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The Chemical Industry

Background

The organic substances first used by humans to make useful materials such as cotton, linen, silk, leather, adhesives, and dyes were obtained from plants and animals and are natural and renewable resources. In the late 19th century, coal tar, a nonrenewable substance, was found to be an excellent raw material for many organic compounds, When organic chemistry developed as a science, chemical technology improved. At **about the same time relatively cheap petroleum became widely available. The industry shifted rapidly to using petroleum as its major raw material.**

The chemical industry's constant search for cheap and plentiful raw materials is now about to come full circle. The supply of petroleum, which presently serves more than 90 percent of the industry's needs, is severely threatened by both dwindling resources and increased costs. It has been estimated that at the current rate of consumption, the world's petroleum supplies will be depleted in the middle of the next century. Most chemical industry analysts, therefore, foresee a shift first back to coal and then, once again, to the natural renewable resources referred to as biomass. The shifts will not necessarily occur sequentially for the entire chemical industry. Rather, both coal and biomass will be examined for their potential roles on a product-by-product basis.[1]

The chemical industry is familiar with the technology of converting coal to organic chemicals, and a readily available supply exists. Coal-based technologies will be used to produce a wide array of organic chemicals in the near future. * Nevertheless, economic, environmental, and technical factors will increase the industry's interest in biomass as an alternative source for raw materials. Applied genetics will **probably** play a major role in enhancing the possibilities by allowing biomass and carbohydrates from natural sources to be converted into various chemicals. Biology will thereby take on the dual role of providing both raw materials and a process for production.

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[1] details see *iologic From* esses, vol. *Processes,* 1, (Washington, D. C.: nology Assessment, Assessment, 1980).

*Most important organic (chemical compounds **used** as **the** basis of commercial products such as ers) **can be obtained** from **coal** . . . methods are **v, methods** ... to convert coal **into** which **gas,** " ... **used** ... sions

Overview of the industry

The chemical industry is one of the largest and most important in the world today. The U.S. market for synthetic organic chemicals alone, excluding primary products made from petroleum, natural gas, and coal tar, exceeded $35 billion in 1978.

The industry's basic function is to transform low-cost raw materials into end-use products of greater value. The most important raw materials are petroleum, coal, minerals (phosphate, carbonate), and air (oxygen, nitrogen). Roughly two-thirds of the industry is devoted to producing inorganic chemicals such as lime, salt, ammonia, carbon dioxide, chlorine gas, and hydrochloric and other acids.

The other third, which is the target for biotechnology, produces organic chemicals. Its output includes plastics, synthetic fibers, organic solvents, and synthetic rubber. (See figure 24.) In general, petroleum and natural gas are first converted into "primary products" or basic organic chemicals such as the hydrocarbons ethylene and benzene. These are then converted into a wide range of industrial chemicals. Ethylene

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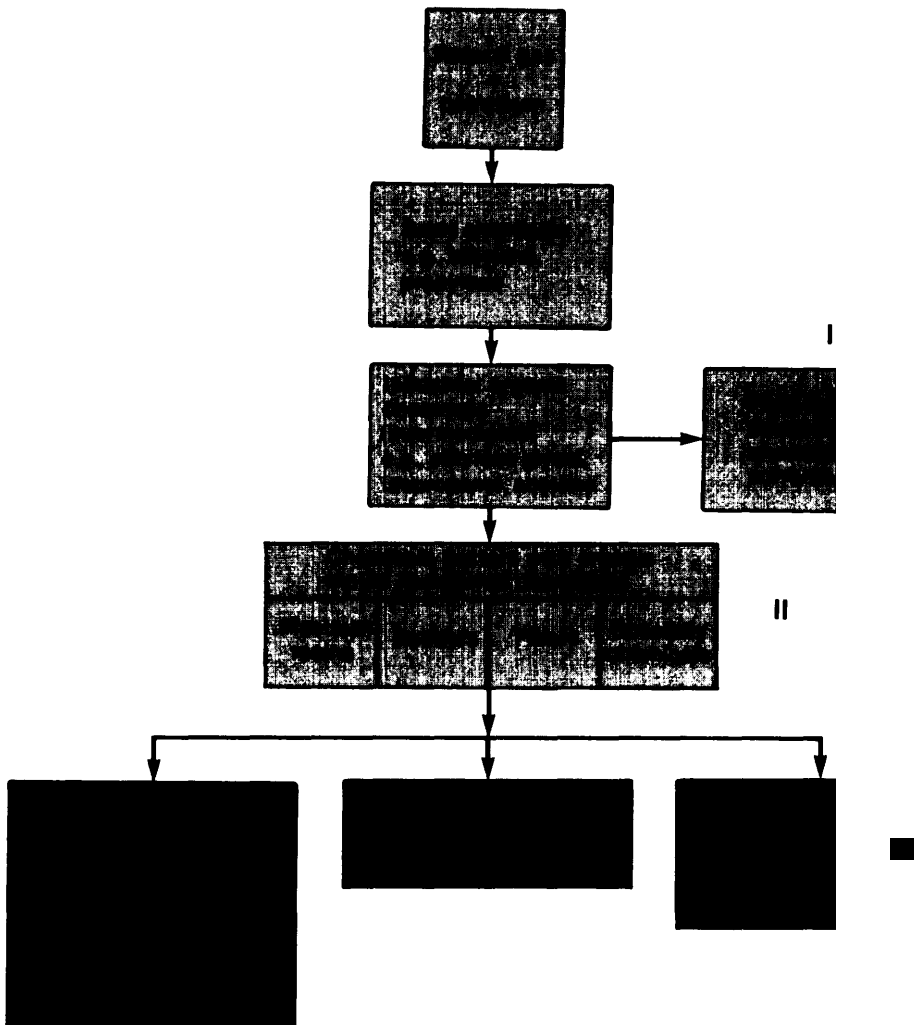
Figure 24.-Flow of Industrial Organic Chemicals From Raw Materials to Consumption



Organic resources

80% raw material from petroleum/ natural gas

20°/0 raw material from coal, coke, and renewable resources

SOURCE: *U.S.* SOURC *Outlook dustrial Outlc* **D. C.: Department of Commerce, 1978);** *Industry,* **Fairfield, N.J., adapted from Tong, 1979.**

alone serves as the basic chemical for the manufacture of half of the largest volume industrial chemicals. Each of the steps in a chemical conversion process is controlled by a separate reaction, which is often performed by a separate company.

Evaluating the competitiveness both of a process and of the market is critical for the chemical industry, which is intensive for capital, energy, and raw materials. Its plants use large amounts of energy and can cost hundreds of millions of dollars to build, and raw material costs are generally 50 to 80 percent of a product's cost. If a biological process can use the same raw materials and reduce the process cost by even 20 percent, or allow the use of inexpensive raw materials, it could provide the industry with a major price break.

Fermentation and the chemical industry

The production of industrial chemicals by fermentation is not new. Scores of chemicals have been produced by micro-organisms in the past, only to be replaced by chemical production based on petroleum. In 1946, for example, 27 percent of the ethyl alcohol in the United States was produced from grain and grain products, 27 percent from molasses, a few percent each from such materials such as potatoes, pineapple juice, cellulose pulp, and whey, and only ***36*** percent from petroleum. Ten years later almost 60 percent was derived from petroleum.

Even more dramatically, fumaric acid was at one time produced on a commercial scale through fermentation, but its biological production was stopped when a more economical synthesis from benzene was developed. Frequently, after a fermentation product was discovered, alternative chemical synthetic methods were soon developed that used inexpensive petroleum as the raw material.

Nevertheless, for the few chemical entities still produced by fermentation, applied genetics has contributed to the economic viability of the process. The production of citric and lactic acids and various amino acids are among the processes that have benefited from genetics. Lactic acid is produced both synthetically and by fermentation. Over the past 10 to 20 years, manufacture by fermentation has experienced competition from chemical processes.

The organisms used for the production of lactic acid are various species of the bacterium ***Lactobacillus.*** Starting materials may be glucose, sucrose, or lactose (whey). The fermentation per se is efficient, resulting in 90 percent yields, depending on the original carbohydrate. Since most of the problems in the manufacture of lactic acid lie in the recovery procedure and not in fermentation, few attempts have been made to improve the industrial processes through genetics.

Citric acid is the most important acidulant, and historically has held over 55 to 65 percent of the acidulant market for foods. * It is also used in pharmaceuticals and miscellaneous industrial applications. It is produced commercially by the mold ***Aspergillus niger.*** Surprisingly little work has been published on improving citric acid-producing strains of this micro-organism. Weight yields of 110 percent have recently been reported in ***A. niger*** mutants obtained by irradiating a strain for which a maximum yield of 29 percent had been reported.

Amino acids are the building blocks of proteins. Twenty of them are incorporated into proteins manufactured in cells, others serve specialized structural roles, are important metabolic intermediates, or are hormones and neurotransmitters. All of the amino acids are used in research and in nutritional preparations, with most being used in the preparation of pharmaceuticals. Three are used in large quantities for two purposes: glutamic acid to manufacture monosodium glutamate, which is a fla-

● **The other two important** acidifying **, or acidifying agents, phosphoric acid** nt) **to 25 percent)** (5 percent **acid percent),**

vor enhancer particularly in oriental cooking;* and lysine and methionine as animal feed additives.

Conventional technology for producing glutamic acid is based on pioneering work that was subsequently applied to other amino acids. The production employed microbial strains to produce amino acids that are not within their normal biosynthetic capabilities. This was accomplished by using two methods: 1) manipulating microbial growth conditions, and 2) isolating naturally occurring mutants.

Although microbial production of all the amino acids has been studied, glutamic acid and L-lysine* * are the ones produced in significant quantities by fermentation processes. (See table 9.) The production of L-lysine is an excellent ex-

"Monosodium glutamate is the sodium salt of odium s acid. In 1978, about 18,000 tonnes were manufactured in the United States and about 11,000 tonnes imported. The food industry consumed 97 percent. The fermentation plant of the plant Chemical Co. in San Jose, in S is the sole U.S. producer. The microbes used in us acid fermentation fermentation (*Corynebacteriu* and *lileum*, and *Brevibacl* produce it in 60 percent of theoretical yield. Thus, there is some but not great potential for the use of applied genetics to improve the yield. Many of the genetic approaches have already been thoroughly investigated y i industrial scientists.

" *The lack of a single amino acid can retard protein synthesis, and therefore growth, in a mammal. The limiting amino acid is a function of the animal and its feed. The major source of animal feed in the United States is soybean meal. The limiting amino acid for feeding swine is ling s the limiting amino acid for feeding poultry is poultry i Because of increased poultry demand, world demand for l dem is climbing, e is climbi is spending $27 million to double its production capacity in n capac France, to 10 thousand tonnes. The Asian and Mideast markets eat markets to increase to thousand tonnes in 1985. Some 1985. produce the g at over 90 percent of theoretical yield, retic genetic improvement is likely in this conversion yield, however, significant improvement can be made in the rate and final concentration.

Table 9.—Data for Commercially Produced Amino Acids[a]

Amino acid	Price March 1980 (per kg pure L)	Present source	Production 1978 (tonnes)	Potential for application of biotechnology (de novo synthesis or bioconversion; organisms and enzymes)
Alanine	$ 80	Hydrolysis of protein; chemical synthesis	10-50(J) [b]	–
Arginine	28	Gelatin hydrolysis	200-300 (J)	Fermentation in Japan
Asparagine	50	Extraction	10- 50(J)	–
Aspartic acid	12	Bioconversion of fumaric acid	500-1,000 (J)	Bioconversion
Citrulline	250		10-90 (J)	Fermentation in Japan
Cysteine	50	Extract ion	100- 200(J)	–
Cystine	60	Extraction	100- 200(J)	–
DOPA (dihydrophenylalanine)	750	Chemical	100- 200(J)	—
Glutamic	4	Fermentation	10,000-100,000 (J)	De novo: *Micrococcus gutamicus*
Glutamine	55	Extraction	200-300 (J)	Fermentation in Japan
Histidine	160	—	100-200	Fermentation in Japan
Hydroxyproline	280	Extraction from collagen	10-50	—
Isoleucine	350	Extraction	10-50 (J)	
Leucine	55	—	50-100(J)	Fermentation in Japan
Lysine	350	Fermentation (800A) Chemical (20%)	10,000 (J)	(80% by fermentation) De novo: *Corynebacterium glutamicum* and *Brevibacterium flavum*
Methionine	265	Chemical from acrolein	*17,000(D,L)* [c] *20,000*(D,L) (J)	—
Ornithine	60	—	10-50 (J)	Fermentation in Japan
Phenylalanine	55	Chemical from benzaldehyde	50-100 (J)	Fermentation in Japan
Proline	125	Hydrolysis of gelatin	10-50 (J)	Fermentation in Japan
Serine	320	—	10-50 (J)	Bioconversion in Japan
Threonine	150	—	50-10 (J)	Fermentation in Japan
Tryptophan	110	Chemical from emica	55 (J)	
Tyrosine	13	Extraction	50- 100(J)	-
Valine	60	—	50-100 (J)	Fermentation in Japan

[a] Produ from Japan because of relative Small U.S. production.

'Japan.

C, and L forms.

SOURCE: Massachusetts Institute of Technology.

ample of the competition between chemical and biotechnological methods. Fermentation has been gradually replacing its production by chemical synthesis; in 1980, 80 percent of its worldwide production is expected to be by microbes. It is not produced in the United States, which imported about *7,000* tonnes in 1979, mostly from Japan and South Korea. Recent estimates of primary U.S. cost factors in the competing production methods are summarized in table 10. Fermentation costs are lower for all three components of direct operating costs: labor, material, and utilities.

Table 10.—Summary of Recent Estimates of Primary U.S. Cost Factors in the Production of L= Lysine Monohydrochloride by Fermentation and Chemical Synthesis

	Cost factors in Production of 98% L-lysine monohvdrochloride					
	By fermentation			By chemical synthesis		
	Requirement (units per unit (product)	Estimated 1976 cost per unit product		Requirement (units per unit product)	Estimated 1976 cost per unit product	
		Cents/lb	Cents/kg		Cents/lb	Cents/lb
Total labor[c]	—	8	18	—	9	20
Materials						
Molasses	44	7	16	—	—	—
Soy beanmeal, hydrolyzed	0.462	4	9	—	—	—
Cyclohexanol	—		—	0.595	17	37
Anhydrous ammonia	—	—	—	0.645	6	14
Other chemicals[d]	—	7	15	—	4	10
Nutrients and solvents	—	—	—	—	4	8
Packaging, operating, and maintenance materials		10	22	—	9	21
Total materials	—	28	62	—	45	90
Total utilities	—	6	12	—	7	16
Total direct operating cost	—	42	92	—	56	126
Plant overhead, taxes, and insurance	—	10	21	—	10	21
Total cash cost	—	52	11	—	66	147
Depreciation	—	16	35	—	13	28
Interest on working capital	—	1	3	—	1	3
Total cost[g]	—	69	151	—	80	178

a 23-percent yield on

bAssumes a 65-percent yield on

maintenance, and control laboratory

both th of fermentation and assumed of (36 percent) and mn percent) percent). For fermentation For fermentation includes

potassium ammonium urea, ammonium carbona calcium carbonate, and magnesium sulfate. For chemical synthesis also includes sulfuric chloride, sulfuric acid, and a credit for ammonium sulfate byproduct.

for both processes include cooling water. steam process water, and electricity. For chemical gas is also natural gas is also included.

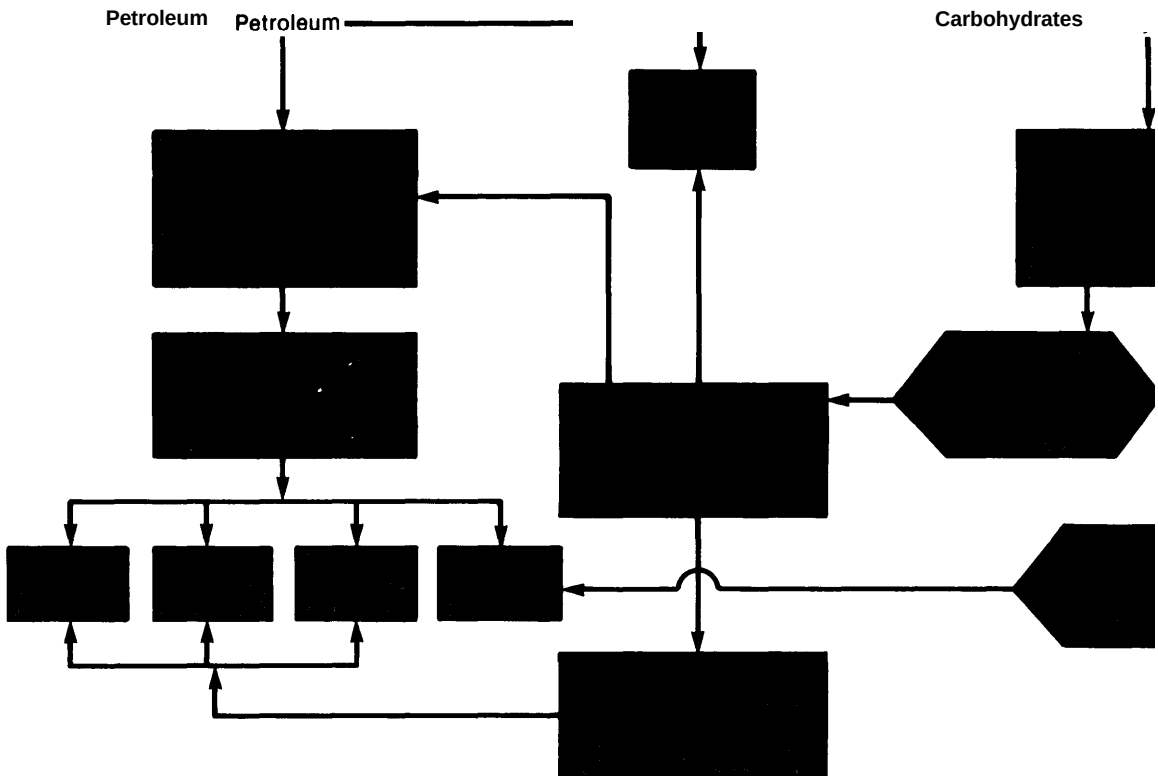
fren fixed per ilt in 197 plant built in at assumed capital cost of $36.6X and $32.5 x 10 and $32.5x for chemical synthesis exclusive of land costs.

SOURCE: Stanford Research Institute, *Chemical Economics Handbook* May 1979.

New process introduction

The development of biotechnology should be viewed not so much as the creation of a new industry as the revitalization of an old one. Both fermentation and enzyme technologies will have an impact on chemical process development. The first will affect the transition from nonrenewable to renewable raw materials. The second will allow fermentation-derived products to enter the chemical conversion chains, and will compete directly with traditional chemical transformations. (See figure 25.) **Fermentation, by replacing various production steps, could act as a complementary technology in the overall manufacture of a chemical.**

Figure 25.—Diagram of Alternative Routes to Organic Chemicals



followed by number owed by number of carbon chain.
SOURCE: E. Tong, "industrial Chemicals From Fermentation Enzymes," ...ation Enzymes," Voi. 1,1979, PP. 173-179.

Characteristics of biological production technologies

The major advantages of using commercial fermentation include the use of renewable resources, the need for less extreme conditions during conversion, the use of one-step production processes, and a reduction in pollution. A micro-organism might be constructed, for example, to transform the cellulose in wood directly into ethanol. * (App. 1-D, a case study of the impact of genetics on ethanol production, elaborates these points.)

RENEWABLE RESOURCES

Green plants use the energy captured from sunlight to transform carbon dioxide from the atmosphere into carbohydrates, some of which are used for their own energy needs. The rest are accumulated in starches, cellulose, lignins, and other materials called the biomass, which is the foundation of all renewable resources.

The technologies of genetic engineering could help ease the chemical industry's dependence on petroleum-based products by making the use of renewable resources attractive. All micro-organisms can metabolize carbohydrates and convert them to various end products. Extensive research and development (R&D) has already been conducted on the possibility of using genetically engineered strains to convert cellulose, the major carbohydrate in plants, to commercial products. The basic building block of cellulose—glucose—can be readily used as a raw material for fermentation.

"If ... Advisory ill ... mittl 25, 1980 Sept. 25.

other plant carbohydrates include cornstarch, molasses, and lignin. The last, a polymer found in wood, could be used as a precursor for the biosynthesis of aromatic (benzene-like) chemicals, making their production simpler and more economical. Nevertheless, the increase in the price of petroleum is not a sufficient reason for switching raw materials, since the cost of carbohydrates and other biological materials has been increasing at a relative rate.

PHYSICALLY MILDER CONDITIONS

In general, there are two main ways to speed chemical reactions: by increasing the reaction temperature and by adding a catalyst. A catalyst (usually a metal or metal complex) causes one specific reaction to occur at a faster rate than others in a chemical mixture by providing a **surface on** which that reaction can be promoted. Even using the most effective catalyst, the conditions needed to accelerate industrial organic reactions often require extremely high temperatures and pressures—several hundred degrees Celsius and several hundred pounds per square inch.

Biological catalysts, or enzymes, on the other hand can speed-up reactions without the need for such extreme conditions. Reactions occur in dilute, aqueous solutions at the moderate conditions of temperature, pressure, and pH (a measure of the acidity or alkalinity of a solution) that are compatible with life.

ONE-STEP PRODUCTION METHODS

In the **chemical synthesis of compounds, each reaction must take place separately. Because most chemical reactions do** not yield pure products, the product of each individual reaction must be purified before it can be used in the next step. This approach is time-consuming and expensive. If, for example, a synthetic scheme that starts with ethylene (a petroleum-based product) requires 10 steps, with each step yielding *90* percent product (very optimistic yields in chemical syntheses), only about one-third of the ethylene is converted into the final end product. Purification may be costly; often, the chemicals involved (such as organic solvents for extractions) and the byproducts of the reaction are toxic and require special disposal.

In biological systems, micro-organisms often complete entire synthetic schemes. The conversion takes place essentially in a single step, although several might occur within the organisms, whose enzymes can transform the precursor through the intermediates to the desired end product. Purification is not necessary.

REDUCED POLLUTION

Metal catalysts are often nonspecific in their action; while they may promote certain reactions, their actions are not ordinarily limited to making only the desired products. Consequently, they have several undesirable features: the formation of side-products or byproducts; the incomplete conversion of the starting material(s); and the mechanical and accidental **loss** of the product.

The last problem occurs with all types of synthesis. The first two represent inefficiencies in the use of the raw materials. These necessitate the separation and recycling of the side-products formed, which can be difficult and costly because they are often chemically and physically similar to the desired end products. (Most separation techniques are based on differences in physical properties—e.g., density, volatility, and size.)

When byproducts and side-products have no value, or when unconverted raw material cannot be recycled economically, problems of waste disposal and pollution arise. Their solu**tion requires ingenuity, vigilance,** energy, and dollars. Many present chemical processes create useless wastes that require elaborate degradation procedures to make them environmentally acceptable. In 1980, the chemical industry is expected to spend $883 million on capital outlays for pollution control, and well over **$200 million on R&D for** new control techniques and replacement products. These figures do not include the millions of dollars that have been spent in recent years to clean up toxic chemical dumps and to compensate those harmed by poorly disposed wastes, nor do they include the cost of energy and labor required to **operate** pollution-control systems.

A genetically engineered organism, on the other hand, is designed to be precursor- and

product-specific, with each enzyme having essentially 100-percent conversion efficiency. An enzymatic process that carries out the same transformation as a chemical synthesis produces no side-products (because of an enzyme's high specificity to its substrate) or byproducts (because of an enzyme's strong catalytic power). Consequently, biological processes eliminate many conventional waste and disposal problems at the front end of the system-in the fermenter. This high conversion efficiency reduces the costs of recycling. In addition, the efficiency of the biological conversion process generally simplifies product recovery, reducing capital and operating costs. Furthermore, by their nature, biologically based chemical processes, tend to create some waste products that are biodegradable and valuable as sources of nutrients.

Specific comparisons of the environmental hazards produced by conventional and biological systems are difficult. Data detailing the pollution parameters for various current chemical processes exist, but much less information is available for fermentation processes, and few compounds are produced by both methods. However, in most beverage distilling operations, pollution has been reduced to almost zero with the complete recovery of still slops as animal feeds of high nutritional value. Such control procedures are generally applicable to most fermentation processes. (App. I-C describes the pollutants that may be produced by current chemical processes and those expected from biologically based processes.)

The Environmental Protection Agency has estimated that the U.S. Government and industry combined will spend over $360 billion to control air and water pollution in the decade from 1977 through 1986. The share of the chemical and allied industries is about $26 billion. Genetic engineering technology may help alleviate this burden by offering cleaner processes of synthesis and better biological waste treatment systems. The monetary savings could be tremendous. As pure speculation, if just 5 percent of the current chemical industry were affected, spending on pollution could be reduced by about $100 million per year.

Industrial chemicals that may be produced by biological technologies

Despite the benefits of producing industrial chemicals biologically, thus far major fermentation processes have been developed primarily for a few complex compounds such as enzymes. (See table 11.) Biological methods have also been developed for a few of the simpler commodity chemicals: ethanol, butanol, acetone, acetic acid, isopropanol, glycerol, lactic acid, and citric acid.

Two questions are critical to assessing the feasibility or desirability of producing various chemicals biologically:

1. Which compounds can be produced biologically (at least theoretically)?
2. Which compounds may be primarily dependent on genetic technology, given the costs and availability of raw materials?

In principle, virtually all organic compounds can be produced by biological systems. If the necessary enzyme or enzymes are not known to exist, a search of the biological world will probably uncover the appropriate ones. Alternatively, at least in theory, an enzyme can be engineered to carry out the required reaction. Within this framework, the potential appears to be limited only by the imagination of the biotechnologist—even though certain chemicals that are highly toxic to biological systems are probably not amenable to production.

Three variables in particular affect the answer to the second question: the availability of an organism or enzymes for the desired transformation; the cost of the raw material; and the cost of the production process. When specific organisms and production technologies

Table 1 1.—Some Commercial Enzymes and Their Uses

Enzyme	Source	Industry and application
Amylase	Animal(pancreas)	Pharmaceutical digestive aids
		Textile: desizing agent
	Plant(barley malt)	Baking: flour supplement
		Brewing, distilling, and industrial alcohol mashing
		Food: precooked baby foods
		Pharmaceutical digestive aids
		Textile: desizing agent
	Fungi (Aspergillus niger,A. *oryzae)*	Baking: flour supplement
		Brewing, distilling, and industrial alcohol mashing
		Food: precooked baby foods, syrup manufacture
		Pharmaceutical digestive aids
	Bacteria (Bacillus subtilis)	Paper starch coatings
		Starch: cold-swelling laundry starch
Bromelin	Plant (pineapple)	Food: meat tenderizer
		Pharmaceutical digestive aids
Cellulase and hemicellulase	Fungi (Aspergillus niger)	Food: preparation of liquid coffee concentrates
Dextransucrase	Bacteria(Leuconostoc mesenteroides)	Pharmaceutical preparation of blood-plasma extenders, and dextran for other uses
	Plant (fig latex)	Pharmaceutical: debriding agent
Glucose oxidase (plus catalase or peroxidase)	Fungi (Aspergillus niger)	Pharmaceutical test paper for diabetes
		Food: glucose removal from egg solids
	Yeast (Saccharomyces cerevisiae)	Candy: prevents granulation of sugars in soft-center candies
		Food: artificial honey
Lactase	*Yeast (Saccharomyces fragilis)*	Dairy: prevents crystallization of lactose in ice cream and concentrated milk
Lipase	Fungi (Aspergillus niger)	Dairy: flavor production in cheese
Papain	Plant(papaya)	Brewing: stabilizes chill-proof beer
		Food: meat tenderizer
	Fungi (Aspergillus niger)	Wine and fruit juice: clarification
Penicillinase	Bacteria(Bacillus cereus)	Medicine: treatment of allergic reaction to penicillin, diagnostic agent
Pepsin	Animal (hog stomach)	Food: animal feed supplement
Protease	Animal (pancreas)	Dairy: prevents oxidized flavor
		Food: protein hydrolysates
		Leather: bating
		Pharmaceutical: digestive aids
		Textile: desizing agent
	Animal (pepsin)	Brewing: beer stabilizer
	Animal (rennin, rennet)	Dairy: cheese
	Animal (trypsin)	Pharmaceutical: wound debridement
	Fungi (Aspergillus oryzae)	Baking: bread
		Food: meat tenderizer
	Bacteria (Bacillus subtilis)	Baking: modification of cracker dough
		Brewing: clarifier
Streptodornase	*Bacteria (Streptococcus pyrogenes)*	Pharmaceutical: wound debridement

SOURCE: David mentatic "The Fermentation Industries," *American Society Microbiology News* 1973, p. 653.

have **been developed, the cost of raw materials becomes the limiting step in production. If a strain of yeast, for example, produces 5 percent ethanol using sugar as a raw material, the process might become economically competitive if the** cost of sugar drops or the price of petroleum rises. Even **if prices remain stable, the micro-organisms might be genetically improved to increase their yield; genetic manipulation might solve the problem of an inefficient** organism. Finally, the production process itself is a factor. After fermentation, the desired product must be separated from the other compounds in the reaction mixture. As an aid to recovery, the production conditions might be altered and improved to generate ***more*** **of a desired** compound.

More than one raw material can be used in a fermentation process. If, in the case of ethanol,

the price of sucrose (from sugarcane or sugar beets) is not expected to change, the production technology is being run at optimum efficiency, and the micro-organism is producing as much ethanol as it can, the hurdle to economic competitiveness might be overcome if a less expensive raw material—cellulose, perhaps—were used. But cellulose cannot be used in its natural state: physical, chemical, or biological methods must be devised to break it down to its glucose (also a sugar) components.

The constraints vary from compound to compound. But even though the role of genetics must be examined on a product-by-product basis, certain generalizations can be made. Overall, genetic engineering will probably have an impact on three processes:

- Aerobic fermentation, which produces enzymes, vitamins, pesticides, growth regulators, amino acids, nucleic acids, and other speciality chemicals, is already well-established. Its use should continue to grow. Already, complex biochemical like antibiotics, growth factors, and enzymes are made by fermentation. Amino acids and nucleotides—somewhat less complicated molecules—are sometimes produced by fermentation. Their production is expected to increase.
- Anaerobic fermentation, which produces organic acids, methane, and solvents, is the industry's area of greatest current growth. Already, 40 percent of the ethanol manufactured in the United States is produced in this way. The main constraint on the production of other organic acids and solvents is the need for cheaper methods for converting cellulose to fermentable sugars.
- Chemical modification of the fermentation products of both aerobic and anaerobic fermentation, which to date has rarely been used on a commercial scale, is of great interest. (See table 12.) Chemical production technologies that employ high temperatures and pressures might be replaced by biological technologies operating at atmospheric pressure and ambient temperature. A patent application has already been filed for the biological production of one of these products, ethylene glycol, by the Cetus Corp. in Berkeley, Calif. The process is claimed to be more energy efficient and less polluting. If it proves successful when run at an industrial scale, the technology could become significant to a [J. S. market totaling $2 1/2 billion per year.

Table 12.—Expansion of Fermentation Into the Chemical Industry

	Examples
Aerobic fermentation	
Enzymes	**Amylases, proteases**
Vitamins	**Riboflavin**
Pesticides	*Bacillus thuringiensis*
Growth regulators	**ors**
Amino acids	**lysine**
Nucleic acids	
Acids	**Malic acid, citric acid**
Anaerobic fermentation	
Solvents	**Ethanol, acetone, n-butanol**
Acids	**Acetic, propionic, acrylic**

SOURCE: Office of Technology Assessment.

The chemical industry produces a variety of likely targets for biotechnology. Tables I-B-27 through 1-B-32 in appendix I-B present projections of the potential economic impacts of applied genetics on selected compounds that represent large markets, and the time frames for potential implementation. Table I-B-7 lists one large group of organic chemicals that were identified by the Genex Corp. and Massachusetts Institute of Technology (MIT) as amenable to biotechnological production methods. They are in agreement on about **20 percent of the products cited, which underscores the uncertain nature of attempting to predict so far into the future.**

Fertilizers, polymers, and pesticides

Gaseous ammonia is used to produce nitrogen fertilizers. About 15 billion tonnes of ammonia were produced chemically for this purpose, in 1978; the process requires large amounts of natural gas. Nitrogen can also be converted, or "fixed," to ammonia by enzymes in micro-organisms; about 175 billion tonnes are fixed per year. For example, one square yard of land planted with certain legumes (such as soybeans) can fix up to 2 ounces of nitrogen, using bac-

teria associated with their roots. Currently, microbial production of ammonia from nitrogen is not economically competitive. Aside from the difficulties associated with the enzyme's sensitivity to oxygen and the near total lack of understanding of its mechanism, it takes the equivalent of the energy in 4 kilograms (kg) of sugar to make 1 kg of ammonia. Since ammonia costs $0. 13/kg and sugar costs $0.22/kg, it is unlikely that the chemical **process will be replaced** in the near future. On the other hand, the genes for nitrogen fixation have now been transferred into yeast, opening up the possibility that agriculturally useful nitrogen can be made by fermentation.

A large segment of the chemical industry engaged in the manufacture of polymers is shown in table 13. A total of 4.3 million tonnes of fibers, 12 million tonnes of plastics, and I. I million tonnes of synthetic rubber were produced in the United States in **1978.** All were derived from petroleum, with the exception of the less than 1 percent derived from cellulose fibers. The most likely ones are polyamides (chemically related to proteins), acrylics, isoprene-type rubber, and polystyrene, Because most monomers, the building blocks of polymers, are chemically simple and are presently available in high yield from petroleum, their microbial production in the next decade is unlikely.

While biotechnoloqy is not ready to replace the present technology, its eventual impact on polymer production will probably be large. Biopolymers represent a new way of thinking. Most of the important constituents of cells are polymers: proteins (polypeptides from amino acid monomers), polysaccharides (from sugar monomers), and polynucleotides (from nucleotide monomers). Since cells normally assemble polymers with extreme specificity, the ideal industrial process would imitate the biological production of polymers in all possible respects—using a single biological machine to convert a raw material, e.g., a sugar, into the monomer to polymerize it, then to form the final product. A more likely application is the development of new monomers for specialized applications. Polymer chemistry has largely consisted of the study of how their properties can be modified.

Table 13.—The Potential of Some Major Polymeric Materials for Production Using Biotechnology

Product	Domestic production 1978 (thousand tonnes)
Plastics	
Thermosetting resins	
Epoxy	135
Polyester	544
Urea	504
Melamine	90
.....	727
Thermoplastic resins	
Polyethylene	
Low density	3,200
High density	1,890
Polypropylene	1,380
Polystyrene	2,680
Polyamide, nylon type	124
Polyvinyl alcohol	57
Polyvinyl chloride	2,575
Other vinyl resins	88
Fibers	
Cellulosic fibers	
Acetate	139
Rayon	269
Noncellulosic fibers	
Acrylic	*327*
Nylon	
.....	311
Polyester	1,710
Textile glass	418
Other	7
Rubbers	
Styrene-butadiene	628
Polybutadiene	170
Butyl	69
.....	33
Polychlorophene	72
Ethylene-propylene	78
Polyisoprene	62

SOURCE: Office of Technology Assessment.

Conceivably, biotechnology could enable the modification of their function and form.

Pesticides include fungicides, herbicides, insecticides, rodenticides, and related products such as plant growth regulators, seed disinfectants, soil conditioners, and soil fumigants. The largest market (roughly $500 million annually) involves the chemical and microbial control of insects. Although microbial insecticides have been around for years, they comprise only 5 percent of the market. However, recent successes in developing viruses and bacteria that produce diseases in insects, and the negative publicity given to chemical insecticides, have encouraged the use of microbial insecticides.

Of the 15,000 known species of insects, only 200 are harmful enough to warrant control or destruction. Fortunately for man, most of them are sensitive to certain micro-organisms which, if they are not toxic to man, nontarget animals, and plants, can be used as commercial insecticides.

Approximately 100 known species of bacteria are pathogenic (disease causing) to insects, but only three—*Bacillus popilliae, B. thuringiensis* and *B. moritai*—have been developed into commercial insecticides. *B. popilliae* is found and produced only in the larvae of Japanese beetles. The other two species can be produced by conventional fermentation techniques. They have been useful because they form spores that can be mass-produced easily and are stable enough to be handled commercially. The actual substances that cause toxicity to the insect are toxins synthesized by the microbes.

Genetic engineering should make it possible to construct more potent bacterial insecticides by increasing the dosage of the genes that code for the synthesis of the toxins involved. Mixtures of genes capable of directing the synthesis of various toxins might also be produced.

Constraints on biological production techniques

The chief impediments to using biological production technology are associated with the need for biomass.[2] They include:

- competition with food needs for starch and sugar;
- cyclic availability;
- biodegradability and associated storage problems;
- high moisture content for cellulosics, and high collection and storage costs;
- mechanical processing for cellulosics;
- the heterogeneous nature of cellulosics (mixtures of cellulose, hemicellulose, and lignin); and
- The need for disposal of the nonfermentable port ions of the biomass.

For food-related biomass sources, such as sugar, corn, and sorghum, few technological barriers exist for conversion to fermentable sugars; but subsidies are needed to make the fermentation of sugars as profitable as their use as food. For cellulosic biomass sources such as agricultural wastes, municipal wastes, and wood, technological barriers exist in collection, storage, pretreatment, fermentation, and waste disposal. In addition, biomass must always be transformed into sugars by either chemical or enzymatic processes before fermentation can begin.

A second major impediment is associated with the purification stage of production. Most chemical products of fermentation are present in extremely dilute solutions, and concentrating these solutions to recover the desired product is highly energy-intensive. Problems of technology and cost will continue to make this stage an important one to improve.

The developments in genetics show great promise for creating more versatile micro-organisms, but they do not by themselves produce a cheaper fuel or plastic. Associated technologies still require more efficient fermentation facilities and product separation processes; microbes may produce molecules, but they will not isolate, purify, concentrate, mix, or package them for human use.

The interaction between genetic engineering and other technologies is illustrated by the problems of producing ethanol by fermentation. The case study presented in appendix I-D identifies those steps in the biomass-to-ethanol scheme that need technological improvements before the process can become economical.

Genetic engineering is expected to reduce costs in many production steps. For certain ones—such as the pretreatment of the biomass to make it fermentable—genetics will probably not play a role: physical and chemical technologies will be responsible for the greatest advances. For others, such as distillation, genetic

[2] *Energy From Biological Processes*, op. cit.

technologies should make it possible to engineer organisms that can ferment at high temperatures *(82° to 85° C) so* that the fermentation and at least part of the distillation can both take place in the same reactor. Various technologies, such as the immobilization of whole cells in reactor columns, could be developed in parallel with genetic technologies to increase the stability of cells in fermenters.

ethanol produc... already been described ... The ... ion, ... nt: fer ... (?ill ...anisms described as ... ii!+ (1'OSS ... taminatic ... teria. can ... at 70° ... 700 (:.

'I"llt? uch thermophilic fermentations are signifi... ion time is considerably is duced; the risk of con... nearly eliminated; and cooling requirements are ... higher temperature of the fermenting broth ... 1)1'0111.

An overview of impacts

The cost of raw materials may become cheaper than the petroleum now used—especially if cellulose conversion technologies can be developed. The source of raw materials would also be broader since several kinds of biomass could be interchanged, if necessary. For small quantities of chemicals, the raw material supply would be more dependable, particularly because of the domestic supply of available biomass. For substances produced in large quantities, such as ethanol, the supply of biomass could limit the usefulness of biotechnology.

Raw **materials,** such as organic wastes, could be processed both to produce products and reduce pollution. Nevertheless, the impact on total imported petroleum will be low. Estimates of the current consumption of petroleum as a raw material for industrial chemicals is approximately 5 to 8 percent of the total imported.

Impacts on the process include relatively cheaper production costs for selected compounds. For these, lower temperatures and pressures can be used, suggesting that the processes might be safer. Chemical pollution from biotechnology may be lower, although methods of disposal or new uses must be found for the micro-organisms used in fermentation. Finally, the biological processes will demand the development of new technologies for the separation and purification of the products.

impacts on the products include both cheaper existing chemicals as well as entirely new products. Since biotechnology is the method of choice for producing enzymes, new uses for enzymes may expand and drive this sector of the industry.

Impacts on other industries

Although genetic engineering will develop new techniques for synthesizing many substances, the direct displacement of any present industry appears to be doubtful: Genetic engineering should be considered simply another industrial tool. As such, any industry's response should be to use this technique to maintain its positions in its respective markets. The point is illustrated by the variety of companies in the pharmaceutical, chemical, and energy industries that have invested in or contracted with genetic engineering firms. Some large companies are already developing inhouse genetic engineering research capabilities.

The frequent, popular reference to the small, innovative "genetic engineering companies" as a major new industry is somewhat misleading. The companies (see table 14) arose primarily to convert micro-organisms with little commercial use into micro-organisms with commercial potential. A company such as the Cetus Corp. initially used mutation and selection to improve strains, whereas other pioneers such as Genentech, Inc., Biogen, S. A., and Genex Corp. were founded to exploit recombinant DNA (rDNA) technology. Part of their marketing strategy includes the sale or licensing of genetically engineered organisms to large established commercial producers in the chemical, pharmaceutical, food, energy, and mining industries. Each engi-

Table 14.—Some Private Companies With Biotechnology Programs

Company	Founded	Approximate employees 1979	Ph. D.s 1979	Research capacity	
				Recombinant DNA	Hybridomas
Atlantic Antibodies	1973	50	2		x
Bethesda Research Laboratories	1976	130		x	x
Biogen	1978	30 (50[b])	(18[b])[(3)(5)]	x	x
Bens Bio Logicals	1979	15	10	x	x
Centocor	1979	20(1)-10(4)			x
Cetus	1972	250	50	x	x
Clonal Research	1979	6	1		x
Collaborative Research[c]	1961	85	15	x	x
(Collaborative Genetics)	(1979)	(4)	(3)	x	
Genentech	1976	90	30	x	
Genex	1977	30	12	x	
Hybritech	1978	33[(1)]	6		x
Molecular Genetics	1979	6(4)		x	x
Monoclinal Antibodies	1979	6			x
NewEngland Biolabs	1974	22(22)-5 (4)		x	

[a] estimates.
[b] Expected by ...
Research ...orative Researc... of Collaborative Genetics. Thedivision batweenthem ...on between them

SOURCES: SOURCE...(1) Scien... 1960(52 ... 692-693, 1980 (52 people) to expa...
(2) *Science 206,* p. 692-693, 19S0 (20 senior ... 1980 ...
(3) *Science 206,* p. *692-693,* 1960(16 scientists, 30 employees).
(4) Dun & Bradstreet, Inc.
(5) *Engineering News,* Mar. 19,1960.
Office of Technology Assessment.

neering firm also intends to manufacture some products itself. It is likely that the products reserved for inhouse manufacture will be low-volume, high-priced compounds like interferon.

Genetic engineering by itself is a relatively small-scale laboratory operation. Consequently, genetic engineering firms will continue to offer services to companies that do not intend to develop this capacity in their own inhouse laboratories. Specifically, a genetic engineering company may contract with a firm to develop a biological production method for its products. At the same time, larger companies might establish inhouse staffs to develop biological methods for both old and new products. (Several larger companies already have more inhouse genetic engineering personnel than some of the independent genetic engineering companies.)

In addition, suppliers of genetic raw materials may decide to expand into the production of genetically engineered organisms. Suppliers of restriction endonuclease enzymes for example, which are used in constructing rDNA, have already entered the field. Diagnostic firms could develop new bioassays for which they themselves would guarantee a market. Finally, companies with byproducts or waste products are beginning to examine the possibility of converting them into useful products. This approach (which is somewhat more developed in Europe) assumes that with the proper technology the waste materials can become a resource.

Some industries, including manufacturers of agitators (drives), centrifuges, evaporators, fermenters, dryers, storage tanks and process vessels, and control and instrumentation systems, might profit by producing equipment associated with fermentation.

Impacts on university research

From the beginning, genetic engineering firms established strong ties with universities. These were responsible for providing most of the scientific knowledge that formed the basis for applied genetics as well as the initial scientific workforce:

- Cetus Corp. established a pattern by recruiting a prestigious Board of Scientific Advisors who remain in academic positions.
- Genentech, Inc., cofounded by a professor at the University of California at San Fran-

cisco, initially depended largely on outside scientists.
- Biogen, S. A., was organized by professors at Harvard and MIT plus six European scientists, and placed R&D contracts with academic researchers.
- Collaborative Genetics has a Nobel prize winner from MIT as the chairman of its scientific advisory board.
- Hybritech, Inc., has as its scientific nucleus a University of California, San Diego, professor complemented by scientists at the Salk Institute.

In addition to these companies, others have also been establishing closer ties with the academic community.

Much of the research that will be useful to industry will continue to be carried out in university laboratories. At present, it is often difficult to decide whether a research project should be classified as "basic" (generally more interesting to an academic researcher) or "applied" (generally more interesting to industry). E.g., a change in the genetic code, which increases gene activity, would be just as exciting to a basic scientist as to an industrial one.

This dialog between the universities and industry—both through formal and informal arrangements–has fostered innovation. Although the number of patents applied for is not a direct reflection of the level of innovation, it is still one indication. By the end of **1980,** several hundred patent applications were filed for genetically engineered micro-organisms, their products, and their processes.

University research has clearly affected industrial development, and has in turn been affected by industry. Although the benefits are easily recognized, some drawbacks have been suggested. The most serious is the concern that university scientists will be restrained in their academic pursuits and in their exchange of information and research material. To date, anecdotal information suggests that some scientists are being more circumspect about sharing information. Still, secrecy is not new to highly competitive areas of biomedical research. In addition, scientists in other academic disciplines useful to industry-such as chemistry and physics—have managed to achieve a balance between secrecy and openness.

The social impacts of local industrial activity

Despite the extensive media coverage of rDNA and other forms of genetic engineering, there is little evidence that people who live near companies using such techniques are still greatly concerned about possible hazards. This may be partly owing to a lack of awareness that a particular company is doing genetic research and partly because companies thus far have adhered to the National institutes of Health (NIH) Guidelines. Some companies have placed individuals on their institutional biosafety committees who are respected and trusted members of the local community. By involving the local citizens with no vested corporate interest, a mechanism for oversight has been provided. (For a more detailed discussion, see ch. 11.)

Impacts on manpower

Two types of impacts on workers can be expected:

- The creation of jobs that replace those held by others. E.g., a worker involved in chemical production might be replaced by one producing the same product biologically.
- The creation of new jobs.

Workers in three categories would be affected:

- those actually involved in the fermentation-production phase of the industry;
- those involved in the R&D phase of the industry, particularly professionals; and
- those in support industries.

Projections of manpower requirements are only as accurate as the projections of the level of industrial activity. In the past 5 years, about 750 new jobs have been created within the small ge**netic engineering firms (including monoclinal antibody producers). Of these, approximately one-third hold Ph. D. degrees.**

Data obtained through an (OTA survey of 284 firms indicate that the pharmaceutical industry employs the major share of personnel working in applied genetics programs. (See table 15.) The average number of Ph. D.s in each industry is given in table *16.* A rough estimate of professional scientific manpower at this level includes: 6 in food, 45 in chemical, 120 in pharmaceutical, and **18** in specialty chemicals-a total of 189. If the number of research support personnel is approximately twice the number of Ph. D.s, the total rises to about 570. If $165,000 per year is required to support one Ph. D. in industry, the total value of such manpower is approximately **$31** million.

Estimates of the number of companies engaged in applied genetics work in 1980 can be compared with the total number of firms with fermentation activities. A tabulation of firms on a worldwide basis in 1977 revealed 145 companies, of which 27 were American. (See table 17.) These companies produced antibiotics, enzymes, solvents, vitamins and growth factors,

Table 15.—Distribution of Applied Genetics Activity in Industry

Classification	Distribution of applied genetics activity by company class[a]	Percent of total
Food	(6146)	13
Chemical	(9/52)	17
Pharmaceutical	(12/25)	48
Specialty chemical[b].	(6/68)	9

firing specializing in genetic research.
ingredients, reagents, enzymes.

SOURCE: of Technology Assessment.

Table 16.—Manpower (low.(average)-high) Distribution of a Firm With Applied Genetics Activity

	Ph. D.	M.S.	Bachelors
Food.		0-(1)-2	O-(2)-8
Chemical	3-(5)-7	0-(1)-2	2-(5)-7
Pharmaceutical.	2-(10)-24	I-(4)-9	1-(8)-20
Specialty.	I-(3)-8	I-(3)-4	2-(2)-4
Biotechnology			
Genetic engineering.	3-(15)-32	2-(1 1)-20	5-(15)-25
Hybridoma.	I-(3)-6	0-(2)-0	0-(20)-0
Other	O-(2)-4	2-(4)-6	8-(10)-13
Average	.1-(6)-12	I-(4)-6	3-(8)-12

SOURCE: Office of Technology Assessment.

Table 17.—Index to Fermentation Companies

1. Abbott Laboratories, North Chicago, or
2. American Cyanamid, Wayne, ami
3. Anheuser-Busch, Inc., St. Louis, Mo.
4. Bristol-Myers Co., Syracuse, N.Y.
5. Clinton Corn Processing Co., Clinton, Iowa
6. CPC International, Inc., Argo, Ill.
7. Dairyland Laboratories, Inc., Waukesha, W
8. Dawe's Laboratories, Inc., Chicago Heights, Ill.
9. Grain Processing Corp., Muscatine, Iowa
10. Hoffman-LaRoche, Inc., Nutley, In
11. IMC Chemical Group, Inc., Terre Haute, Ind.
12. Eli Lilly & Co., Indianapolis, Ind.
13. Merck & Co., Inc., Rahway, Inc
14. Miles Laboratories, Inc., Elkhart, Ind.
15. Parke, Davis & Co., Detroit, Mich.
16. S. B. Penick & Co., Lyndhurst, N.J.
17. Pfizer, Inc., New York, N.Y.
18. Premier Malt Products, Inc., Milwaukee, Wis.
19. Rachelle Laboratories, Inc., Long Beach, Cal if.
20. Rohm & Haas, Philadelphia, Pa.
21. Schering Corp., Bloomfield, N.J.
22. G. D. Searle & Co., Skokie, Ill.
23. E. R. Squibb& Sons, Inc., Princeton, N.J.
24. Standard Brands, Inc., New York, N.Y.
25. Stauffer Chemical Co., Westport, Corm.
26. Universal Foods Corp., Milwaukee, Wis.
27. The Upjohn Co., Kalamazoo, Kal
28. Wallerstein Laboratories, Inc., Morton Grove, Ill.
29. Wyeth Laboratories, Philadelphia, Pa.

SOURCE: Office of Technology Assessment.

nucleosides, amino acids, and miscellaneous products. (See table 18.) The only chemical firm listed was the Stauffer Chemical Co. Ten firms are listed as having the ability to produce food and feed yeast. (See table 19.) Correcting for firms listed twice, at least 38 U.S. firms were engaged in significant fermentation activity for commercial products, excluding alcoholic beverages, in 1977. Not all have research expertise in fermentation or biotechnology, much less a regular genetics program: 10 to 20 were in the chemical industry; 25 to 40 in fermentation (enzyme, pharmaceutical, food, and specialized chemicals); and 10 to 15 in biotechnology (genetic engineering)—or about 45 to 75 firms in all.

If average manpower numbers are used, the total number of professionals involved in commercial applied genetics research is:

Ph. D.s: 300-450
Others: 600-900
900-1,350

The number of workers that will be involved in the production phase of biotechnology repre-

Table 18.-Fermentation Products and Producers

Product	Some producers
Amino acids	
L-alanine	
L-arginine	
L-aspartic acid	
L-citrulline	
L-glutarnic acid	25
L-glutamine	
L-glutathione	
L-histidine	
L-homoserine	
L-isoleucine	
L-leucine	
L-lysine	
L-methionine	
L-ornithine	
L-phenylalanine	
L-proline	
L-serine	
L-threonine	
L-tryptophan	
L-tyrosine	
L-valine	
Miscellaneous products and processes	
Acetoin	
Acyloin	13
Anka-pigment(red)	
Blue cheese flavor	7
Desferrioxamine	
Dihydroxyacetone	17,21,28
Dextran	
Diacetyl (from acetoin)	
Ergocornine	
Ergocristine	
Ergocryptine	
Ergometrine	
Ergotamine	
Bacillus thuringiensis insecticide	1
Lysergic acid	
Paspalic acid	
Picibanil	
Ribose	
Scteroglucan	
Sorbose(from sorbitol)	10,17
Starter cultures	7,13,14
Sterol oxidations	22,27
Steroid oxidations	21,23,27,29
Xanthan	13,17
Antibiotics	
Adriamycin	
Amphomycin	
Amphotericin B	23
Avoparcin	2
Azalomycin F	
Bacitracin	11,16,17
Bambermycins	
Bicyclomycin	
Blasticidin S	
Bleomycin	
Cactinomycin	
Candicidin B	16
Candidin	
Capreomycin	
Cephalosporins	4,12
Chromomycin A_3	
Colistin	
Cycloheximide	27
Cycloserine	11
Dactinomycin	13
Daunorubicin	
Destomycin	
Enduracidin	
Erythromycin	17,27
Fortimicins	
Fumagiliin	
Fungimycin	
Fusidic acid	
Gentamicins	21
Gramicidin A	28
Gramicidin J(S)	
Griseofulvin	
Hygromycin B	12
Josamycin	
Kanamycins	4
Kasugamycin	
Kitasatamycin	
Lasalocid	10
Lincomycin	27
Lividomycin	
Macarbomycin	
Mepartricin	
Midecamycin	
Mikamycins	
Mithramycin	17
Mitomycin C	4
Mocimycin	
Monensin	
Myxin	10
Neornycins	16,17,23,27
Novobiocin	27
Nystatin	23
Oleandomycin	17
Oligomycin	
Paromomycins	15
Penicillin G	4,12,13,17,23,29
Penicillin V	1,4,12,17,23,29
Penicillins(semisynthetic)	4,13,17,23,29
Pentamycin	
Pimaricin	
Polymyxins	17
Polyoxins	
Pristinamycins	
Quebemycin	
Ribostamycin	
Rifamycins	
Sagamicin	
Salinomycin,	
Siccanin	
Siomycin	
Sisomicin	21
Spectinomycin	27
Streptomycin	13,17,29
Tetracyclines	
Clortetracycline	19

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Table 18.-Fermentation Products and Producers

Product	Some producers	Product	Some producers
Demeclocycline	2	Lactase	28
Oxytetracycline	17,19	Lipase	20
Tetracycline	2,4,17,19,23,27	Microbial rennet	17,28
Tetranactin		Naringinase	28
Thiopeptin		Pectinase	20,28
Thiostrepton	23	Pentosanase	20,28
Tobramycin	12	Proteases	14,17,18,20,28
Trichomycin		Streptokinase-streptodornase	2
Tylosin	12	Uricase	
Tyrothricin	16,28	Organic acids	
Tyrocidine		Citric acid	14,17
Uromycin		Comenic acid	17
Vaildamycin		Erythorbic acid	
Vancomycin	12	Gluconic acid	4,17,18
Variotin		Itaconic acid	17
Viomycin		2-keto-D-giuconic acid	17
Virginiamycin		acid	
Enzymes		Lactic acid	5
Amylases	5,19,20,24,28	Malic acid	
Amyloglucosidase	5,6,14,28	Urocanic acid	
Anticyanase		Solvents	
L-asparaginase		Ethanol	9
Catalase	8,14	2,3-butanediol	
Cellulase	6,20,28	Vitamins and growth factors	
Dextranase		Gibbereliins	1,12,13
'Diagnostic enzymes'		Riboflavin	13
Esterase-lipase	28	Vitamin B_{12}	13
Glucanase	28	Zearalanol	11
Glucose dehydrogenase		Nucleosides and nucleotides	
Glucose isomerase	3,5,14,24	5-ribonucieotides and nucleosides	
Glucose oxidase	8,14	Orotic acid	
Glutamic decarboxylase	18	Ara-A-(9-B-D-arabino-furanosyl)	15
Hemi-celiulase	14,20,28	6-azauridine	
Hespiriginase			
Invertase	24,26,28		

[a]Blank meal in 10 U.S. produce in 1977; therefore, is produ foreign ne or more foreign firms (from a firms).

SOURCE: SOURCE: O Assessment.

sents a major impact of genetic engineering. To estimate this number these two calculations must be made:

- the value or volume of chemicals that might be produced by fermentation, and
- the number of production workers needed per unit volume of chemicals produced.

Any prediction of the potential volume of chemicals is necessarily filled with uncertainties. The approximate market value of organic chemicals produced in the United States is given in appendix I-B. Total U.S. sales in 1979 were calculated to be over $42 billion. On the basis of the assumptions made, $522 million worth of bulk organic chemicals could be commercially produced by genetically engineered strains in 10 years and $7.1 billion in 20 years. Table I-B-l0 in appendix I-B lists the potential markets for pharmaceuticals. Excluding methane production, the total potential market for products obtained from genetically engineered organisms is approximately $14.6 billion.

If the production of chemicals having this value is carried out by fermentation, it impossible to calculate how many workers will be needed. Data obtained from industrial sources reveal that 2 to 5 workers, including those in supervision, services, and production, are required for $l million worth of product. Hence, 30,000 to 75,000 workers would be required for the estimated $14.6 billion market.

Table 19.—U.S. Fermentation Companies

Producers of Baker's yeast and food/feed yeast in the United States in 1977
Baker's yeast:
American Yeast Co., Baltimore, Md.
Anheuser-Busch, Inc., St. Louis, Mo.
Federal Yeast Co. (now Diamond Shamrock), Baltimore, Md.
Fleischmann Yeast Co., New York, N.Y.
Universal Foods Corp., Milwaukee, Wis.
Food/feed yeast:
Amber Laboratories, Juneau, Wis.
Amoco Foods Co., Chicago, Ill.
Boise-Cascade, Inc., Portland, Oreg.
Diamond Mills, Inc., Cedar Rapids, Iowa
Fleischmann Yeast Co., New York, N.Y.
Lakes States Yeast Co., Rhinelander, Wis.
Stauffer Chemical Co., Westport, Corm.
Enzyme producers, *1977*
Clinton Corn Processing Co., Clinton, Iowa
Miles Laboratories, Inc., Elkhart, Ind.
Premier Malt Products, Inc., Milwaukee, Wis.

SOURCE: Compiled by Society for Microbiology News 43:2, 1977, pp 82-89.

Since the chemicals considered above are currently being produced, any new jobs in biotechnology will displace the old ones in the chemical industry. Whether the change will result in a net loss or gain in the number of jobs is difficult to predict. However, a rough estimate indicates that approximately the same number of workers will be required per unit of output.

Estimates of the number of workers are divided into: 1) workers directly involved in the growth of the organisms; and 2) workers involved in the "recovery" phase, where the organisms are harvested and the chemical product is extracted, purified, and packaged. Based on industry data, the number of workers in the fermentation phase is approximately 30 percent of the total, and those in recovery approximately 50 percent. Hence, about 9,000 to 22,500 workers might be expected to hold jobs in the immediate fermentation area, and about 15,000 to 37,500 workers would be involved in handling the production medium (with or without the organisms).

Estimates of the number of totally new jobs that would be created are highly speculative; they should allow for estimates of increases in the quantity of chemicals currently being produced and the production of totally new compounds. According to estimates by Genex, the new and growth markets may reach $26 billion by the year 2000, which would add 52,000 to 130,000 jobs to the present number.