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Altered Biochemical Content

Genetic engineering allows scientists to manipulate the biochemical content of plants in unprecedented ways. The ability to access and alter the expression of biochemicals in seeds and other harvested components will be of particular importance to biobased crop research. The majority of grain crops do produce diverse carbohydrates, oils, and proteins. To exploit this chemical diversity, scientists will need to gain a more detailed knowledge of the plant genes and enzymes regulating these biochemicals.

Carbohydrates

Significant progress has occurred in altering the carbohydrate chemistry of agricultural crops. For example, potatoes containing novel carbohydrates have been commercialized and similar technologies are being applied to corn and wheat (Kishore and Somerville, 1993). While potatoes produce less starch than grain crops on a per-acre basis, starch-enhanced potatoes are being commercialized in some value-added markets such as food processing (see Box 2-4). Potatoes producing amylose-free starch are providing a desirable starch source for some markets because these modified potatoes contain only amylopectin rather than a mixture of amylose and amylopectin. Potatoes capable of fructan production will yield a new polymer based on fructose instead of glucose. Microbes can metabolize fructose and industrial processes can convert fructose to a wide range of organic compounds. Fructose is an example of the many sugars that are becoming important feedstock to the chemical industry.

Other polysaccharides such as cellulose, pullulan, hyaluronic acid, guavan, and xylans have interesting material, polymer, and fiber properties. The genes and enzymes involved in the biosynthesis of specific molecules will need to be identified and expressed in their natural hosts or engineered into other organisms. In some cases, genes may be modified to alter enzyme substrate specificity and accumulation of new polymers with different ionic charge, chemical reactivity and stability, solubility, melting, and other thermoplastic properties. The availability of genetic mutants in *Arabidopsis*, corn, and other plants will accelerate this research. A complete understanding of plant carbohydrate metabolism in unmodified and modified plant tissues will promote application of these sophisticated engineering technologies to other applications.

Lipids

Researchers have identified several plant genes and enzymes involved in lipid metabolism over the past five years, enabling development of

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modified oilseed rape cultivars for the biotechnology industry. Because of the similarity in lipid metabolism across plant species, similar oil research is under way with soybean, sunflower, and corn crops. Genes have been identified that affect carbon chain length, degree of unsaturation, and substituents in the fatty acid hydrocarbon chain (Topfer et al., 1995). Numerous fatty acids have been identified by screening the composition of various plant species. These plant species will provide a gene source for creating cultivars of major agronomic crops that produce fats and oils of value to the chemical industry as lubricants, fuels, and detergents. Introduction of additional functionalities, such as hydroxy or epoxy groups or double- and triple-carbon bonds, into plant fatty acids will enable synthesis of new molecules in major oilseed crops.

Many benefits may be derived from research that improves productivity and biochemical characteristics of some oil-producing crops. For example, the ricinoleic acid present in castor bean oil can be used for the production of nylon 11; the erucic acid found in crambe and rapeseed oils can be used for nylon 13 production; and the petroselenic acid present in coriander can be used for the production of nylon 66. High-linolenic oils present in the seed can be used to produce various coatings, drying agents, and printing inks. Significant opportunities may exist to improve the agronomic productivity of some of these oil crops and develop applications for the fatty acids and byproducts.

The oil pathway of plants may serve as a platform for the production of novel biopolymers. Industrial scientists have recently succeeded in transferring genes from the bacterium *Alcaligenes eutrophus* into the plant *Arabidopsis*. This modification led to plant production of poly(hydroxybutyrate) (PHB); this is an example of biopolymer engineering that can be performed on plants (Poirier et al., 1995). PHB constitutes nearly 20 percent of leaf dry matter in the genetically engineered *Arabidopsis*. Researchers at Zeneca and Monsanto are now transferring PHB genes into oilseed rape and soybean seeds for production of the polymer. Scientists anticipate that cotton fiber quality could be improved if PHB genes could be introduced into cotton plants. Future work will expand beyond PHB and focus on the production of diverse polymers that vary in carbon chain length and substitution. This work will require a more detailed understanding of fatty acid metabolism and the microbial pathways involved in polymer formation. Related research leading to identification of inexpensive processes for the extraction and separation of these polymers also will be critical for developing industrial applications.

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BOX 2-4
Genetic Engineering to Increase Starch Biosynthesis

Starch is the main storage carbohydrate in most plants. It is a major harvest component of several crops and thus directly affects yield. Industrial starch demand has increased dramatically over the past decade, primarily because of growth in the production of high-fructose corn syrups and bio-ethanol. In addition, various specialty starches, such as amylose and waxy starch, are being recognized for their superior material and nutritional properties as well as biodegradability.

Plant breeders have worked to increase the starch content of potatoes for a number of years; however, breeders typically do not achieve large changes. When large changes do occur, they prove difficult to work with since they can involve multiple genetic loci. The genetic engineering work described here involved a single gene and dramatically increased starch production, and thus harvested biomass per acre, without any apparent harmful effects on the plant.

The high-starch potato is one of the first genetic engineering products that targets industrial needs. Dry matter content (mostly starch) is the most important characteristic of potatoes for the processing industry because starch content affects processing cost, efficiency, and yield. For the food industry, high-starch potatoes are expected to improve efficiency and consume less oil during frying, thereby yielding fried products with more potato flavor, improved texture, reduced calories, and less greasy taste.

The strategy taken by Monsanto researchers was to increase starch content by enhancing the rate of starch biosynthesis. Starch biosynthesis in plants (and glycogen biosynthesis in bacteria) requires the enzymes ADPglucose pyrophosphorylase (ADPGPP), starch synthase, and branching enzyme. These enzymes

Proteins

Little genetic engineering research has focused on proteins other than enzymes, although there are several advantages to using protein polymers for biobased production:

- Plant proteins generally are more diverse than other plant polymers.
- Molecular weight and amino acid sequences of protein polymers can be precisely regulated.
- Proteins can catalyze reactions or be hydrophobic, hydrophilic, neutral, acidic, or basic reactants.
- Proteins can form higher-order structures such as multimers of polymers.
- Plant proteins are generally inexpensive.
- Certain proteins, such as silk and wool, have long histories in the textiles industry.

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build the large starch molecule. The ADPGPP catalyzes formation of ADPglucose from glucose 1-phosphate and ATP. The ADPglucose subsequently serves as the substrate for starch synthase. Plant cells tightly regulate the activity of ADPGPP, turning the enzyme "on" when excess carbohydrates are present and shutting it "off" when starch biosynthesis is not needed. The researchers reasoned that, since ADPG-PP controls the amount of starch produced, addition of another enzyme that is not subject to control by the cell would cause more carbohydrate to flow into starch. Scientists at Michigan State University had utilized such an enzyme from the common enteric bacterium, *Escherichia coli*; this enzyme was previously discovered at the Pasteur Institute. The mutant enzyme GlgC16 causes *E. coli* to accumulate high levels of glycogen because the bacterial cells do not regulate its metabolic state (glycogen is similar to starch). The Monsanto group obtained the gene encoding GlgC16 designed it to be active only in tubers and transferred it into russet Burbank potato plants (the dominant potato variety in North America).

In some cases, tubers from transgenic plants containing the GlgC16 gene contained on average 25 percent to 30 percent more starch than tubers lacking the gene. Extensive U.S. field testing has shown the high-starch trait is stable in a number of different potato-growing environments. Furthermore, the trait has had no negative effect on plant growth or tuber yield, but, since the tubers contain more starch, the harvested dry matter per acre is substantially increased. The starch molecule in the transgenic potatoes, while more abundant, is structurally unchanged—important because the molecule's structure determines its end-use properties. The starch enhancement technology has now been extended to tomato and canola.

SOURCES: Leung et al. (1986), Stark et al. (1992).

Other Biochemicals

The biochemicals that may be manufactured by plants are not limited to carbohydrates, oils, and proteins. Rubber is an important hydrocarbon produced by certain plants, and genetic engineering could enhance the amount and quality of rubber from these sources. Worldwide demand for rubber is growing at a dramatic rate as automobiles are becoming more common in the emerging economies of Asia. The opportunity to meet this need from renewable resources is real and deserves attention. Thus, genetic engineering could significantly enhance the biochemical diversity of the plant world and address some major issues in plant-based industries.

Although this chapter focuses primarily on plant biotechnology, developments in microbial biotechnology will also be key to the expansion of biobased production. Research on microbial systems is addressing the processing of plant products as well as the handling of society's wastes. Increased understanding of metabolic control in microorganisms is point-

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TABLE 2-2 Crops with Potential Uses for Industrial Products

Crop	Current Acreage	Primary Products	Uses	Comments
Castor	Unknown (Major toxin-free seed is being accumulated in the U.S.)[a]	Ricinoleic acid (Castor seeds contain over 50% oil on a dry-weight basis and almost 90% of the oil is ricinoleic acid)[a]	Lubricants, plastics, coatings, sealants	Because of widely fluctuating world supplies and the structure of the world market, prices for castor oil vary considerably. This affects cash flow, makes corporate planning difficult, and discourages investment in new products. Commercial production of transgenic canola containing 15% ricinoleic acid is currently under way.
Crambe	35,000–40,000[b]	Erucic acid	Lubricants, waxes, paints, nylon 1313	Major competition by industrial rapeseed. Seed shattering and agronomy are major issues.
Cuphea	Unknown	Capric and lauric acids	Soaps, detergents, lubricants	A potential substitute for tropical oil.
Guayule	Unknown	Natural rubber	Rubber products, tires, surgical gloves, nonallergenic rubber products	Need to increase rubber content and utilize more of the plant.
Jojoba	16,000[c]	Wax esters	Cosmetics, lubricants, waxes	Needs more research into processing and use.
Kenaf	8,000[d]	Short and long fibers	Rope, newsprint, paper products	Potentially meant for replacing newsprint; most well-studied alternative crop.
Meadowfoam	5,000	High-value oils	Personal care products	Other uses under development; unsaturated chemical bonds confer

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Kenaf	8,000[d]		Short and long fiber[e]	Rope, newsprint, paper products	Potentially meant for replacing newsprint; most well-studied alternative crop.
Meadowfoam	5,000		High-value oils	Personal care products	Other uses under development; unsaturated chemical bonds confer unusually stable oil product.
Milkweed	<100[e]		Floss	Down quilts, pillows	Possibly large potential if nonwoven and yarn markets materialize.
Herbaceous crops (switchgrass, etc.)	600,000[f]		Biomass	Fermentable sugars, liquid fuels	30 to 40 million acres may supply up to 25% of U.S. liquid fuel needs.
Silviculture crops (short rotation, woody species such as hybrid poplar)	130,500[g]		Biomass	Fermentable sugars, liquid fuels, chemicals	30 to 40 million acres may supply 10 to 20% of U.S. liquid fuel needs.

[a] During the 1950s and 1960s, approximately 85,000 acres of castor were grown annually in the United States. Since then domestic production decreased and was abandoned in 1972 due to disagreement on an annual contract between castor seed processors and castor oil buyers. Source: USDA (1992).

[b] Source: Personal communication with John Gardner, Agro-Oils, Inc., Carrington, North Dakota, July 20, 1998.

[c] Source: USDA (1992).

[d] Estimated value. Source: ERS (1997b).

[e] Source: Personal communication with Herbert Knudsen, Natural Fibers Corp., Ogallala, Nebraska, July 17, 1998.

[f] Switchgrass is currently used by the livestock industry primarily for summer grazing in the Midwest and Great Plains. Source: Personal communication with Ken Vogel, U. S. Department of Agriculture, Agriculture Research Service, September 25, 1998.

[g] There are no hybrid poplar crops grown specifically for energy uses. Approximately 62,500 acres of hybrid poplar are planted in the Pacific Northwest; 54,000 poplars, sycamores, and sweetgum are planted in the Southeast; and 14,000 acres of hybrid poplar are planted in the North Central region for production of paper, boards, etc. To a limited extent, some of the residuals are being used for energy if the trees are planted very close to the mill. Source: Personal communication with Lynn Wright, U.S. Department of Energy, Bioenergy Feedstock Development Program, Oak Ridge National Laboratory, September 24, 1998.

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ing to new ways to genetically modify organisms for industrial conversion of plant-derived feedstocks.

Introduction of New Crops

Most of the agricultural research in the United States focuses on major agronomic crops and developing applications for existing biochemicals extracted from these crops. Although this work is worthwhile and should continue, it will be equally important to develop new crops that have the potential to produce desired biochemicals. In addition to selecting and designing crops to meet certain industrial chemical needs, enhanced productivity should be a major goal of crop development efforts. This section briefly explores issues and opportunities associated with the introduction of new crops. Other analyses have described potential markets and botanical details of alternative crops (e.g., Harsch, 1992). Table 2-2 summarizes data for some new crops that have received initial scientific and commercial investments.

Basic technical factors often create difficulties in the commercialization of new crops. Many alternative crops lack characteristics that would result in high yields because they have been neither intensively cultivated nor subject to research and development for improved agronomic traits. Well-tended experimental plots may demonstrate useful genetic potential. However, the absence of directed plant breeding and underlying scientific knowledge generally makes for a long development period prior to major production of a new crop. In contrast the value of traditional crops is continuously being enhanced by technological advances resulting from major investments in research and development.

Biobased crops should be selected based on their productivity of the desired product as well as specific biochemical characteristics. Plant breeding may be necessary to introduce new biomolecules or enhance total biomass production. Sugar cane provides a useful example. Cultivars of sugar cane, called "energy cane," have been developed for ultimate conversion of the sucrose, cellulose, and hemicellulose contents to ethanol. Plant breeders developed cultivars having lower sucrose contents because the higher biomass yields of the cultivars more than compensated for the lower sucrose levels, thereby reducing the raw material's final cost.

Plants of natural origin and genetically engineered crops should be considered during the crop selection process. Castor provides an instructive example. The large-scale reintroduction of this crop is largely driven by a desire to replace the $30 million annual importation of castor oil with a reliable, cost-effective, domestic supply of ricinoleic acid. However, crops that produce high levels of oleic acid, such as sunflower or rape-

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seed, are being engineered to contain the gene required to produce hydroxyleic acid, thereby yielding the desired ricinoleic acid in an established agronomic crop.

Over the near term the acreage of traditional crops will continue to dwarf that of new crops. In the long-term, alternative crops can make important contributions in the industrial and agricultural sectors—if they can compete in the marketplace with traditional crops. Industrial crops that will be successful will be those with sufficient registered crop protection chemicals, appropriate infrastructure, optimized manufacturing processes and equipment, and byproduct utilization systems.

SUMMARY

If appropriate and sufficiently low-cost processing technologies were developed, there is enough unused biomass to satisfy all domestic demand for organic chemicals that can be made from biological resources (approximately 100 million tons per year) and all of the nation's oxygenated fuel requirements (use of oxygenated gasoline) in areas that did not meet the federal ambient air standard for carbon monoxide as mandated by the Clean Air Act Amendments of 1990. Production of biobased crops on land presently idled could, given low-cost technologies for converting these crops, provide an additional source of U.S. liquid fuels. A few new crops have received initial scientific and commercial investments, but various factors impede their commercial adoption. Nevertheless, certain nontraditional crops, such as switchgrass and hybrid poplar, are valuable because of their high yields.

Classical plant breeding and genetic engineering techniques will continue to be used by scientists for the development of new crops and improvement of well-established crops. Genetic engineering offers unprecedented opportunities to manipulate the biochemical content of specific plant tissues and design a raw material for easier processing—an advantage not enjoyed by fossil feedstocks. However, much more remains to be done to provide the raw materials for expanding biobased industries.

Over the long term, a major research priority is to maintain a commitment to fundamental and applied research in the biology, biochemistry, and genetics of plants and microorganisms. It is necessary to gain an understanding of underlying processes associated with gene expression, growth and development, and chemical metabolism. Improved methods of plant transformation and new promoters that further refine gene expression are needed to hasten the development of crops suitable for biobased industries. A sound scientific base in these fundamental areas will be critical to formulating strategies to supply future raw materials for biobased industries.

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Future development of agricultural and forest crops for a biobased industry will strengthen the ties between agriculture and industrial production. The change will depend not only on continued improvement of traditional crops but also on the development of alternative crops, genetically engineered cultivars, and separation and fermentation processes that can make use of biomass. Making the transition to a competitive biobased industry will require close coordination between plant scientists and process engineers to develop cost-effective biological and industrial processes for the conversion of raw materials into value-added products.

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3

Range of Biobased Products

At the turn of the century most nonfuel industrial products—dyes, inks, paints, medicines, chemicals, clothing, synthetic fibers, and plastics—were made from trees, vegetables, or crops. By the 1970s, organic chemicals derived from petroleum had largely replaced those derived from plant matter, capturing more than 95 percent of the markets previously held by products made from biological resources, and petroleum accounted for more than 70 percent of our fuels (Morris and Ahmed, 1992). However, recent developments are raising the prospects that many petrochemically derived products can be replaced with industrial materials processed from renewable resources. Scientists and engineers continue to make progress in research and development of technologies that bring down the real cost of processing plant matter into value-added products. Simultaneously, environmental concerns and legislation are intensifying the interest in agricultural and forestry resources as alternative feedstocks. Sustained growth of this burgeoning industry will depend on developing new markets and cost-competitive biobased industrial products.

Numerous opportunities are emerging to address industrial needs through the production and processing of biological materials. Today's biobased products include commodity and specialty chemicals, fuels, and materials. Some of these products result from the direct physical or chemical processing of biomass—cellulose, starch, oils, protein, lignin, and terpenes. Others are indirectly processed from carbohydrates by biotechnologies such as microbial and enzymatic processing. Table 3-1 shows

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TABLE 3-1 Increase in Worldwide Sales of Biotechnology Products, 1983 and1994[a]

	1983 ($ millions)[b]	1994[c] ($ millions)
Fuel and industrial ethanol	800[d]	1,500[e]
High-fructose syrups	1,600	3,100
Citric acid	500	900
Monosodium glutamate	600	800
Lysine	200	700
Enzymes[f]	400	1,000
Specialty chemicals[g]	1,300	3,000
Total	5,400	11,000

[a] Table excludes pharmaceutical products.
[b] Data from Hacking (1986).
[c] Data from John VicRoy, Michigan Biotechnology Institute, Market Analysis, 1994.
[d] Data based on Hacking (1986): 1983 ethanol price = $1.70 per gallon and volume = 180 million bushels corn (approximately 2.5 gallons ethanol per bushel). Total ethanol sales = $0.8 billion.
[e] Data based on February 21, 1994, Ethanol Profile, Chemical Marketing Reporter: 1994 industrial ethanol (fermentation) price = $1.70 per gallon and volume = 75 million gallons; fuel ethanol price = $1.1 per gallon and volume = 1.2 billion gallons. Total ethanol sales = $1.5 billion.
[f] Includes feed grades.
[g] Includes diverse products such as gums, vitamins, and flavors.

worldwide markets for several biobased industrial products (excluding pharmaceuticals) made from microbial and enzymatic conversion of carbohydrates. The gross annual sales of these biochemicals in 1994 exceeded $13 billion (Datta, 1994). Analyses of historical and present market growth rates suggest that the worldwide market for specialty chemicals will grow 16 percent per year (Datta, 1994).

A wide range of biobased industrial products and technologies will be introduced to diverse industrial markets. Ethanol and oxygenated chemicals derived from fermentable sugars will be key precursors to other industrial chemicals traditionally dependent on petroleum feedstocks. In the long term, with advances in genetic engineering, large-scale fuel production from lignocellulosic plant materials may become cost competitive with petroleum fuels. In other cases, biobased technologies such as enzyme catalysts are promising replacements for more hazardous industrial chemical processes. Increasingly, niche markets will be sought for a wide array of custom-engineered plant polymers (e.g., chiral compounds) not available in petrochemical-based products.

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COMMODITY CHEMICALS AND FUELS

Biobased industries of the future will include plant-derived commodity chemicals (those selling for under $1.00 per pound) to provide transportation fuels and intermediate chemicals for industrial processing. Ethanol is critical because this oxygenate can serve as a transportation fuel and also is a precursor to many other industrial chemicals. For example, corn starch fermentation yields ethanol, which then can be dehydrated for production of ethylene, the largest petroleum-based commodity chemical. The U.S. Department of Agriculture (USDA) estimated for 1996 to 1997 that 12 million metric tons of corn of a total 252 million metric tons of corn grain produced in the United States were put into ethanol fuel production—about 1.1 billion gallons of ethanol fuel (ERS, 1997b).

Ethanol

Large imports of foreign crude oil in the 1960s and 1970s stimulated interest in fuel ethanol (Harsch, 1992). In the United States the primary approach taken was gasohol, a blend of 10 percent ethanol in gasoline. Researchers found that ethanol and its derivative, ethyl *tert*-butyl ether, work as octane enhancers, increasing the efficiency of burning gasoline in an internal combustion engine. Similar interest in ethanol occurred in Brazil, and, with subsidies from the government, Brazil forged ahead with ethanol production. Until six years ago nearly 95 percent of the cars produced in that country ran on ethanol. Since then the price of crude oil has dropped and Brazil has converted to ethanol-gasoline blends (Anderson, 1993).

In the United States, ethanol occupies a niche in the transportation fuel market as an oxygenate in urban areas that do not attain U.S. Environmental Protection Agency air quality standards for carbon monoxide in response to the Clean Air Act Amendments of 1990. Gasoline is blended with an oxygenate fuel such as ethanol or methyl *tert*-butyl ether (MTBE) to increase the combustion efficiency of gasoline and decrease carbon monoxide emissions in cold weather. Due to its lower cost in comparison to ethanol, MTBE has been the primary oxygenate used, and its use ranges from 63 to 81 percent of the total demand for oxygenates (EIA, 1997). Total estimated U.S. production of MTBE in 1995 was 8 billion kilograms; estimated ethanol production for 1994 was 4.3 billion kilograms (Committee on Environment and Natural Resources, 1997).

An interagency panel assessed the air quality, groundwater and drinking water quality, fuel economy and engine performance, and the potential health effects of MTBE and other oxygenates (Committee on Environment and Natural Resources, 1997). In its review of the draft

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federal report, the National Research Council concluded that the cold-weather air pollution effects of oxygenated fuels were unclear. While data on the occurrence of MTBE in groundwater and drinking water are scarce, MTBE has been detected in groundwater (Squillace et al., 1996), stormwater (Delzer et al., 1996), and drinking water (Committee on Environment and Natural Resources, 1997). Because MTBE is very soluble in water, is not readily sorbed by soil and aquifer materials, and generally resists degradation in groundwater, the interagency group recommended that there be an effort to obtain more complete monitoring data, behavior and fate studies, and aquatic toxicity tests for wildlife and to establish, if warranted, a federal water quality criterion.

Specific well-targeted research will be needed to answer questions about potential tradeoffs in using these chemicals as additives to gasoline (NRC, 1996b). Demand for starch-based ethanol is influenced by the commodity market price for corn. During the 1995 to 1996 marketing year, high demand for corn grain drove up corn prices to record levels, leading to high input costs and a downturn in ethanol fuel production. Many ethanol producers opted to suspend ethanol production and do maintenance on their manufacturing facilities. Other producers diverted ethanol fuel production to the alcoholic beverage market. The USDA expects that producers will need to reestablish long-term contracts with blenders to regain market share lost when corn markets experienced a period of high input pricing in 1995 to 1996 (ERS, 1997b).

In the long term, large-scale production of fuel ethanol from lignocellulose materials could become technically feasible and economically favorable. A key will be demonstrating that recent and anticipated technical innovations work at larger scales with representative raw materials. The cost of bioethanol must drop significantly if it is to penetrate a much larger fraction of the transportation fuel market. This change will occur only if economical lignocellulose conversion technologies are developed—a long-sought achievement. Use of these alternative feedstocks with new conversion processes may reduce production costs sufficiently to allow access to the commodity fuel market, even without subsidies or tax incentives. The case study of lignocellulose-ethanol processing described in this chapter illustrates one approach toward reducing the costs of ethanol production.

Biodiesel

Biodiesel is a fuel that likely will not be an economically viable product in the near term. Vegetable-based diesel fuels are appealing in part because these biobased fuels confer some potential environmental benefits. Because production costs for soy-based diesel currently are ex-

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tremely high, soy-based diesel fuel faces stiff competition in most petroleum-based diesel fuel markets. For example, in Europe biobased diesel is more popular because incentives are offered to encourage its use. Further research and development may increase the demand for biobased diesel fuel in the long term.

Biodiesel is made by transesterifying plant oil(s) with methanol in the presence of a catalyst to produce fatty acid methyl esters. Methanol for the reaction is readily available from biomass, natural gas, or coal. Oils that can be processed into biodiesel include soybean, canola, and industrial rapeseed (Harsch, 1992). If the reacted oils have the correct carbon chain length, the fatty acid methyl esters will have chemical characteristics similar to those of conventional diesel fuel when they combust in modern diesel engines. Biodiesel is usually mixed with petroleum-based diesel fuel in a ratio of 20 percent biodiesel to 80 percent diesel fuel (B20). The U.S. Department of Energy (DOE) has moved to the rule-making process for inclusion of B20 as an approved alternative fuel under the Energy Policy Act of 1992. If this acceptance occurs, government-owned fleets of small diesel engines will be able to meet alternative fuel guidelines with biodiesel under that act.

Biodiesel does confer some environmental benefits. One advantage of biodiesel over petroleum-derived diesel is the virtual absence of sulfur and aromatic compounds (Abbe, 1994). Further, combustion of biodiesel produces lower emissions of carbon monoxide, unburned hydrocarbons, and particulate matter than combustion of petroleum-based diesel (Abbe, 1994). Consideration of emissions is particularly important in urban areas suffering from poor air quality. Biodiesel may be valuable in the future because the fuel can be used in today's diesel engines without modification and in various blends without negative impacts on engine performance (Hayes, 1995).

An increased focus on biodiesel largely results from its success in Europe. The crop of choice in Europe has been rapeseed, and the European Union has implemented subsidies for farmers growing oilseed crops to promote biodiesel production. European production of biodiesel and implementation of government policies to promote its use have progressed relative to the United States. A gallon of biodiesel requires 7.35 pounds of soybean oil and other inputs valued between $0.50 and $0.70. If soybean oil costs $0.25 per pound, biodiesel must cost at least $2.33 per gallon excluding taxes, or at least four times the cost of tax-free petroleum-based diesel (Hayes, 1995). The USDA estimated a hypothetical market price of $4.25 per gallon for biodiesel (ERS, 1996b). As a result of these high costs, biodiesel may be used only where it is mandated (i.e., in urban transit fleets and government-owned diesel vehicles), which limits the ultimate market size and encourages vehicle owners to seek less ex-

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pensive alternatives (Hayes, 1995). Some research on other plant-based diesel fuel alternatives may be warranted. Direct substitution of plant oils for diesel fuel would be cheaper than the manufacture of biodiesel because the transesterification process imposes significant additional costs. Unfortunately, the high viscosity of the oils causes poor atomization and creates flow characteristics that are generally incompatible with present-day diesel engines (Harsch, 1992). A different lower-cost alternative that merits consideration is the use of ethanol or butanol solvents for transesterification of plant oil.

In the United States, biodiesel would be unlikely to completely replace petroleum-based diesel. Even if all of the vegetable oil currently produced in the United States (about 3.1 billion gallons per year) went into biodiesel production, plant-based diesel production could provide only 6.4 percent of the nation's annual diesel consumption of 45 billion gallons (Harsch, 1992). Production of 3 billion gallons of biodiesel necessary for agricultural uses would require farmers to dedicate 40 million to 60 million acres to biodiesel crops (Harsch, 1992). Introduction of biodiesel as a blend with conventional diesel fuel is a more feasible goal in the United States and one that could have significant benefits in areas where the environment is sensitive to disruption by conventional diesel emissions or spills.

INTERMEDIATE CHEMICALS

Intermediate chemicals play an integral role in the U.S. economy. Organic chemicals are synthesized primarily from petroleum for production of numerous nonfuel industrial products such as paints, solvents, clothing, synthetic fibers, and plastics. Without these products the United States could not maintain its modern way of life. When petroleum supplies are interrupted, price volatility occurs in international petroleum markets. These events can have widespread economic consequences on oil-importing nations. Increasing the diversity of strategic feedstocks with biobased raw materials could help mitigate economic downturns created by oil shortages. Thus, intermediate chemicals are an important market targeted by the biobased industry.

Ethylene

Ethylene is perhaps the most important petrochemical because of the value of its numerous derivatives such as polyethylene, ethylene dichloride, vinyl chloride, ethylene oxide, styrene, ethanol, vinyl acetate, and acetaldehyde. Before the new lignocellulose conversion technology came on the horizon, the ethylene market was considered inaccessible to

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TABLE 3-2 Hypothetical Production Cost Comparisons for Ethylene

Commodity	Year	Average Variable Cost[a] ($/lb.)	Average Fixed Cost[b] ($/lb.)	Average Total Cost ($/lb.)	Price[c] ($/lb.)
Petroethylene	1993	0.02	0.08	0.10	0.21
Projected petroethylene	2005	0.06	0.08	0.14	
Biobased ethylene[d]	1993	0.13	0.01	0.14	

[a] Average variable costs include costs for labor, inputs, and energy in the case of biobased ethylene, but labor is omitted in the case of petroethylene because the figure was not available. This will raise the average total cost for the petroethylene somewhat but by only approximately 4 percent. In the case of petroethylene, the input material was naptha, and credit was given for the propylene and gasoline that would be coproduced.

[b] Average fixed costs include costs for land and capital.

[c] Price for ethylene on December 23, 1993, as quoted in *Chemical Marketing Reporter*. Prices will vary annually.

[d] Cost data for biobased ethylene were developed using Donaldson and Culbertson (1983) estimates of input requirements, yields, and plant costs—combining input requirements with 1993 price data to estimate material and utility expenditures, updating capital expenditure data with a price index for plant and equipment, and giving annual payment for a 15-year mortgage. The ethanol production cost of $0.46 per gallon (see Appendix A, Table A-2) converts to 6.6 pounds of ethanol per gallon = $0.12 per pound (ethanol cost for the ethylene process).

SOURCE: Callagher and Johnson (1995).

biobased production (Lipinsky, 1981). Today, biobased ethylene production based on ethanol derived from corn stover still is not cost competitive with petroethylene sources. In the near term, ethylene based on lignocellulose fermentation could move into the margin of competition against petrochemical sources (see Table 3-2). Petroethylene costs are expected to be $0.14 per pound by 2005 based on increasing cost projections for oil prices, using long-term projections developed by the World Bank. Bioethanol costs likely will remain stable owing to a slowly growing demand for agricultural products. Ethylene would be produced in large-scale operations that already process ethanol, thus enabling manufacturers to manage the costs from sluggish marketing periods. With rising petroleum prices or further improvements in the biobased ethylene route, the cost advantage of petroethylene could erode.

Acetic Acid

Acetic acid could be a large-volume chemical target for the biobased industry. It is used primarily as a raw material in the production of vinyl

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acetate, acetic anhydride, cellulose acetate, acetate solvents, terephthalic acid, and various dyes and pigments and as a solvent in the chemical processing industry. The food, textiles, and pharmaceuticals industries also use acetic acid in their manufacturing processes. In 1992, 1.9 million tons of acetic acid were produced in the United States (Ahmed and Morris, 1994). Acetic acid may be combined with dolomite lime to produce calcium magnesium acetate, an important deicing agent for the transportation industry. Biobased acetic acid may be produced by fermenting corn starch or cheese whey waste or as a byproduct of the sulfite wood pulping process. A better understanding is needed of the relative costs of production of acetic acid from renewable resources as compared to petroleum-based feedstocks.

Fatty Acids

Fatty acids, readily available from plant oils, are used to make soaps, lubricants, chemical intermediates such as esters, ethoxylates, and amides. These three important classes of intermediates are used in the manufacture of surfactants, cosmetics, alkyd resins, nylon-6, plasticizers, lubricants and greases, paper, and pharmaceuticals (Ahmed and Morris, 1994). Of the approximately 2.5 million tons of fatty acids produced in 1991, about 1.0 million tons (40 percent) were derived from vegetable and natural oils; the remaining 1.5 million tons were produced from petrochemical sources. Twenty-five percent of all plant-derived fatty acids used in the coatings industry comes from tall oil (a byproduct of kraft paper manufacture). The range of compounds in tall oil is quite large and unique, including long-chain unsaturated fatty acids.

SPECIALTY CHEMICALS

Specialty chemical markets represent a wide range of high-value products. These chemicals generally sell for more than $2.00 per pound. Although the worldwide market for these chemicals is smaller than those for bulk and intermediate chemicals, the specialty chemicals market now exceed $3 billion dollars and is growing 10 to 20 percent annually (Datta, 1994). Examples of biobased specialty chemicals include bioherbicides and biopesticides; bulking and thickening agents for food and pharmaceutical products; flavors and fragrances; nutraceuticals (e.g., antioxidants, noncaloric fat replacements, cholesterol-lowering agents, and salt replacements); chiral chemicals; pharmaceuticals (e.g., Taxol); plant growth promoters; essential amino acids; vitamins; industrial biopolymers such as xanthan gum; and enzymes.

Specialty chemicals can be made using fermentation and enzymatic

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processes or directly extracted from plants. Genetic engineering has now made possible microbial fermentations that can convert glucose into many products and can yield an essentially unlimited diversity of new biochemicals (Zeikus, 1990). Likewise, one could engineer plants to produce some of these same chemicals. Furthermore, industrial researchers are discovering that plants can be altered to produce molecules with functionalities and properties not present in existing compounds (e.g., chiral chemicals). It is anticipated that advances in biotechnologies will have significant impacts on the growth of the specialty chemicals market.

Enzymes

Fermentation of biological materials will continue to be a primary source of most enzymes used today and new enzymes produced in the future. Enzymes serve two major purposes. Some function as biological catalysts in industrial processing of food ingredients, specialty chemicals, and feed additives. Others are components in end products such as laundry detergents, diagnostics, laboratory reagents, or digestive aids.

Worldwide enzyme sales totaled $650 million in 1989 (Layman, 1990) and grew to approximately $1 billion in 1993 (Thayer, 1994). European companies dominate world enzyme production; the largest company, Novo Nordisk, currently supplies 40 to 50 percent of world sales (Thayer, 1994). Analysts predict enzyme sales will grow 10 percent annually over the next few years for traditional markets and new uses. The three largest markets for enzymes are the detergent, starch, and dairy industries. The enzyme market in 1989 broke down into 40 percent for detergents, 25 percent for starch conversion, and 15 percent for dairy applications (Layman, 1990). The remaining 20 percent included leather, pulp and paper, and animal feed manufacture. This last category is of particular interest because it includes industries that historically have caused adverse environmental impacts and, consequently, may have incentive to use more environmentally benign processes like those based on enzymes.

Soaps and Detergents

Industrial production of soaps and detergents in the United States totaled $14.9 billion in 1993 (Ainsworth, 1994). Almost half of the laundry detergents in the United States and 90 percent of those in Europe and Japan contain enzymes. The partial ban in the United States of water-polluting phosphates from detergents in 1982 led to increased use of enzymes in soaps and detergents (Ahmed, 1993). The replacement of traditional chlorine bleach with peroxygen-based bleach additives (such as perborate bleach) also has enabled enzymes to play an important role in

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the soap and detergent industry due to their compatibility with the newer additives (Ainsworth, 1994).

Enzymes are naturally diverse and function in various cleaning agent roles. Protease, lipase, and cellulase enzymes are used in soaps and detergents to break down and help remove dirt stains. Celluzyme, a Novo Nordisk product, removes microfibrils that emerge from cotton fibers after use and cause an "old and gray" appearance (Falch, 1991). In addition, detergent enzymes reduce energy use because they are effective in much cooler wash waters.

Food Processing Enzymes

The largest use of enzymes as catalysts is in the production of high-fructose syrup from starch. Amylases break down starch to glucose; then glucose isomerase is used to isomerize the glucose into fructose. The resulting mixture of glucose and fructose is used as a sweetener in soft drinks. Enzymes also have several uses in the dairy industry. The enzyme rennin coagulates milk protein and is used to make dairy products such as cheeses. Lactase is used to produce lactose-free milk.

Cellulase Enzymes

Relatively small amounts of cellulase enzymes are used now, primarily in the food industry. A large-scale fermentation industry based on lignocellulosic materials will require huge volumes of cellulases, much larger amounts than for any other enzyme, at much lower enzyme prices than currently available. Reducing the costs of cellulase enzymes is a key research priority for reducing the costs of industrial processing of biobased raw materials.

Other Uses for Enzymes

Various industries use enzymes as end products or biocatalysts at a smaller scale. The leather manufacturing industry has traditionally used lime and sodium sulfide mixtures to dissolve hair on animal skins—a process that is polluting and unpleasant to work around. Proteases provide an alternative treatment that loosens and removes the hair, allowing it to then be filtered off. Proteases also result in a better-quality end product (Falch, 1991). The pulp and paper industry also uses enzyme technologies, especially xylanases for bleaching to replace chlorine. The textile industry uses cellulases for making "stonewashed" jeans (Wrotonowski, 1997).

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Animal Feed Industry

The animal feed industry is currently developing beneficial applications of enzymes on a large scale. Certain antinutritional compounds are present in animal feeds. Beta-glucans create viscous mixtures after being solubilized, and these impair animal digestion by causing poor absorption, poor diffusional rates of solutes in the digestive tract, and a low rate of nutrient uptake. Addition of beta-glucanases (enzymes that degrade beta-glucans) to animal feeds removes the beta-glucans and their associated problems. This technique makes it possible to produce efficient animal feeds from grains that are high in beta-glucans, such as barley and oats. It also decreases the amount of manure produced by animals consuming the feed.

Enzymes may lessen the contribution of animal feeds to phosphate pollution. Phytic acid, the major plant storage compound for phosphate, comprises about 60 to 65 percent of the phosphorus content in animal feeds made from cereal grains. Phytic acid forms complexes with iron and zinc ions and makes these metal ions less available for assimilation by animals. Moreover, animals cannot degrade phytic acid, so producers add inorganic phosphate to animal feed as a supplement, although most of the supplemental phosphate is excreted. The estimated 100 million tons of animal manure produced each year in the United States is thought to liberate 1 million tons of phosphates, contributing significantly to phosphate pollution. Addition to animal feeds of phytase, an enzyme that degrades phytic acid, allows animals to digest the phytic acid and better assimilate the iron and zinc ions. Less phosphorus consequently needs to be added to the feed, thereby reducing the contribution of animal feed to phosphate pollution. The animal feed industry can benefit from the addition of a variety of enzymes to feed mixes. It is important to note that modifications of feed composition can be made through genetic engineering of plants to allow for optimization of the feed directly.

BIOBASED MATERIALS

Increased consumer demands for environmentally benign products are leading to numerous opportunities in the biobased materials market. Diverse materials are produced from agricultural feedstocks, including wood and paper; cotton, kenaf, and other textiles; industrial starches; and specialty polysaccharides such as xanthan, fats and oils, and proteins (Narayan, 1994). Also under development are biobased composites such as one made of soybean protein and waste paper.

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Bioplastics

Renewable resources such as industrial starches, fatty acids, and vegetable oils can serve as sources for bioplastics. Biodegradable thermoplastics—such as starch esters, cellulose acetate blends, polylactide, thermoplastic proteins (e.g., zein), and poly(hydroxybutyric acid)

BOX 3-1
Plastics from Plants and Microbes

Poly(hydroxybutyrate) (PHB) and its variants, generally known as polyhydroxyalkanoates, are natural polymers commonly produced by plants and microbes. PHB is a truly biodegradable plastic material that is naturally and efficiently degraded to carbon dioxide and water by many common soil bacteria. It is also a common food storage material in bacteria that accumulates inside bacterial cells when carbon is in excess but some other nutrient limits growth. In bacteria such as *Alcaligenes eutrophus*, PHB may represent as much as 90 percent of the total cell mass under the appropriate growth conditions. PHB is derived from acetyl-CoA, a component of primary metabolism, by a process involving three enzymes. The enzyme beta-ketothiolase condenses two molecules of acytl-CoA to yield acetoacetyl-CoA. This compound is reduced to beta-hydroxybutyryl-CoA by acetoacetyl-CoA reductase and then condensed to a nascent polymer chain by PHB polymerase.

Commercial production by fermentation is currently under way for poly-3-hydroxybutyrate-3-hydroxyvaleate (PHB-V), a PHB that has characteristics similar to polypropaline or polyethelene. Nevertheless, a broader commercial use of these natural polymers will require new biological and engineering technologies to enable large-scale production. One possible approach is to increase and improve synthesis in the host bacterium by mutating the existing biosynthetic pathway. Another is to move the genes for PHB synthesis into other bacteria, plants, or yeasts for increased production. At Michigan State University, Sommerville and colleagues pioneered this approach using the common weed *Arabidopsis* as a "bioreactor." The researchers manipulated genes for PHB synthesis in *Arabidopsis* and showed the plant produced PHB at a low level. Moving the genes to the target expression in a different part of the plant cell (i.e., from the cytoplasm to the chloroplast) dramatically increased PHB production.

Increased understanding of the basic science underlying the plant and bacterial metabolic and biosynthetic pathways has made possible another exciting development. New polymer structures can now be engineered by manipulating the PHB metabolic pathway in various plants and microbes. For example, less brittle plastics may result if low amounts of poly(hydroxyvalerate) are coproduced in bacterial or plant cells that manufacture PHB. These polymers are readily biodegradable and have properties that make them a suitable substitute for petrochemical-derived thermoplastics. The new-found ability to "engineer" chemical derivatives of such polymers in living cells holds the promise of a truly environmentally benign bioprocess.

SOURCE: Poirier et al. (1995).

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(PHB)—show great promise for replacing the plastics derived from petrochemicals that generally are not biodegradable (see Box 3-1). Graft plastic polymers (plastics based on plant materials and petrochemicals) are less bio- degradable than plant-based bioplastics. Bioplastics comprise about 5 percent of the total polymer, plastics, and resin market (Ahmed and Morris, 1994).

The bioplastics industry has generated new markets for industrial starches. Starch can be directly manufactured into products such as biodegradable loose-fill packaging to replace nondegradable polystyrene-based packaging peanuts. Fermenting starch into lactic acid or PHB yields other starch-derived thermoplastics. The Cargill Company has introduced polylactide-based thermoplastics for single-use disposable products such as utensils, plates, and cups. ICI Corporation has commercialized biodegradable PHB plastics for shampoo bottles and other higher-cost disposables. Plant matter also provides a new material for direct processing into plastic and polymeric resins.

A graft copolymer of latex and starch is used to make coated papers. Certain starch-based plastics are also in commercial use, as are various graft polymers between starch and synthetics. One class of graft polymers absorb many times its weight in water and has many applications such as absorbent soft goods (e.g., absorbents for body fluids, disposable diapers, hospital underpads, and related products), hydrogels, and agricultural products (such as seed and bare root coatings and hydromulcher) (Doane et al., 1992). These hydrophilic graft polymers are prepared using polyacrylonitrile in which the nitrile substituents have been hydrolyzed with alkali. Many new starch-based polymers and applications are expected to appear soon in commercial uses.

Soy-based Inks

Soybean oil-based inks were introduced to U.S. markets in the 1970s in response to the oil shortages. More recently increased emphasis on improving worker safety and reducing environmental emissions has spurred interest in alternatives to petroleum-based inks. Soybean oil is a carrier for a pigment in ink formulations. Plant-derived inks require less use of hazardous chemicals during equipment maintenance, produce lower evaporative emissions of volatile organic hydrocarbons, and are biodegradable. Soybased inks are more desirable because the lighter color of soybean oil enhances the true color of colored ink pigments compared to petroleum-based inks. Black soy-based inks typically require a larger proportion of oil than pigment in comparison to colored printing inks. Because soybean oil costs more than petroleum, black soybased inks are at a cost disadvantage. Some research indicates that soy inks can spread

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BOX 3-2
Biopolymers

The great majority of all biomass consists of natural polymers, and the great majority of all biomass is carbohydrate in nature. This means that the majority of all biomass is in the form of carbohydrate polymers, called polysaccharides. These natural polymers (biopolymers) can be used both as nature provides them and as the skeletal framework of other derived polymers. By far the most abundant of these carbohydrate polymers is cellulose, the principal component of cell walls of all higher plants. It is estimated that 75 billion tons of cellulose are biosynthesized and disappear each year, most of the disappearance being through natural decay.

Cellulosic plant materials are used as fuel, lumber, and textiles. Cellulose is currently used to make paper, cellophane, photographic film, membranes, explosives, textile fibers, water-soluble gums, and organic-solvent-soluble polymers used in lacquers and varnishes.

The principal cellulose derivative is cellulose acetate, which is used to make photographic film, acetate rayon, various thermoplastic products, and lacquers. The world's annual consumption of cellulose acetate is about 750,000 tons, 400,000 to 450,000 tons being produced in North America. Cellulose acetate products are biodegradable.

While use of biopolymers, largely polysaccharides, as is and in modified form is now considerable, only a infinitesimal amount of that available is now utilized commercially in applications also served by petroleum-based polymers; so the potential is enormous. Broader application of such preformed polymeric materials awaits research and development.

plant fiber composed of 90 percent cellulose. The long fibers of cotton make it an ideal material for weaving and spinning into cloth. Cotton confers qualities on fabrics that are difficult to duplicate with synthetic fabrics. Demand for cotton products has resurged in recent years, and the United States harvested approximately 18 million bales of raw cotton in 1996 to 1997 marketing year (USDA, 1997a). Advances in biotechnology and genetic engineering are now enabling development of cotton cultivars with improved pest resistance, yield, and quality, thereby potentially reducing production costs and better matching cotton characteristics to specific applications.

Natural fibers other than cotton occupy various U.S. niche markets, such as specialty fabrics, papers, cordage, and horticultural mulches and mixes. Heightened environmental concerns are helping natural fibers find their way into new markets as well. Jute, hemp, sisal, abaca, coir fibers, and products derived from these fibers are currently being imported but could be produced domestically.

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TARGETING MARKETS

This section identifies opportunities for replacing products made from nonrenewable fossil feedstocks with biobased chemicals and materials. In the midterm, biobased products will be primarily oxygenated chemicals and materials; petroleum will remain a more competitive feedstock for hydrocarbon-based liquid fuels and aromatic and alkane chemicals. Over the longer term, adoption of biofuels and biobased aromatic and alkane chemicals could grow significantly, given investment in the necessary research and development and perhaps carefully chosen incentives. The manufacture of chemicals is now dominated by fossil fuel sources; this market may represent the greatest opportunity for replacement of petrochemicals with biobased material. Only about 10 percent of the 100 million metric tons of chemicals marketed in the United States are biobased. The remaining 90 million tons of organic chemicals currently derived from fossil fuels potentially could be replaced by renewable resources.

Biomass processing—fermentation of starch or cellulose accompanied by additional chemical, thermal, and physical processing steps—can produce a number of oxygenated intermediate chemicals, including ethylene glycol, adipic acid, ethanol, acetic acid, isopropanol, acetone, butanol, citric acid, 1,4-butanediol, methyl ethyl ketone, N-butanol, succinic acid, itaconic acid, lactic acid, fumaric acid, and propionic acid. These intermediate chemicals have uses in the manufacture of such polymers as nylon, polyesters, and urethanes; of various plastics and high-strength composites; and of solvents, coatings, and antifreeze. Numerous chemical markets may be filled by agricultural feedstocks.

Development of fermentation industries over the next few decades could be accomplished in three progressive phases: (1) glucose from corn feedstock, (2) sugars from lignocellulosic crop residues from silviculture and agriculture, and (3) establishment of a large "carbo-chemistry" industry using sugars derived from the most cost-effective local sources. Another approach would be to produce industrial chemicals in genetically engineered plants. These chemicals and materials could then be separated from the plant matter and upgraded by processing, possibly biological processing in some cases.

Apart from pulp and paper, ethanol fuel is probably the largest single biobased industrial product. The United States produced about 1.1 billion gallons of ethanol in the 1995 to 1996 marketing year (ERS, 1997b), less than 1 percent of annual domestic gasoline consumption. The United States used 1.8 billion tons of mostly fossil fuels in 1989, triple the amount of all of the plant matter consumed for food and nonfood purposes combined (Ahmed, 1993). Large-scale production of ethanol fuel from lignocellulose may become economically feasible with new processing technologies, although this may take decades to materialize.

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Specialty chemicals represent a rapidly growing and diverse group of high-value industrial products. The benefits of some of these biobased products are well known (e.g., enzymes). At the same time, rapid advances occurring in the life and materials sciences will lead to discoveries of plant compounds that cannot be produced with petroleum feedstocks. Industry will vigorously pursue the most promising candidates for further development and commercialization. Since some of these products will be successful and others will not, this market will be constantly evolving. It will be important for academic and industrial scientists to monitor market trends and technological breakthroughs to identify promising target areas for future research.

Significant opportunities exist to increase markets for biobased materials. Because most industrial materials can be produced from agricultural and forestry feedstocks, markets for biomaterials and biopolymers likely will increase. For example, the United States manufactures annually more than 5 billion pounds of industrial starches for multiple uses, including making paper and paperboard. Several biodegradable polymers—such thermoplastics as polylactide and poly(hydroxybutyrate)—have been developed and are now sold commercially in small quantities. It is likely that biobased materials, including biopolymers, will serve as important and diverse resources for a growing biobased industry.

CAPITAL INVESTMENTS

A substantial investment of capital will be required to commercialize biobased products. Capital investment figures estimated for nine biobased chemicals are shown in Table 3-3. The private sector currently is investing in lactic acid production for use in lactic acid polyester formation, a polymer that can substitute for polystyrene in many cases. The capital required for developing the remaining eight chemicals would be more than $6 billion.

Scale-up and commercialization costs are significant barriers in moving laboratory discoveries into the market. Industrial researchers estimate that the relative costs of discovery, scale-up, and commercialization are 1:10:100. Hence, $1 million invested in basic research generates sufficient promising technologies to justify $10 million invested in scale-up and risk reduction efforts that, in turn, are sifted through to find sufficient proofs of concept to warrant $100 million invested in commercial-scale manufacturing facilities. Applying these ratios to the eight chemicals listed in Table 3-3 suggests that $600 million dollars would be required to adequately demonstrate promising production technologies at a pilot scale and that $60 million would be required to support research aimed at solving the technical issues that have the greatest impact on processing costs.