Develop efficient catalysts and processes to derivatise platform chemicals
Sugars	Organic acids, alditols, butyro lactone, ethanol, butanol, PHAs	
Oils	Glycerol	
Plants	To be identified	

EU REACH Directive

Restricted availability of formulation ingredients

Formulation Industries

Variability of renewable sources

Reformulation
- rapid analysis
- predictive modelling

Aqueous formulations

Hydrophilic Ingredients

Understand carbohydrate control of cell-cell recognition

High-value carbohydrate-derived products

Carbohydrate modification

Chiral Carbo hydrates

Oleochemicals Industry

₵Improved immobilised lipases for trans esterification

Medium-length fatty acids similar to petrochems

₵Metathesis

Medium-length fatty acids; end double bond

Attach other functionality

Free radical polymerisation

Oil

Ozonolysis

Biodiesel

₵Hydroformylation

Complete catalyst recovery

Polyaldehydes

₵

1^{Y} Alcohols Polycarboxylic acids, Polyamine

Polymers

Fatty acids

₵Improved activity, selectivity and stability of epoxidation catalysts

₵Improved phase transfer catalysts and enzymes to functionalise fatty acids

Expand oleochemicals manufacturing industry

Adapt oleochemistry to produce heterocycles

Promote secretion
Use differentiated cells
Select high-yield strains
Add precursors
Combine with biotransformation
Use elicitors (infection or stress)
Immobilise product and/or cells
Optimise fermenter design
& conditions

Mediated release

Permeabilise cells

Organ cultures
Triggered differentiation
Hairy root cultures
Hydroponics

FP7 Plants for the future programme

Specialist crops

possibly in protected environments

Existing skills in horticulture suitable for hydroponics

Flexible & responsive science base (plant science; catalysis)

UK strengths in plant science, agonomy & pharmaceuticals

Build library of N-and O-heterocycles from plant sources

Extract & possibly derivatise metabolites; extract recombinant proteins

⊗

Produce specialist chemicals from specialist crops

Produce chemicals from commodity crops UK can grow well:
wheat
oil seeds
sugar beet

Add value to imported platform chemicals

Supply or license catalysts separation systems other process technologies

Provide consulting, legal, financial and other services

Produce low volume, high-value products e.g. pharmaceuticals, secondary metabolites, immobilisation materials surfactants

INFRA STRUC TURE

Green Chemistry Network
CNAP

Pro-Bio Crystal Impact

National Non-Food Crops Centre

Database of available materials, processes, suppliers

CoEBio3

Strategy Group

Knowledge Transfer Network

Evaluate & Report Overseas Developments

Monitor & Evaluate Energy Economy

Implement Strategy

Update & deepen roadmap

KTN in Marine Biotechnology
KTN in Design Simulation & Modelling

Identify UK niches

BBSRC and EPSRC Strategies
- Harness UK catalysis & plant scientists
- Develop educational & training material
- Academic networks
- Risk-taking culture:
  - academic research reviews
  - few, large research budgets
  - innovation in supply chains

Demonstration projects

Develop robust supply chains

Co-ordinated Govt. & RC support for research, development & demonstration

Government Procurement Stimulates Vision