Introduction 1

Throughout history, humans have relied extensively on biological materials like wool, leather, silk, and cellulose.[1] Today, such natural polymers can be tailored to meet specific needs. The advent of modern biotechnology has fundamentally transformed the way scientists view organisms and the materials they produce. For example, the genetic manipulation of some plant species could give rise to a new source of structural polymers that supplant traditional commodity plastics. By harnessing the enzymes found in nature, or transforming agricultural or marine feedstocks, a new class of biodegradable, biocompatible, and renewable materials is on the horizon.

Polymers play a central role both in the natural world and in modern industrial economies. Some natural polymers, such as nucleic acids and proteins, carry and manipulate essential biological information, while other polymers such as the polysaccharides—nature's family of sugars-provide fuel for cell activity and serve as structural elements in living systems. With advances in chemistry and materials science, a vast array of novel synthetic polymers has been introduced over the past century. Synthetic polymers such as nylon, polyethylene, and

1 These four materials are natural polymers. Polymers are substances composed of repeating structural units that are linked together to form long chains.

polyurethane have transformed daily life.[2] From automobile bodies to packaging, compact discs to clothing, and food additives to medicine, man-made polymers pervade virtually every aspect of modern society.[3]

However, the growing reliance on synthetic polymers has raised a number of environmental and human health concerns. Most plastic materials, for instance, are not biodegradable and are derived from nonrenewable resources.[4] The very properties of durability and strength that make these materials so useful also ensure their persistence in the environment and complicate their disposal. In addition, the synthesis of some polymeric materials involves the use of toxic compounds or the generation of toxic byproducts.[5]

These problems have focused increased attention on polymers that are derived from biological precursors or are produced by using the methods of modern biotechnology.[6] Such *biopolymers* may prove to have a variety of environmental benefits. Possible applications range from agriculturally or bacterially derived thermoplastics that are truly biodegradable, to novel medical materials that are biocompatible, to water treatment compounds that prevent mineral buildup and corrosion.[7] However, because materials typically have many different properties, in certain applications biopolymers may not necessarily provide environmental advantages over conventional polymers.[8] In practice, it is extremely difficult to develop testing methods that assess the environmental characteristics of materials.[9]

In recent years, a number of significant technical developments, particularly in the area of genetic engineering, have enhanced the commer-

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[2] These materials have been widely adopted because they are lightweight, strong, versatile, damage-resistant and chemically inert.

[3] In 1990, the United States produced 46.8 billion pounds of thermoplastics (e.g., polypropylene, polystyrene, polyethylene), 8,6 billion pounds of thermosetting plastics (e.g., urethanes and epoxy compounds), 8.1 billion pounds of synthetic fibers (e.g., nylon and polyester), and 0.5 billion pounds of cellulosic fibers (e.g., rayon) (data compiled by BioInformation Associates, Boston, MA).

[4] A biodegradable material is a material in which degradation results from the action of naturally occurring microorganisms such as bacteria, fungi, and algae.

[5] Although toxic intermediatcs are sometimes used in the manufacture of polymers, *the* final polymer products themselves are rarely toxic. Few commercially important polymers have any toxicity at all, thus they are used in a broad range of applications from food packaging to medical care. It is important to note that toxicity is often determined by the dose or concentration of a substance, so many compounds that pose health or ecological risks at very high concentrations may pose little risk at low concentration.

[6] Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, improve plants or animals, or develop micro-organisms for specific uses. Biotechnology also includes the development of materials that emulate the molecular structures or functions of living systems. For a comprehensive discussion of developments in this emerging field, see U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology:* An International Analysis, OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984); U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy,* OTA-BA-494 (Washington, DC: U.S. Government Printing Office, October 1991); and Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, Biotechnology~or *the* 21st *Century* (Washington DC: U.S. Government Printing Office, February 1992).

[7] Conventional water treatment chemicals employed as flocculants, corrosion inhibitors, and antiscalants are generally used at very low concentrations where they are not known to produce toxic effects. However, these compounds are not typically biodegradable.

[8] Little research has been done concerning the potential environmental impacts of biopolymers that are used in large quantities, It is possible that the widespread use of some biopolymers may have unanticipated effects on ecosystems or waste streams. It should be noted that some naturally occurring polymers have varying degrees of toxicit y. Some examples of natural toxicants include the protein toxins from pathogenic bacteria, and certain plant proteins that act as natural pesticides. *See Regulatory Toxicology and Pharmacology,* vol. 12, No. 3, December 1990, pp. S11-s77.

[9] For example, the biodegradability of a particular material is determined by a set of complex factors such as material shape and surface-to-volume ratio, as well as environmental conditions such as nutrient concentration, bacterial-fungi inoculation, pH, moisture level, and temperature. Any or all of these factors may vary from location to location. For a discussion of the problems associated with environmental evaluation methods, see U.S. Congress, Office of Technology Assessment, *Green Products by Design: Choices for a Cleaner Environment, OTA-E-541* (Washington, DC: U.S. Government Printing Office, October 1992).

cial prospects of biologically derived polymers .10 The advent of recombinant DNA technology has allowed researchers to exercise unprecedented control over the purity and specific properties of polymers. [11] Advances in genetic engineering have also enabled scientists to study how biological systems produce complex polymers. It is remarkable that living organisms are able to create sophisticated materials (e.g., spider silk) at normal temperature and pressure, without causing environmental disruption. This is certainly not the case for many man-made materials. *2 Thus, biopolymer research could also lead to the development of new environmentally sensitive manufacturing methods.

Biopolymers area diverse and versatile class of materials that have potential applications in virtually all sectors of the economy. For example, they can be used as adhesives, absorbents, lubricants, soil conditioners, cosmetics, drug delivery vehicles, textiles, high-strength structural materials, and even computational switching devices. Currently, many biopolymers are still in the developmental stage, but important applications are beginning to emerge in the areas of packaging, food production, and medicine. Some biopoly - mers can directly replace synthetically derived materials in traditional applications, whereas others possess unique properties that could open up a range of new commercial opportunities. Novel biopolymer compounds are being investigated by established agricultural and chemical firms, as well as small biotechnology enterprises.

Yet despite the promise of these new materials, a series of economic and engineering hurdles may impede their introduction to the market in the near term. Even if some biopolymers are shown to have environmental characteristics that are preferable to conventional polymers, much work needs to be done to bring down the costs of biologically derived materials. Commercially available biopolymers are typically two to five times more expensive than synthetic resins. In only a few specialized applications, such as biomedicine, are the relatively high costs of biopolymer materials not likely to impede market growth. Since many biopolymers are in the early phases of development, it is difficult to determine whether economy-of-scale manufacturing will be able to bring down their current high production costs. The commercialization difficulties facing biopolymers in many ways resemble the problems confronting other emerging technologies such as photovoltaic cells and fuel cells.[13]

At present, government-sponsored research and development efforts in the biopolymer area are relatively small in scope, but many ongoing Federal activities in biotechnology and agriculture have an indirect bearing on biopolymer science. Unlike Japan and the European Community, the United States does not have a well-defined biopolymer policy. The United States is, for the moment, well positioned in some areas of biopolymer development because of its strong agricultural base, expertise in polymer engineering, and active biotechnology sector. However, the relative competitive position of the United States could be enhanced by fostering greater collaboration among researchers in government, industry, and academia. Fundamental research barriers in the biopolymer field could also be better addressed by bringing greater coherence to

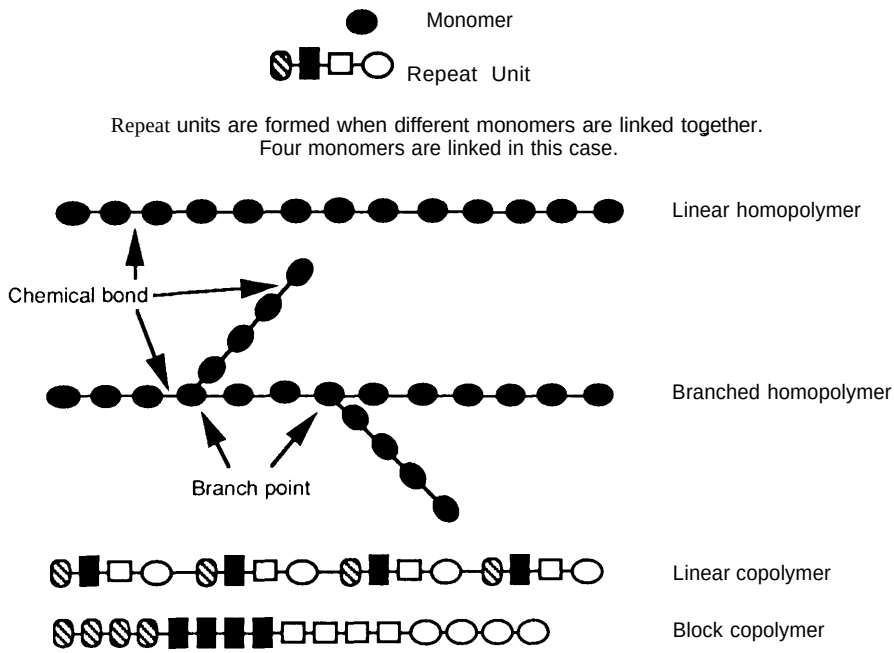
[10] Advances have also occurred in the development of chemical analogues of natural polymers (see Ch. 2).

11 Recombinant DNA technology allows direct manipulation of the *genetic material* of individual *cells. The* ability to direct which genes arc used by cells permits extraordinary control over the production of biological molecules. See discussion below.

[12] Many advanced materials are synthesized at extremely high temperature and pressure, and require toxic substances at various stages of processing.

[13] Technologies that convert or use renewable energy face a number of commercialization barriers. Some barriers are technical, while others relate to the high costs of production. There is a ‘ ‘chicken and egg’ problem of developing a market. Lower costs might be achieved through economy-of-scale manufacturing, but without market demand, it is not possible to make the investments necessary to achieve those low costs. Since fossil fuels are relatively inexpensive, it has been difficult for renewable energy technologies to make significant commercial inroads.

Figure 1-1—Some Basic Structural Features of Polymers



SOURCE: Office of Technology Assessment.

the research and development (R&D) efforts of different Federal agencies. The formidable economic and technical obstacles facing biopolymers, as well as the interdisciplinary nature of the biopolymer field itself, pose difficult challenges for policymakers and industry managers alike.

POLYMERS: A PRIMER

Polymers are a class of "giant" molecules consisting of discrete building blocks linked together to form long chains. Simple building blocks are called monomers, while more complicated building blocks are sometimes referred to as ''repeat units' (see figure l-l). When only one type of monomer is present, the polymer is referred to as a homopolymer. Polyethylene—the material commonly used in plastic bags—is a homopolymer that is composed of ethylene building blocks. A copolymer is formed when two or more different monomers are linked together. The process by which the monomers are assembled into polymers, either chemically or biologically, is referred to as polymerization. Polymers can **be** either linear or branched (figure l-l).

The distinguishing features of a polymer are determined by the chemical properties of the monomeric units (i.e., what the polymer is specifically composed of), the way in which the monomeric units are linked together, and the size or molecular weight of the polymer. (The size of the polymer is determined by the number of monomers linked together.) Each of these parameters contributes to the physical properties of the polymer product. Understanding the relationship between polymer structure and physical properties remains one of the most active and challenging areas of current research. In practice, polymers that are created by conventional chemical approaches lack uniformity in length, composition, and spatial orientation. Thus, a central aspect of polymerization techniques is statistical

Table 1-1—Biopolymers Found in Nature and Their Functions

Polymer	Monomers	Function(s)
Nucleic acids (DNA and RNA)	Nucleotides	Carriers of genetic information universally recognized in all organisms
Proteins	Alpha-ammo acids	Biological catalysts (enzymes), growth factors, receptors, structural materials (wool, leather, silk, hair, connective tissue); hormones (insulin); toxins; antibodies
Polysaccharides (carbohydrates)	Sugars	Structural materials in plants and some higher organisms (cellulose, chitin); energy storage materials (starch, glycogen); molecular recognition (blood types), bacterial secretions
Polyhydroxyalkanoates	Fatty acids	Microbial energy reserve materials.
Polyphenols	Phenols	Structural materials in plants (lignin), soil structure (humics, peat), plant defense mechanisms (tannins)
Polyphosphates	Phosphates	Inorganic energy storage materials
Polysulfates	Sulfates	Inorganic energy storage materials

SOURCE BloInformatlon Associates, contractor report prepared for the Office of Technology Assessment, April 1993

control of key polymer characteristics. Much of modern polymer science is concerned with reducing this variation in polymer properties.[14]

BIOPOLYMERS

The term “biopolymers’ is used to describe a variety of materials. In general, however, biopolymers fall into two principal categories:

- polymers that are produced by biological systems such as microorganisms, plants, and animals; and
- polymers that are synthesized chemically but are derived from biological starting materials such as amino acids, sugars, natural fats, or oils.[15]

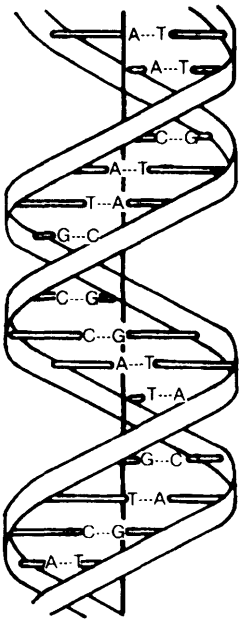
Table 1-1 lists various types of naturally occurring biopolymers defined on the basis of the chemical structure of their monomeric units, and indicates the functions that these polymers serve in living organisms. For example, DNA (deoxyribonucleic acid), which carries the essential genetic information of living systems, is a linear copolymer composed of four monomer nucleotides. [16]The nucleotides are linked together along

[14] Curtis Frank, ‘‘Polmer Materials Science: Novel Synthesis and Characterization of Supermolecular *Structures,* ” *Materials Research Society Bulletin,* vol. 16, No. 7, July 1991.

[15] Polyamides (nylons), some epoxies, and other polymers can be synthesized from naturally occurring fatty acids and oils. For example, ‘*nylon 11, ’ which is derived from castor oil, is now available commerically. The U.S. Department of Agriculture has sponsored a great deal of work in this area (L. Davis Clements, U.S. Department of Agriculture, Cooperative State Research Service, Office of Agricultural Materials, personal communication, July 27, 1993).

[16] The amount of DNA present in a cell is proportional to the complexity of the cell. This was one of the clues that led scientists to confirm that DNA is the bearer of genetic information. DNA can be thought of as a library that contains the complete plan for an organism. If the plan were for a human, the library would contain 3,000 volumes of 1,000 pages each. Each page would represent one gene or unit of heredity and be specified by 1,000 letters. The four nucleotide bases—adenine, cytosine, guanine, and thymine—are the letters of the chemical language. A gene is an ordered sequence of these letters. Any particular sequence specifies the information necessary to create a protein.

Figure 1-2—Structure of DNA



Schematic **diagram of the DNA double helix.**

The DNA molecule is a double helix composed of two chains. Sugar-phosphate backbones twist around around the outside, with paired bases on the inside serving to hold the chains together.

SOURCE: U.S. Congress, Office of Technology Assessment, Com-*mercial Biotechnology:* An International*Analysis,* OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

a pair of helical sugar-phosphate backbones (see figure 1-2). As an industrial polymer, DNA is currently not of commercial interest, although some researchers are beginning to examine this biopolymer for the purpose of assembling nanostructural materials, as well as for its electrical properties. [17]

Proteins-also referred to as polypeptides—are complex copolymers composed of up to 20 different amino acid building blocks. There are virtually a limitless number of proteins that can be formed from these 20 monomers, just as there are a vast number of words that can be made from the 26 letters of the alphabet (see box l-A). Proteins can contain a few hundred amino-acid units or thousands of units. Each protein has a specific chemical composition and three-dimensional shape. The amino-acid building blocks are linked by amide bonds in specific sequences determined by the DNA code of the corresponding gene.[18] Protein polymers are unique in that the sequence of the monomers in the polymer chain is predetermined by the template specific reamer of the polymerization process (i.e., they are copied from a genetic blueprint.)19 The sequence diversity of proteins is responsible for the wide array of functions performed by these materials in living organisms. Proteins typically account for more than 50 percent of the dry weight of cells, and are the primary means of expressing the genetic information coded in DNA. In recent years, researchers have been able to synthesize various polypeptides that are similar to natural proteins found, for example, in biominerals such as shells or bones. Synthetic polypeptides are usually created from amino-acid precursors (e.g., aspartic acid).

Polysaccharides are polymers or macromolecules composed of simple sugars. The polysaccharides have two principal functions. Some, such as starch, store energy for cell activity, and others, such as cellulose, serve as structural

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17 Researchers have used the twisting strands of DNA to construct simple three-dimensional structures. These DNA structures could conceivably be used to encase other molecules or to serve as a molecular scaffolding to which other molecules could be attached. See J. Chen and N. Seeman, ''Synthesis from DNA of a Molecule with the Connectivity of a Cube, " *Nature, vol.* 350, Apr. 18, 1991, pp. 631-633.

18 The term ''gene " is defined as the basic unit of heredity-an ordered sequence of nucleotide bases, constituting a distinct segment of DNA.

19 Each amino acid in a protein chain is represented *by three* nucleotides from the DNA. Thus, different nucleotide combinations give rise to different amino-acid sequences, which give rise to different proteins.

20 Unlike proteins, polysaccharides do not have an information-carrying function. However, when polysaccharides are connected to proteins, they guide proteins to correct locations within a cell—a property that is useful in drug delivery. For more detail on the respective functions of these biopolymers, see Albert Lehninger, *Biochemistry (New* York, NY: Worth Publishers, 1975).

Box I-A–Probability and the "Miracle" of Life

How is it that biological systems are able to produce the polymers that are needed to sustain life? Stated another way, how can a particular kind of polymeric structure be created out of the extraordinarily vast number of structures that are possible? If, for example, a polymer consists of k types of monomers and has a total length N, the number of possible polymeric structures that can be generated is k^N. This number becomes extremely large when the polymer is of even moderate length. For instance, proteins consist of 20 different types of amino acids and are about 100 units long. Therefore, 20^{100} (about 10^{130}, or 1 followed by 130 zeros) possible polymeric configurations exist. For DNA, k = 4 (four types of nucleotides), and N = 1 million, so 4^{106} (about $10^{600,000}$, or 1 followed by 600,000 zeros) structures are possible. Thus, the probability of the right polymer being created by chance alone is fantastically small. However, biological systems are able to generate the desired polymer with a probability virtually equal to 1 (i.e., there is basically a 100 percent chance that the correct polymer will be created). This high probability is due principally to the presence of biological catalysts (enzymes) that eliminate the randomness associated with chemical transformations and thereby ensure the "uniqueness" of biochemical processes. Enzymes play a central role in DNA replication and protein production, as well as in polysaccharide biosynthesis. It should also be noted that some biological monomers have certain chemical tendencies to form "nonrandom" polymers even under simple conditions of formation (e.g., simple thermal polymerization of amino acids gives rise to compounds that have a relatively high degree of order).

SOURCES: V. Averisov et al., "Handedness, Origin of Life, and Evolution," Physics Today, July 1991, pp. 33-41; S. Fox and A. Pappelis, "Synthetic Molecular Evolution and Photocells," The *Quarterly Review of Biology*, vol. 68, No. 1, March 1993.

materials in living systems.[20] After proteins, polysaccharides are among the most diverse and complex group of biopolymers. This is because the bonds linking the sugar monomers can be formed at different positions on the sugar units (illustrated in figure 1-3 for homopolymers of glucose). By simply linking glucose monomers together at different positions, polymers with very different properties are produced (see chapter 2). At least 20 different sugars have been identified in a variety of polysaccharides from biological sources, and thus a great range of polymer structures can be created (see box l-A).

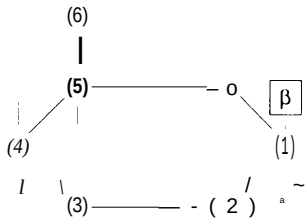
Many polysaccharides contain branched structures and are chemically modified by the addition of other molecules. The monomeric or repeat units are often made up of more than one sugar molecule and consequently can be quite complex. The xanthan gum repeat unit, for example, contains five sugars. The assembly of polysaccharide repeat units and the associated polymerization processes are not dependent on a template or genetic blueprint, but are specified by the enzymes (biological catalysts) involved in an organism's "biosynthetic pathway."[21] This process in biological systems is often referred to as contemplate polymerization.

Other biopolymers include polyhydroxyalkanoates (PHAs), nature's biodegradable thermoplastics[22] (chapter 2); polyphenols, a class of structural materials; and inorganic polyphosphates and

21 The term "biosynthetic pathway" is used to describe the step-by-step conversion of precursor molecules into a final product, with each step in the process being carried out by a specific biological catalyst (enzyme), A pathway consists of a sequence of reactions leading to a final product that is usually quite different from the starting materials.

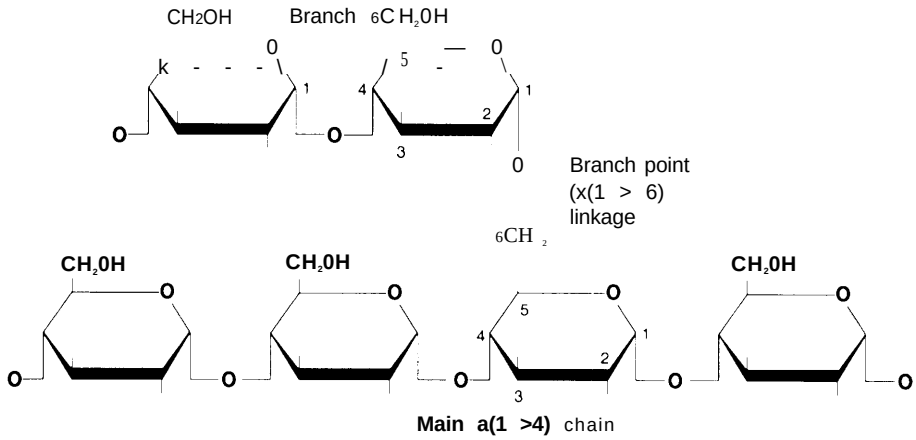
22 Thermoplastics are polymers that will repeatedly soften when heated and harden when cooled.

Figure 1-3-Anatomy of a Natural Sugar



Bond(s)	Polymer
B(1-4)	**Cellulose**
B(1-3), B(1-6)	Yeast glucan
a(l-4), a(1 -6)	Starch

The different types of linkages found in some glucose homopolymers are illustrated. The glucose monomer (above) is made up of six linked carbon atoms. The bond that joins two different sugar units is described by the respective numbers of the carbon atoms that are linked. For example, if the "B1" position of the first sugar monomer is linked to position 4 of the second sugar monomer, the bond would be described as B(1-4). In amylopectin (depicted below), a form of starch, the main polymer chain consists of a(l-4) bonds and the branched chain is connected by a(l-6) bonds.



Amylopectin (a form of starch)

SOURCE: BioInformation Associates, contractor report prepared for the Office of Technology Assessment, April 1993.

polysulfates, which are not discussed in this report.[23]

IMPACT OF GENETIC ENGINEERING ON BIOPOLYMER TECHNOLOGY

Modern biotechnology has given scientists revolutionary tools to probe and manipulate living systems. Genetic engineering permits extraordinary control over the time, place, level, and type of ''gene expression. ''[24] The simplest case applies to protein polymers. Having access to the genetic blueprint (gene) of a particular protein polymer allows one to change both the system that produces the polymer and the composition of

23 These ''inorganic'' polymers have structural backbones that do not contain carbon atoms. However, the polymer side groups often do contain carbon. One type of inorganic polymer family is the polyphosphazenes. These compounds have unique elastic properties.

24 Gene expression is the mechanism whereby the genetic instructions in any particular cell are decoded and processed into a final functioning product, usually a protein. This involves several steps: In a process called transcription, the DNA double helix is locally unzipped near the gene of interest, and an intermediate product, known as ''messenger' RNA, is synthesized. The messenger RNA transmits the instructions found in the DNA code to the protein-synthesizing machinery of the cell, and a protein is created. Proteins are composed of amino acids. Each amino acid in a protein chain is represented by three nucleotides from the DNA. See *Commercial Biotechnology,* op. cit., footnote 6, pp. 34-35.

COURTESY OF DISCOVER MAGAZINE (JULY 1990)

Some bacteria can store energy in polymer-bearing granules (polyhydroxyalkanoates) that can be collected and made into truly biodegradable packaging like these plastic bottles made from Alcaligenes bacteria by Zeneca Bio Products.

the polymer itself. Recombinant DNA techniques permit the creation of polymer chains that are virtually uniform in length, composition, and stereochemistry or spatial orientation[25] (see box l-B). For example, the protein polymer silk that is produced commercially by silkworms can now be made in recombinant microorganisms.[26] The advantage of this new approach is not that the recombinant DNA method is necessarily more economical, but that it is possible to generate polymers of exceptional structural purity, as well as manipulate the biopolymer production system to create new materials. In addition, the recently developed ability to chemically synthesize DNA allows scientists to construct entirely new genes

[25] The three-dimensional arrangement of a biological polymer gives rise to specific types of biochemical activity. For example, the Spatial arrangement of an enzyme results in some reactions being greatly favored over others. It turns out that natural proteins are constructed only from ''left-handed'' amino acids, and nucleic acids are made up only of "right-handed" sugars. Their mirror image structures (e.g., right-handed proteins) are not found in living systems. Although 'left-handed' and 'right-handed' versions (so-called stereoisomers) of any given compound have identical chemical composition and physical properties, they react quite differently biologically and with some reagents. Traditional chemical synthesis techniques usually produce left- and right-handed versions of a polymer, which is undesirable from the perspective of production efficiency.

[26] See David L. Kaplan et al., "Biosynthesis and Processing of Silk Proteins, ' *Materials Research Society Bulletin*, vol. 17, No. 10, October 1992, pp. 41-47.

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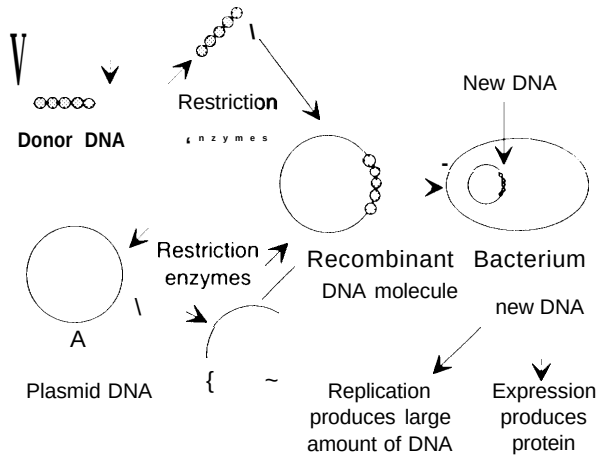
Box l-B–The New Alchemy: Recombinant DNA Technology

Recombinant DNA is formed when **pieces of DNA f from different organisms** are joined together. The basic tech**nique of preparing recombinant** DNA is illustrated in the **diagram shown. Special biological catalysts known as "restric**tion enzymes" are used to cut donor DNA (usually from a higher organism) into fragments, one of which contains the gene of interest. Restriction enzymes recognize certain sites along t he DNA and can chemically cut the DNA at those sites. The resulting DNA fragments are t hen inserted into a "vector,"- a DNA molecule used to introduce foreign genes into host cells. Plasmids, circular segments of DNA **that are not part of chromosomal** DNA, are t he most common types of vectors used. Thus, selected genes from donor DNA molecules are inserted into plasm id DNA molecules to form the hybrid or recombinant DNA. Each plasm id vector **contains a different donor** DNA fragment. These recombinant DNA plasm ids are introduced into host cells in a process called "transformation." When the transformed host cells grow and divide, the plasm ids replicate and partition with the host daughter cells, ultimately providing many host cells that carry the same donor DNA fragment. This process of replication is known as cloning. The cloned genes can then be "switched on, " resulting in the creation of large quantities of the desired protein. Recombinant DNA is grown principally in simple microorganisms such as bacteria and yeast. In recent years, scientists have also developed methods of introducing genetic material into higher plants and animals.



SOURCE: U.S. Congress, Office of Technology Assessment, Commercial *Biotechnology: An /nternationa/* Analysis, OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

SOURCE: U.S. Congress, Office of Technology Assessment, *Commercia/Biotechno/ogy:An Internationa/Ana/ysis,* OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984).

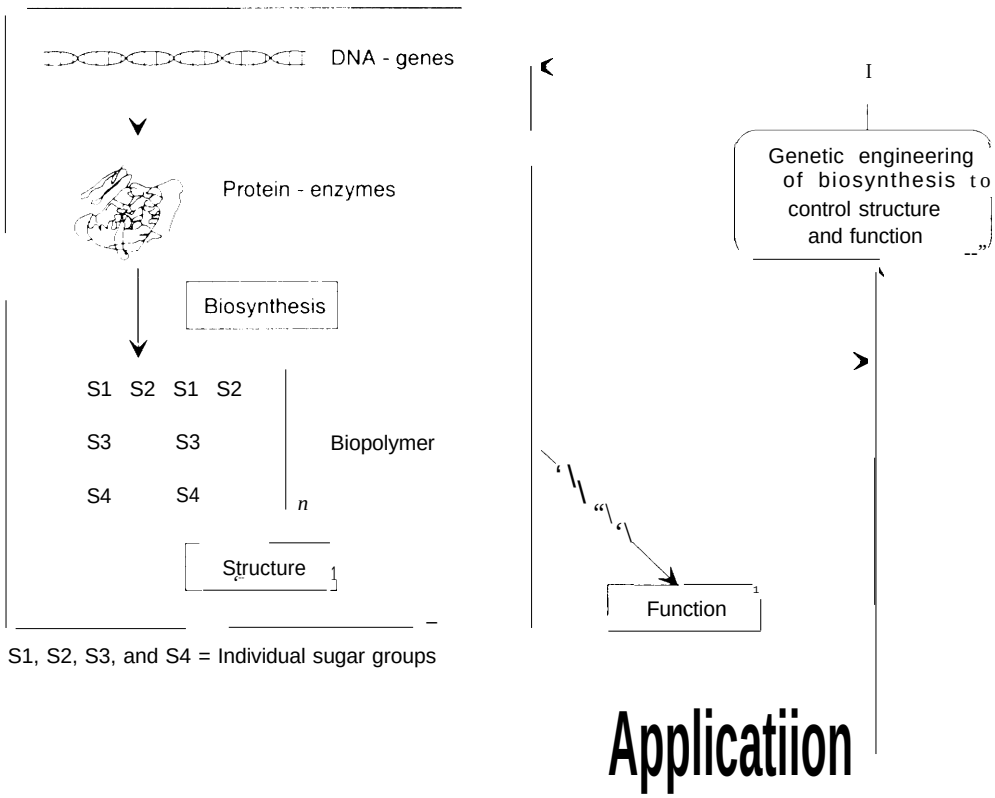
that encode unique protein polymers .27 Researchers are now modifying genes to improve the mechanical and chemical properties of structural proteins such as silk, elastin, and various adhesive polymers.[28]

For biopolymers other than proteins, such as polysaccharides and polyhydroxyalkanoates, the situation is more complicated. In these cases, genetic manipulation permits control of the production of biological catalysts (proteins known as enzymes), which are in turn responsible for the production and polymerization of the building blocks that make up the final polymer products (see figure 1-4). A useful analogy is to view

27 A gene can be synthesized or created directly since the nucleotide sequence of the gene can be deduced from the amino-acid sequence of its protein product.

28 David Tirrell et al., "Genetic Engineering of Polymeric Materials, " *Material sResearch Society Bulletin,* vol. 16, No. 7, July 1991, pp. 23-28.

Figure 1-4-A Genetically Engineered Biopolymer Production System



S1, S2, S3, and S4 = Individual sugar groups

Unlike proteins, polysaccharides and other natural polymers are not created by following a genetic blueprint; rather, an organism outlines a "pathway" of synthesis in which each step of the pathway is carried out by a specific enzyme. Some polysaccharide pathways can have more than ten steps and sometimes as many as a hundred steps. By using recombinant **DNA techniques, enzymes from different** biological sources (i.e. species) can be introduced into host organisms, thereby creating entirely new biosynthetic pathways or polymer assembly lines. These new biological assembly lines could be used to produce greater quantities of a particular polymer, or to design novel polymers with unique physical and functional properties.

SOURCE: BioInformation Associates, contractor report prepared for the Office of Technology Assessment, April 1993.

enzymes as being machines that carry out different steps on a biological assembly line. Throughout the biological world there exists an extraordinary army of different machines (enzymes), all encoded by specific genes. Many of these enzymes are present in only one species or strain of organism. The genes for these enzymes are then the blueprints for the individual pieces of machinery, and remarkably, these blueprints are recognized and translated in the same way in all organisms. By adding the appropriate signals and transferring the gene into a new organism, the organism can then produce a new enzyme, thereby giving the organism the capacity to carry out a particular step in the assembly line process. Genetic engineers now have the ability to add new machines, or remove old ones, in practically any system.

The implications of these genetic techniques are quite profound. It is now possible to genetically modify an organism so that it produces greater quantities of a particular polymer. As an example, the introduction of a specific enzyme has allowed researchers to increase starch produc-

tion in genetically engineered plants.[29] It is also possible to transfer an entire assembly line into a new host organism to improve a production process. One illustration of this procedure is the production of the bacterial thermoplastic polyhydroxybutyrate (PHB) in transgenic plant species.[30] Finally, these new techniques allow organisms to be modified so that truly novel materials can be produced. For instance, a series of genetically engineered xanthan gums has been developed by removing specific enzymes from the xanthan assembly line (ch. 2). Ultimately, it may be possible to construct biological systems for the production of entirely new classes of polymers. This could be accomplished by creating new assembly lines using enzymes from diverse sources and then introducing the correct blueprints into an appropriate host. The long-term objective of this type of research is to design biological systems that produce specific polymers for specific applications. For example, materials might be genetically ''customized' to have a unique combination of mechanical, chemical, and degradative properties.

THE ROLE OF CHEMISTRY IN BIOPOLYMER TECHNOLOGY

Given the advances in genetic engineering, what is the role of traditional chemical synthesis in creating biopolymers? The most widely used polymers, such as polypropylene and polyester, are produced by standard chemical means. But as mentioned previously, the processes used to manufacture these synthetic polymers can sometimes have a number of drawbacks. Although technologies for producing proteins by chemical synthesis have been developed, they are extremely costly. Such methods are used primarily for the production of research chemicals or for very high-value applications such as pharmaceuticals. There is no existing chemical technology capable of producing the complex polysaccharide structures made so readily by biological systems. Because of their structural and chemical specificity, enzymes are extremely efficient at producing polymer compounds with high yield.[31]

Yet, chemistry still has an important role to play in the development of biopolymers. Chemical techniques can be used to modify the properties of biopolymers to expand their range of applications, to polymerize biological starting materials, or to create new gene sequences that can lead to novel protein polymers through the application of recombinant DNA methods. Examples of such chemical methods are presented in chapter 2.

THE POLICY CONTEXT

As noted in previous sections, there have been significant advances in basic biopolymer science, with a wide range of new applications on the horizon. Due to the versatility and potential environmental benefits of biopolymer materials, R&D activities are likely to expand considerably in coming years. While technical progress in the biopolymer field is, for the most part, being driven by academia and industry, the Federal Government directly and indirectly affects biopolymer development. In the following sections, the role of federally funded research and various regulatory issues are discussed.

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29 See David M, Stark et al., ''Regulation of the Amount of Starch in Plant Tissues by ADP Glucose Pyrophosphorylase,' *Science*, vol. 258, Oct. 9, 1992, pp. 287-292.

30 While early work in this area is encouraging, many technical challenges remain. See Yves Poirier et al., ''Polyhydroxybutyrate, a Biodegradable Thermoplastic, Produced in Transgenic Plants,' *Science*, vol. *256*, Apr. 24, 1992, pp. 520-523. Transgenic plants are plants whose hereditary DNA has been augmented by the addition of DNA from other species.

31 However, polymers that are created by biological processes such as fermentation may require further purification before they are suitable for a particular application.

Role of Federal R&D Programs

Although there is not a well-defined biopolymer research program in the United States, many ongoing Federal activities have a bearing on biopolymer science. Several Federal agencies are sponsoring efforts in biopolymer research, as well as related areas such as bioprocessing and genetic engineering (see ch. 4). In February 1992, the White House Office of Science and Technology Policy announced the Biotechnology Research Initiative—a coordinated interagency effort to strengthen and diversify Federal research activities in biotechnology .32 This initiative is designed to extend the ''scientific and technical foundations' of biotechnology, to "accelerate the transfer of biotechnology research" to applications in the commercial sector, and to expand interdisciplinary research between biology and other fields, such as chemistry, physics, or materials science .33 The initiative calls for greater attention to be paid to bioprocessing and manufacturing, including bimolecular materials, biocompatible materials, and metabolic engineering, and thus addresses many aspects of biopolyrner science.

However, the amount of funding specifically targeted for biopolymer programs is relatively small. In FY 1993, only about 3 percent ($124 million) of the total biotechnology budget ($4 billion) is devoted to biologically derived compounds and industrial processing research (see ch. 4); and only a small fraction of that 3 percent goes directly to biopolymer development. Some members of the research community have called for more explicit Federal goals in the biopolymer area, particularly in the biomedical field (see box 4-A). For example, the creation of a national center for biomaterials research at the National Institutes of Health (NIH), as some observers have called for, could lend greater focus to biopolymer programs in the medical area.

It is important to recognize, though, that while many important biopolymer applications are emerging in the medical field, there are also promising applications in the industrial, agricultural, and waste management sectors. As noted in a previous Office of Technology Assessment report, Federal funding for biotechnology in the area of medicine dwarfs the funding directed toward agriculture, chemicals, energy, and other biotechnology applications.[34] To ensure that promising nonmedical biopolymer applications are not ignored, Federal programs could give greater emphasis to areas such as the conversion of agricultural or aquatic materials into useful industrial feedstocks and the production of environmentally sensitive materials .35

Despite the promise of new biopolymer production technologies, this nascent field faces the same problems that have confronted other new technologies: development periods of 5 years or longer, poor prospects for short-term gains, and uncertain demand in the marketplace because of inexpensive alternatives (synthetic polymers are currently much less expensive than agriculturally or microbially derived materials). Although some materials are being used now, many biopolymers face a variety of technical and economic barriers that will take several years to overcome. The efforts of the private sector to overcome some of these barriers might be aided by such Federal

32 *Biotechnology for the 21st Century,* Op. cit., footnote 6.

33 Ibid.

34 Biotechnology in *a Global Economy,* op. Cit., footnote 6.

35 Nonmedical research in the biopolymer area is being carried out or sponsored by the office of Naval Research, the U.S. Army Natick Research, Development and Engineering Center, the U.S. Army Research Office, the U.S. Department of Agriculture's Office of Agricultural Materials, the National Science Foundation, and the National Oceanic and Atmospheric Administration (see ch. 4).

programs as the Advanced Technology Program[36] of the Department of Commerce, or the cooperative research and development programs (CRADAs) of the U.S. Department of Agriculture (USDA) and the various Department of Energy national laboratories.[37]

At present, Federal biopolymer research activities are diffuse and for the most part, not well coordinated. Yet, given that biopolymer materials have an extraordinarily broad range of possible uses, the decentralized structure of the Federal research system should not necessarily be regarded as a barrier to biopolymer development. Many biopolymer applications fall neatly into the research agendas of individual Federal agencies and are already the subject of focused attention. On the other hand, a large number of biopolymer applications involve a range of different scientific disciplines, and thus some areas of biopolymer research could no doubt benefit from increased coordination of Government resources.

The recent White House initiative to classify biotechnology research across the Federal research system is beginning to address this situation and is intended to lead to greater cross-agency cooperation.[38] Creating opportunities for increased collaboration among academic, industrial, and Government researchers is an explicit objective of the initiative. These efforts, even without increased levels of funding, should benefit ongoing biopolymer research activities. Over the long term, Federal R&D programs in the biopolymer area might focus on:

- exploratory work on biopolymer materials that are genetically engineered to have unique physical and functional properties or that could be used as substitutes for the commodity resins currently derived from petroleum sources;
- utilization of agricultural or marine products and byproducts;
- biopolymer processing technologies that could potentially lead to new environmentally sensitive manufacturing methods;
- approaches to lower the costs of production associated with various biopolymer manufacturing technologies;
- research on the environmental impacts (positive or negative) of biopolymers that are introduced into solid and aqueous waste streams or natural ecosystems.

As with other areas of technology development, the challenge for policymakers is to determine where Government can best use its R&D resources to complement, rather than replicate, the activities of the private sector.

Regulatory Issues

A number of existing or potential regulatory factors could affect biopolymer development and commercialization efforts. These include the Food and Drug Administration (FDA) approval process for medical applications that use biopolymers; the development of legal definitions for biodegradable materials, or regulations mandating the use of biodegradable materials for

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36 The Advanced Technology Program (ATP) has granted a small number of awards to companies working in the biotechnology Mm. Some of the recent ATP grants have included biopolymer applications in the medical field. For example, Tissue Engineering, Inc., is developing biopolymers derived from animal and marine sources that can be used as prosthetic devices or vascular grafts (Les Garrick, Tissue Engineering, Inc., personal communication, Aug. 23, 1993).

37 The Agricultural Research Service of the USDA has more active CRADAs than any other Government agency. In addition, the USDA's Alternative Agriculture Research and Commercialization Center works with private industry to promote the commercialization of promising new materials. The Department of Energy has a large general effort in biotechnology at its national laboratories, including projects in mapping the human genome and in structural biology.

38 Another White House initiative that relates to biopolymer research is the Federal Advanced Materials and Processing Program (AMPP). AMPP is designed to encourage multidisciplinary research and new advances in materials science. For example, as part of AMPP, the National Science Foundation is supporting work in ceramics, composites, electronic and magnetic materials, superconductors, and biomaterials and bimolecular materials. See "NSF's Participation in Advanced Materials and Processing program (AMPP)," NSF document 93-68, May 7, 1993.

applications such as packaging; regulations affecting the use of genetically engineered systems for producing biopolymers; and requirements regarding the introduction of new industrial chemicals.

FOOD AND DRUG ADMINISTRATION

The FDA is a regulatory agency responsible for the safety of the Nation's foods, cosmetics, drugs, medical devices, biological products, and radiological products. Since biopolymers have potential uses in virtually all of these areas, the market introduction of many biopolymer compounds will be governed by FDA guidelines.[39] For example, biopolymer crystallization inhibitors such as polyaspartate (see chapter 2) could be used in oral health care as tartar control agents. However, toothpaste and mouthwash additives are considered "drugs," and therefore require FDA approval. The principal biopolymer applications affected, however, will be drug delivery systems and medical devices .40

To enter the U.S. market with a new drug or an advanced drug delivery system that is being packaged with a new or existing drug, an application must be filed with the FDA before a manufacturer can begin human clinical trials.[41] Following this step, a new drug application (NDA) is submitted with supporting evidence as to both safety and efficacy. Even if a proven drug delivery system is packaged with a proven drug, anew application is required. Such safeguards are necessary because a new delivery system-drug combination will have new pharmacological properties. This requirement can obviously affect the rate at which various biopolymer drug delivery systems are introduced into the market.

Medical device implants are also subject to FDA review through the Medical Device Amendments Act of 1976.42 The FDA evaluates the safety and effectiveness of medical devices, but does not necessarily approve biomaterials per se. There is not an FDA list of approved medical materials, but if a material is itself a product, such as bone cement, the material does receive certification. However, the evaluation of materials in medical devices is obviously an important part of the overall review process.[43]

In recent years, medical device manufacturers have expressed considerable concern about the length of time required for FDA approval of medical products.[44] This has resulted in calls to streamline FDA evaluation procedures. In 1989, the Biomaterials Industry Subpanel of the Na-

39 FDA evaluation efforts focus on the development of in vitro (outside the body) assessment methods. This includes the evaluation of cellular and molecular mechanisms of biomedical materials degradation and performance, as well as assessment of host system-medical device interactions. *Biotechnology for the 21st Century,* op. cit., footnote 6.

40 The three main biomedical market segments for biopolymers are wound management products, polymeric drugs and drug delivery systems, and orthopedic repair products. The wound management segment is the most mature of the three markets, with both drug delivery technology and orthopedic devices just beginning to establish a significant commercial presence.

41 A controlled-release drug system is a combination of a biologically active agent (i.e., the drug) and a support vehicle. The support vehicle can be either a matrix or a reservoir device. In a matrix system, an active drug is dissolved or dispersed uniformly throughout a solid polymer. Drug release from the matrix device can be controlled by either a diffusion or an erosion process. In a reservoir system, the polymer acts solely as a barrier that controls the rate of drug delivery by diffusion. Polylactide and some polyamino-acid polymers are currently being evaluated as drug vehicle materials (see ch. 2).

42 In 1990 Congress passed the Safe Medical Device Act, which modified the 1976 act. The 1990 law requires manufacturers to take steps to evaluate medical device performance after a device has been approved and distributed in the marketplace.

43 E. Mueller et al., " 'Regulation of 'Biomaterials' and Medical Devices, ' *Materials Research Society Bulletin, vol.* 16, No. 9, September 1991, pp. 39-41. Also see U.S. Department of Health and Human Services, Tripartite Biocompatibility Guidance for Medical Devices (Washington, DC: 1986).

44 See "FDA Foot. Dragging Stymies Medical Device Makers, " *Wall Street Journal*, June *4, 1993,* p. B2.

tional Research Council made several recommendations[45] for improving the FDA approval process:

- A biomaterials evaluation process should be established to facilitate the use of new materials in medical devices. The material itself, once proven safe and effective, should not be subject to further testing in the event of its use with additional medical devices.
- The FDA should establish a biomaterials advisory committee.
- The FDA should establish biomaterials guidelines and standard test protocols.

Regardless of whether these proposals are adopted, the introduction of procedures that ensure product safety, while reducing evaluation times and costs, will bean important objective of the FDA in years to come.[46]

BIODEGRADABLE MATERIALS

Scientifically based definitions and standards relating to degradability have yet to be legally established. While some studies on degradability have been performed by the Environmental Protection Agency (EPA) and the USDA, Congress has not yet mandated technical standards in this area. However, in Public Law 100-556, Congress required that plastic ring carriers for bottles and cans be made of degradable material. In the proposed rule for this law, EPA does not specify that particular materials be used, but has instead set performance standards for degradable materials.[47] The performance criteria include three factors: a physical endpoint for degradation, a time limit for degradation, and marine environmental conditions.[48] By specifying performance goals rather than particular materials, EPA hopes that industry will have sufficient flexibility to develop new classes of degradable polymers. Currently, beverage ring containers are made only from photodegradable materials, consisting of ethylene-carbon monoxide copolymers.[49] In addition to this Federal action, 27 States have passed legislation prohibiting the use of nondegradable ring carriers.

Although this EPA rule applies to a narrow product category, the precedent of setting performance standards for degradable substances could facilitate the introduction of biopolymer materials. If Federal or State action is taken to expand the range of mandated degradable products (e.g., personal hygiene products or diapers), market opportunities could develop for the new starch, polylactic acid, and microbial polyester biopolymers. However, precise technical definitions and testing methods will be needed to convince both manufacturers and consumers that such new materials are indeed environmentally

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45 See "Report of the Committee to Survey Needs and Opportunities for the Biomaterials Industry," *Materials Research Society Bulletin*, vol. 16, No. 9, September 1991, pp. 26-32.

46 The FDA has taken some steps in this direction with its recently announced "expedited review' process for innovative medical devices. The new procedures are intended to give administrative priority to potential 'breakthrough devices," and to better classify products submitted for FDA approval. In the past, every product submitted for approval was subject to the same administrative procedures. The new procedures will eliminate some of the review steps for relatively simple devices and give greater attention to more complex medical devices (see "Promising Medical Devices To Be Speeded to Market," *Washington Post,* June 25, 1993, p. A2).

47 The proposed EPA rule states that the term "biodegradable plastic" is used to "describe any plastic that is intended to completely assimilate into the environment regardless of the derivation of the material or the combination of degradation processes involved in assimilation" (see *Federal Register,* vol. 58, No. 65, Apr. 7, 1993).

48 Ibid.

49 Scientists are still concerned that these "dqp&ble' materials may seine only to substitute one hazard for another in marine waters. That is, with the use of degradable plastics, the hazard of ingesting plastic fragments may replace the hazard of entanglement in nondegradable plastics. See U.S. Congress, Office of Technology Assessment, *Facing America's Trash: What* Next *for Municipal Solid Waste?* OTA-O-424 (Washington DC: U.S. Government Printing Office, October 1989), pp. 180-183.

superior and do not affect product integrity.[50] In this regard, the efforts of the American Society for Testing and Materials (ASTM) to develop scientific definitions and evaluation methods for degradable materials may serve to allay public concerns.[51]

GENETICALLY ENGINEERED BIOPOLYMER PRODUCTION SYSTEMS

The principal Federal regulatory guidelines dealing with biotechnology were formulated in the 1986 White House Office of Science and Technology Policy report "Coordinated Framework for Regulation of Biotechnology. ' The document describes how novel chemicals, materials, and organisms, produced by the methods of biotechnology, fit into the existing corpus of Federal legislation and regulation. In general, genetically engineered products are regulated on the basis of their intended use, rather than the method or process by which they are made. For example, under current FDA rules, genetically engineered foods are treated the same way as conventional products. The FDA does not require that new products be approved or labeled, as long as such products are essentially similar in composition, structure, and function to food items already available on the market.[52] However, USDA and EPA do regulate field tests of genetically modified plants.[53] As of 1993, more than 400 permits have been granted for the field testing of genetically altered plants and other organisms.[54]

For the short term, genetically engineered biopolymers will be produced in "contained" fermentation systems where standard safety procedures are well established.[55] Thus, microbially derived biopolymer materials are unlikely to face any significant regulatory obstacles.[56] In the future, however, schemes that involve the production of biopolymers through the genetic modification of crops could face greater regulatory scru-

50 For example, the FDA is concerned about the possibility of a shortened shelf life of degradable food-packaging material. In evaluating the safety of new additives in food-contact materials, the FDA must consider potential problems such as enhanced migration of food-packaging components as a consequence of accelerated degradation of a polymer. In the case of some proposed biopolymer packaging materials such as pullulan (ch. 2), there would have to be evidence that the food product is adequately protected. Ibid.

51 The ASTM Degradable Plastics Subcommittee is examining various degradation pathways, including photodegradation, oxidation, chemical degradation, and biological degradation. It has developed standard laboratory test methods that measure the rate and extent of degradation for different materials, and is in the process of establishing a classification and marking system for polymer compounds. ASTM researchers are currently attempting to determine the behavior of degradable polymeric materials in real disposal systems and are correlating these results with ASTM laboratory methods. This work could very well become the de facto industry baseline for defining and evaluating new polymer materials, Already, EPA has used some of ASTM's work in developing proposed performance standards for degradable beverage ring carriers (op. cit., footnote 47; and see Ramani Naryan, "Development of Standards for Degradable Plastics by ASTM Subcommittee D-20.96 on Environmentally Degradable Plastics, ' 1992).

52 Some consumer groups have expressed concerns that genetically engineered foods may be subject to microbial contamination, possess higher levels of toxins, or expose consumers to allergy-producing compounds that are not naturally present in foods. The present consensus among scientists is that the risks associated with genetically altered organisms are similar to those associated with nonengineered organisms or organisms genetically modified by traditional methods (Biotechnology *in a Global Economy*, op. cit, footnote 6).

53 Currently, researchers are required to give 30 days notice to the USDA before beginning field tests. During that time, a determination is made as to whether additional review or inspection is necessary. See *Federal Register,* "Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status, " vol. 58, No. 60, Mar. 31, 1993. Also, EPA considers microorganisms that are released into the environment to be chemical substances subject to the Toxic Substances Control Act of 1976. EPA is currently developing guidelines governing genetically engineered pesticides and other microbes.

54 For a discussion on how scientists are assessing the ecological impacts of genetically altered plants, see M.J. Crawley et al., ''fiolo8Y of Transgenic Oilseed Rape in Natural Habitats, ' *Nature,* vol. 363, June 17, 1993, pp. 620-623.

55 NIH has developed guidelines that prescribe various procedures of containment for genetic experiments. See *Federal Register,* "Guidelines for Research Involving Recombinant DNA Molecules, " vol. 51, No. 88, May 7, 1986.

56 Whether a biopolymer is regulated will to a large degree depend on the application. For example, medical products that contain microbially-derived biopolymers will still be subject to FDA review.

tiny. Several researchers, for instance, are exploring the possibility of producing natural polyesters such as PHB by altering the enzyme machinery of corn or potatoes.[57] Such approaches to biopolymer manufacture will be subject to existing Federal rules governing genetically engineered agricultural organisms.

REGULATIONS RELATING TO INDUSTRIAL CHEMICALS

In response to public concerns over the possible health and environmental implications of widespread chemical use, Congress passed the Toxic Substances Control Act (TSCA) in 1976, Under the provisions of TSCA, EPA is charged with assembling basic data on chemicals, reviewing industry tests of new and existing compounds, and reducing public risk. There are more than 60,000 chemicals currently on the TSCA inventory, and roughly 1,000 new chemicals are proposed for manufacture each year.[58] Before manufacturers can begin production of a new chemical, they must submit a Premanufacture Notice to EPA. Only a small number of the premanufacture notices submitted to EPA are held up for extended review.[59] In the vast majority of cases, manufacturers can begin production of a chemical 90 days after notifying EPA.

Since some of the more interesting biopolymer compounds are new chemical formulations, they will also be subject to TSCA provisions.[60] Yet, given that biopolymers are derived from natural precursors, most biopolymer *products* should not have difficulty meeting current TSCA requirements.[61] For instance, this should be the case for biopolymers that are created by the chemical polymerization of naturally occurring monomers, such as polylactide and the polyamino acids.[62] However, as indicated previously, some of the *processes* used to produce genetically engineered biopolymers may be subject to more detailed regulatory review (e.g., genetic modification of plants).

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57 See "In Search of the Plastic potato, " *Science,* vol. 245, Sept. 15, 1989, pp. 1187-1189.

58 Michael Shapiro, "Toxics Substances Policy, " Paul Portney (cd.), *Public Policies for Environmental Protection* (Washington, DC: Resources for the Future, 1990), p. 208.

59 Often, new chemicals are simply slight modifications of existing substances and are therefore not subjected to a rigorous review. However, if EPA is concerned about a particular chemical, it can take years before definitive toxicity data can be developed. This has led to calls for new procedures in the TSCA chemical evalution process. Ibid.

60 Depending on the types Of applications involved, biopolymers could also be subject to the provisions of the Clean Water Act and the Safe Water Drinking Act. The Clean Water Act regulates contaminants discharged into surface waters, and the Safe Water Drinking Act safeguards drinking water sources and prescribes drinking water standards. For a general discussion of the regulation of water pollutants and treatment chemicals, see "Water Treatment Chemicals: Tighter Rules Drive Demand, " *Chemical & Engineering News,* Mar. 26, 1990, pp. 17-34.

61 However, for most biopolymers, the presumption that they pose little risk to human health and the environment has yet to be conclusively proven.

62 Polyamino acids such as the polyaspartates show considerable promise as water treatment additives. Biodegradable polyaspartate compounds could be used to replace petroleum-derived polymers such as polyacrylate and polyacrylamide. However, it is not known whether the use of large quantities of natural polymers will have any adverse ecological effects.