EPA/600/R-94/125
October 1994

Proceedings

WORKSHOP ON GREEN SYNTHESES AND PROCESSING IN CHEMICAL MANUFACTURING

Omni Netherland Plaza
Cincinnati, Ohio
July 12-13, 1994

Sponsored by the U.S. Environmental Protection Agency:

Office of Research & Development
Risk Reduction Engineering Laboratory
Cincinnati, Ohio 45268

Office of Prevention, Pesticides and Toxic Substances
Washington, D.C. 20460

Co-sponsored by:

National Science Foundation
Arlington, Virginia 22230

Contract No. 68-C0-0068

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FOREWORD

Today's rapidly developing and changing technologies and industrial products and practices frequently carry with them the increased generation of materials that, if improperly dealt with, can threaten both public health and the environment. The U.S. Environmental Protection Agency is charged by Congress with protecting the Nation's land, air, and water resources. Under a mandate of national environmental laws, the Agency strives to formulate and implement actions leading to a compatible balance between human activities and the ability of natural systems to support and nurture life. These laws direct the EPA to perform research to define our environmental problems, measure the impacts, and search for solutions.

The Risk Reduction Engineering Laboratory is responsible for planning, implementing, and managing research, development, and demonstration programs. These provide an authoritative defensible engineering basis in support of the policies, programs, and regulations of the EPA with respect to drinking water, wastewater, pesticides, toxic substances, solid and hazardous wastes, and Superfund-related activities. This publication is one of the products of that research and provides a vital communication link between researchers and users.

The Workshop on Green Syntheses and Processing in Chemical Manufacturing was designed to provide an insight into the state of the art of environmentally benign chemical manufacturing. The recommendations of the workshop are summarized in these proceedings. The perspectives and recommendations coming out of this Workshop will help federal research directors make decisions regarding the support of research and development related to benign synthesis and manufacturing.

E. Timothy Oppelt, Director
Risk Reduction Engineering Laboratory

ABSTRACT

The Workshop on Green Syntheses and Processing in Chemical Manufacturing was held in Cincinnati, Ohio, on July 12 and 13, 1994. The purpose of the workshop was to solicit information from industry, academia, and government regarding research related to the advancement of environmentally benign chemical manufacturing processes.

Keynote addresses in Organic Synthesis, Biosynthesis, Engineering Approaches, and Computer-Based Methods specifically related to benign technology were presented by leading experts. The workshop attendees were subdivided into smaller groups addressing each of these four key areas. Proposed research topics were ranked according to their overall priority; the time frame within which an impact of the proposed research would be felt; what combination of industrial, academic, and government efforts is appropriate; and the need and justification for Federal funding.

FIGURES

FIGURES (continued)

FIGURES (continued)

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I. INTRODUCTION

In recent years, efforts have intensified to identify alternative chemical or biochemical processes that are both environmentally friendly and economically attractive. The chemical and allied industries, broadly defined as those industries employing processes involving chemical reactions that have the potential to cause the formation of undesirable by-products or the emission of toxic compounds, are responsible for the bulk of the environmental pollution associated with manufacturing activities.

To explore issues related to environmentally benign synthesis, a two-day workshop was organized under the joint sponsorship of the U.S. Environmental Protection Agency's (EPA's) Office and Research and Development (ORD), EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS), and the National Science Foundation (NSF). This meeting, entitled "Workshop on Green Syntheses and Processing in Chemical Manufacturing," was held in Cincinnati, Ohio, on July 12 and 13, 1994. At this workshop, more than 50 chemists, biochemists, and chemical engineering experts representing industrial, academic, and government institutions met to discuss the research needed to advance the development and adoption of environmentally benign chemical manufacturing processes (see Appendix A).

An overview of the background and goals of the workshop was provided by Thomas Powers of ORD's Water and Hazardous Waste Research Treatment Division, who chaired the opening session. Following several administrative announcements, T. Powers introduced Subhas Sikdar, Director of the Water and Hazardous Waste Treatment Research Division. After welcoming participants to Cincinnati, Dr. Sikdar described the workshop as part of an ongoing joint effort through which EPA and NSF are attempting to develop an integrated program in

support of environmentally benign chemical manufacturing. As stated by Dr. Sikdar, the specific goal of the workshop was to identify critical areas of research and development (R&D) in which government assistance and/or partnerships with industry and academia could be expected to offer the greatest benefit in meeting the dual goal of maintaining the economic vitality of the chemical manufacturing industry while at the same time reducing the industry's disproportionate contribution to environmental pollution. The case for so-called green chemistry has attracted a great deal of attention in the past year, beginning with a white paper entitled "Chemistry for a Clean World," published by the European Community's Chemistry Council in June, 1993. More recently, green chemistry has been the subject of articles in professional journals such as *Science* and *Chemical and Engineering News.* The scope of this workshop would be somewhat broader, moving beyond chemical processes *per se* to include chemical engineering and economic feasibility issues.

Dr. Sikdar concluded his introductory presentation by reviewing the proposed agenda for the two-day meeting (Appendix B). The first afternoon of the workshop would be devoted to an overview of issues in advanced manufacturing as seen from the perspective of the National Science and Technology Council, followed by a series of formal presentations on issues related to green syntheses and manufacturing processes. The following morning, the workshop would break into smaller workgroups that would attempt to answer four questions related to general areas covered in the plenary speakers' presentations:

- ***Question #1:*** *What research and development must be exploited to accelerate the development of benign organic synthesis?*
- ***Question #2:*** *What research and development must be exploited to accelerate the development of benign biosynthesis?*
- ***Question #3:*** *What engineering methods must be developed to aid in the cost-effective manufacturing of chemicals by benign routes?*

- ***Question #4:*** *What models, databases, and algorithms must be developed to make benign manufacturing more facile?*

At the end of the second day of the meeting, the group was scheduled to reconvene as a whole to discuss the conclusions and recommendations reached by the workgroups, particularly as those conclusions related to the need for short-, medium-, and long-term government assistance. These recommendations will be helpful to both EPA and NSF in their decision-making process for federal funding in this area.

II. PRESENTATIONS – OPENING PLENARY SESSION

Next Generation Manufacturing Systems and the Environment:
The Federal Agenda

Joseph Bordogna, National Science Foundation

A schematic representation of the variety of issues that currently impinge on thinking about research and development priorities at the federal level is depicted in Figure 1. Much effort is being invested in issues related to manufacturing and the environment. With the establishment of the National Science and Technology Council (NSTC) in November, 1993, there is a centralized structure for decisions about how to allocate the $70 billion the federal government spends on research and development each year. The

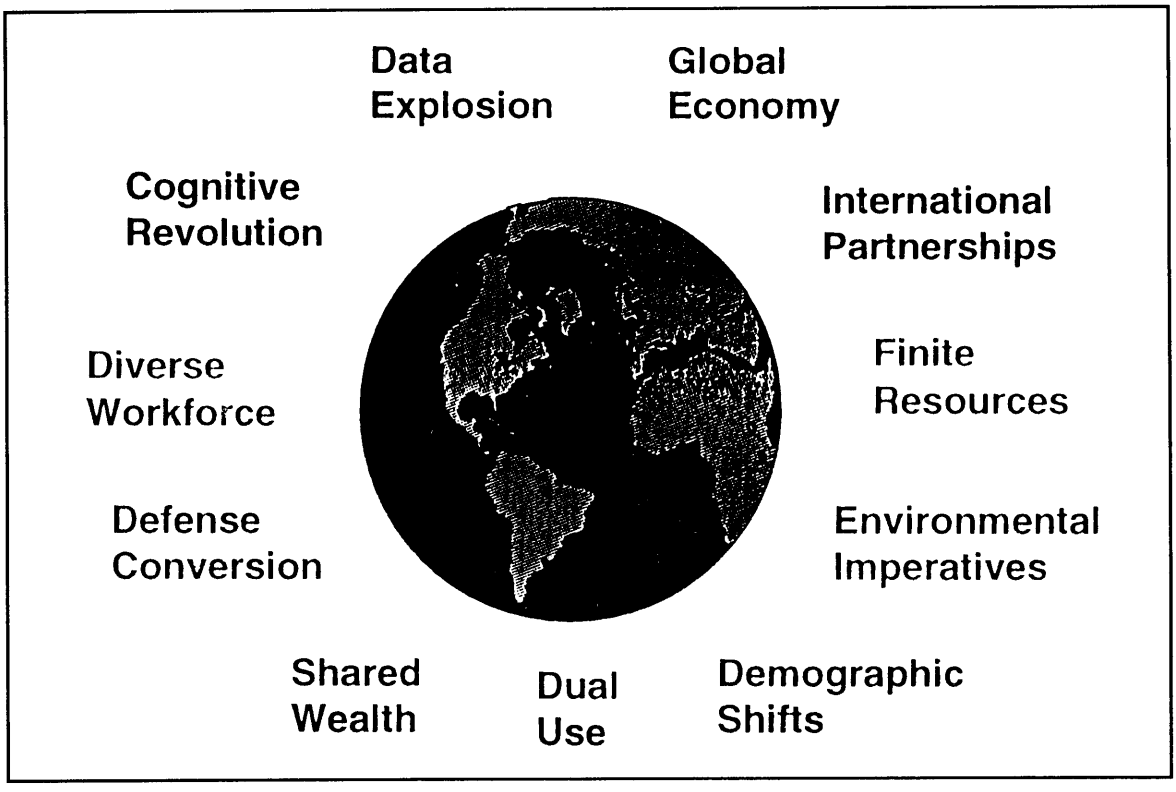


Figure 1. R&D Issues in a Changed World

proceedings of this workshop will be very useful to guide the decisions of NSTC, particularly to the extent that workshop participants could address the full spectrum of issues from discovery to regulation that fall under the combined aegis of the EPA and NSF.

Decisions concerning the allocation of federal R&D funding are presently being evaluated by two main criteria: the extent to which proposed efforts promote innovation and the extent to which these efforts contribute to the creation of wealth in the United States (see Figure 2). In this regard, a distinction is to be made between innovation, defined as new knowledge applied to things you did not know how to do before, and productivity, new knowledge that helps you do better things you already know how to do. In the context of

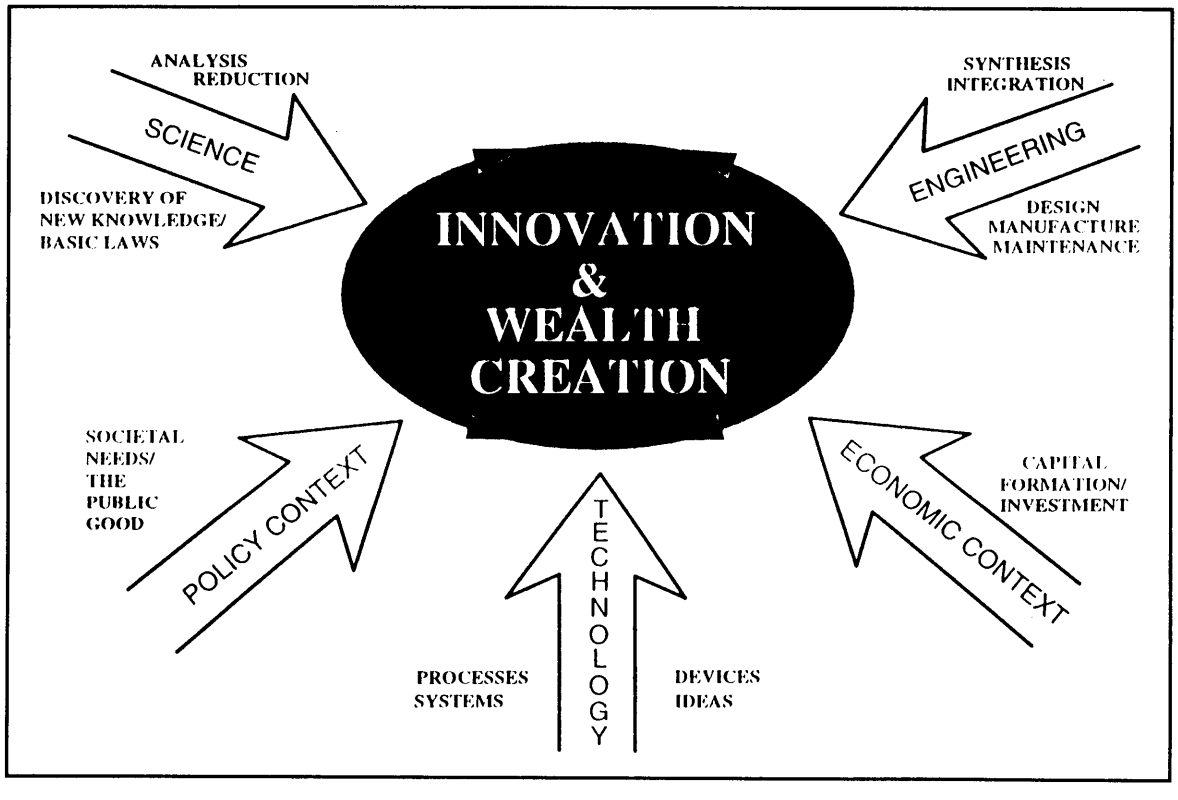


Figure 2. Concurrent Integration of Innovation and Wealth Creation

wealth creation, innovation is key, for innovation and wealth creation to go hand-in-hand. However, it is not sufficient just to have the science and engineering elements in place; for wealth creation to occur, it is also necessary for the resulting technology to fill a need in terms of prevailing economic and policy contexts. Moreover, for a process to realize its wealth-creating potential, all five aspects of the process (i.e., the science, engineering, technology, policy context, and economic context) must develop in parallel.

To illustrate the changing economic and political context for manufacturing in the United States, the change in demands on industry over the past several decades are described. For much of the 20th century, it was sufficient for manufacturers to pick two of three desirable attributes: good, fast, and cheap. Beginning in the 1980s, it became necessary for manufacturers to assure that processes met all three of these criteria. For the 1990s and beyond, a fourth criterion – clean – has been added to the list. From this point forward, environmental considerations must become part of the front-end design process for any manufacturing interest.

Perhaps the best indication of the federal government's increasing awareness of the importance of science and technology to the overall well-being of the United States was the November 1993, Executive Order, which established the National Science and Technology Council within the Executive Office of the President. The NSTC was organized to offer advice directly to the President in a manner similar to that previously provided only by the National Security Council and the National Economic Council. The most important undertaking of the NSTC is to decide how the federal R&D budget allocation should be used. In the past, federal R&D expenditures have been summarized on a single page in the budget, where R&D outlays were divided into four general categories: basic research, applied research, development, and facilities. In lieu of this somewhat "fuzzy" breakdown, one goal of the NSTC is to look at federal R&D expenditures

in terms of their impact on functions that the government exists to fulfill. Thus, the NSTC has organized itself into nine committees, one dedicated to each of these priority functions (see Figure 3). Each of these Committees is chaired by an Executive Branch member.

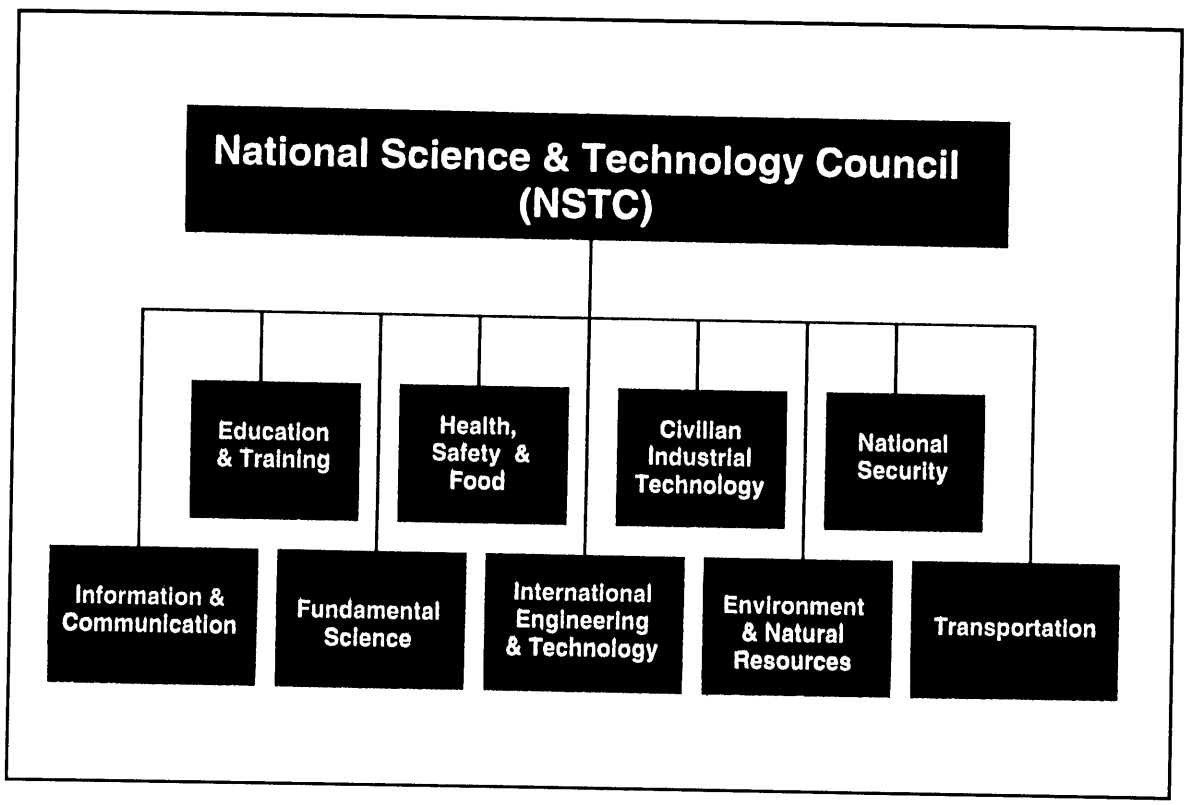


Figure 3. *Organization of the National Science and Technology Council (NSTC)*

Manufacturing issues fall within the purview of the NSTC Committee on Civilian Industrial Technology. The Civilian Industrial Technology Committee is an extremely important one, because it is the only committee in government that has representatives from both the private and public sectors working together. One initiative, the Partnership for a New Generation of Vehicles, involves executive vice presidents from the "Big Three" automobile manufacturers as well as representatives from seven government agencies.

The Subcommittee on Manufacturing Infrastructure has five working groups, each dedicated to an area the Subcommittee views as particularly worthy of federal support:

- Manufacturing Systems, dedicated to the advancement of next-generation manufacturing systems (e.g., agile/flexible manufacturing, intelligent manufacturing systems, quality initiatives)
- Engineering Tools for Design and Manufacturing, which will attempt to answer the question of how best to deal with the decline in the machine tool industry (e.g., concurrent engineering, virtual prototyping)
- Manufacturing Processes and Equipment, the working group that will promote the development of environmentally benign processes; rapid physical prototyping; and intelligent sensors, controls, and actuators
- Manufacturing Education and Training (e.g., TRP projects, teaching factories)
- Manufacturing Technology Deployment (e.g., MTCs, TRP projects)

An NSTC Committee of relevance to the issues being discussed at the workshop is the Committee on the Environment and Natural Resources, the organizational structure of which is illustrated in Figure 4. This committee has a Subcommittee on Technology and Engineering Research, the purview of which cuts across numerous areas of environmental concern, including air quality, toxic substances, and others. Currently, this subcommittee's efforts are focused in two main areas. The first, determining how to facilitate the commercialization of extant environmental technologies that for various reasons have not yet reached the market, is probably about a $100 million effort.

The other main interest of this subcommittee – long-term environmental technology research and development needs – is also the subject of a document entitled "Technology for a Sustainable Future." This document outlines the three

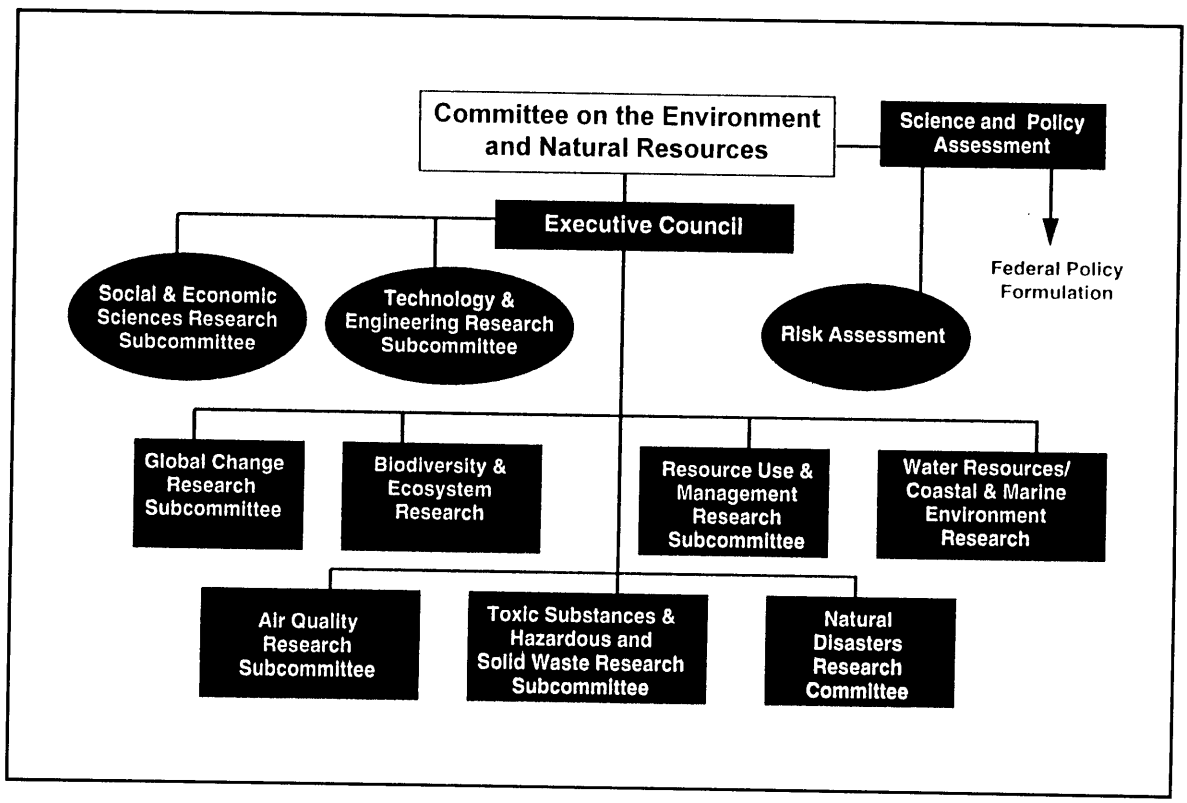


Figure 4. *Organization of the NSTC Committee on the Environment and Natural Resources*

main goals that will guide the Administration's efforts to develop an integrated, long-term environmental technology strategy:

- Encourage development of avoidance technologies and adoption of the low-waste/no-waste tenets of industrial ecology
- Forge stronger public-private partnerships to foster rapid diffusion of research results to environmental technology users
- Foster use of environmentally sound and socially appropriate technologies worldwide

The definition of sustainable development set forth by the Bruntland Commission in 1987 ("development that meets the needs of the present without compromising

the ability of future generations to meet their own needs"), was used as a basis for environmental technology as "technology that advances sustainable development by reducing risk, enhancing cost-effectiveness, improving process efficiency, and creating products and processes that are environmentally beneficial or benign." In this context, technology includes hardware, software, systems, and services. With a vision of long-term economic growth that creates jobs while improving and sustaining the environment, the overall thrust of the contemplated program is to move the environmental technology paradigm from one of cleanup and control to one of anticipation, avoidance, and assessment.

The "Technology for a Sustainable Future" document is expected to be the focus of extensive interaction among representatives from industry, academia, and government over the next year. Based on these interactions, the President will enunciate an Environmental Technology Strategy for the U.S. on Earth Day, 1995.

Noting that it is common for people in government to think about manufacturing primarily if not exclusively in terms of parts assembly, it will be important for the chemical manufacturing community to make its R&D needs known to policymakers. Among areas of research and development considered to be at the leading edge of chemical technology and manufacturing are the following:

- Environmental Technology
- Biotechnology
- Chemical Processes
- Process Design

- Process Equipment, Analytic Devices and Sensors, and Materials of Construction
- Microtechnology and Microsystems Technology

Given the stiff competition for federal research dollars, it will be important for chemists and chemical engineers to make a case for environmental technologies as a potential source of wealth creation. Toward this end, Robert Wellek of the NSF has estimated that the global market for environmental technologies amounted to nearly $300 billion in 1992 and that this market could grow to roughly $425 billion per year by 1997.

Turning to the issue of pollution prevention, there remains considerable debate regarding the potential of pollution prevention strategies as a catalyst for innovation, new market opportunities, and wealth creation. On the one hand, U.S. businesses spent $91 billion in 1989 for pollution control and abatement, and it was recently estimated that cleanup of Superfund hazardous waste sites could cost as much as $700 billion, much of which will also come from U.S. businesses. In light of these and other costs, avoidance of problems through pollution prevention has become an option of choice for many U.S. chemical manufacturers. On the other hand, responding to environmental challenges has almost always been a costly and complicated proposition in which "win-win" solutions are rare. Because of this, some globally managed corporations have elected to move their production facilities out of the U.S. to areas that place a lower value on less polluting manufacturing. Given these conflicting viewpoints, this emphasizes that there is a great deal of wealth that can be made through green manufacturing, and an important part of that process is obtaining the funding needed for research in this area.

It is important that the activities of the NSTC Committee on Environment and Natural Resources mesh with NSF's ongoing Environment and Manufacturing

Initiatives. Within the Environment Initiative, emphasis is placed on the development of new products, materials, and processing methods to minimize pollution, while the Manufacturing Initiative concentrates on environmentally conscious means of scaling up production, actual plant processing and equipment design, and reuse of by-products for reducing manufacturing costs. Often, the same R&D skills are used in both research initiatives, leading to opportunities for cooperative and synergistic planning.

Recently, a number of integrating themes have been developed as priority areas for the NSF Environmental Initiative; these integrating themes include Biodiversity, Water and Watersheds, Environmental Technology, and Resource Use and Management. The Environmental Technology theme is that fundamental research in environmentally conscious technologies, monitoring technologies, and remediation technologies increases our capabilities with regard to environmentally benign manufacturing, materials, water and energy technologies, and the application of existing technologies to new environmental problems. In support of this theme and in partnership with other agencies – including EPA – NSF plans to initiate cooperative research efforts supporting the design and development of new products and materials, especially those that involve streamlining synthetic methods and enhancing product biodegradability.

Benign Organic Synthesis

James Bashkin, Washington University

The state of the art of synthetic organic chemistry is often equated with the tremendous advances that are occurring in the synthesis of highly complex natural products of known or potential pharmaceutical importance. An example of this type of advance is the synthesis of Taxol, an anti-cancer agent derived from the bark and needles of yew trees (Figure 5). Achieving total synthesis of Taxol is

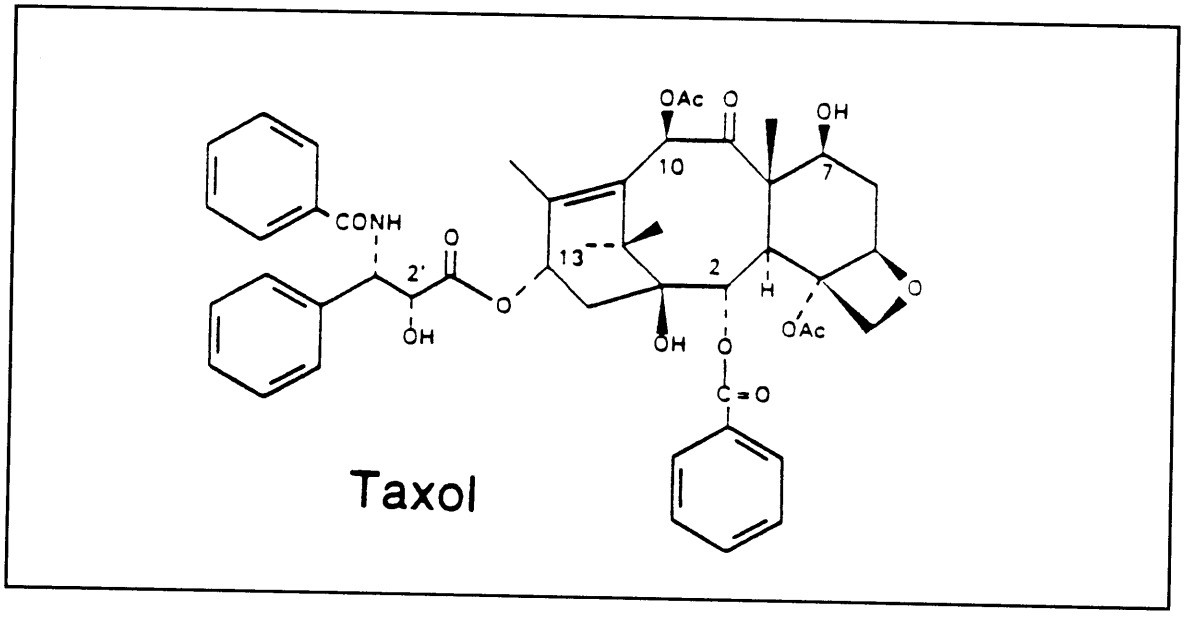


Figure 5. Chemical Structure of Taxol

remarkable not only because of the complex structure of the target molecule, but also because of the number and complexity of chemical transformations that make up the synthetic process (see Figure 6).

While not disputing the importance of synthesizing compounds of pharmaceutical value, the broadening of our view of state-of-the-art organic synthesis to include the synthesis of commodity and specialty chemicals might afford the opportunity to develop equally impressive advances in the form of new versions of old reactions that do not carry the "environmental baggage" of traditional industrial processes. Moreover, new organic synthetic techniques can be brought to bear in the manufacturing of many materials that are prepared via organic chemical reactions. Examples of the breadth of areas in which synthetic organic chemistry and organic chemical reactions impact on manufacturing and society are:

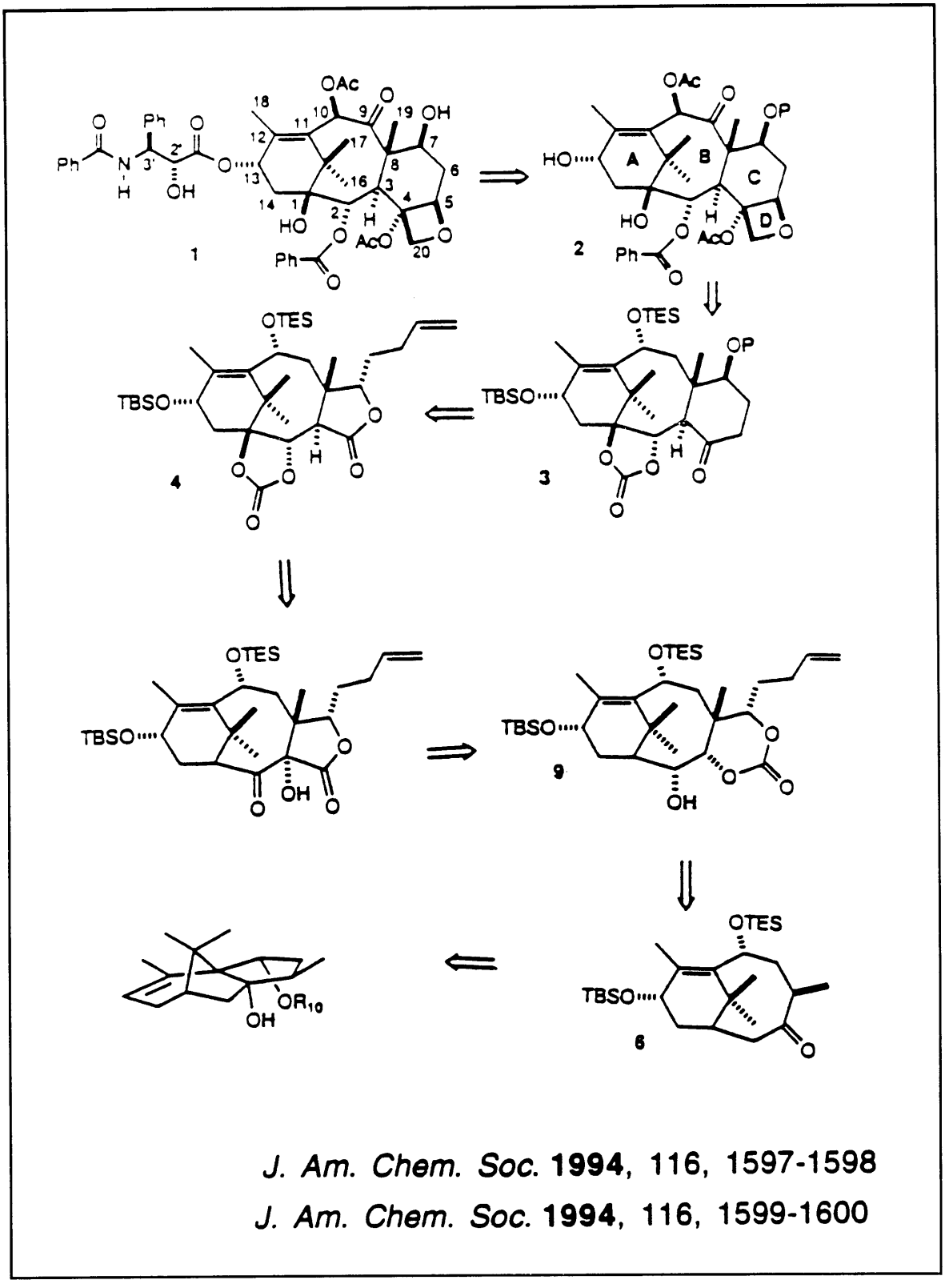


Figure 6. Holton's Synthesis of Taxol

- Natural, semisynthetic, and synthetic fibers used in clothing
- Paper pulp used to form paper
- Polyurethane coatings that protect automobiles
- Structural plastics used to build medical devices and other equipment
- Rubber chemicals used in the manufacture of automobile tires and other products
- Specialty fluids necessary to the operation of the Space Shuttle

Chemical processes involved in the preparation of materials for these purposes include the bleaching of paper pulp, the uv-stabilization and crosslinking of polymers, protection of automobile tires from oxidative breakdown, and modification of fibers to improve stain resistance and wear.

Given the wide-ranging importance of commodity and specialty chemicals to society, another "leading edge" of organic synthesis is embodied in attempts to replace traditional synthetic processes with environmentally benign alternatives. It is possible to develop benign organic syntheses that eliminate the waste of the old process while at the same time offering a more economically viable method of producing the target molecule. Because of this, the economics of benign synthesis can be very attractive even without considering costs related to the environmental elements of the equation.

One important barrier to the development of environmentally benign syntheses has been the tendency of organic chemists to focus exclusively on the target molecule (product). Many organic chemists feel successful if they are able to synthesize a target molecule – even if the yield is small and the synthetic process requires a large number of intermediate steps. In almost every such process, however, by-products other than the target molecule are also generated. In the past, chemical manufacturers have typically viewed these by-products as

annoying but not terribly important wastes. In academic pursuits, where even very low-yield syntheses may represent important intellectual advances, reaction by-products do not always receive much attention. As awareness of the environmental impact of chemical processes has increased, it becomes clearer that all of the by-products of chemical reactions must be taken into account. Although many organic chemists are working on the synthesis of very complex molecules, few people are engaged in the development of new synthetic methods that replace traditional bond-making and bond-breaking reactions or oxidation reactions with environmentally acceptable alternatives.

To promote the development of new organic reactions that meet environmental criteria, the application of the concept "the conservation of useful mass" could help. The key tenet of this concept is to incorporate all of the atoms in the starting materials in the product to the extent possible. Where reaction by-products are unavoidable, these by-products should themselves be benign compounds.

To illustrate the conservation of useful mass concept in a simplistic manner, two different methods of producing water were outlined in Figure 7. Using traditional methods, a mixture of an acid and a base produces water; both organic or inorganic reactants could be used in this process. Although this type of reaction has the desired effect of producing water, it does not meet the criteria of conserving useful mass, since one equivalent of salt is produced for each equivalent of water. If the goal of the process is synthesizing water, salt is a waste product that will have to be dealt with in some way. Alternatively, water could be synthesized via a reaction between hydrogen and oxygen. This pathway results in a full conservation of useful mass, since all of the atoms of the starting materials are incorporated in the product.

The Synthesis of Water. 1.

Acid + Base = Salt + Water

An Inorganic example:

$HCl + NaOH = NaCl + H_2O$

Using an Organic Acid:

$$MeCOOH + [NMe_4^+]OH^- = [MeCO_2^-][NMe_4^+] + H_2O$$

Water is produced, but so is an equivalent of salt.

The Synthesis of Water. 2.

$$H_2 + 1/2O_2 = H_2O$$

There is no wasted mass. All of the mass of the starting materials is incorporated into the product.

Figure 7. *Traditional versus Environmentally Benign Methods of Synthesizing Water*

A more sophisticated example of environmentally benign alternatives to traditional reaction processes could be the oxidation reactions such as those used in the bleaching of paper pulp. Traditionally, these reactions have been carried out using a variety of chlorine-based bleaches (Figure 8). In these reactions,

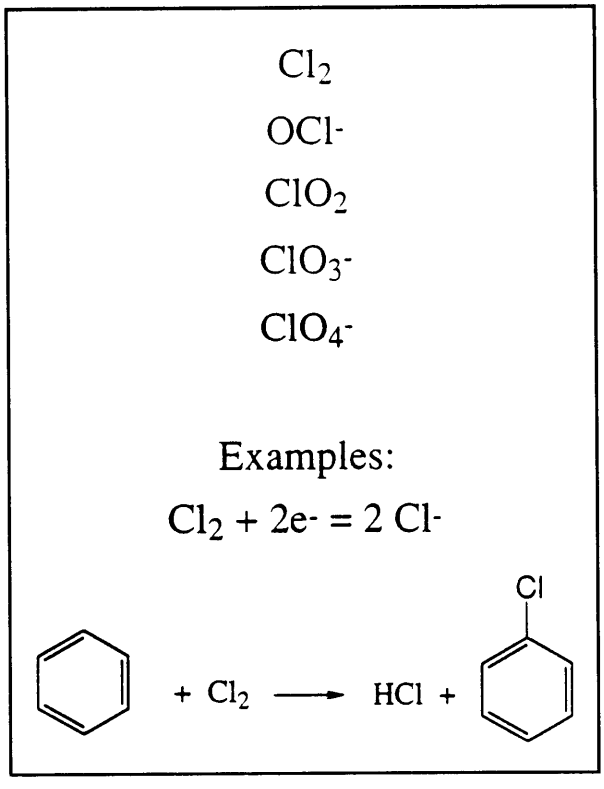


Figure 8. Traditional Cholorine-Based Oxidation Reactions

chlorine gas acts as an oxidizing agent by accepting two electrons, in the process generating two equivalents of chloride ion. Although effective in achieving the desired oxidation, the halogen-based bleaching process produces waste chloride anion and chlorinated organics that will have to be dealt with in some manner. Similarly, chlorine gas is commonly used in the functionalization of benzene, generating starting materials for nucleophilic aromatic substitution reactions. Waste products associated with these types of reactions include two equivalents of chloride waste: one in the form of hydrochloric acid and the other in the form

of chloride that will act as a leaving group during the nucleophilic displacement step of the reaction.

To accomplish the same goal in a more environmentally benign way, oxygen and hydrogen peroxide could be used as oxidizing agents in place of halogen-based compounds. As Figure 9 illustrates, the only by-products of such oxidations would be two equivalents of water. All of the atoms of the starting materials are incorporated in the reaction products, so this process, too, satisfies the criteria for conservation of useful mass.

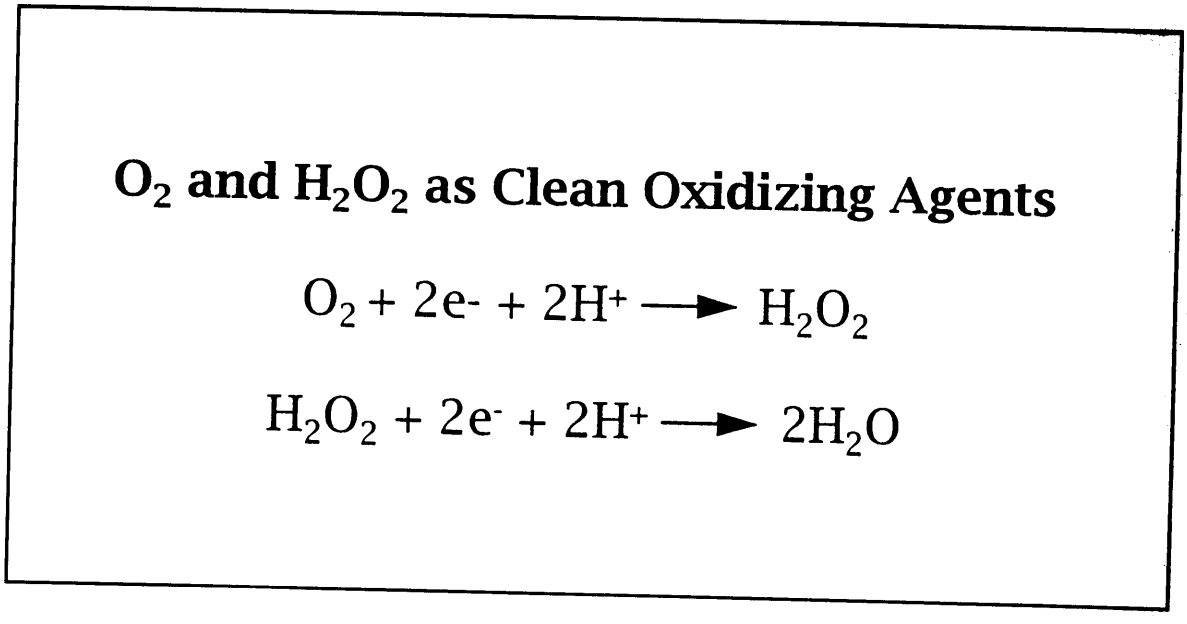
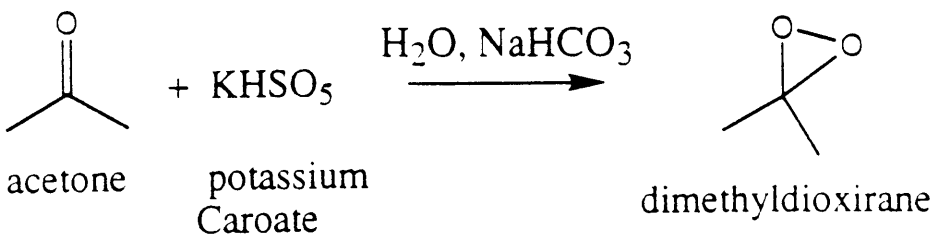


Figure 9. Oxygen and Hydrogen Peroxide as Clean Oxidizing Agents

There are a number of difficulties in attempting to use oxygen and hydrogen peroxide as oxidizing agents, most involving the problem of how to control the oxidation reaction once it begins. Normally, such reactions require the use of a catalyst that helps modify the reactivity and selectivity of oxygen. It is extremely difficult to avoid overoxidation to carbon dioxide or carbon monoxide in a methane-to-methanol conversion, for example, unless the reaction is carried

out in the presence of methane monooxygenase, a metalloenzyme that acts to control the rate and extent of the oxidation reaction. Development and industrial exploitation of metal catalysts that can replace environmentally dangerous oxidizing agents should be an area in which increased efforts have a great deal of potential. In some cases, such catalysts have already been developed and need only be exploited by industry. One example of such catalyst development is the use of a manganese dimer to accelerate the decomposition of sodium perborate, allowing the bleaching of fabrics to take place at low temperatures.

Another approach to modulating oxidation reactions involves the use of highly-oxygenated reactive intermediates. The development of a distillable oxidizing agent, dimethyldioxirane, by Murray and colleagues at the University of Missouri, St. Louis, is shown in Figure 10. Because it is distillable, this oxidizing



1. Murray, R. W.; Jeyaraman, R., *J. Org. Chem.* **1985**, *50*, 2847.
2. Waldemar, A.; Hadjiarapoglou, L.; *Top. Curr. Chem.* **1993**, *164*, 45-62.

Figure 10. *Preparation of Murray's Dimethyldioxirane as a Clean Oxidizing Agent*

agent can be readily separated from organic by-products, and because it uses a regenerable acetone as the oxygen carrier, it can also be recycled. By providing

an oxidation pathway that is totally devoid of inorganic by-products, this kind of reagent is currently receiving very serious attention in industry.

An example of green chemistry, which can be economically as well as environmentally rewarding, is an alternate pathway to 4-nitro dybenzylamine. A precursor, 4-nitro dyphenylamine, used in making the additives that prevent the oxidative breakdown of automobile tires by ozone, can be made by traditional means (see Figure 11). In this process, benzene is functionalized via an oxidative chlorination reaction. The resulting chlorobenzene is nitrated, producing water and a para-chloronitrobenzene intermediate. Finally, aniline or formaniline is added in the presence of a base, where it acts as a nucleophile to displace the chloride leaving group and form the target product.

The traditional synthetic pathway is limited by the formation of an equivalent of salt, also produced for each equivalent of para-nitrodiphenylamine produced. Given that compounds based on para-nitrodiphenylamine are produced on a scale of approximately 300 million pounds per year worldwide, the associated salt waste stream represents a significant challenge. The problem is complicated further by the fact that the waste salt is contaminated by aromatic amine impurities that are structurally related to benzidine, a known human carcinogen.

To evaluate the potential for environmental and human health risks associated with conventional methods of producing para-nitrodiphenylamine, an attempt was made to devise a synthetic pathway through which the target compound could be produced without generating any salt. The major problem that had to be overcome was finding a way to perform a nucleophilic substitution reaction without a leaving group, or using hydride as a leaving group. Direct nucleophilic attack of the nitrobenzene produces a Meisenheimer complex that is

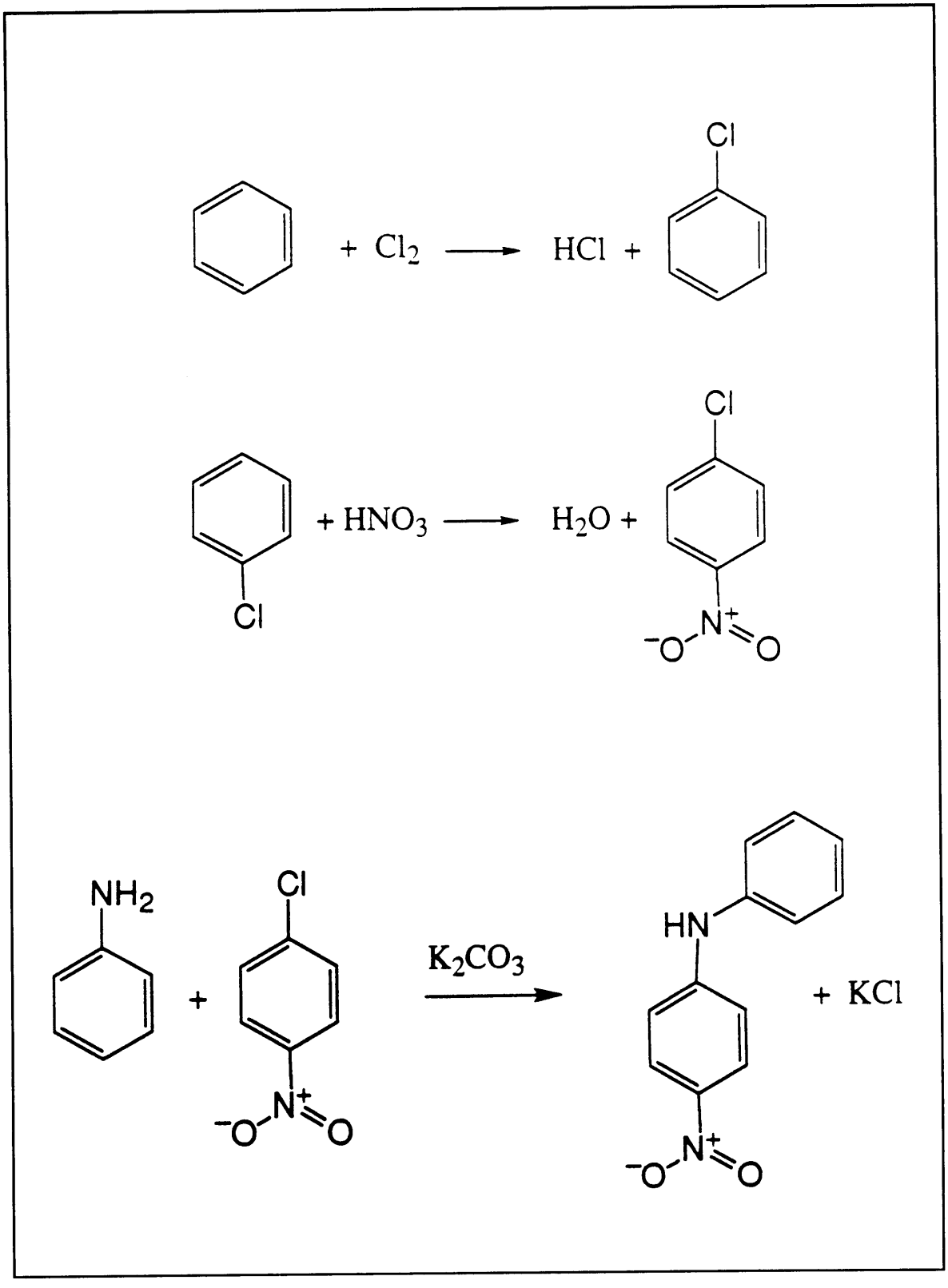


Figure 11. *Conventional Pathway for Synthesizing para-Nitrodiphenylamine*

structurally similar to that produced in the chlorination reaction, except that the structure does not include a good leaving group (Figure 12).

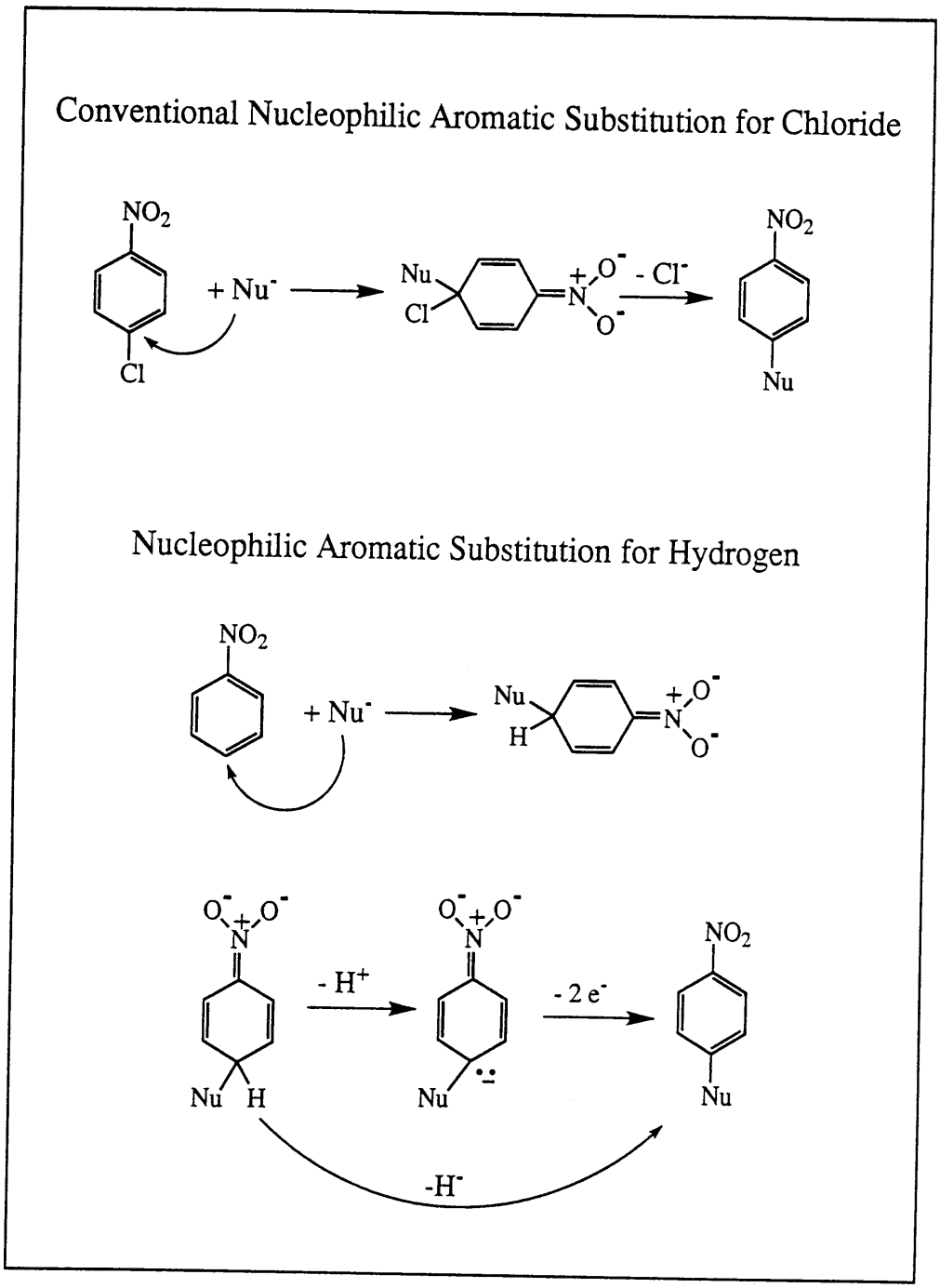


Figure 12. Generation of a Meisenheimer Intermediate via Chlorobenzene versus Direct Nucleophilic Attack

To achieve the desired product, a method had to be found to replace a hydride – whether in the form of a proton plus two electrons, a hydrogen radical and an electron, or a hydride ion – in order to aromatize the ring. The method chosen was to use aniline as a starting material in the presence of a catalytic base, tetramethylammonium hydroxide (see Figure 13). In this system, the catalytic base deprotonates aniline, generating an anilide nucleophile. This nucleophile attacks the nitrobenzene molecule, forming a Meisenheimer complex in which the no-longer aromatic nitro group can act as a hydride acceptor. Depending on the concentration of nitrobenzene present, the reaction yields varying combinations of para-nitrosodiphenylamine, para-nitrodiphenylamine, and azobenzene. The nitro and nitroso compounds are readily hydrogenated, generating more of the desired para-nitrodiphenylamine product. Azobenzene can be hydrogenated to produce aniline, which can be recycled in the reaction. Thus, the only by-product of the reaction is distilled water.

The overall stoichiometry of the catalyzed reaction is summarized in Figure 14. In this reaction, nitrobenzene plus anilide in the presence of a catalytic base yields para-nitrosodiphenylamine plus water. This reaction avoids both the chlorination of nitrobenzene and the subsequent removal of the chloride ion during the nucleophilic substitution step, and the only by-product of the process is distilled water. The oxygen atom in the water comes from the nitro group, one hydrogen comes from the aniline, and the other comes from the Meisenheimer intermediate.

The overall synthetic yield of the nitro and nitroso compounds is 90% or greater, depending on the aniline:nitrobenzene ratio of the reaction mixture (Figure 15). Since nitrobenzene is much cheaper than para-chloronitrobenzene, this route not only avoids environmental clean-up problems but is actually more cost-effective than the conventional process for synthesizing para-

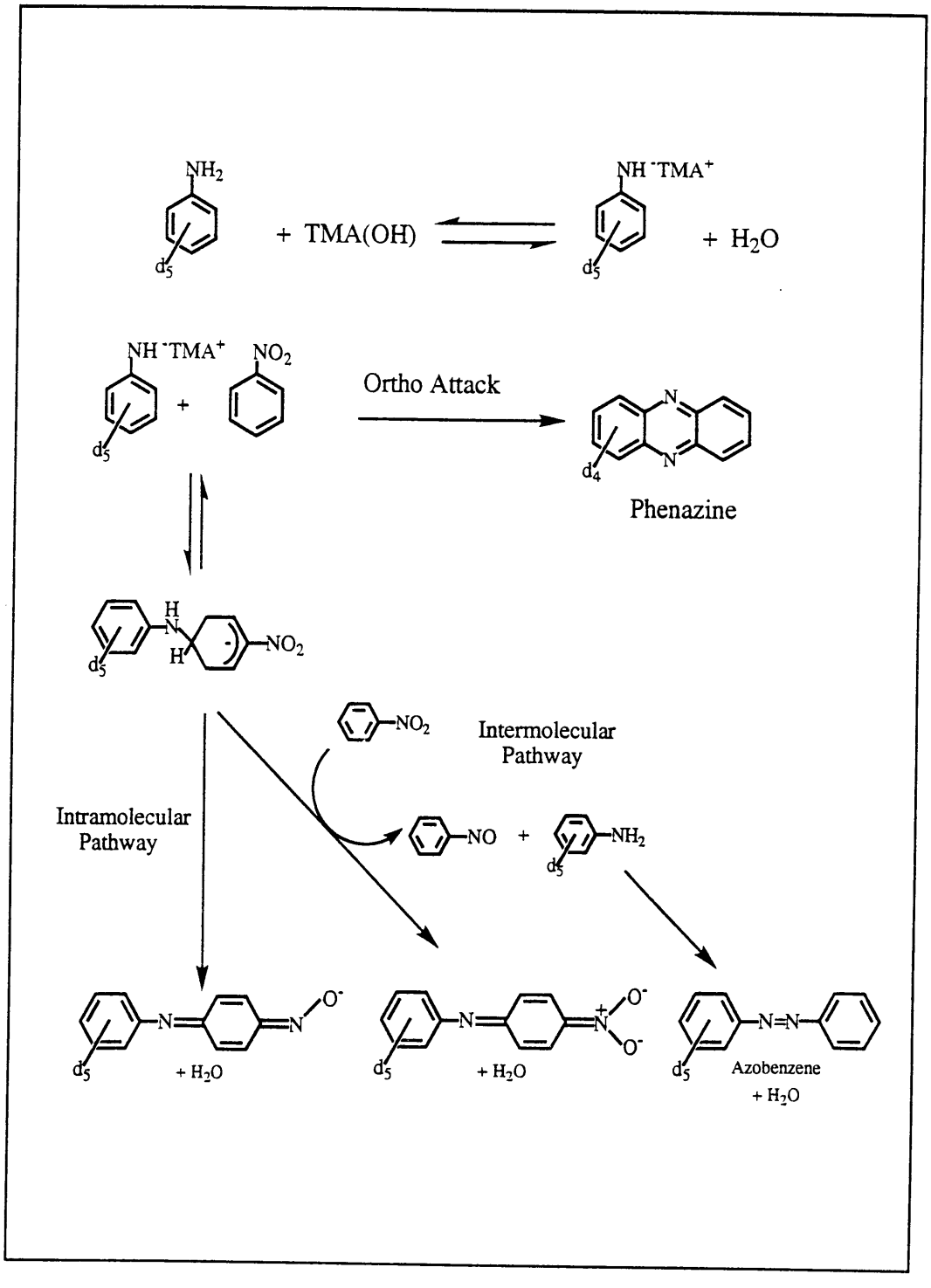


Figure 13. *Synthesis of para-Nitrodiphenylamine Without Using Chlorobenzene*

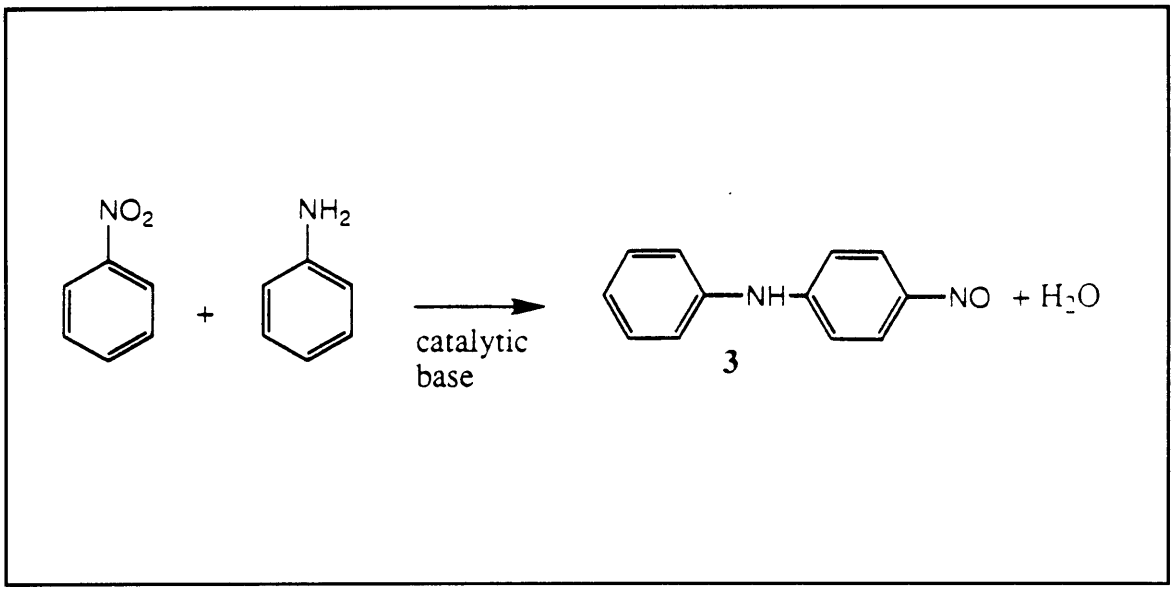


Figure 14. *Overall Stoichiometry of the Tetramethylammonium Hydroxide-Catalyzed Synthesis of para-Nitrosodiphenylamine*

Mole Ratio Aniline:Nitrobenzene	% Yield[a] 3	4
1.32	15	80
11.9	55	35
51.5	86	9

[a]Reverse phase HPLC was used to analyze the reaction mixtures. The external standard method was used to quantitate reaction yields using a Vydac 210HS54 (4.6 X 250 mm) column and UV detection at 254 nm. Yields are normalized to total moles of 4-NODPA and 4-NDPA produced at each AN:NB ratio.

Figure 15. *Percent Yield of Nitro and Nitroso Diphenylamine Products with Varying Aniline: Nitrobenzene Ratios*

nitrodiphenylamine. Monsanto has taken this alternative mode of synthesis to a pilot plant stage, and the economics of the process thus far look very promising.

There are a number of nucleophiles other than aniline that can be used in aromatic substitution reactions designed to avoid the use of chlorobenzenes. For those interested in more information, the following references are offered:

- "Methods of Preparing Anti-ozonants for Rubber Chemicals," M.K. Stern and J.K. Bashkin, U.S. Patent 5,117,063.
- "The Direct Coupling of Aniline and Nitrobenzene: A New Example of Nucleophilic Aromatic Substitution for Hydrogen," M.K. Stern, F.D. Hileman, J.K. Bashkin, *J. Am. Chem. Soc.,* **1992,** *114,* 9237-9238.
- "Process for preparing *p*-nitroaromatic amides and products thereof," J.K. Bashkin, M.K. Stern, U.S. Patent 5,331,099.
- "Amination of Nitrobenzene via Nucleophilic Aromatic Substitution for Hydrogen: Direct Formation of Aromatic Amide Bonds," M.K. Stern, B.K. Cheng, *J. Org. Chem.,* **1993,** *58,* 6883-6888.

There is information relating to green processes currently sitting on shelves in universities and industry. The main obstacle to commercial application of some processes is the difficulty of raising the capital needed to build new chemical plants. Federal assistance in this area – perhaps in the form of new guidelines regarding the tax treatment of capital expenditures – would provide a useful counterbalance to penalties that are rightly imposed for chemical processes that pollute. In addition, federal funding should play an important role in educating academic scientists about and supporting research on the standard bond-making and bond-breaking reactions that need to be re-examined from the perspective of environmentally benign organic synthesis.

Benign Biosynthesis

Jerome Schultz, University of Pittsburgh

Since the term benign biosynthesis is a relatively new one, the area may be approached from two distinct points of view. First, benign biosynthesis can be defined in terms of utilizing what might otherwise be considered waste; included within this definition would be efforts involving the use of biotechnology to convert agricultural wastes to chemical feedstocks (e.g., lignocellulose to ethanol) or to treat conventional feedstocks in ways that reduce their potential to pollute (e.g., desulfurization of coal). Second, it is important to keep in mind that most of conventional biotechnology is based in aqueous systems, which could pose problems for large-scale manufacturing in that most of these systems are relatively dilute. Another definition of benign biosynthesis, therefore, involves exploring ways in which enzymes and other biotechnologic approaches to chemical synthesis might be applied to non-aqueous systems.

To set a general framework for the discussion, a table from the July, 1994 issue of *Chemical and Engineering News* lists most of the organic chemicals currently produced in the United States (see Figure 16). This table raises two important issues regarding biosynthetic approaches to organic chemistry. First, most of the chemicals on the list are produced in the range of millions to billions of pounds. One question, therefore, is whether biotechnologic techniques can realistically be expected to achieve production levels in this range. Second, most chemicals on the list are low molecular weight compounds, whereas the efforts of the biotechnology industry have been focused mainly on production of large pharmaceutical compounds. Thus, a second question concerns how adaptable existing biotechnologic techniques will be to the production of smaller molecules.

1993 United States Organic Chemcial Production
Chem and Eng News - July 1994

	Millions Pounds	% change (1983-1993)
Acetic Acid, synthetic	3656	23
Acetone	2462	24
Acrylonitrile	2508	19
Aniline	1011	34
Benzene	13416	27
Bisphenol A	1286	50
1,3-Butadiene	3092	24
1-Butanol	1328	37
Caprolactam	1359	28
Chloroform	476	24
Cumene	4489	25
Cyclohexane	2000	17
Dioctyl phthalate	245	-18
Ethanol, synthetic	740	-31
Ethanolamines	706	34
Ethylbenzene	11758	33
Ethylene	41244	30
Ethylene dichloride	17945	36
Ethylene glycol	5228	15
Ethylene oxide	5684	3
2-Ethylhexanol	688	44
Formaldehyde	3041	28
Isobutylene	1146	34
Isopropyl alcohol	1236	2
Maleic anhydride	424	29
Methanol, synthetic	10542	24
Methyl tert-butyl ether	24053	97
Methyl chloride	849	52
Methyl ethyl ketone	556	4
Methyl methacrylate	1088	22
Methylchloroform	452	-23
Methylene chloride	354	-39
Perchloroethylene	271	-50
Phenol, synthetic	3718	29
Phthalic anhydride	854	2
Propylene	22398	38
Propylene glycol	885	45
Styrene	10063	32
Terephthalic acid	7837	28
Toluene	6664	6
Vinyl acetate	2827	31
Vinyl chloride	13746	50
o-Xylene	884	12
p-Xylene	5757	29
Total	240966	

Figure 16. Production of Organic Chemicals in the United States, 1993

To address the issue of biomass feedstocks, Figure 17 shows data developed by Charles Scott and colleagues at the Oak Ridge National Laboratory. These data indicate that millions of tons of waste materials could potentially be used to replace petroleum as a feedstock for chemical production. With potential feedstocks in the 3 trillion ton range, the volume of biomass resources is large enough to have a significant impact on the production of industrial organic chemicals. Altogether, chemicals that could be synthesized from agricultural feedstocks have a total value of approximately $110 billion per year. Most promising in this regard, 25% of these chemicals that represent oxidation products could potentially be produced by microorganisms.

The potential use of wastepaper as a chemical feedstock offers another example of an evolving biotechnology. Because wastepaper is already being "harvested," raw material costs should be vanishingly small. At the same time, the amount of wastepaper currently processed is enough to produce on the order of 4 million gallons of ethanol per year, and at a competitive price (i.e., less than $1/gallon). As such, use of wastepaper as a feed material for the production of ethanol may well represent the first entry into the industrial market of a lignocellulose-based commodity chemical.

For a chemical manufacturing plant to be built around a bioprocess, two important criteria must be met. First, the proposed feedstock must be able to compete with the fluctuating and currently low cost of fossil materials, and secondly, an adequate supply of the feedstock must be assured. From this perspective, waste materials may be the most useful feedstocks for initial market penetration. Second, the manufacturer must have the advanced technology required to process this material. In this regard, research directed toward development of more effective biocatalysts and more advanced bioprocessing systems may be especially useful.

FEEDSTOCK	PRODUCTION (Millions of Dry Tons/Yr) Current	Potential
CROPS:		
LIGNOCELLULOSE	391	1565*
STARCH CROPS	103	1575*
FORAGE GRASSES	26	414
WASTE:		
AGRICULTURAL	390	390
LIVESTOCK	290	325
INDUSTRIAL	60	60
MUNICIPAL	125	160
FORESTRY	110	140
TOTAL	1495	3064*

*Since some of the same land area may be required by both lignocellulose and starch crops, the quoted potential biomass for each could be mutually exclusive. The total potential feedstock includes only one of these sources.

Figure 17. Current and Potential Biomass Feedstocks in the United States (Source: "Production of Organic Chemicals via Bioconversion," U.S. DOE Report EGG-2645, 1991.)

From a biochemical engineering perspective, the most effective approach is to consider the entire biosynthetic process (Figure 18). Particularly if benign biosynthesis is the goal, it is no longer sufficient to think of the acquisition of feedstocks and the disposal of waste products as separate processes; rather, it is necessary to consider the system as a whole, from input to output. Not only must chemical engineers consider the material balance around an entire plant, but it is also becoming increasingly important to think of material balances around the economy as a whole. From this broader perspective, it may well turn out that waste materials produced by one industrial sector are ideal feedstocks for another.

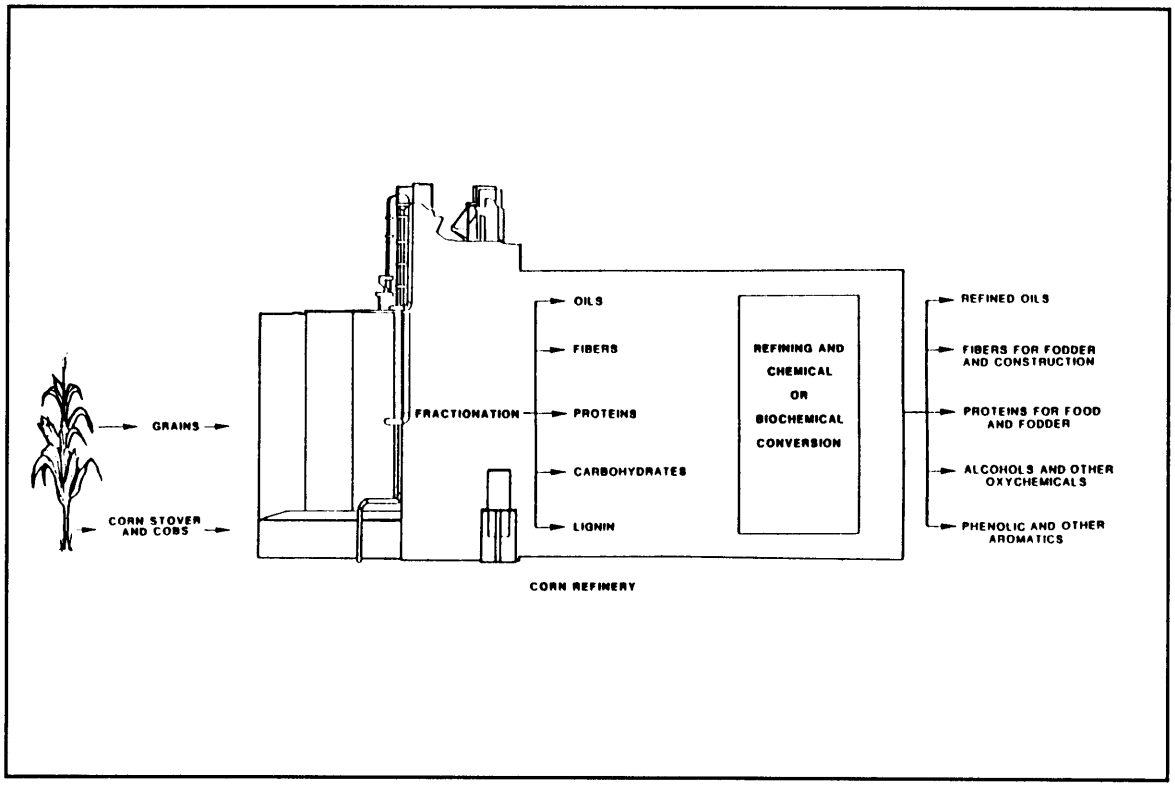


Figure 18. *A Total-System Perspective on Bioprocessing (Source: Dr. Charles Scott.)*

Another important consideration in biochemical processing is scale, since catalyst-based processes often involve flow dynamics that are not easily scaled up to the larger systems required for production in the millions of gallons or millions of tons range. In the petrochemical industry, similar problems have been overcome by development of fluidized bed technologies (Figure 19). Using the

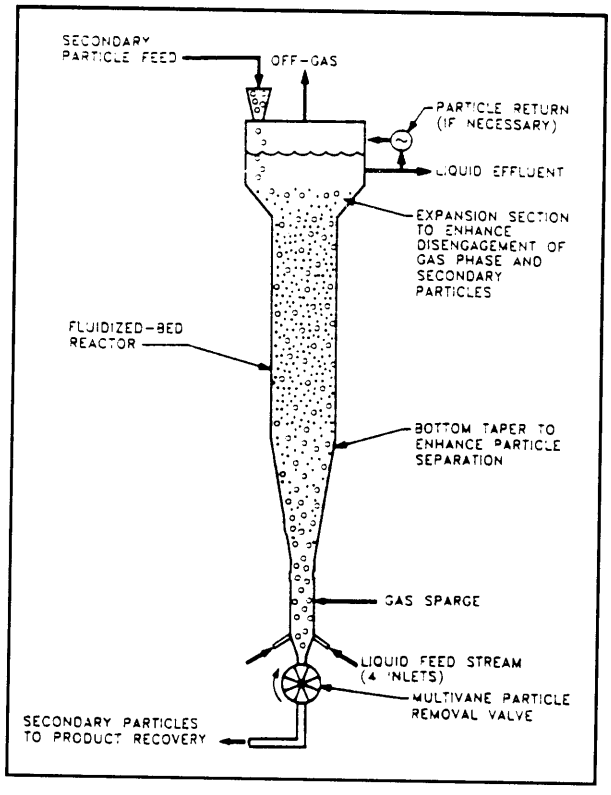


Figure 19. *A Biparticle Fluidized Bed Operating in Countercurrent Mode (Source: Dr. Charles Scott.)*

fluidized bed model, it is usually possible to construct very large systems that behave very similarly to smaller, pilot-scale systems. If fluidized bed behavior can be adapted to biochemical processing, it might be possible for advanced separation systems such as adsorption to replace or augment less efficient processes such as distillation. At the same time, it might also be possible to combine two or more processing steps.

Figure 20 illustrates how fluidized bed bioreactors could be incorporated into a biochemical production process. In this case, ethanol is produced from

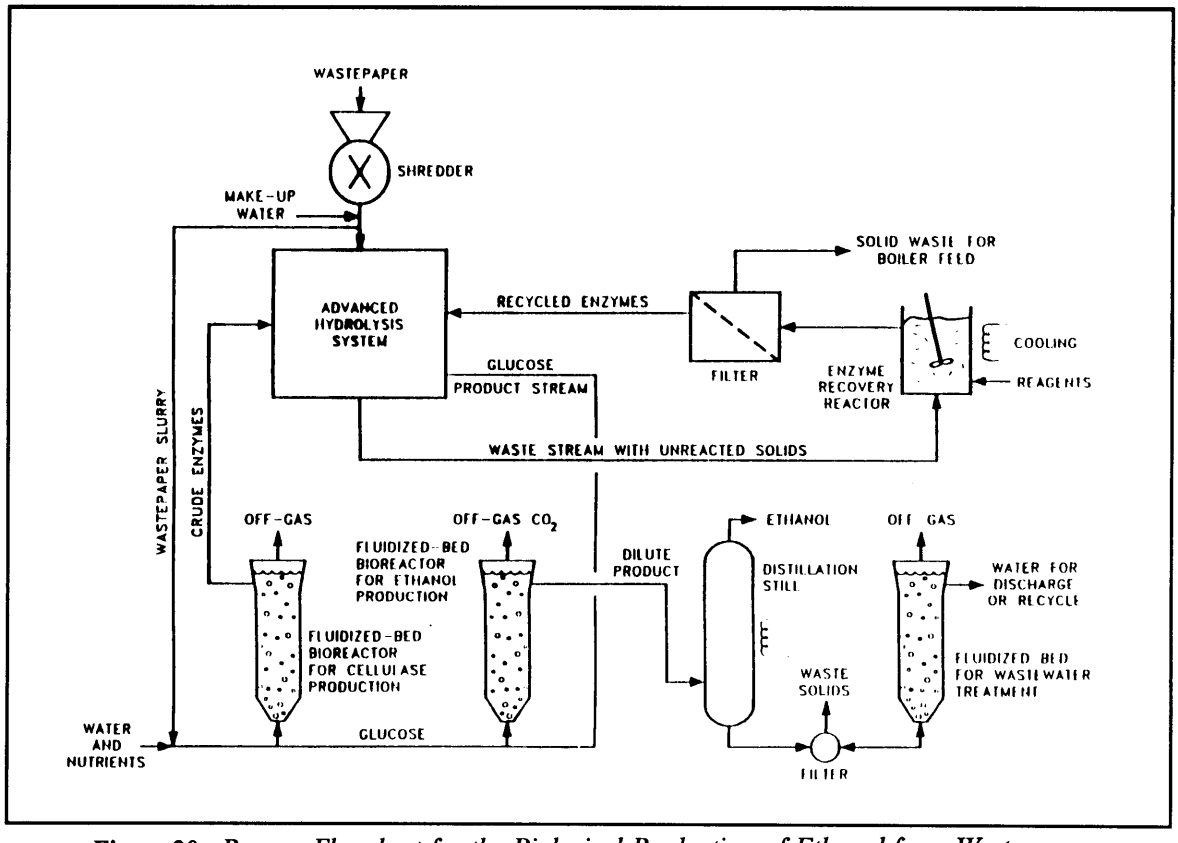


Figure 20. *Process Flowsheet for the Biological Production of Ethanol from Wastepaper (Source: Dr. Charles Scott.)*

wastepaper feedstocks. The flow chart in Figure 20 illustrates the basic difference in viewpoint between chemists and chemical engineers, in that chemical engineers must consider both the energy and mass balances of industrial processes. Thus, to gain a perspective on the process as a whole, a chemical engineer must consider all streams coming into and going out of the plant. To a chemical engineer, energy must be viewed as a cost in much the same way that materials are a cost of the process as a whole.

Another obstacle to the development of biochemical industrial processes arises from the relative lack of in-house biochemical engineering expertise in the chemical manufacturing industry. Although most manufacturing interests have experts in chemical or petrochemical engineering on hand, relatively few employ individuals with training in biochemical engineering. As a result, it is common for engineers unfamiliar with biochemical unit processes to overestimate the costs of biological elements of the process. Intuitively, chemical engineers are likely to expect enzymes or microorganisms for biosynthetic processes to comprise a large part of the total cost of the process. In fact, as Figure 21 illustrates, costs

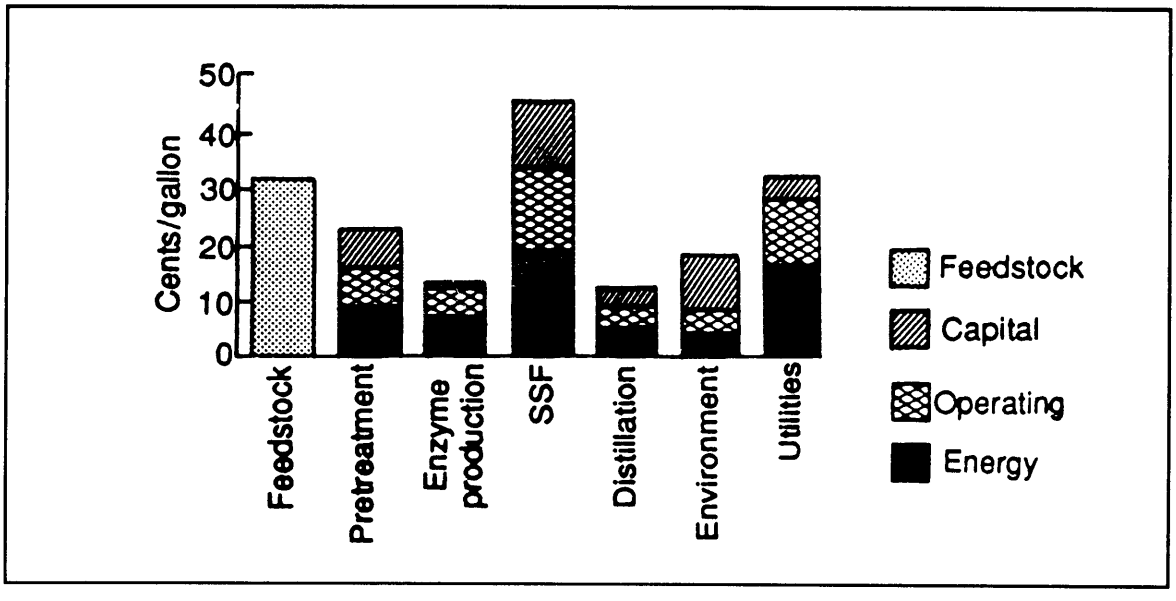


Figure 21. Breakdown of Ethanol Production Costs by Process Area (Source: Chemical Engineering Progress.)

associated with biochemical elements comprise only a small fraction of total process costs. In this particular process, which involves using hydrolytic enzymes to produce ethanol from a cellulose feedstock, the costs associated with feedstock, treatment, and utilities are significantly higher than those associated with production of the enzyme. Thus, economics of the process are far more

dependent on materials and energy costs than on the cost of the catalyst or other biological components.

A sensitivity analysis of the same production process (Figure 22) confirms that major benefits in terms of process improvements lie not in reducing the cost

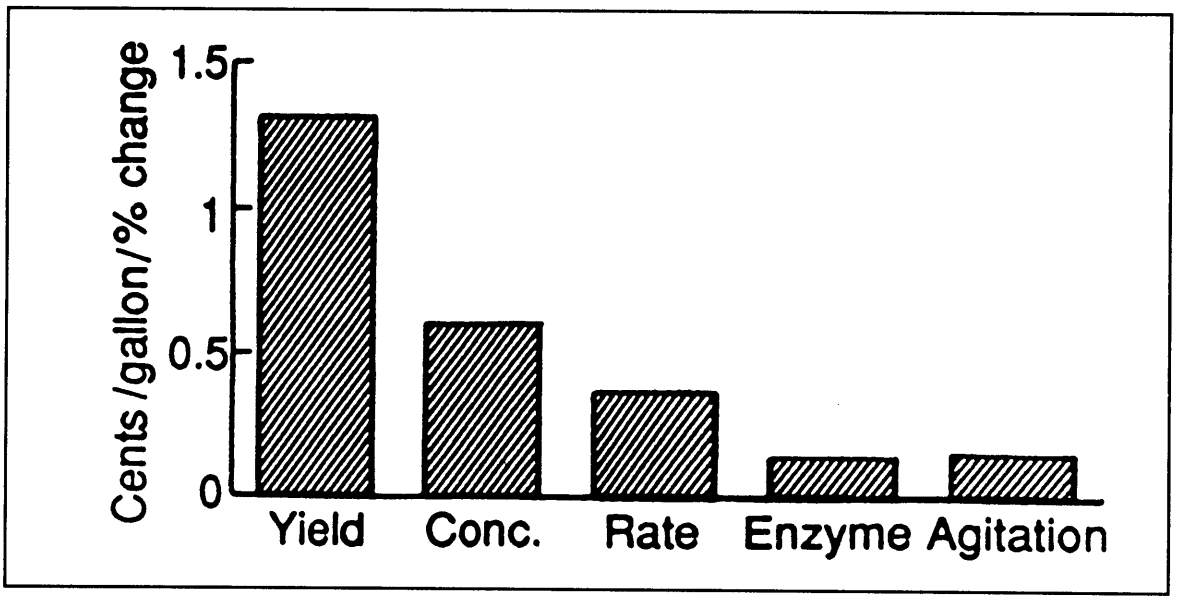


Figure 22. Sensitivity of Ethanol Selling Price to Major Process Parameters (Source: Chemical Engineering Progress.)

of the enzyme but rather in increasing the yield of the conversion and/or concentration of the product. These two parameters, which together comprise recovery cost of the product, represent an especially important component of total biosynthetic costs, since microorganisms used in aqueous biochemical processing typically grow only in very dilute solutions. As a result, industrial processes currently using microorganisms tend to have very low yields – in most cases lower than 10% (Figure 23).

Product	Concentration ($g\ l^{-1}$)
Acetone/butanol/ethanol mixture	18–20
Antibiotics by established processes (e.g., penicillin G)	10–30
Cyanocobalamin	0.02
Enzymes (e.g., serum protease)	2–5
Ethanol	70–120
Lipids	10–30
Organic acids (e.g., citric acid, lactic acid)	40–100
Riboflavin	10–15
Single-cell proteins (e.g., yeast where entire dry biomass is product)	30–50

Figure 23. Typical Concentrations of Products Leaving Fermenters (Source: Handbook of Biochemical Engineering.)

The inverse relationship between product concentration and selling price is illustrated in Figure 24. When the concentration of product is low, as is the case with many pharmaceutical biotechnology products, the selling price tends to be high. Conversely, only compounds that can readily be produced at high concentrations can be marketed at low selling prices. By the same token, when economies of scale can be achieved, biological products can be competitive on a price per weight basis (Figure 25). The obvious conclusion is that efficient and economical bioprocessing will require methods of producing materials at higher concentrations than can be obtained using conventional biochemical processes.

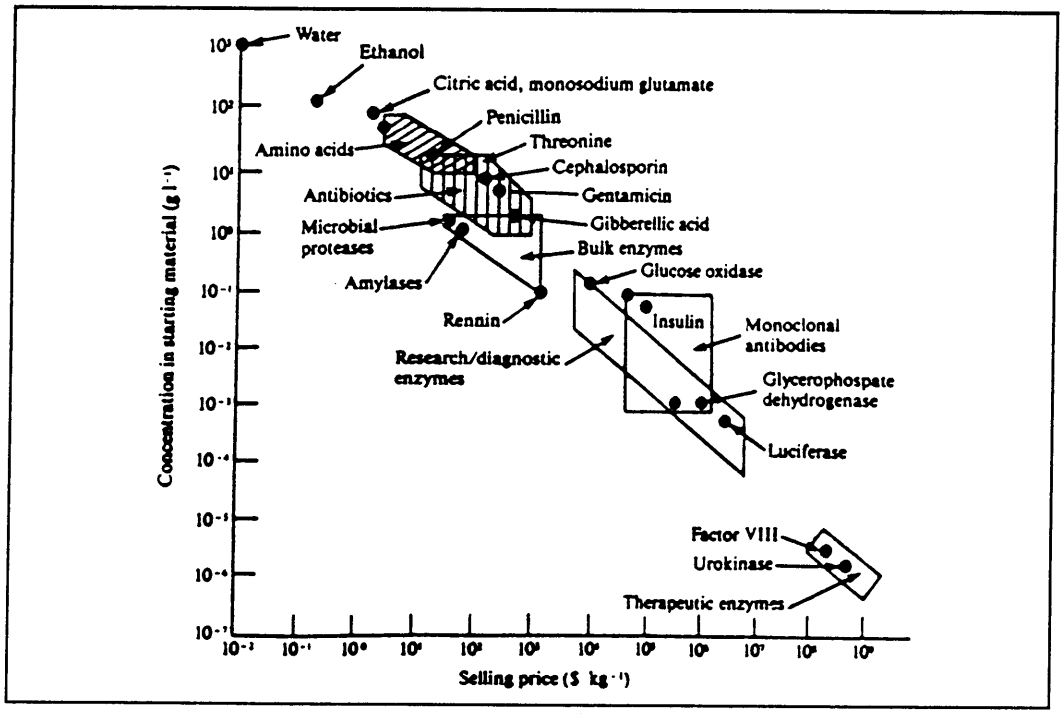


Figure 24. Relationship Between Product Concentration and Selling Price (Source: Handbook of Biochemical Engineering.)

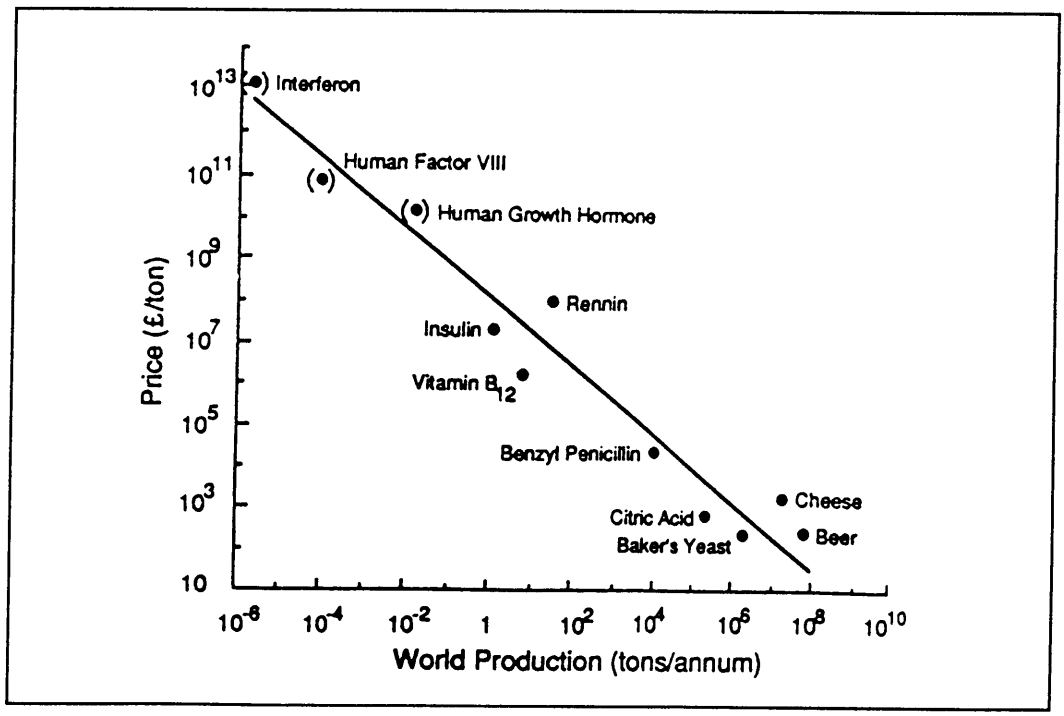


Figure 25. Relationship Between Selling Price and Worldwide Production of Various Fermentation Products (Source: Handbook of Biochemical Engineering.)

Production of high-fructose corn syrup through the enzymatic conversion of glucose to fructose (Figure 26) represents an example of a successful large-scale process using biochemical methods. Worldwide, the total market for high-fructose corn syrup is about 6 million tons per year, which translates to roughly

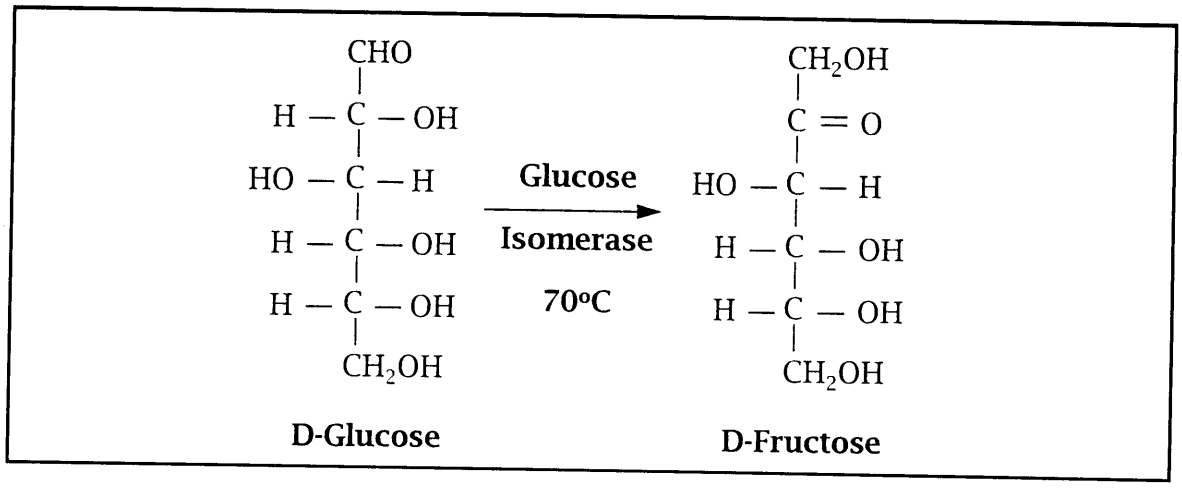


Figure 26. Production of High-Fructose Corn Syrup by Enzymatic Methods

$20 billion. As in the earlier example, analysis of the economics of high-fructose corn syrup production indicates that the biological component – enzyme – accounts for only a small fraction of the total production cost (Figure 27).

Turning to a different area of biochemical processing, consider the issue of enzymes as tools in environmentally benign chemical processing. To illustrate the broad variety of areas in which enzymes might play a role in benign processing, Figure 28 shows a list of potential applications prepared by Alan Russell of the University of Pittsburgh.

Production cost of HFCS	US (cents/lb)
a. Raw corn cost (1980)	9.03
b. Return from by-products	
Oil	1.38
Feed (Gluten)	2.79
Meal (Gluten)	0.75
c. Net raw material cost, a-b	4.11
d. Other costs	
Enzyme	0.40
Operating Labor	2.00
Utilities	0.70
e. Total variable cost	7.31
f. Fixed overhead costs	2.00
Freight	1.75
g.Total	11.06
h.Capital investment cost	2.40 - 4.50
i. Total (42% HFCS)	13.46 - 15.56
j. Total (55% HFCS) + 15%	15.48 - 17.89

Figure 27. Economics of High-Fructose Corn Syrup Production (Source: Dr. Alan Russell.)

The remainder of this presentation focuses on four general areas:

- Enzymes as Catalysts
- Enzymes in Supercritical Fluids
- Enzymes in the Gas Phase
- Enzyme Catalysis in Pure Reactants

Regarding the use of enzymes as catalysts, Figure 29 presents data showing the enhancement of chemical reaction rates possible with use of enzymes as alternative to heavy metal catalysts. In one set of data, addition of a pig liver

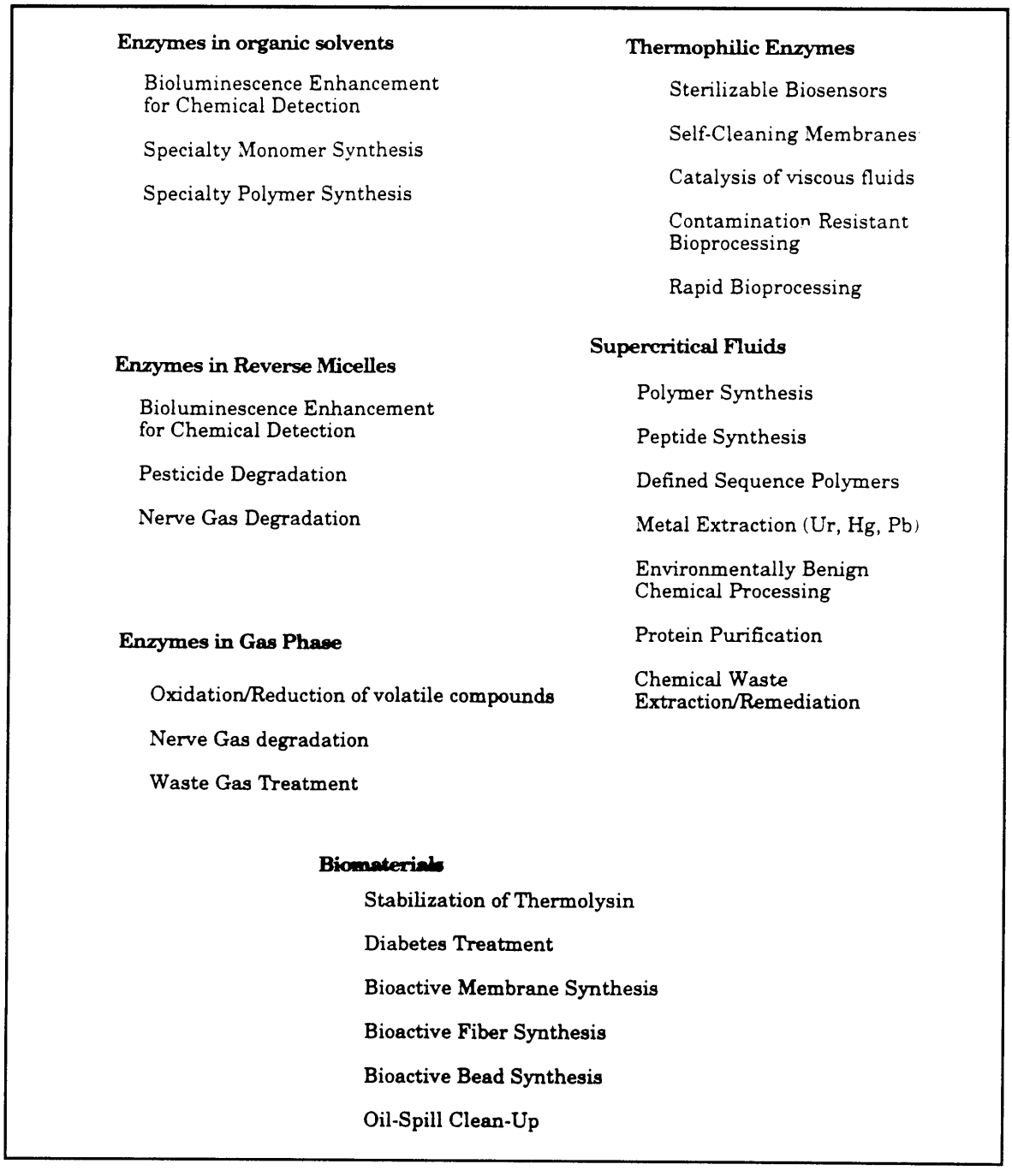


Figure 28. Potential Applications of Enzymes in Environmentally Benign Chemical Processing

Substrate	Catalyst	Rate Constant	Temperature
		M^{-1} sec^{-1}	°C
Ethyl Butyrate (Hydrolysis)	H_2O	10^{-5}	100
	OH^-	10^{-4}	25
	Pig Liver Esterase	10^{4}	25

Enzyme	Substrate	Product	Enzyme Catalyzed Rate / Un-Catalyzed Rate
Hexokinase	Glucose, ATP	Glucose-6-P	$> 10^{10}$
Phosphorylase	Glucose-P, $Glycogen_n$	$Glycogen_{n+1}$	$> 10^{11}$
Alcohol	Ethanol, NAD	Acetaldehyde	$> 10^{9}$

Figure 29. Enzymatic Enhancement of Chemical Reaction Rates (Source: Dr. Alan Russell.)

esterase increased the rate of ethyl butyrate hydrolysis by 8 orders of magnitude compared with a hydroxide catalyst. Other enzymes have been demonstrated to increase reaction rates between 9 and 11 orders of magnitude in comparison withuncatalyzed rates for a variety of other types of biochemical reactions, including phosphorylation reactions, polymerizations, and acetaldehyde production.

Next, supercritical fluids may be used as solvents to carry out biochemical reactions. Thermodynamic properties of supercritical fluids, which are gases compressed to a level at which they behave as fluids, offer more degrees of freedom than can be obtained using conventional solvents. Although supercritical

fluids have been used in extraction processes, their use as solvents for biochemical reactions is relatively new. The advantage of supercritical fluids is that separations can be made markedly more efficient and inexpensive by changing the pressure at the end of a reaction to convert the solvent to a gas.

Figure 30 shows an example of the potential value of supercritical fluids as solvents for enzyme-catalyzed reactions. A polymerization reaction that Alan

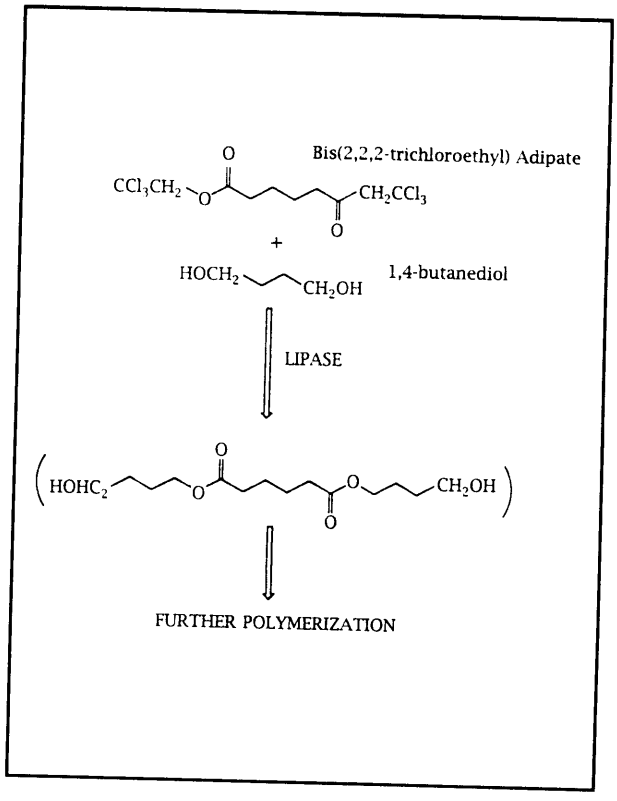


Figure 30. *Lipase-Catalyzed Polymerization Reaction (Source: Dr. Alan Russell.)*

Russell has been exploring where an adipate and a butanediol are exposed to a lipase that promotes the polymerization reaction is depicted. When using supercritical fluoro-form as a solvent, it is possible to control the reaction to

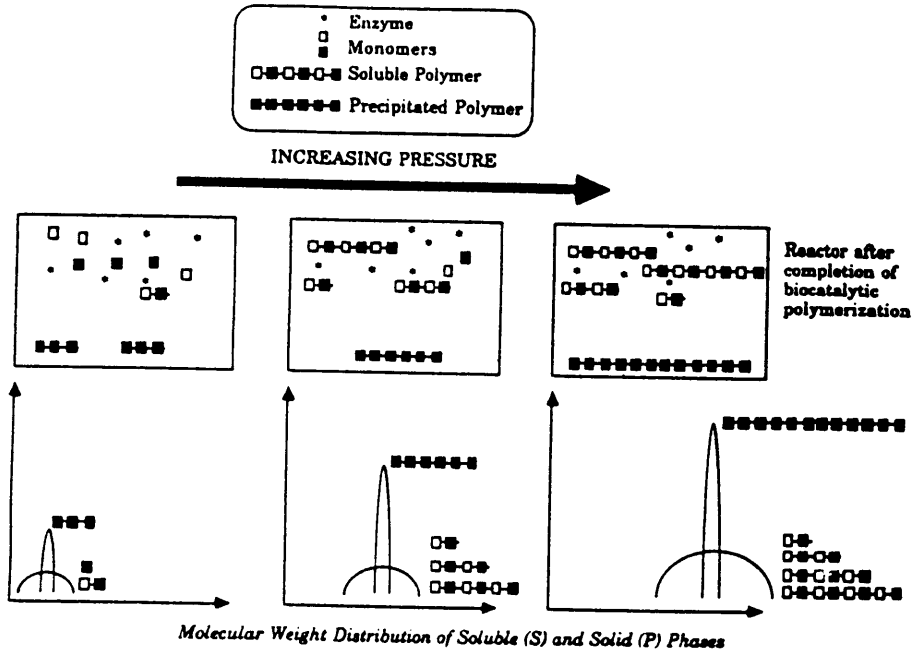
produce polymers of a defined molecular weight (Figure 31). In this system, the polymer grows as a function of time, but changing pressure of the supercritical fluid changes solubility of the polymer, eventually causing it to precipitate out of solution. Thus, it is possible to generate polymers of any desired molecular weight simply by adjusting the pressure under which the reaction is conducted.

A third example of potential biosynthetic applications of enzymes deals with use of enzymes on solid supports as catalysts for gaseous substrates (Figure 32). This approach is especially useful for oxidation-reduction reactions, where a proton acceptor or exchanger must be present. In a redox reaction, the enzyme is supported on a solid matrix to which some type of solvent or fluid also adsorbs, and the reactant is present in the gas phase. The advantage of this system is that the nicotinamide cofactor stays with the enzyme and can be recovered for reuse. As a result, this expensive cofactor can be recycled, whereas in an aqueous system the cofactor would be lost.

A final example involves benign synthesis that does not use a catalyst at all – i.e., a system in which the reactants themselves are the liquid phase. To illustrate this concept, consider a reaction in which methyl methacrylate and hexanol are mixed together as pure liquids (Figure 33). When the lipase catalyst is added to the mixture, methacrylate can be separated out and the remaining reactants can be recycled. Thus, in this system, a concentrated form of reactants is used to generate a concentrated product without unwanted by-products.

In summary, this presentation has focused on three main ideas:

- For biochemical engineering to have a significant impact on industrial processes, it must function on a scale capable of generating products in large volumes, which for most industrial chemicals is in the millions of pounds range.



Pressure (psi)	Maximum Molecular Weight of the Soluble Polymer	Average Molecular Weight and Dispersity of the Soluble Polymer	Average Molecular Weight and Dispersity of the Precipitated Polymer
900	[a]987	[a]937 (1.07)	[a]1020 (1.02)
1600	1424	1037 (1.11)	1677 (1.03)
2400	2586	1371 (1.18)	2774 (1.03)
3000	2849	1762 (1.23)	3357 (1.05)

The alcoholysis of bis(2,2,2-trichloroethyl) adipate by 1,4-butanediol catalyzed by porcine pancreatic lipase suspended in fluoroform at 50 °C. The error in determination of polymer molecular weights is ±5 %. [a]The extractions for the biocatalysis experiment performed at 900 psi were performed in a supercritical fluid extractor in which the minimum pressure achievable is 1200 psi.

Figure 31. Relationship Between Pressure and Degree of Polymerization in a Supercritical Solvent System (Source: Dr. Alan Russell.)

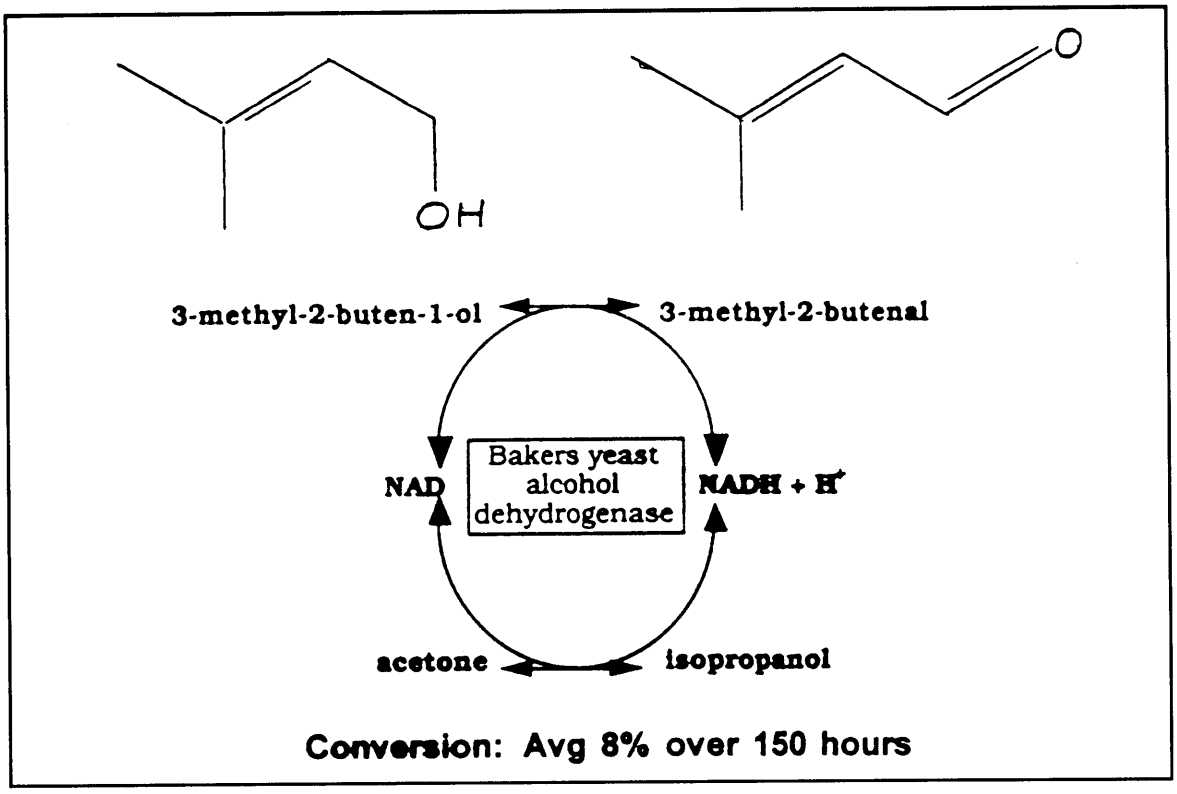


Figure 32. Enzymatic Catalysis in the Gas Phase

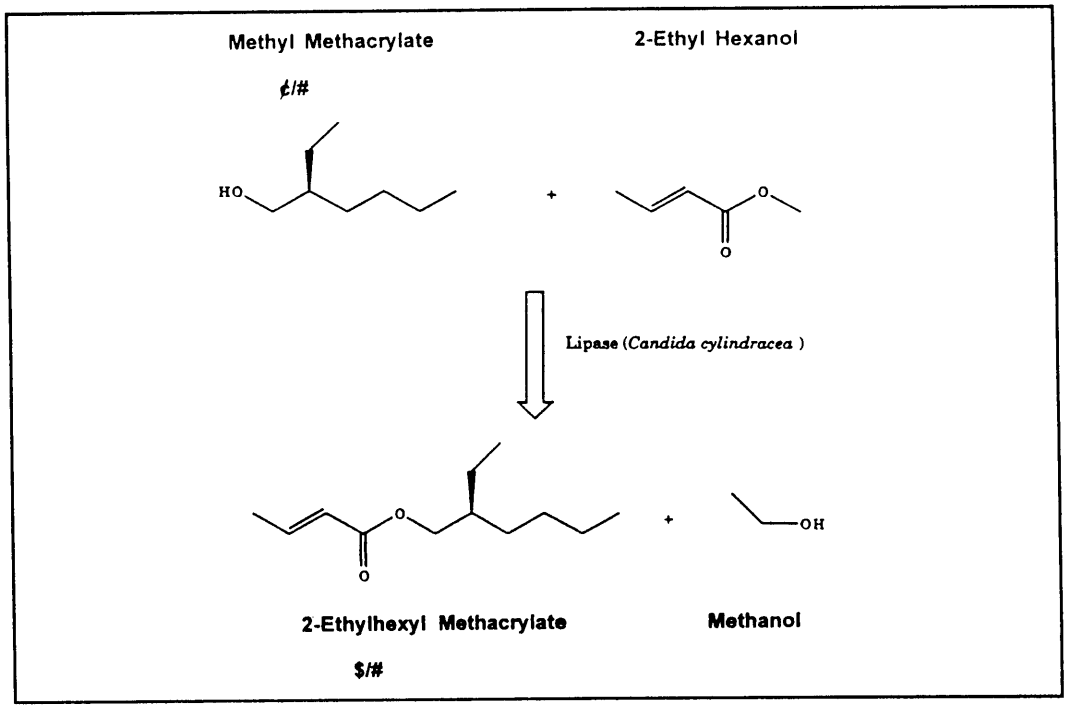


Figure 33. Enzymatic Catalysis in Pure Reactants

- Problems with dilute aqueous chemistry remain to be resolved, but promising methods for dealing with these problems have begun to be developed.

- With development of new technologies, enzymes can be used as catalysts in organic syntheses, but these applications will require new thinking on the part of industrial chemists and chemical engineers.

Regarding the last point, the most likely scenario for broader use of enzymes as catalysts involves joint efforts between the traditional organic chemistry industry and the emerging biotechnology industry. In this scenario, the smaller biotechnology companies could create and provide the needed catalysts to larger chemical companies engaged in industrial-scale organic synthesis.

Benign Engineering Approaches

C. Thomas Sciance, DuPont Experimental Station

The concept of engineering paradigms was defined as "patterns that determine the rules of the game." Since ideas and concepts outside the prevailing paradigm usually remain invisible, behaviors that have been rewarded in the past are reinforced even in the face of considerable evidence that the future will be different.

Figure 34 outlines the paradigms that have defined the boundaries of chemical engineering over the past several decades. For many years, chemical engineering was dominated by a growth-centered paradigm in which rewards came from increasing capacity and solving problems quickly. Under this paradigm, it was often better to proceed simultaneously on several possible solutions to a technical problem rather than to waste time attempting to determine which solution was best. Technical mistakes were corrected during subsequent expansions, and economies of scale dominated capital decisions.

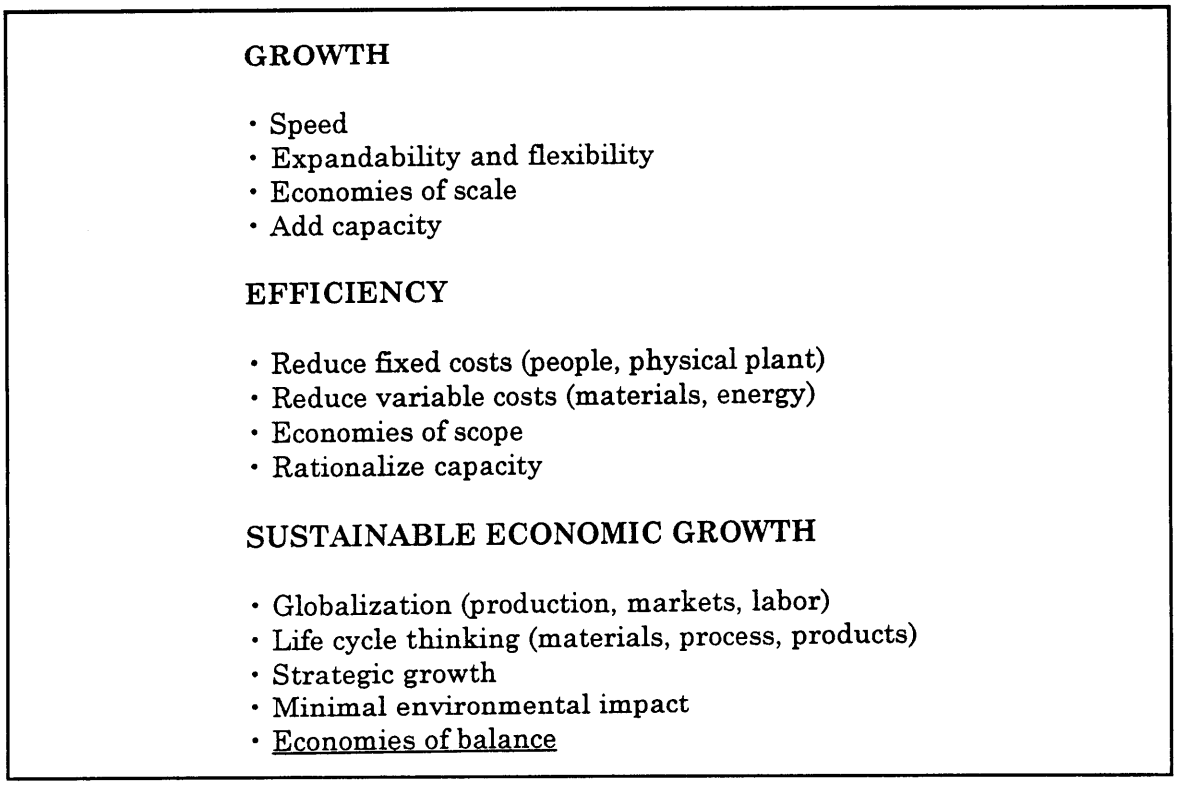


Figure 34. *Evolution of Engineering Paradigms*

In recent years, as the global chemical industry suffered hard times, the growth-centered paradigm was supplanted by a new paradigm centered on efficiency. This new paradigm emphasized differentiation of products through quality and customer service, reducing costs, and various types of rationalization such as disinvestment, mergers, and downsizing. Under the efficiency-centered paradigm, excess capacity became a burden rather than an opportunity. At the same time, rewards were more likely to come from cost-conscious management than from economies of scale. As a result, technical options and innovations have been studied more carefully and implemented more cautiously than in the past.

Chemical engineering is currently under-going another paradigm shift, this time to a paradigm that has sustainable economic growth as its central organizing

principle. Rewards in the next decade and beyond will come from strategic thinking that leads to an economically viable compromise between business and societal needs. Technology will play an essential role in this process, but it will have to take into account many more variables than ever before. Under this paradigm, effective management will consist of learning how to cooperate effectively in order to compete more effectively. A multidisciplinary approach will be required, not only because of the complexity of the technology but also because of the variety of interests that must be considered. At the same time, new tools and techniques will be needed to improve the selection and execution of research and development programs.

To describe the situation, testimony to a Congressional committee by Braden Allenby of AT&T in May of 1994 is quoted:

> In leading industrial firms, we are moving conceptually beyond end-of-pipe and emission control technologies, beyond even pollution prevention and waste reduction programs. It is not that we are reducing such activities in an absolute sense. Rather, we are recognizing that they are not, by themselves, adequate to allow us to live in equilibrium with natural systems. They are an important dimension of the solution, but by no means the only one.
>
> This understanding is leading to a fundamental change in the way the environmental impacts of materials and products are being managed around the world. Most importantly, it is now clear that any environmental assessment of materials must include consideration of impacts across the lifecycle of materials – from their mining or initial production, to their use in commerce and products and return of the components or materials to the economy. Fixating on any single lifecycle state of a material runs the risk of failing to recognize more serious risks posed at other stages.

The logical conclusion is that decisions in the future will have to take into account a longer time horizon and a much broader scope than was ever necessary in the past. This necessity may in turn lead to some reversal of the trend toward

decision-making at lower and lower levels of industrial organizations. In the future, it will be necessary for those in leadership positions to view a wider field and operate in a longer time horizon than is currently the norm.

A graph from a report prepared by a Dutch government group studying the time horizon likely to be involved in achieving the development of sustainable technology is illustrated by Figure 35. This group found that, starting from a new situation, it may take 10 years or more to progress to some form of sustainable technology. From an existing situation, several decades may be required. Using DuPont's five adipic acid plants as an example, it would cost billions of dollars and take more than a decade to replace this investment, even if technologically and economically attractive options were currently available.

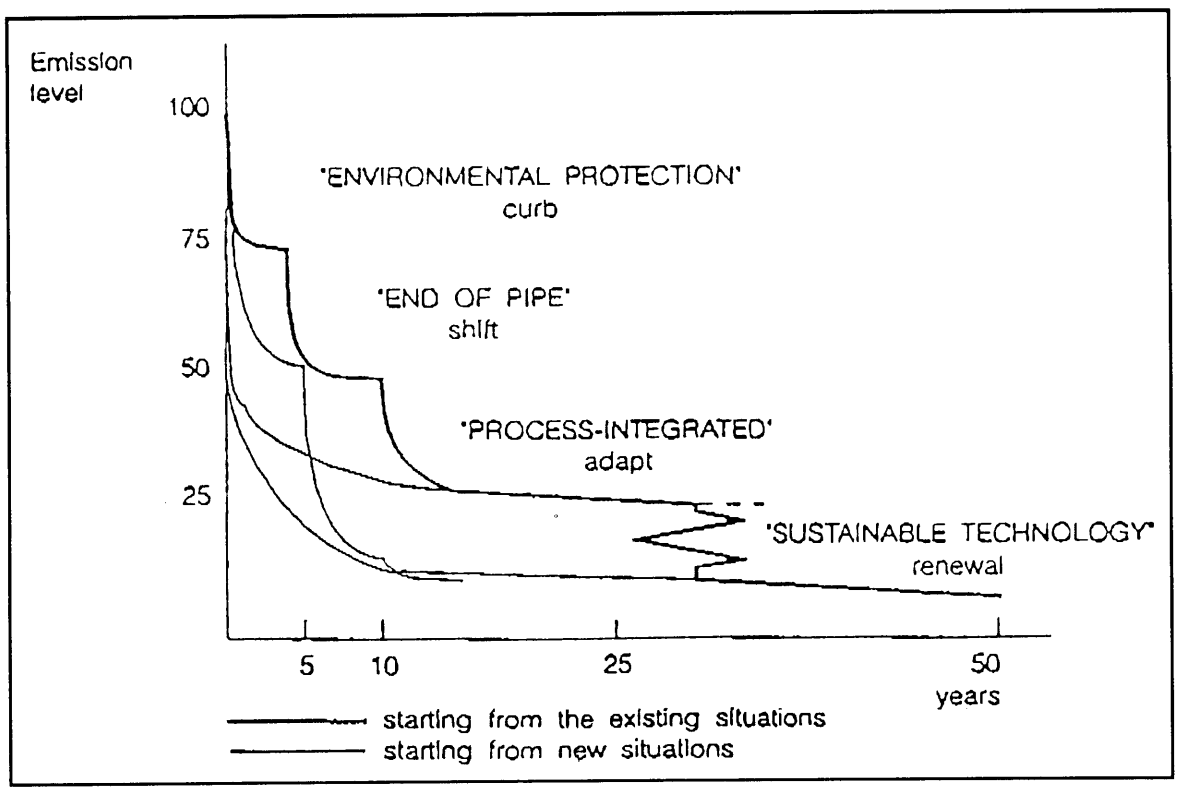


Figure 35. Predicted Time Course for Developing Sustainable Technologies (Source: "Sustainable Development: a Challenge to Technology!" J.L.A. Jansen and Ph. J. Vergragt, 6-92. Ministry for Housing, Physical Planning and Environment. Technical University of Delft, Netherlands.)

It is important to keep in mind that not every good technical idea that would improve the environment is economically viable. Without economic viability a good technical idea is not a technology at all – it is merely a fact or a bit of knowledge. Clearly there is room for technical improvements that are both environmentally advanced and that meet the economic criteria necessary to implement them. Economic growth and environmental protection are inextricably linked, however, and competent engineers are going to have to learn how to deal with both.

One area having a great deal of potential value is generic science related to pollution prevention. The only example of truly generic research in this area that a group of chemists and chemical engineers at a meeting several years ago of the Council for Chemical Research (CCR) were able to cite, concerned work at UCLA on avoiding making aerosols in the range of droplet sizes that are difficult to collect. Concluding that most waste prevention or avoidance work is extremely process-specific, and that prevention is both conceptually and intellectually a more difficult problem than clean-up, the CCR and NSF jointly published a list of areas in which basic pollution prevention research is needed. Items listed in the joint program announcement included the following:

- New chemistries and methodologies for on-demand, on-site production and consumption of toxic intermediates for use in manufacturing
- New, more highly selective catalysts to increase product yield and reduce by-product formation in chemical manufacturing
- Low-energy separation technologies for feedstock purification and recycling
- Improved membranes and membrane/molecular sieve technologies that integrate transport and reaction to enhance specificity
- Alternative chemical syntheses that bypass toxic feedstocks and solvents such as chloro- and nitrocarbons

- New processing methods that eliminate production of hard-to-entrap micron-sized aerosols
- Alternative chemical syntheses that eliminate or combine process steps, resulting in a net reduction of pollutants
- Design of novel low-temperature or other energy-efficient methods for chemical synthesis and processing

Approaching the same problem from a slightly different perspective, the Chemical Manufacturers' Association (CMA) has published as part of its Responsible Care™ series a book called *Designing Pollution Prevention into the Process.* Whereas the CCR/NSF list begins from technologies and their possible applications, the CMA document contains an appendix listing pollution prevention ideas from a perspective that is more process-oriented (see Figure 36). This appendix is another good source for stimulating thinking about waste prevention.

One of the most difficult tasks in process design is asking the right questions to begin with. Three areas were presented in which asking the right questions is particularly important:

- Fundamental beliefs and assumptions (e.g., What business are we in? Why are we making this product? Why do we use the materials we do?)
- Factors that govern investment behavior (e.g., Is management willing to innovate? Is capital available? What is the time scale? Is there an investment hurdle rate?
- What we "know" that may not be right (e.g., What were our past "failures" and have the reasons for failure changed? Could cooperation help? Could leveraging help?)

The Strategic Decisions Group (which attempts to apply mathematical methods such as decision tree analysis to decisions about research and development) advocates separating the probability of technical success from the probability of

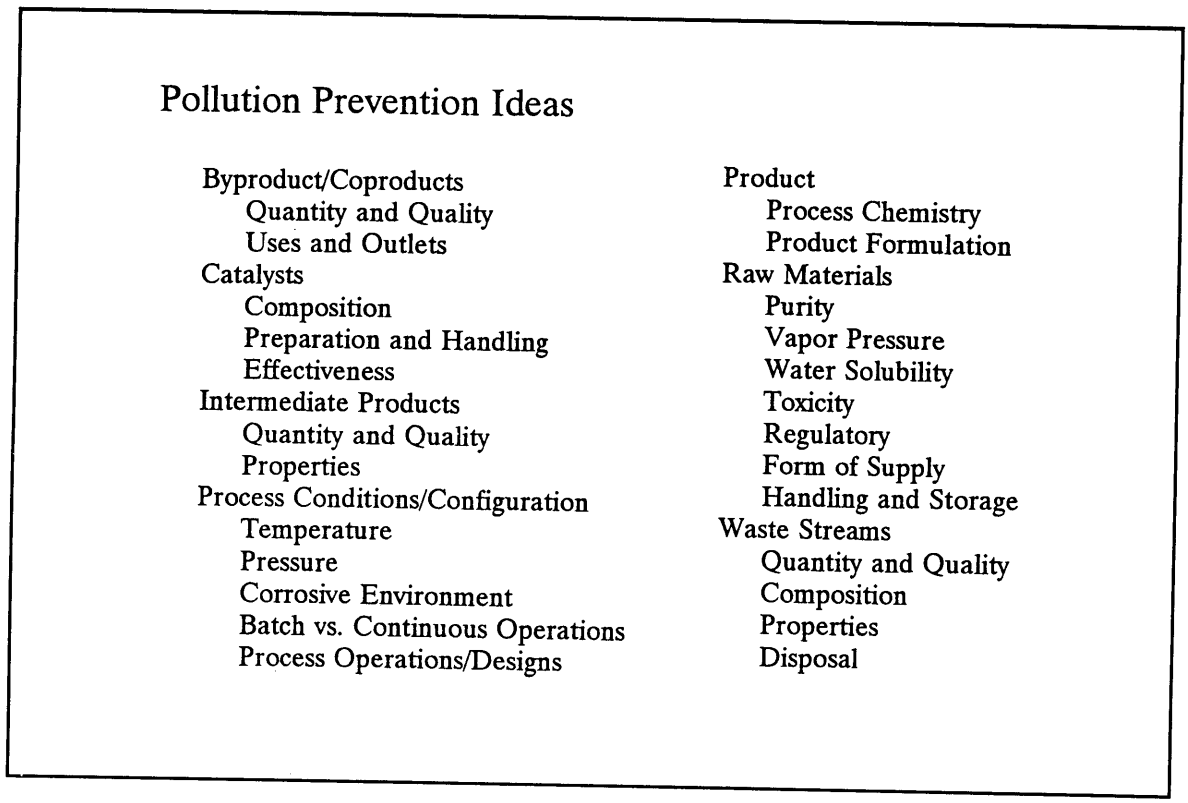


Figure 36. *Pollution Prevention Ideas (Source: Chemical Manufacturers' Association, Designing Pollution Prevention into the Process)*

commercial success/given technical success. If the probability is low that a technical success will be implemented in the industrial R&D community, it usually makes more sense to look for something else to do.

An example of a situation in which benign engineering played a significant role in process selection, is DuPont's experience in synthesizing adiponitrile, a nylon intermediate. Thirty years ago, adiponitrile was made by chlorinating butadiene and then reacting the product with sodium cyanide to make adiponitrile and salt. The selection of butadiene as a feedstock got the process off to an environmentally good start, since butadiene is a by-product of ethylene manufacturing. On the other hand, buying caustic and chlorine, making salt, and

then throwing it away is neither an especially cost-effective nor a very green thing to do.

DuPont had been trying since 1939 to directly produce hydrocyanate butadiene, but the company was unable to produce a linear isomer. It was not until they tried a new type of catalysis which had not previously been industrially applied that this problem was solved. This process, which was the first industrial application of coordination catalysis, eliminated the use of chlorine and the salt waste stream. As a result, this process at one time comprised the most valuable set of patents in DuPont's possession. This invention led DuPont to embark on the largest commercial process development on new chemistry in the company's history. Over a short period of time, plants using the older technology fell off one by one, and the new process was adopted throughout the company. As with any entirely new process, of course, a whole host of other problems arose that required a constant stream of further innovations over the next 25 years – but the process remains a fine example of the fact that economic and environmental concerns do not have to oppose one another. In fact, it is the continual stream of innovation and creativity rather than the invention or catalyst *per se* that makes or breaks such a process conversion.

The importance of thinking as far into the future as possible is illustrated by the various catalysts and reactor types that have been used in the hydrogenation of adiponitrile to produce hexamethylenedi-amine. DuPont had concentrated on developing a cheap high-pressure catalyst that minimized the cost of synthesis but, because of its slightly lower yield, required a large refining train. One competitor used a very expensive high-pressure catalyst that had exceptionally high yield and thus minimized the refining investment. Another competitor used a slurry process that was intermediate in yield, minimizing energy consumption and investment. All of these companies improved their processes for years, and all became economically equivalent. From the perspective of 50

years ago, all of these processes seemed about the same. From today's perspective, however, the high-yield process that does not make impurities to begin with would certainly be preferred. Because of their early investment decisions and hard-won expertise in their own processes, however, all companies are locked in to continuing their current methods. The point is that once a company starts on a particular path of capital investment, the choices of generations of successors may be significantly constrained. Minimizing such constraints requires thinking as far into the future as possible before selecting a process.

Another example of new process development is the process developed for producing tetrahydrofuran (THF). Because the existing process required energy-intensive and reactive starting materials and because it was expensive, DuPont wanted to develop a new process for THF synthesis. This example is particularly relevant to this workshop since the process selected required innovations in engineering as well as in chemistry.

As Figure 37 illustrates, one intermediate in the THF pathway is maleic anhydride. Using a fixed bed system, this compound can be made from readily available hydrocarbons, but the fixed bed process has a number of limitations, including the high cost of the fixed bed reactor. To address this problem, DuPont engineers determined that three major new inventions or developments would be required:

- A transport bed reactor that would allow the reaction to take place while at the same time using a flywheel mechanism to regenerate the catalyst
- An attrition-resistant catalyst (since the catalyst would be moving around so much in the system)
- A hydrogenation catalyst for the final step of the reaction

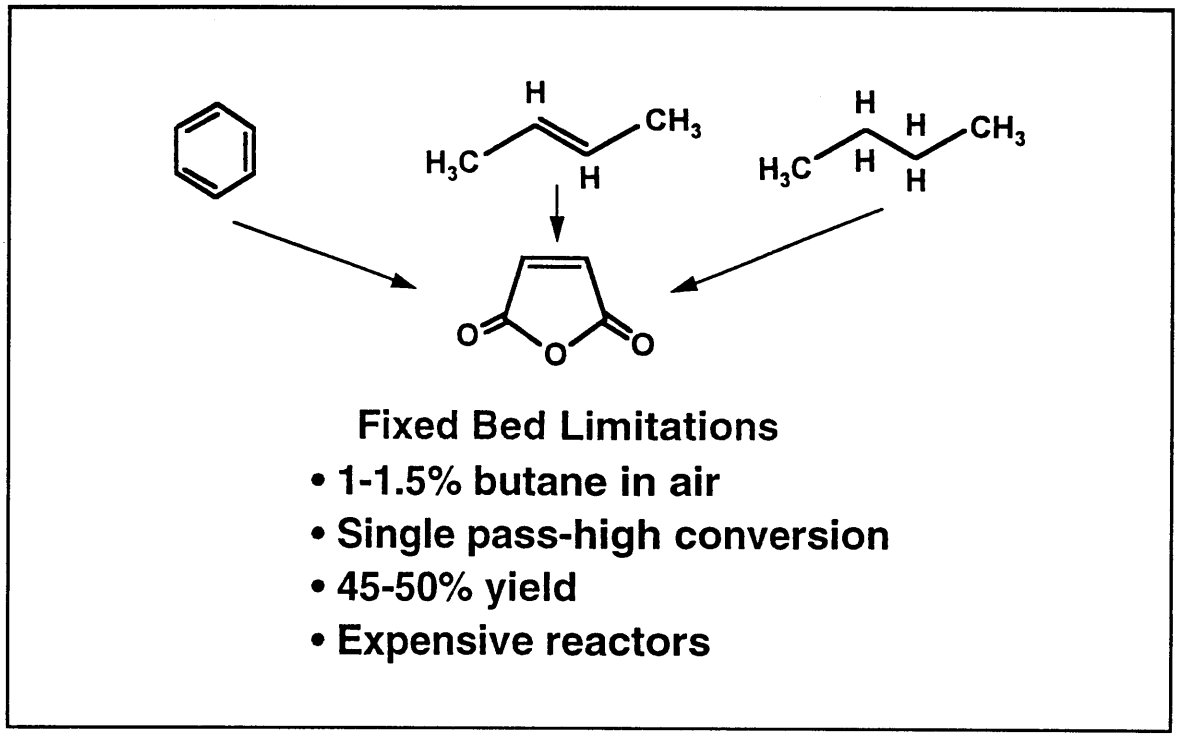


Figure 37. Limitations Inherent to the Production of Maleic Acid via a Fixed Bed Reactor

The relationship of these advances to the proposed synthetic pathway are illustrated in Figure 38.

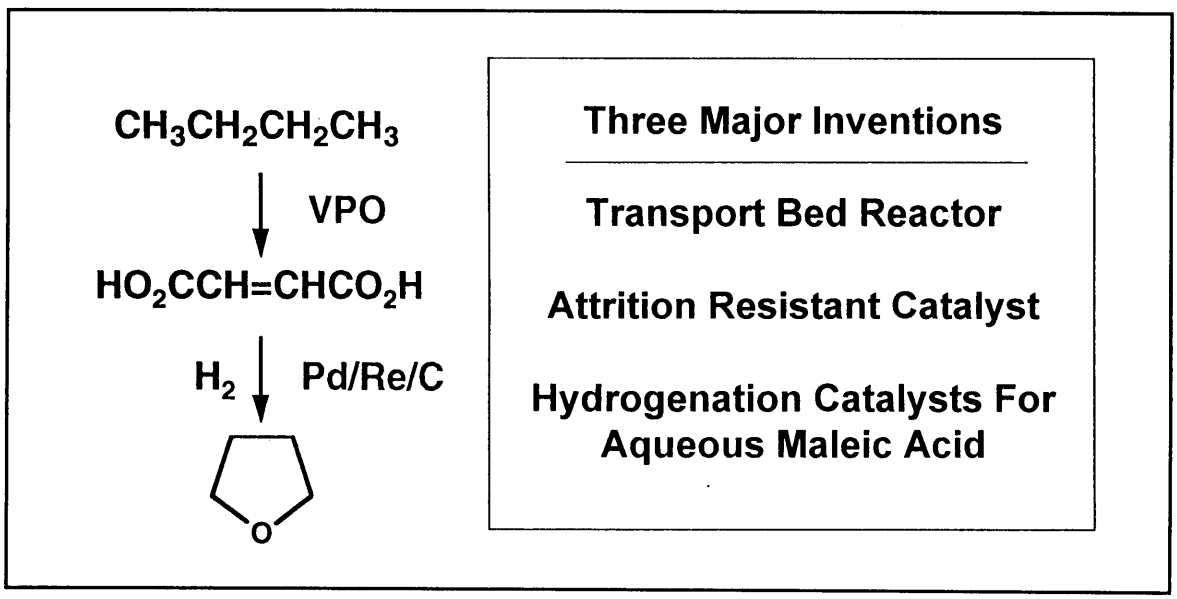


Figure 38. Innovations Required for the New Synthetic Pathway

Figure 39 illustrates the role of lattice oxygen chemistry in the new synthetic pathway. In essence, the process involves pumping oxygen through an

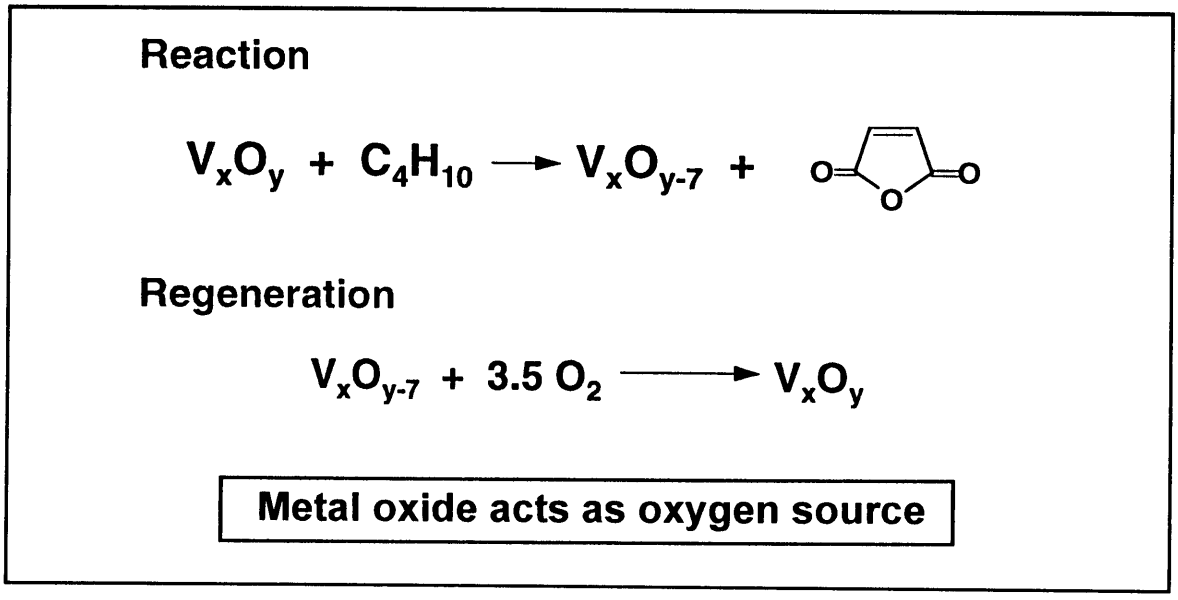


Figure 39. The Role of Lattice Oxygen Chemistry in the New Synthetic Pathway

oxide catalyst and then regenerating it. That is, the metal oxide is used to pump oxygen into the butane, and then separately – but in the same piece of equipment – is regenerated. The reactor itself is illustrated in Figure 40. Conceptually, the reactor is relatively simple; the reaction itself takes place in one part of the reactor, while the catalyst is regenerated in another part of the reactor and fed back into the reaction chamber.

Advantages of the riser reactor over fluidized bed oxidation reactions include advances in both the safety and the greenness of the process. The incorporation of separate catalyst redox zones offers independent control. In addition, selectivity is better at higher conversion, and oxygen levels are lower

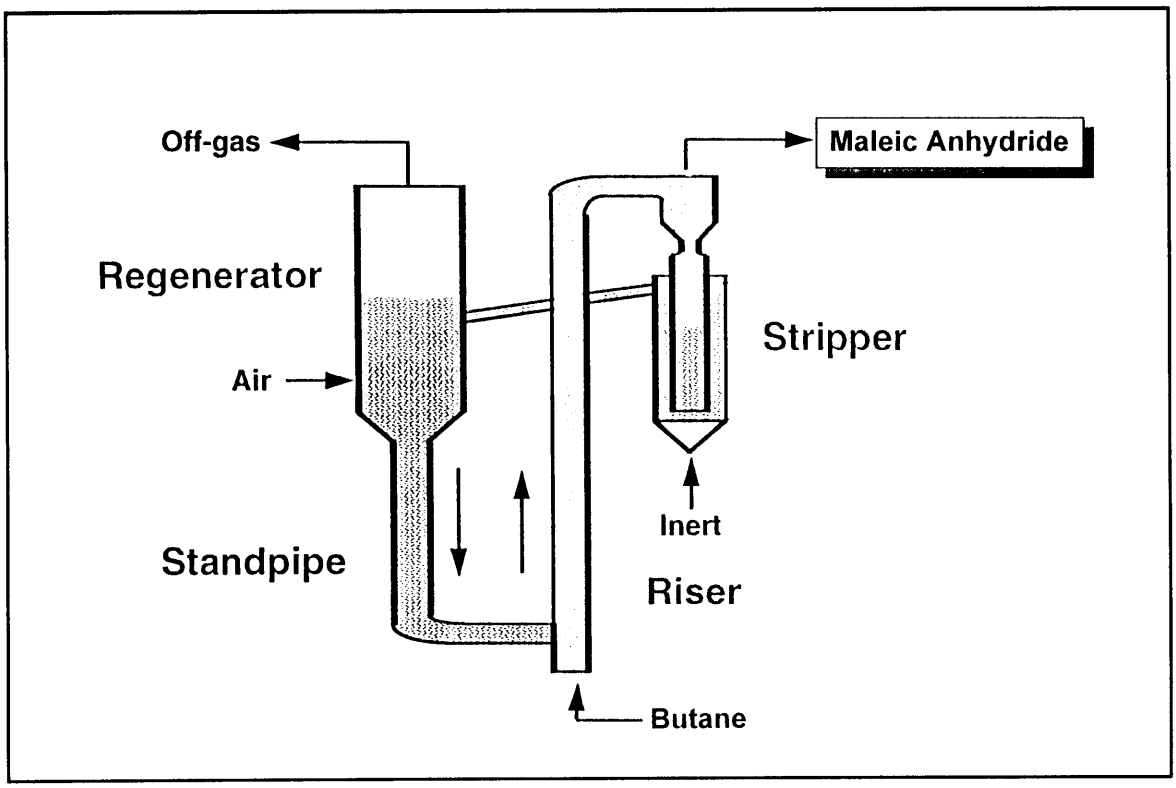


Figure 40. Riser Reactor Developed for the New Synthetic Pathway

(see Figure 41). At the same time, the riser reactor offers a more concentrated product stream, high throughput, a low catalyst inventory, and a reduced risk of explosions. Its main limitations lie in the operational complexity of the system, which is a problem only if the complexity precludes a solution, and in the need for an attrition-resistant catalyst. To meet the latter need, DuPont has developed a special encapsulated catalyst with an attrition-resistant shell that still permits the mass transfer required.

At least at the pilot level, the new process clearly works better than the old one. Getting everything to keep working as intended, however, is an enormous engineering problem – particularly when it comes to scale-up. DuPont is currently building a plant in Spain for industrial-scale testing of the new process.

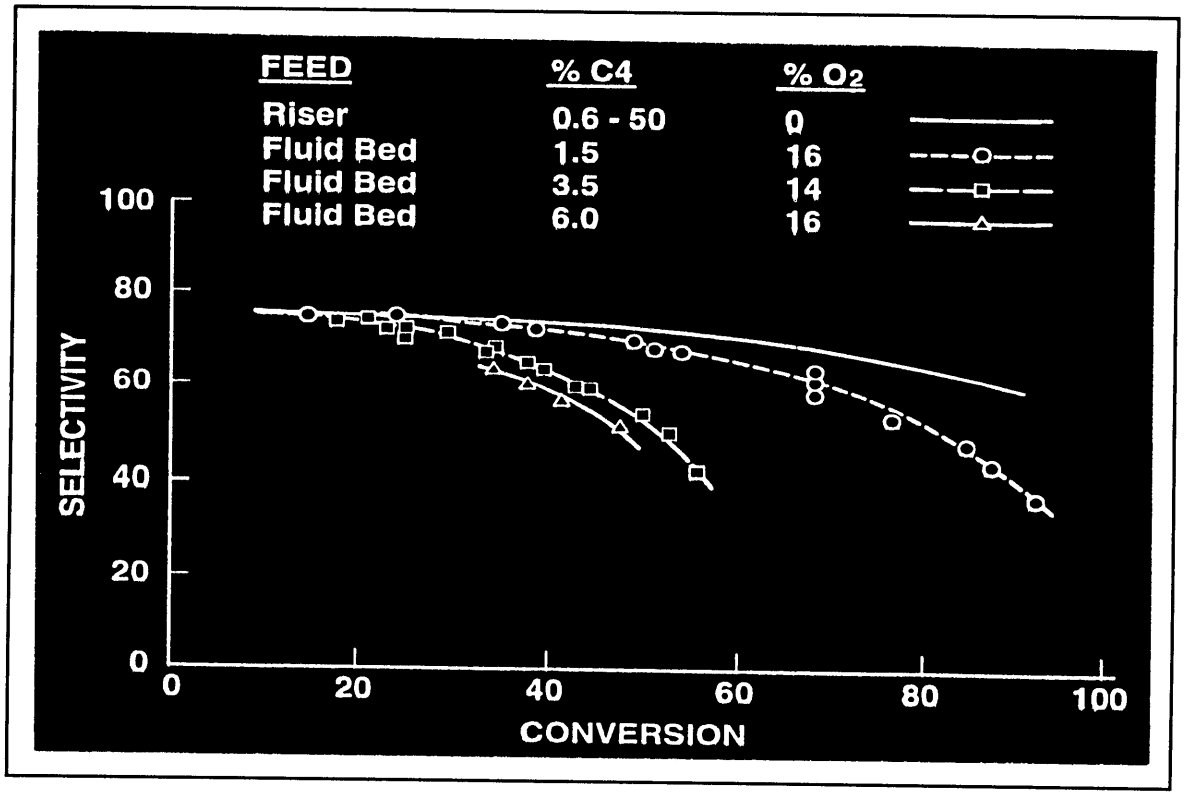


Figure 41. Riser versus Fluid Bed Oxidation

This exercise is expensive, but if the process works as envisioned it will offer an important new option for engineers to apply in the design of other alternative synthetic processes.

As a final example of process selection, the alternative methods of manufacturing hydrogen cyanide (HCN) come to mind. The two methods that are widely used in industry are the Andrussow process, which is the most economical for large-scale production of HCN, and the Degussa process, which is most appropriate for intermediate-scale production (see Figure 42). Although DuPont uses the Andrussow process for its own HCN production, some of the company's process development people have begun to think about the needs of small-scale HCN users. Although HCN is a useful, reactive material, it is poisonous and will explosively polymerize if allowed to become too acidic or too

basic. If shipped, it must be inhibited, which may introduce problems related to removing the inhibitor. In addition, HCN is difficult to make because it is a very endothermic reaction carried out at high temperature. Thus, to accommodate the needs of small-scale users, the ideal process would provide a controllable, safe process for making small amounts of HCN at the point of use.

The process that DuPont engineers have proposed for this purpose is depicted in the lower portion of Figure 42. The essence of the process is using microwave energy to generate the necessary heat *in situ.* The idea is that if the heat can be generated in a fixed bed, it should be possible to make HCN with no waste streams and no need to recycle ammonia. The process should be relatively easy to control, and should greatly reduce inventory. In fact, if the reaction is done in a carbon bed, only ammonia need be fed to the system continuously. Although it is not yet clear whether this process can be made economical, it is another example of how thinking in terms of balance might lead to entirely new synthetic pathways.

It is not usual for industrial engineers to be given the opportunity to develop and commercialize completely new processes. It is far more common for innovation to be required within the constraints of an existing system. For this reason, a list of individual process improvements that might be expected to broaden the range of environmentally attractive and economically viable choices available to engineers confronted with this type of task follows:

- Improvements related to feedstocks
- Improvements related to ordinary chemical processes (e.g., mechanical separations, optimum networks/model-based control)
- Improvements related to unusual reactions or reaction conditions (e.g., supercritical water oxidation, "Bioprocessing Plus")

Degussa vs Andrussow HCN

Degussa ($\Delta H°_{298}$= ~60 kcals/mole)

$CH_4 + NH_3 \longrightarrow HCN + 3H_2$

- external heating and heat exchangers
- high yield and investment
- medium scale

Andrussow ($\Delta H°_{298}$= ~ –50 kcals/mole)

$CH_4 + NH_3 + [O_2/N_2] \longrightarrow HCN + [H_2O]$

- internal combustion for heat
- lower yield and investment
- high capacity but more waste

Microwave HCN Process

$$CH_4 + NH_3 \xrightarrow{1200° C,\ Pt/Al_2O_3} HCN + 3H_2$$

Advantages

- Quick startup and shutdown (rapid heating)
- On-site production and consumption
- Reduced potential for exposure
- High yield (>95%)
- Essentially no waste stream

Figure 42. Alternative Processes for HCN Production

- Improvements related to unusual separations (e.g., pressure-recovery desalination, solids transfer columns, melt crystallizations, physical and physicochemical separations)

- Methods of avoiding separations (e.g., heterogeneous versus homogeneous catalysis, chemical reactions, avoiding or substituting solvents, precise reaction control)

It is recommended that government and private industry select some of the more promising of these possibilities for concerted joint efforts that in many cases would need to be both long-term and multidisciplinary. Candidate projects attractive in this regard include developing alternative methods of producing a vacuum, producing better tools both for modeling and developing processes that already have environmental considerations embedded in them, promoting research into advanced oxidation treatment systems (particularly supercritical water oxidation), developing chemically resistant polymeric membranes and tailored asymmetric structures for unusual separations, and investigating the applicability of solvent-free melting and freezing purifications to the chemical industry.

Specific examples of process improvements that are already being addressed are the effects of feed purity and conversion, the use of heterogeneous catalysts, and process improvements related to the treatment of biosludge.

Figure 43 shows the effect of inert substances in feedstocks. In this case, inert substances comprise 10% of the feedstock in a process that runs a 50% conversion. The need to purge inert substances from the feedstock causes an additional 10% loss of feedstock materials. Because of this, the reaction system is three times as large as it might otherwise be, and a great deal of energy is consumed merely circulating the impure feedstock through the system. Since low feed purity increases losses, equipment costs, energy consumption, and waste, the use of a purer feedstock might well be worth the extra cost. Similarly, since low

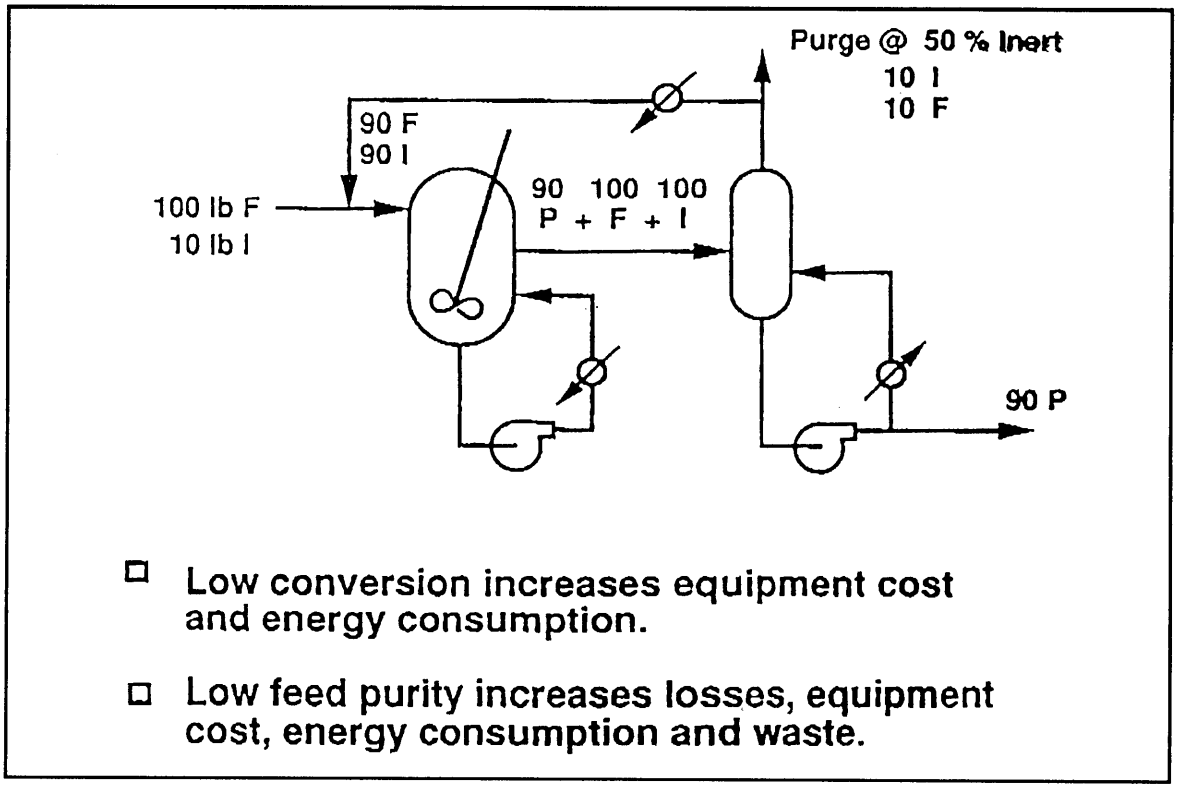


Figure 43. Effect of Feed Purity and Conversion

conversion increases equipment costs and energy consumption, higher conversion might be worth some loss of yield or investment in a different catalyst.

While homogeneous catalysts are often very selective, the need to recover and recycle the catalyst and solvents can often outweigh the advantages of a homogeneous system. Because of this, heterogeneous catalysts may be preferable in some situations, particularly those involving acid-based conversions. Figure 44 shows a simple fixed bed system of the sort described earlier for small-scale production of hydrogen cyanide. Although somewhat more complex, a slurry system would provide many of the same benefits.

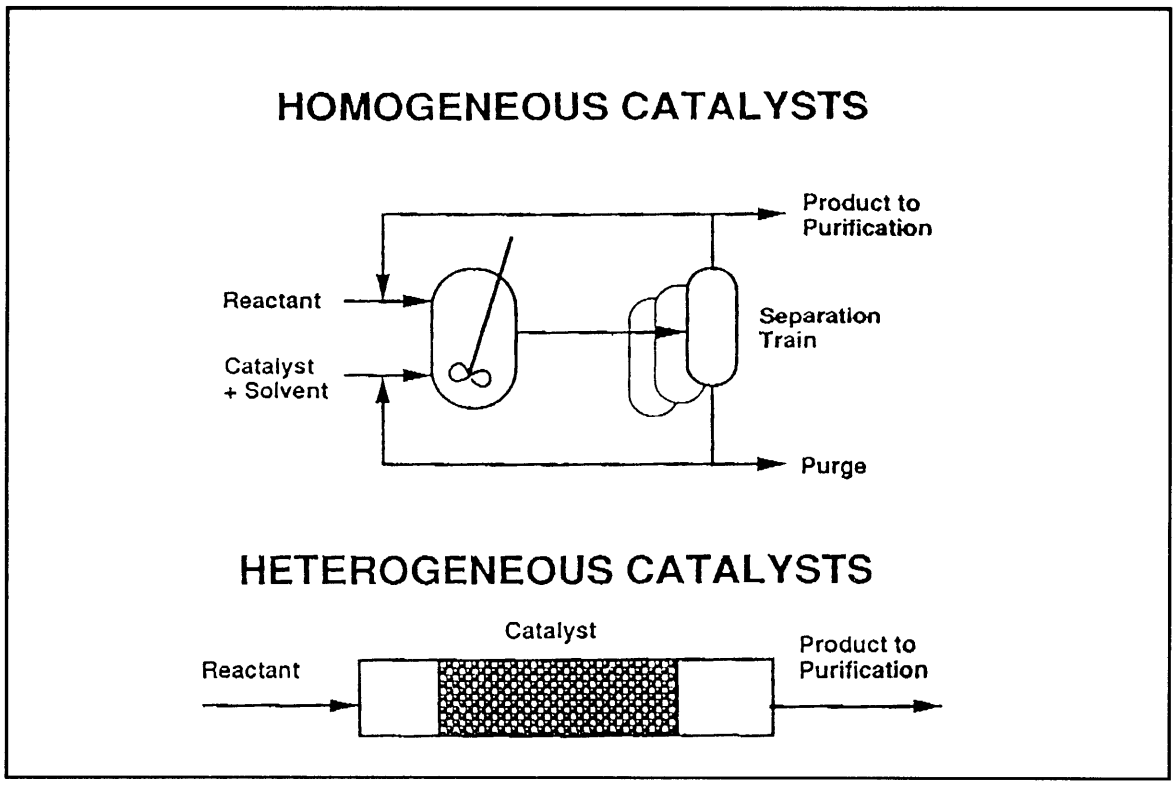


Figure 44. Homogeneous versus Heterogeneous Catalysts

In the area of biosludge treatment, Figure 45 is a flow chart illustrating a process currently being contemplated for the acid-catalyzed hydrolysis of biosludge. As a step toward DuPont's corporate goal of zero-discharge processing, this process could be used for the treatment within plant boundaries of biosludge that may contain various industrial contaminants such as trace metals. The goal is to eliminate the purge stream.

A good rule of thumb in new process design appears to be to seek methods of solving problems that make the process simpler rather than more complicated. It might be very fruitful to go back and take a second look at processes that were developed but not exploited in the past because they were not considered economically viable at the time they were developed. Many of these

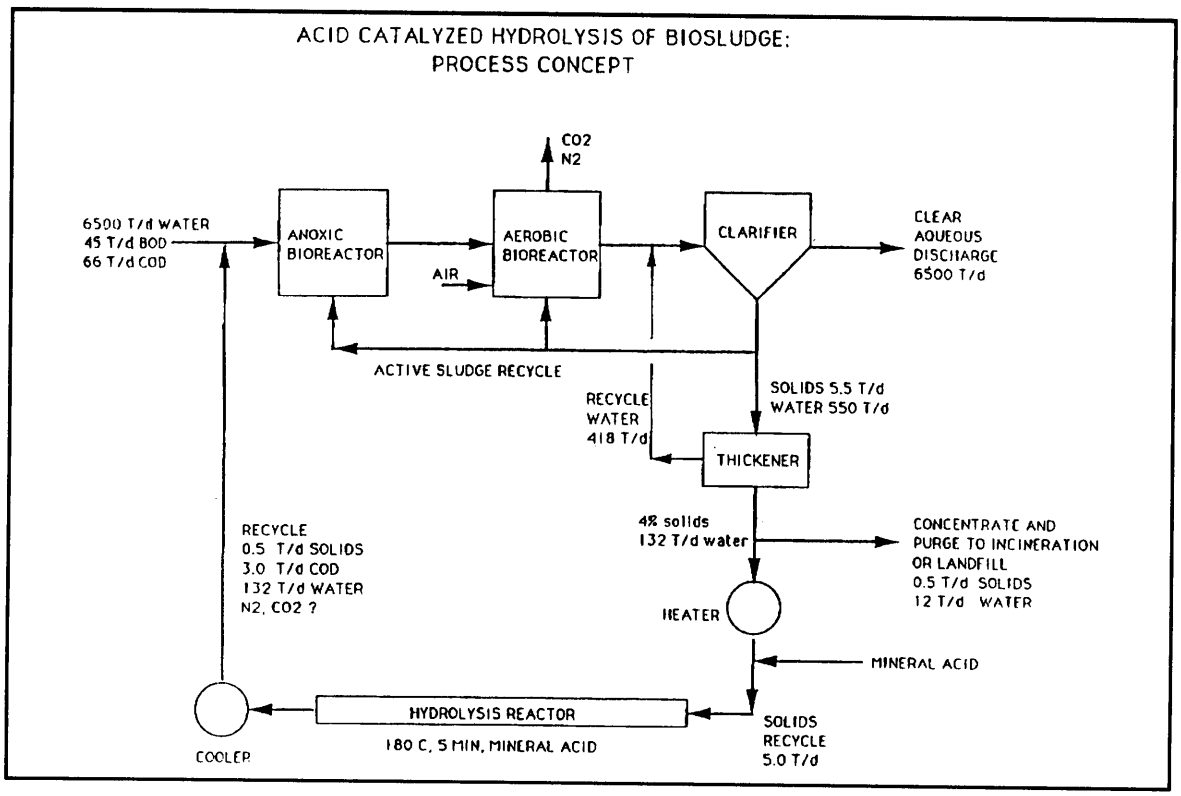


Figure 45. *Process Concept: Acid-Catalyzed Hydrolysis of Biosludge*

processes may be much more appealing in the context of current goals and priorities. Most important is the need to expand the scope of our thinking to include larger, more complex systems, more disciplines, and a longer time scale. Although attention to unit parts and unit operations will remain an important part of chemical engineering, the demands of sustainable development will increasingly require this broader view.

Computer-Based Methods for Finding Green Synthesis Pathways and Industrial Processes for Manufacturing Chemicals: A View From 10,000 Feet

Peter P. Radecki, Center for Clean Industrial and Treatment Technologies/Michigan Technological University

A graphic depicting the trade-offs between unit costs and pollution prevention associated with various types of approaches to the problem of making chemical manufacturing processes greener is shown in Figure 46. Most current approaches fall into the general category of management practices. These approaches, which include pollution audit activities such as inventory control, materials management, and energy utilization analysis, may reduce unit production costs in some instances but may increase these costs in others. At the

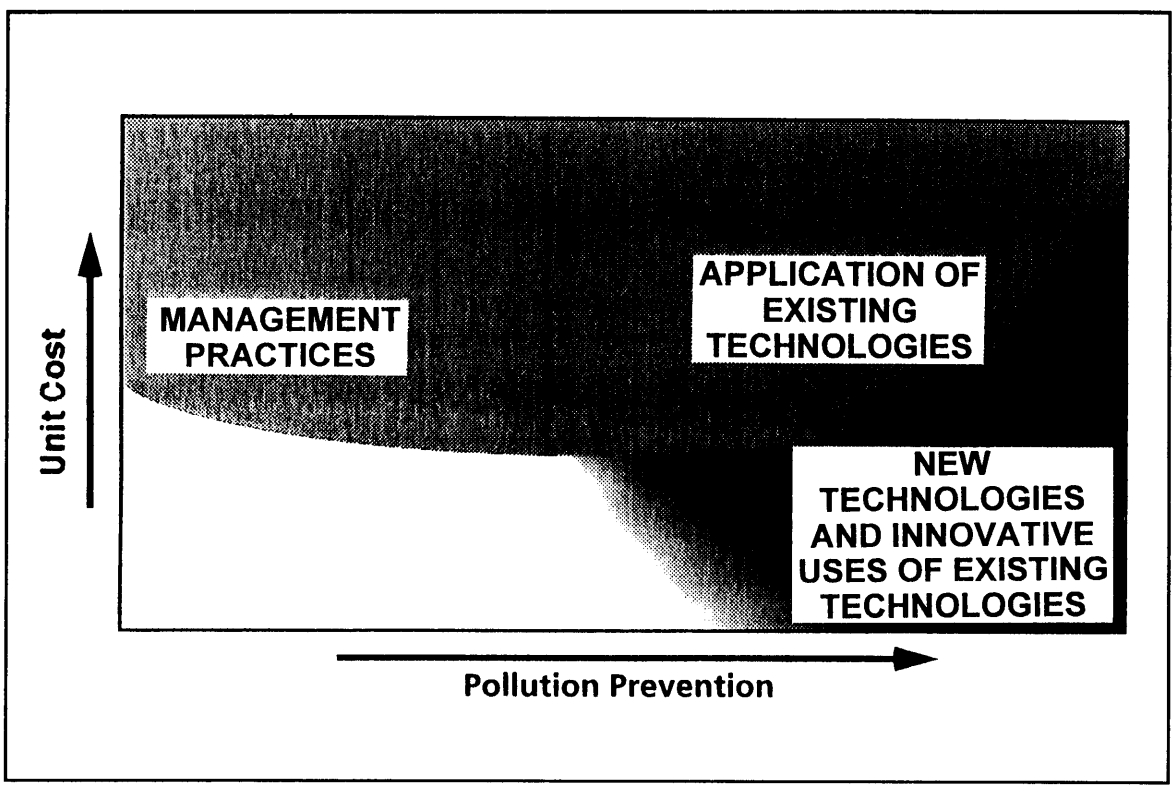


Figure 46. Clean Technology Targets

same time, these approaches offer only modest improvements from the perspective of pollution prevention.

The goals of the workshop are more closely related to the right side of the diagram – that is, finding ways of applying existing technologies that will provide large payoffs in pollution prevention while maintaining production costs at an acceptable level. The ideal that we are moving toward is represented in the lower-right quadrant of the diagram – a situation in which the development of new technologies or the innovative use of existing technologies enhances pollution prevention while at the same time decreasing the production costs of the material in question. Thus, the ultimate goal of benign process development is to achieve source reduction in such a way that unit production costs remain constant or go down.

Current reality is far from this ideal. In many cases, for example, advances in industrial process design are held as corporate secrets. As a result, what scientists in academic or government laboratories consider state-of-the-art may actually be quite different from what is already being implemented in industry. In addition, the results of a Hoechst Celanese study in which 80% of about 200 pollution prevention projects spanning a whole range of chemical processes were found to have a high cost impact. Thus, while maintaining or even reducing production costs is a goal of green chemistry, the reality is that most of the projects we are talking about are going to cost money. Processes described as "the low-hanging fruit" have already been picked by the large chemical companies who have been proactive in the area of process pollution prevention. Despite impressive engineering capability, going beyond these projects is not likely to occur on a large scale in the near future due to the combination of market forces, structural barriers, political considerations, and emphasis on short-term funding that all come to bear on the issue.

Two of the main barriers to the sort of holistic development that is necessary to attain the goal of environmentally benign manufacturing are the "culture of verification" that currently pervades our thinking about environmental issues, and the emphasis on highly quantitative, single-medium, chemical-by-chemical measurements that characterize our thinking about monitoring and regulation. These inhibit environmental impact-based approaches and favor low-risk, end-of-pipe solutions to environmental problems. Some means of measuring progress is needed, and the techniques needed to measure progress in pollution prevention may be very different from those developed to measure progress in areas related to chemical-by-chemical monitoring and regulation.

Another important barrier to holistic development has to do with corporate realities in an age of compliance. In some ways this is related to the issue of verification, in that monies spent on chemical-by-chemical monitoring and reporting are not available for long-range research and development or other types of green planning. This is true not only in industry, but also in the public sector, since the tax dollars required to run federal and state environmental agencies charged with establishing regulations and monitoring compliance are also part of the financial equation. The focus on compliance also results in a corporate structure that separates treatment and environmental expertise from process design expertise. With the relevant individuals in different parts of a company, it should not be surprising that environmental considerations are not routinely incorporated in new process design. The costs of compliance induce investment in oil producing countries and elsewhere to turn oil into chemicals. Increasingly, overseas interests are providing the value added to basic resources instead of this being done in the United States.

A series of diagrams outlining the major stages of new process development and implementation are shown in Figure 47. It is estimated that construction of entirely new plants, and therefore, the synthesis steps shown in

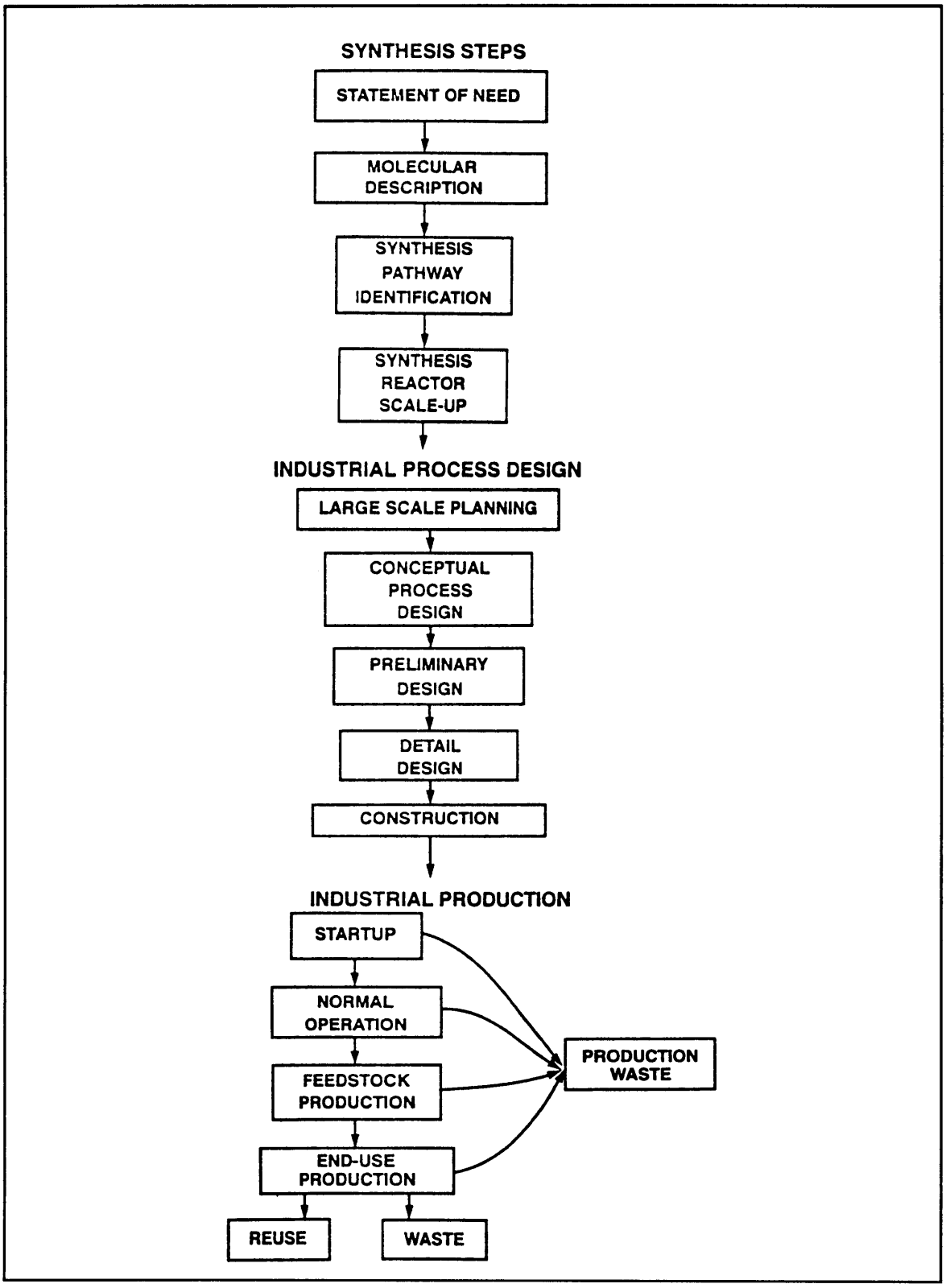


Figure 47. Stages of Process Development and Implementation

this figure, account for about 5% of capital expenditures in any given year, while industrial process design and production in plant revamps account for the bulk of the remaining 95%. This distribution reflects the fact that it is not often the case that one gets the opportunity to design a new process from the ground up. Much more common are situations in which engineers are asked to modify an existing system so that the system will fulfill more or different needs.

Figure 48 lists computer tools that might be of use during the preliminary stages such as molecular description, synthesis pathway identification, and synthesis reactor scale-up. Although in this diagram the computer-based approaches and the development steps to which they apply generally correlate, a direct, one-to-one relationship does not necessarily hold.

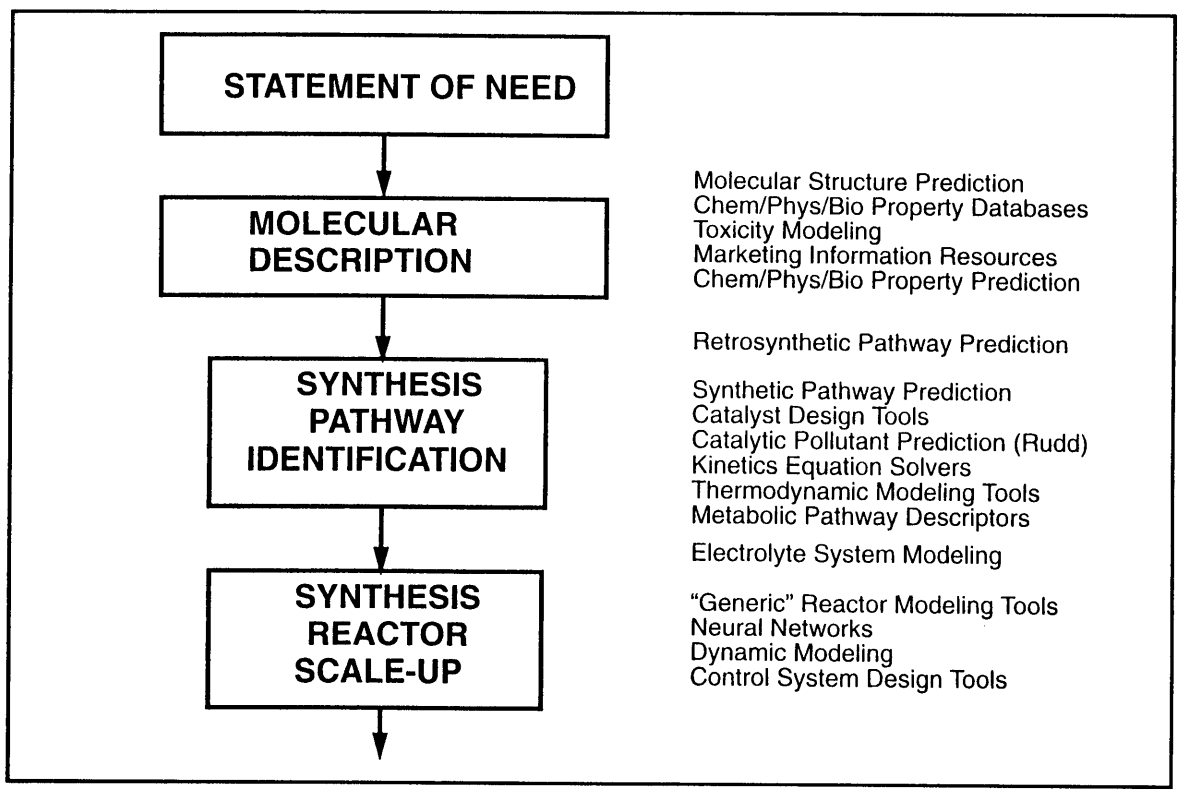


Figure 48. *Computer-Based Tools for Use in the Early Planning Stages of Process Design*

In terms of the computer-based tools available for use in the early planning stages of process design, there is a distinction between those that are available for more or less generic application and those more likely to be developed in-house and considered highly proprietary. Examples of the former include molecular structure prediction packages and consortia-funded databases of physical-chemical biological properties. When the development process reaches the stage of catalyst design, design of the reactor itself, or design of control systems, however, computer-based tools tend to be "home grown" packages developed by academic or industrial researchers for use in a specific manufacturing situation; as such, these tools are much less likely to be available outside the sponsoring company. There is a fair amount of movement in the direction of creating generic reactor modeling tools that would allow chemical engineers to experiment with variables such as reaction conditions, the inclusion of additives or inhibitors, and so on. With such tools, engineers could relatively easily evaluate a half-dozen different types of reactors to determine which might work best for a given synthetic pathway.

Computer-based tools that might be used during the industrial process design stage are listed in Figure 49. For the most part, the goal of the large-scale planning tools is to allow a means of taking a proactive look at potential impacts over the 40- or 50- or 100-year lifetime of the contemplated process. This is an important advance over existing programs most of which involve after-the-fact analysis of problems only after it is too late to do anything about them.

As a specific example of the types of tools envisioned as particularly useful, a project to develop a program which would enable corporate planners to view a matrix of industrial processes used to manufacture a given feedstock from the perspective of an environmental inventory has been proposed. This matrix would allow planners, particularly those with multinational operations, to determine where it might make economic sense to reduce output from one plant and

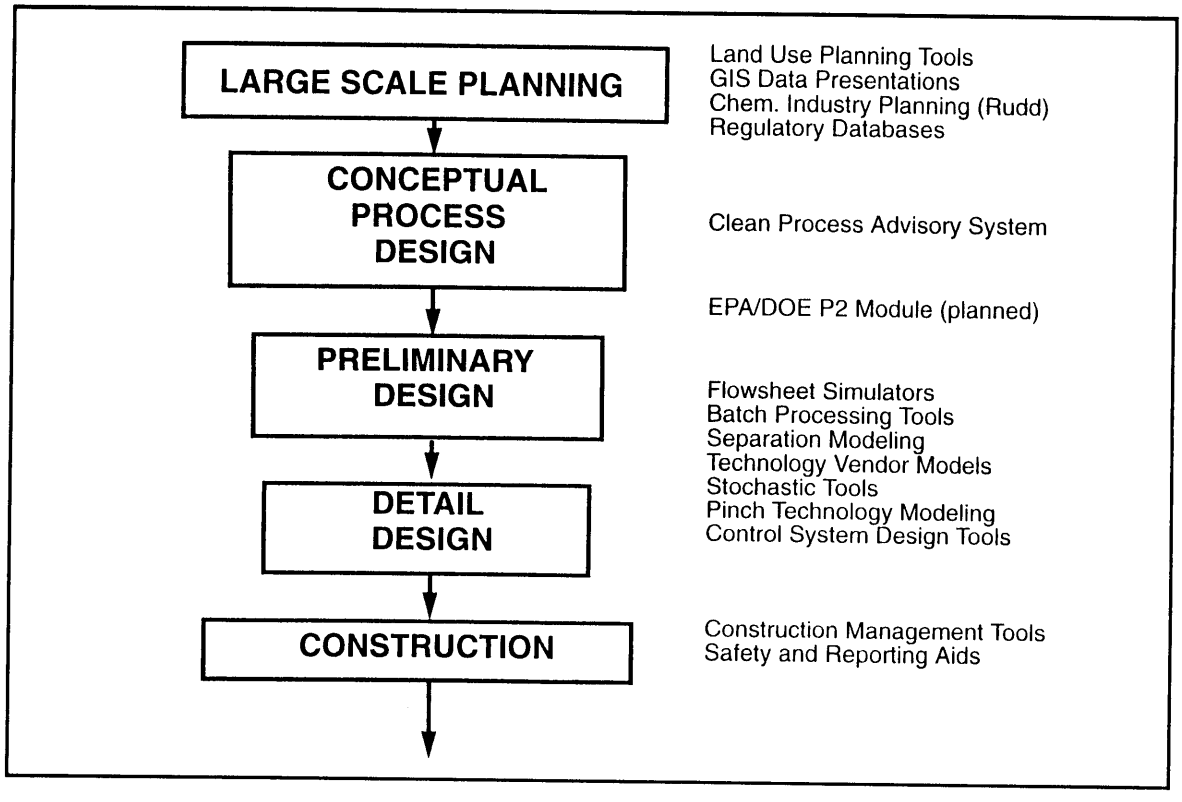


Figure 49. Computer-Based Tools for Use in Industrial-Scale Process Design

increase output from another. Similarly, such a matrix would help identify areas in which environmentally-motivated changes in process design are economically viable versus areas in which they are not.

The Clean Process Advisory System is a program through which CenCITT and two industrial consortia, the Center for Waste Reduction Technologies and the National Center for Manufacturing Sciences, are attempting to assure that information about process options is made more widely available to process engineers. At present, the designer's awareness of options for achieving a particular process goal are often limited to information that he or she happens to hear about from other process designers. The goal of the Clean Process Advisory System, which is currently about a year old, is to make available a comprehensive

list of all the options that are available to achieve a specific goal – for example, ways of separating materials which result in less environmental impact. Thus, for example, if someone comes up with a new membrane separation process that could be used to replace an energy-consuming distillation process, the Advisory System would make this information available to process engineers who may be confronted with a parallel situation in which distillation is not the best or most desirable way of achieving the targeted separation.

Another example is a multi-million-dollar, multi-year program that the Water and Wastewater Research Division of the Risk Reduction Engineering Laboratory is trying to develop in conjunction with the Department of Energy. This program which falls somewhere between conceptual process and preliminary design, would attempt to develop a pollution prevention module that could be tied to conventional process flow sheet simulators. The availability of such a module would make it much easier for environmental considerations to be taken into account during each step of the design process.

Regarding the potential of pinch technology in the context of environmentally benign manufacturing, efforts are currently under way to develop tools to look at mass exchange in much the same way that pinch technologies for energy conservation look at heat exchange.

Turning to the industrial production stage, most existing computer-based tools apply to this final segment of the development process as shown in Figure 50. Many gains have already been realized from tools available in the areas of pollution auditing, total quality management, and safety assessments. In the area of environmental impact, however, most existing packages focus on chronic emissions and other problems from an after-the-fact perspective. An important goal will be to get similar types of information made available for use earlier in the design process.

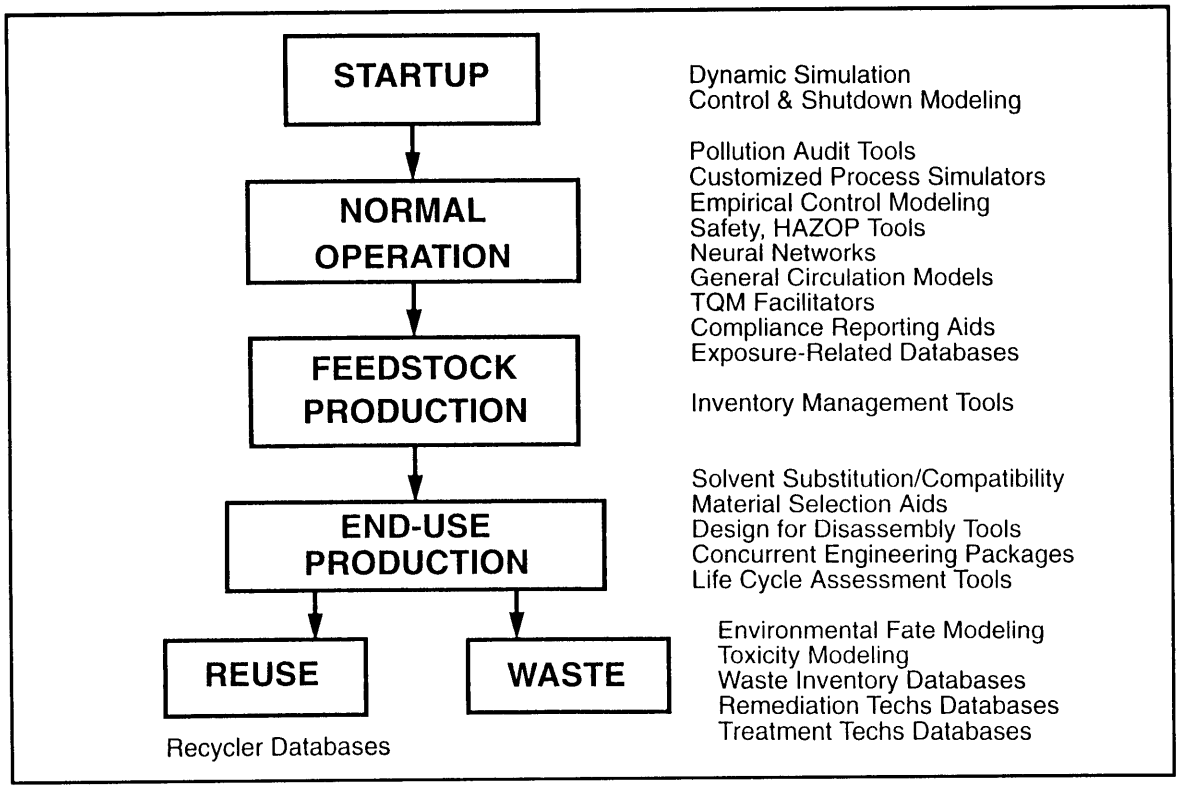


Figure 50. Computer-Based Tools for Use During the Industrial Production Stage

As an example of an area in which many tools are available but integration is needed, the programs designed to facilitate decisions related to solvent substitution and solvent compatibility are available. There are at least a half-dozen different efforts under way in this area, including several at National Labs, several at various industrial consortia, and at least one being funded by EPA. Because these systems were developed in parallel, however, there may be overlap among them as well as problems related to the fact that the various programs cannot "talk" to one another. Currently, the National Center for Manufacturing Sciences is trying to come up with a way to tie all of these systems together, but this is a very costly undertaking. Better front-end planning might have resulted in tremendous cost savings for everyone involved.

A few more general observations about current computer-based tools can be made. For the most part, existing programs are independent, stand-alone tools, each of which can only offer limited benefits in terms of making process design more environmentally friendly. In addition, commercial software development is going to tend to focus on marketable products, whether or not these products address the most important aspects of green process design. As a result, federal funding should be earmarked for programs in areas in which market forces alone cannot be expected to provoke sufficient interest on the part of software developers.

New releases of commercially available programs generally tend to focus on front-end features such as user interface, robustness, and speed. What is really needed, however, is advancement of the "workhorse" databases that underlie these programs. Data acquisition programs only rarely have significant commercial potential; as a result, almost all currently available tools focus on issues of treatment, liability, compliance, or management.

The greatest capability of existing chemical synthesis tools is in dealing with high-purity systems. In these systems, it is sometimes possible to make synthetic and retrosynthetic predictions related to a single chemical. When it comes to predicting the behavior of real-world chemical feedstocks, however, the utility of these systems falls off dramatically, even for very standard feedstocks. It has been only recently that a good surrogate for gasoline has appeared in the literature, and that analysis received funding only because there was a great deal of interest in leaking underground storage tanks at the time. The coarseness of modeling tools for commodity chemicals is perhaps best reflected in the fact that it is not at all uncommon for predictions about the physical properties of mixed-species feedstock components to have errors on the order of 20-30%, and these errors are compounded many times over when the predicted values are propagated through an entire process. Therefore, while molecular modeling

techniques and molecular-level surface chemistry tools may be useful in providing conceptual insights, correlation with actual industrial experience is rare, and meaningful stochastic analyses are virtually impossible.

In the area of data acquisition and management, these types of programs are almost never profitable enough for commercial software houses to develop and maintain. Those programs that do generate data are almost always consortia-funded, but it is very difficult to arrange for long-term stewardship of these programs. When funding is obtained, duplication of efforts is often a problem, and projects that integrate data and methodologies are exceedingly rare.

Left to its own, the commercial software industry will continue to focus on advances in numerical methods, user interfaces, computing power, and communications and networking – despite the fact that information management acquisition and retrieval is the area that offers the greatest potential for meaningful advances in this field. The single biggest obstacle to improved information management is in developing protocols for effective information transfer from one unit operation to the next or even from one step to the next within a single unit operation. The only such program he is aware of aware of, Mr. Radecki said, is an effort by the Process Data Exchange Institute of AIChE, which is supported at a level of about $100,000 per year. For comparison, Mr. Radecki noted he has been told that Japanese spending in this area is currently about $5 million per year. Advocating a long-term federal commitment to environmental information acquisition and management, the current model of support through short-term projects will not be adequate to maintain the edge the U.S. has historically held in information management systems. Information management strategies would benefit from a more object-oriented approach that would allow parallel rather than stepwise development of the range of components needed to address a given technologic problem (see Figure 51).

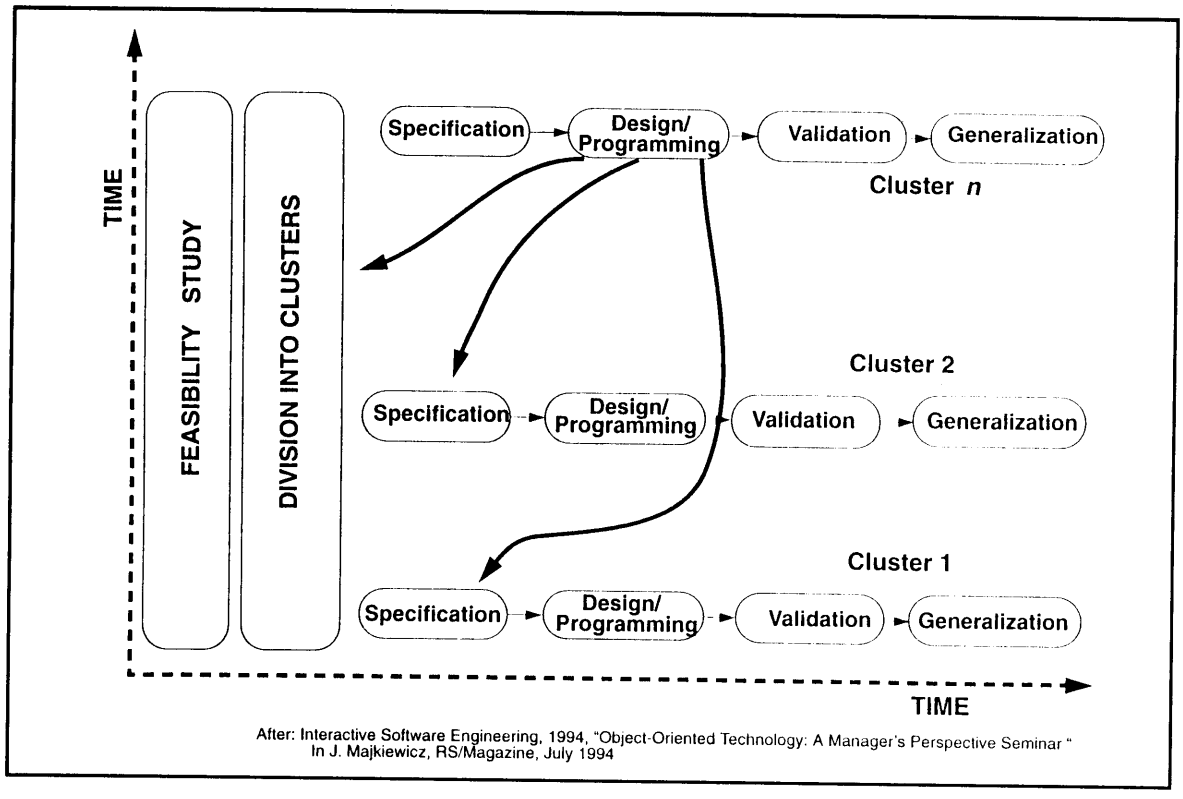


Figure 51. *Object-Oriented Programming and Concurrent Software Development*

In the search to identify and fill critical R&D needs, the focus should be on the industrial designer, who is in a far better position than government regulators or academic scientists to know what type of information would be of greatest practical benefit. At the same time, greenness should be measured on a broad spectrum, so that movement in the right direction is valued over advances that echo the "bean-counting" approach of monitoring and compliance.

A summary list of elements that should guide research and development in the area of green process design follows:

- Facilitate the convergence of process design and environmental understanding within the corporate structure
- Make it easy to learn about the green synthesis and process design options that are already available
- Target those information needs not likely to be filled by the market
- Emphasize long-term stewardship over short-duration projects
- Promote the development of common R&D goals of multiple organizations

III. BREAKOUT SESSIONS

During the morning and early afternoon of the second day of the workshop, participants met in four smaller breakout groups to discuss and make recommendations regarding research needs in the four general areas addressed by the plenary speakers:

- Benign Organic Synthesis
- Benign Biosynthesis
- Benign Engineering Approaches
- Computer-Based Methods

In addition to workshop attendees who had preregistered to participate, each breakout group included a facilitator responsible for guiding the discussion and making sure all participants got a chance to express their views, a chart writer responsible for capturing the main points of discussion on a flip chart, and an EPA writer responsible for taking detailed notes of the breakout group proceedings. Minutes of the proceedings for each breakout group are contained in Appendix C of this document.

In making recommendations about needed research and development within their assigned area, breakout group members were asked to address four main questions:

- Whether the priority assigned to each area of recommended research was high, medium, or low

- Whether the recommended research could be expected to produce an impact within a long (>10 years), medium (5-10 years), or short (0-5 years) timeframe

- Whether the research would most appropriately be undertaken by industry (I), government (G), academia (A), or some combination of the three

- Whether and why government funding is or is not needed to support the recommended research

In addition, workgroups were asked to using a voting procedure to assign relative priority scores to each area of recommended research.

IV. PRESENTATIONS – CLOSING PLENARY SESSION

Following the completion of individual breakout sessions, the workshop reconvened as a whole. During this closing plenary session, representatives from each of the workgroups made presentations summarizing the discussions that took place and the recommendations reached in their respective groups.

Workgroup on Engineering Approaches

Facilitator: A. Ford, Lamar University

The recommendations of the workgroup are summarized in Table 1. Due to its large size, this workgroup was divided into several smaller groups to address the various areas of research initially identified by the workgroup. Summaries of discussion and findings of each of these groups were presented by members of the smaller workgroups.

P. Biswas presented recommendations regarding research needed in the area of high temperature processes. Examples of synthetic routes that might be good candidates for further investigation are fume silica and titanium pigments (both involving gas phase/aerosol synthesis). The rationale for the group's recommendation for fundamental study of high-temperature chemistry was the need for a better understanding of the mechanisms of both product and pollutant formation, which may permit better control of pollutants, despite the instance where formation of these by-products cannot be totally avoided. Finally, an emphasis on both research and development was deemed important to permit control of processes within narrow operating windows and to trigger a shut-down if the process falls outside the prescribed operating constraints.

Table 1: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN ENGINEERING APPROACHES

Category	Priority	Time-frame	Who Does Research?	Federal Funding Needed?	Priority Score
High Temperature Processes					7
• Investigate gas phase/aerosol synthesis routes for production of novel materials such as advanced ceramics, electronic materials, nanophase materials	High	Medium	I/G/A*	Yes	—
• Fundamental study of high-temperature chemistry to understand product and pollutant formation	High	Short	I/G/A*	Yes	—
• Develop real-time/in-situ diagnostic techniques for high-temperature process monitoring (e.g., optical diagnostics)	High	Short	I/G/A*	Yes	—
By-Products					
• Recovery of products (polymers, paper, metals); recovery of raw materials; inert (ceramic) products; land uses	Medium	Short-Medium	I/G/A*	Yes	7

Table 1: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN ENGINEERING APPROACHES (continued)

Category	Priority	Time-frame	Who Does Research?	Federal Funding Needed?	Priority Score
Containment					10
• Plant-wide confinement strategies (e.g., encapsulation)	High	Medium	I*	No	—
• Multi-phase confinement (e.g., solids charging or discharging in the presence of volatile organics)	High	Medium	I/G*	Yes	—
• Novel shaft-sealing techniques	High	Medium	I/G*	Yes	—
Catalysis					11
• Achieving higher concentration of product	High	Short-Medium	I/G/A[1]*	Yes	—
• Separations (catalytic membranes)	High	Medium-Long	I/G/A*	Yes	—
• Non-toxic (benign) catalysts	High	Medium	I/G/A*	Yes	—
• Attrition of catalysts (fluidized beds)	Medium	Medium	I*	No	—

[1] The Benign Engineering Approaches Workgroup specified that industry should fund and conduct research related to specific products; government and academic involvement should focus on more generic products.

Table 1: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN ENGINEERING APPROACHES (continued)

Category	Priority	Time-frame	Who Does Research?	Federal Funding Needed?	Priority Score
Process Synthesis					11
• Promote "mass/energy" pinch computational technology to identify process inefficiency and point to improved process schemes	High	Long	I/G*	Yes	—
• Augment traditional pinch technology to include emissions debits/credits	Medium	Long	I*	No	—
Sensors					9
• Develop techniques to gather hard data to document zero emissions and to measure effectiveness of improvements	High	Medium	I/G/A*	Yes	—

Table 1: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN ENGINEERING APPROACHES (continued)

Category	Priority	Time-frame	Who Does Research?	Federal Funding Needed?	Priority Score
Unit Operations					
• Develop low-energy chemical separations (e.g., removal of H_20 from dilute products; avoid phase change when possible; better freezing and/or crystallization methods)	High	Short	I/A*	Yes	11
• Develop membrane systems with better selectivity, higher flux, and longer life; for polymer-based membranes, develop more solvent-resistant membrane materials	High	Short-Medium	I/A*	Yes	3
• Develop more effective physical methods for selectively separating phases (solid-solid, solid-fluid, and fluid-fluid)	High	Short-Medium	mainly I; some A/G*	Yes	5
• Develop novel combinations of unit operations (i.e, hybrid unit operations) for separations	High	Short	I*	Yes	2

Table 1: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN ENGINEERING APPROACHES (continued)

Category	Priority	Time-frame	Who Does Research?	Federal Funding Needed?	Priority Score
Unit Operations (continued)					
• Develop better understanding and use of mathematical models for evaluating, selecting, synthesizing, and optimizing the performance of unit operations	Medium	Medium	A/I/G*	Yes	5

* I = Industry
A = Academia
G = Government

C. Sciance identified "front-end" issues that they considered important:

- Define benign technologies and "greenness" to help all parties develop and enunciate a "green vision"
- Develop tools and technology to facilitate selection of environmental alternatives (e.g., life cycle analysis, risk/benefit analysis, environmental full-cost accounting, databases and heuristics, methods of quantifying "greenness")
- Promote progress toward benign processing (e.g., programs addressing the unique needs of small companies, programs addressing the common needs of related industries, programs identifying suppliers of needed equipment, services, and so on)
- Develop innovative ways to promote more effective cooperation, and identify and prioritize research needs to serve industry; seek complimentary roles and responsibilities and work with government to secure funding
- Promote professional and public education and continuing workplace training on values, ethics, and sustainability as well as benign technologies

C. Nassaralla presented findings related to waste issues. By-products were selected to mean solid wastes such as incinerator ash, tar, dust, biosolids, and any other solid wastes produced during a synthetic process. The goals of the recommended research were to avoid the formation of solid waste or to transform the wastes into useful products. Recognizing that it is currently not economical to recycle much of this material, the group felt that diminishing landfill space and increasing government regulation were likely to change this situation.

E. Nauman presented the workgroup's findings related to containment issues, noting that there was not universal agreement on this point, but a general opinion among workgroup members that greenness ought to be judged on the basis of what goes into and comes out of a plant, not on the basis of what might

be within the boundaries of the plant itself. Research into ways of "keeping the nasties locked up" should be part of an overall program that has zero- or near-zero emissions as its goal.

T. Foust presented the recommendations in the area of catalysis. The catalysis group believed work on separations and developing non-toxic catalysts was rated as relatively high-risk, while research into methods of achieving higher product concentrations and reducing catalyst attrition were rated as lower-risk undertakings.

W. Schmeal presented the recommendations regarding research needs in the area of process synthesis. Creative thinking about process synthesis using a rationale for classifying these efforts as long-term should be promoted. Attempting to apply pinch computational technologies to the issue of mass transfer may be significantly more difficult than applying them to energy conservation – which itself was not an easy or quick process. Instead of a single commodity (energy), an environmentally-based pinch technology approach would have to take substances of many different chemical compositions into account.

J. Watson presented the workgroup's recommendations in the area of unit operations. Low-energy separations are particularly important in the context of biotechnology products, which tend to be made in very dilute solutions. Examples of the types of physical separations the group thought particularly worthy of consideration were (1) removing toxic materials from wastes, (2) removing impurities from feedstocks, and (3) various types of de-misting processes. The objective of hybrid unit operations research should be to come up with novel combinations of unit operations that lower operating costs, reduce energy consumption, reduce capital requirements, and/or minimize product degradation.

Following the presentations, one workshop participant (Bashkin) expressed some confusion about the relationship between fundamental studies of high temperature chemistry and benign processing. It was concluded that the products of high-temperature chemistry often have very narrow or controlled properties, so that even a slight change in processing conditions can significantly affect the extent to which solid wastes or toxic emissions are created. A better understanding of the chemistry would make it possible to minimize the formation of these undesirable products.

Workgroup on Biosynthesis

Facilitators: J. Frost, Michigan State University and
P. Elankovan, Michigan Biotechnology Institute

The recommendations of the Workgroup on Benign Biosynthesis are summarized in Table 2. The workgroup's findings were presented by D. Cameron, who noted that there was a fair amount of overlap between the recommendations of this and the Engineering Approaches workgroup. Cameron said that this was encouraging, since it probably meant that there really is some consensus about the types of projects that should be funded.

Regarding the group's recommendation that renewable feedstocks be investigated, some of the examples discussed were carbohydrates, carbon dioxide, methane, mixed organic wastes, and lipids. Already some companies have begun efforts to design specialized starches and lipids for use as chemical feedstocks. In addition, the group felt that more attention should be given to non-carbon-based activities of biological systems. Nitrogen fixation, conversion of minerals into unique materials like ceramics, and water-splitting reactions represent examples of biological processes that might be relevant to feedstock selection.

Table 2: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN BIOSYNTHESIS

Category	Priority	Time-Frame (Risk)	Who Does Research?	Federal Funding Needed?	Priority Score
Feedstocks					
• Investigate the use of renewable feedstocks for the production of chemicals	High	Short	J*	Yes	47
• Investigate methods of customizing feedstocks to produce chemicals	Low	Long	J*	Yes	20
• Investigate the use of non-carbon-based feedstocks in biosynthesis	Low	Long	J, A*	Yes	23
Pathway Engineering					
• Investigate methods of genetically modifying lifeforms with respect to attributes related to chemical production	High	Long	J*	Yes	35
• Investigate methods of expanding and utilizing biocatalyst diversity (e.g., organisms, enzymes, catalytic antibodies, genes, ribozymes)	High	Long	A*	Yes	32
• Develop tools for pathway engineering (e.g., pathway modeling, database development)	High	Medium	A*	Yes	23

Table 2: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN BIOSYNTHESIS (continued)

Category	Priority	Time-Frame (Risk)	Who Does Research?	Federal Funding Needed?	Priority Score
Reaction Engineering					
• Investigate methods of stabilizing enzymes with respect to temperature, solvents, pH, pressure, and electrolytes	Medium	Short	J*	Yes	30
• Investigate alternative methods of electron transfer	Medium	Long	J*	Yes	23
• Develop methods needed to improve the productivity and selectivity of biocatalytic conversions	Medium	Medium	J*	Yes	37
Processing					
• Develop databases that address the physical/chemical properties of aqueous and aqueous/organic systems as well as process alternatives	Medium	Short	G*	Yes	13

Table 2: RECOMMENDATIONS OF THE WORKGROUP ON BENIGN BIOSYNTHESIS (continued)

Category	Priority	Time-Frame (Risk)	Who Does Research?	Federal Funding Needed?	Priority Score
Processing (continued)					
• Develop databases that help evaluate the economics of biosynthetic processes	High	Short	J*	Yes	17
• Develop improved methods of separation and purification	High	Medium	J*	Yes	28
• Investigate methods for better monitoring and control of biosynthetic processes	Medium	Medium	I*	Yes	8
• Improve reactor design and modeling	Medium	Medium	J*	Yes	9
• Investigate methods of integrating biosynthetic and traditional synthetic processes	High	Short	J*	Yes	15

* I = Industry
A = Academia
G = Government
J = Joint venture in some combination of I,A,G

As discussed by the Biosynthesis group, pathway engineering was defined as taking advantage of advances in molecular biology to modify the metabolism of organisms, making them better producers of chemicals they already produce or causing them to produce chemicals that they otherwise would not. The types of work that need to be done in this area, the group felt, have to do with improving the yield, selectivity, tolerance, productivity, titer, and robustness of these biologically-based systems. Among tools that would help advance pathway engineering, the group discussed databases providing information on enzymatic activity and genes; models capable of integrating thermodynamics, kinetics, and stoichiometry; and databases containing information about the thermodynamics of various materials within the aqueous cellular environment.

In contrast with pathway engineering, which the group had defined to include large, integrated systems of reactions, reaction engineering was defined as having to do with modifying and improving single reaction sequences or enzymatic reactions. Regarding the identified need for work on alternative methods of electron transfer, the group thought that, in addition to cofactor regeneration, research should focus on ways of coupling electron transfers with electrochemical or photochemical reactions. Among the methods discussed to improve the productivity and selectivity of biocatalytic conversions, the Biosynthesis group listed phase transfer catalysis; use of non-aqueous media, including specialized media such as supercritical fluids; catalyst immobilization; post-translational modification, and substrate and product transport through the catalytic system.

The greatest area of overlap with the Engineering group was in the Biosynthesis group's consideration of issues related to processing. Noting that large databases are available only for the physical and chemical properties of chemicals in organic systems, the group felt that comparable databases should be developed for the behavior of chemicals in aqueous or mixed aqueous/organic systems and for process alternatives in aqueous systems. In the area of

monitoring, the group was particularly interested in methods of monitoring substrate concentrations, product concentrations, and biomass or catalyst concentration and activity on line. Regarding new methods of integrating biosynthetic and traditional synthetic processes, the group was particularly interested in comparative analyses of immobilized systems versus suspension biocatalysts and of batch versus continuous processing. The group also felt that integrations of organic and biological synthesis offer many unique opportunities in process development. Examples of integrated reactions included the fermentative production of lactic acid followed by chemical formation of an ester and chemical hydrolysis of feedstocks and sugars followed by fermentation processes.

Following Cameron's presentation, a workshop participant (Bashkin) asked about the group's inclusion of nitrogen fixation as a non-carbon-based reaction that might be exploited biosynthetically. From the questioner's perspective, biological nitrogen fixation is a poor competitor for standard chemical processes of nitrogen fixation, since biological fixation consumes large amounts of ATP and large numbers of protons and is associated with uncontrolled hydrogen production. The only advantage of biological nitrogen fixation, this participant suggested, is that it works at atmospheric pressure and room temperature. Cameron indicated that the group had wanted to make sure that they did not neglect non-carbon-based chemistry in their consideration of biosynthetic processes, and that some members of the group thought that there might be some interesting nitrogen-based chemistry that could be done with microorganisms. While agreeing that nitrogen fixation might not be the best example of such a process, large-scale nitrogen fixation by plants is, in fact, a pretty benign form of chemical processing.

Another participant (Sciance) asked whether the group had discussed sulfur, noting that a number of people in refining are interested in bioprocessing as a way to remove sulfur from feedstocks. Cameron emphasized that the group

had focused mainly on synthetic processes, but he agreed that biological desulfurization of oil and coal is a very promising area. The questioner pointed out that sulfate esters are an example of a biosynthetic process involving sulfur. Another member of the workgroup (Bradford) noted that the group had talked about both sulfur and phosphorus in terms of esterification reactions that could be of value in organic synthesis. As an example, he said that it might be possible to oxidize elemental sulfur or some other substrate *in situ* to generate a sulfate ester, and then to use this ester in the manufacture of surfactin or other sulfur-containing compounds.

Another workshop participant (Lee) expressed interest in the group's call for the development of new databases and asked what types of thermodynamic information are needed. Cameron responded that the group had discussed two different types of needs. First, there is a need for information about the nature of thermodynamic equilibrium in a cellular environment, the concentration of reaction intermediates within cells, and other types of similarly rudimentary baseline information. Second, the group felt there to be a great need for more information about the thermodynamic properties of various compounds in an aqueous environment. Examples offered included octanol/water partition coefficients and vapor pressure and equilibrium constants for organic acids in water or in ionic media that more closely resemble the solutions found in living systems.

The question was also posed (Radecki) whether the group had discussed the use of organisms for extracting toxic materials out of various types of streams; this questioner noted that bioaccumulation might be a very energy-efficient way to detoxify various types of materials. Cameron related that the group had agreed that microorganisms represent an important resource for clean-up and remediation, but that they had decided to focus strictly on issues related to biosynthesis.

Workgroup on Chemical Synthesis

Facilitator: P. Anastas, U.S. Environmental Protection Agency

The technical recommendations of the Workgroup on Chemical Synthesis are summarized in Table 3. The workgroup's findings were presented by T. Collins, who noted that the group had decided to rename itself the Workgroup on Environmentally Benign Synthesis, since there was general agreement that much of the research needed in this area would also apply to inorganic syntheses.

Regarding the group's recommendation that robust and selective homogeneous oxidants be developed, Collins noted that many of the species currently used in oxidation reactions are metals that have the potential to generate toxic by-products. Because of this, the group felt that high priority should be placed on developing recyclable alternatives, especially for catalytic purposes. The group's recommendation regarding the development of new solvents and/or solventless systems reflected a consensus regarding the need to find alternatives to chlorinated solvents and other solvents that represent health hazards.

The group's recommendation regarding long-term research on oxide-based catalysts for NO_x abatement had to do with finding an alternative to the "lose-lose" situation faced with existing internal combustion engines. If a rich mixture is run through these engines, the exhaust contains an excessive amount of hydrocarbon by-products. With the use of a lean mixture, production of nitrogen oxides increases. Because of this dilemma, there is currently a great deal of interest in the automobile industry in developing a solid catalyst for NO_x abatement.

Some detail was presented about the group's recommendation related to the development of functional models of enzymes. Enzymes are currently

Table 3: RECOMMENDATIONS OF THE WORKGROUP ON CHEMICAL SYNTHESIS

Category	Priority	Time-Frame	Who Does Research?	Federal Funding Needed?	Priority Score
Benign Reaction Design					
• Develop robust homogenous oxidants	High	Medium	I/A/G*	Yes	9
• Develop safer solvents to replace those currently used, or develop solventless systems	High	Short	I/A/G*	Yes	6
• Develop methods of selective, clean oxidative functionalization (bond-making processes) in order to reduce the use of substitution processes	High	Medium	I/A/G*	Yes	9
• Investigate novel media and/or reaction systems to enhance the selectivity of chemical transformations	Medium	Medium	I/A/G*	Yes	5
• Develop and promote the use of solid acid catalysts (heterogenizing processes)	High	Medium	I/A/G*	Yes	3
• Design processes, including new separation techniques, for the recovery of reagents	Low	Medium	I/G*	Yes	5
• Conduct long-term research on oxide-based catalysts for NO_x abatement	Medium	Medium	I/A/G*	Yes	3

Table 3: RECOMMENDATIONS OF THE WORKGROUP ON CHEMICAL SYNTHESIS (continued)

Category	Priority	Time-Frame	Who Does Research?	Federal Funding Needed?	Priority Score
Benign Reaction Design (continued)					
• Develop functional models of enzymes	High	Long	I/A/G*	Yes	10
• Investigate means to increase enantio-selective synthetic methods (particularly catalysis)	Medium	Short	I/A*	Yes	2
• Investigate biocatalytic, enzymatic, and microbiological transformations	Medium	Short	I/A/G*	Yes	4
• Promote photochemistry and electrochemistry for benign synthesis	High	Medium	I/A/G*	Yes	5
• Investigate the use of supercritical fluids in catalytic and biocatalytic reactions	High	Short	I/A/G*	Yes	6
• Molecular design for advanced separations	Low	Long	I/A/G*	Yes	4
• Develop in situ or more benign analytic sensors/monitors	Medium	Medium	I/A/G*	Yes	2
• Promote benign reactor design	Low	Long	I*	No	3
• Develop generic reagent-based strategies	Medium	Medium	I/A/G*	Yes	4
• Promote the use of renewable feedstocks	Low	Long	I/G*	Yes	6

* I = Industry A = Academia G = Government

receiving a great deal of attention from many different perspectives. Of particular interest to the workgroup was the fact that in addition to optimizing reaction rates, we are getting closer and closer to developing "smart" molecules – that is, multifunctional molecules that are capable of carrying out a transformation involving more than one reaction at more than one reaction site. The workgroup felt that support of these types of efforts has a very great potential for advances in our ability to make synthetic reactions more benign.

In addition to its technical recommendations, the workgroup offered a number of broader suggestions for promoting the development of environmentally benign syntheses. In the area of education and training, for example, the workgroup identified a number of efforts that it felt had significant potential for short-term impacts. These efforts included:

- Developing a list of 250 of the top processes that provide opportunities for pollution prevention, so that academic chemists will better understand which alternative pathways offer the greatest potential benefit
- Including benign chemistry as a core tenet of the chemistry curriculum, and teaching young chemists that responsible chemistry and creative chemistry are not two different things
- Developing educational approaches to familiarize chemists with separations and processes (physical/chemical isolation)
- Developing a database and/or information network on benign synthesis
- Promoting special issues of journals to disseminate information on benign synthesis to scientists in many different disciplines
- Disseminating information on benign synthesis to the public and promoting chemistry as a source of solutions to environmental problems
- Gaining a better understanding of industrial processes that could benefit from environmentally benign synthesis

The workgroup had also considered issues related to the implementation of environmentally benign synthetic pathways, and it was here that the workgroup felt that the government must play a major role. Elements of this effort might include any or all of the following:

- Promoting the implementation of benign methods in industry
- Identifying barriers to the implementation of benign methods
- Clearly stating a stable commitment to long-term research in synthetic chemistry
- Developing evaluative tools to assess the environmental and economic impact of synthetic methods at both the bench and process scales
- Developing means of funding interdisciplinary teams of scientists who can collaborate to address key problems in research and education

Like its recommendations related to education and training, the workgroup felt that efforts in this area have a great deal of potential to impact the development of benign synthesis over the short term. Particularly important in this regard is the commitment to long-term research. The group felt strongly that moving in and trying to find short-term projects to fund would retard rather than advance progress in this area. They agreed that long-term funding, particularly in the academic sector, is essential to building a solid research base for benign synthesis.

The workgroup had two general recommendations that it felt likely to promote the development of many different types of benign products. First, they suggested that a goal of benign synthesis should be to design target molecules that preserve the desired function and then to mitigate the toxicity of these compounds by modifying their physical and chemical properties. Second, the group thought that it would be useful to develop a functional group understanding of health and environmental hazards, since chemists are most adept at learning and comprehending chemistry through a functional group

approach. The working group felt that both of these general principles would help pull together broad areas of knowledge and would give people a much-needed intellectual framework for thinking about environmental problems.

Workgroup on Computer-Based Methods

Facilitator: C. Brunner, U.S. Environmental Protection Agency

The recommendations of the Workgroup on Computer-Based Methods are summarized in Table 4. The workgroup's findings were presented by P. Radecki, who began by noting that the group had a general concern about the compartmentalization of knowledge related to environmentally benign syntheses. People who understand process and synthesis design either do not have a good grasp of environmental issues or they are unable to obtain the data they need to implement that understanding in a quantifiable way. By addressing this problem from a number of different perspectives, the group felt that all of the research they recommended has the potential for significant impact at the application stage over the next 5 years.

In assigning the various research tasks to industry, government, or academia, the group had used fairly broad definitions of these terms. In addition to universities, for example, the group included "think tanks" and various other types of research institutions that may or may not be located at universities in its assignment of specific tasks to academia. Similarly, the group had considered industrial consortia to be the most appropriate sponsors for some of the tasks assigned to industry.

Regarding the category of integrating activities, the sense of the group was that there are some types of information needs that are not tied to a specific model. Rather, these are areas in which it will be necessary to develop some sort

Table 4: RECOMMENDATIONS OF THE WORKGROUP ON COMPUTER-BASED METHODS

Category	Priority[1]	Time-Frame	Who Does Research?	Federal Funding Needed?[2]	Priority Score[3]
Integrating Activities					
• Develop protocols for information transfer	High	Short	I/A/G*		24
• Develop approaches for long-term maintenance of software and databases	High	Short	I/A/G*		25
• Develop consistent engineering module descriptors	Medium	Short	I/A*		11
Decision-Making Tools					
• Design decision-making tools that are useful in retrofit process design	High	Short	I/A*		17
• Develop methods of tracking error propagation (uncertainty) through process models	High	Short	I/A*		15
• Develop an expert system shell that could incorporate experience-based information and compliance rules	High	Short	I/A*		15

[1] Medium priority was assigned where the priority score showed a significant break from the highest scores. No categories were judged to be low priority.
[2] Some federal support was considered necessary for all items. A "Yes" in this column indicates a need for significant federal funding.
[3] Although there is some variability, the total number of votes in each main category should be 60.

Table 4: RECOMMENDATIONS OF THE WORKGROUP ON COMPUTER-BASED METHODS (continued)

Category	Priority[1]	Time-Frame	Who Does Research?	Federal Funding Needed?[2]	Priority Score[3]
Decision-Making Tools (continued)					
• Develop improved optimization techniques (e.g, techniques involving multiple processes, multiple reactor components, or multiple areas of plant)	Medium	Short	I/A*		11
Expanded Process Simulation					
• Promote development of small-customer modules (e.g., membrane v. distillation separations) that are unlikely to be developed by large software firms	High	Short	I/A*	Yes	19
• Develop dynamic process simulations and promote integration with existing steady-state models	High	Short	I/A*		16
• Develop integrated models of energy and mass transfer networks	High	Short	I/A*		16
• Investigate the applicability of artificial intelligence techniques in process simulation	Medium	Short	I/A/G*		9

Table 4: RECOMMENDATIONS OF THE WORKGROUP ON COMPUTER-BASED METHODS (continued)

Category	Priority[1]	Time-Frame	Who Does Research?	Federal Funding Needed?[2]	Priority Score[3]
Decision Support					
• Develop integrated, product-based computer models	High	Short	I/A/G*	Yes	9
• Investigate ways of incorporating life cycle assessment issues into process design	High	Short	I/A*		11
• Develop methods to make information about environmental concerns available to process designers at the conceptual design stage	High	Short	I/A*		8
• Develop methods of regulatory forecasting	High	Short	I/A/G*		12
• Develop tools for use in total cost assessment (including environmental factors) on a unit-by-unit or process-by-process basis	High	Short	I/A*		8
• Develop tools for applying industrial ecologic concepts at the process design stage	Medium	Short	I/A*		5
• Develop tools to facilitate environmental impact analysis in terms of pollution prevention energy and economics	Medium	Short	I/A/G*		5

Table 4: RECOMMENDATIONS OF THE WORKGROUP ON COMPUTER-BASED METHODS (continued)

Category	Priority[1]	Time-Frame	Who Does Research?	Federal Funding Needed?[2]	Priority Score[3]
Decision Support (continued)					
• Develop tools that translate toxicity data to terms that are useful to process engineers	Medium	Short	I/A/G*		3
Reaction Engineering					
• Develop methods to better predict the formation of trace contaminants	High	Short	I/A*	Yes	17
• Develop methods to facilitate more realistic reactor design	High	Short	I/A*		16
• Design new and improved catalysts	Medium	Short	I/A/G*		11
• Investigate potential for solvent substitution within a reaction process	Medium	Short	I/A/G*		8
• Investigate alternative synthetic reaction pathways	Medium	Short	I/A*		10
Data and Characterization					
• Develop improved methods of data acquisition and prediction	High	Short	I/A/G*		16
• Develop improved methods of structure-based data predictions	High	Short	I/A/G*		17
• Develop improved methods of data retrieval	Medium	Short	I/A/G*		8

Table 4: RECOMMENDATIONS OF THE WORKGROUP ON COMPUTER-BASED METHODS (continued)

Category	Priority[1]	Time-Frame	Who Does Research?	Federal Funding Needed?[2]	Priority Score[3]
Data and Characterization (continued)					
• Develop improved methods of toxicity data retrieval and prediction	Medium	Short	I/A/G*		8
• Develop process simulators that can be used in aqueous and mixed-phase systems	Medium	Short	I/A/G*		7
• Develop programs to facilitate selection of surrogate feedstocks	Medium	Short	I/A/G*		4

* I = Industry
A = Academia
G = Government

of consensus regarding the best way to get information out to the people who need it. Particularly important in this regard, the group thought, were efforts to coordinate software packages and to provide long-term maintenance of databases once they are developed.

In the area of decision-making tools, the workgroup had focused on programs that would facilitate the process of comparing one process design with another. Especially important in this regard is the development of tools that are useful in the retrofitting approach that characterizes most process design in this country. Unfortunately, many of the currently available programs assume that process design is starting from scratch, when in fact most efforts have considerably fewer degrees of freedom than these packages assume.

In its discussion of expanded process simulation, the group was concerned about what they referred to as "small-customer modules." The group was interested in promoting green processes in areas where financial backing for research and development is not readily available. As a leading example, membrane systems development was cited as almost exclusively the domain of very small and highly specialized firms. Because of this, major process simulation houses are unlikely to consider it cost-effective to build a generic membrane module and include it in a larger process simulation package. The group felt that federal funding in this area should be a very high priority, since it would go a long way toward providing engineers with ways of looking at alternative processes. Without small-customer modules, a process engineer has no way to evaluate the membrane system in comparison with a distillation column, for example.

Similarly, the group had felt it important to promote the development of dynamic process simulations to complement existing packages that focus on steady-state conditions. Often a company's biggest pollution problems are

associated with start-ups and shutdowns rather than steady-state operation of the facility.

The workgroup spent a great deal of time discussing computer-based tools for decision support, and a broad range of needs were identified. In particular, the group's recommendation regarding the need to investigate ways of incorporating life cycle assessment into process design was described. This is an especially important area since legislative initiatives are increasingly including language requiring life cycle assessments, yet there are very few tools that allow these assessments to be done on any kind of consistent or large scale. In addition, there is a fairly strong likelihood that the next round of amendments to the General Agreement on Trade and Tariffs (GATT) will include language similar to that which has begun to appear in domestic initiatives.

Regarding the need for tools that could be used in total cost assessment, the group had been concerned about the tendency of existing packages to include the costs of environmental compliance in the general category of overhead. More useful, it was concluded, would be tools that enable managers to look at environment-related expenses on a unit-by-unit or process-by-process basis, as well as tools that would associate the costs of waste management with specific streams instead of the facility as a whole. Using such tools, managers could then make decisions about process improvements from the perspective of knowing what cost savings could be expected from the adoption of specific benign processes.

Most of the workgroup's recommendations related to reaction engineering, and therefore echoed the needs expressed by other breakout workgroups. One exception was the Computer-Based Methods group's focus on solvent substitution within the reaction system rather than at the end-product production stage. By exploring ways of modifying the reaction system itself, it might be possible to

identify more benign or less energy-intensive alternatives earlier in the synthetic pathway.

One workshop participant (Sciance) commented that in developing new computer-based tools it will be important to assure that the packages developed are not user-hostile programs that can be run on only one type of equipment. While agreeing that computer-based tools are important and valuable, this participant urged that the programmers keep the end user in mind throughout their development efforts and that they define the universe of potential users as broadly as possible.

V. CLOSING REMARKS

At the conclusion of the workgroup presentations, Dr. Sikdar asked Dr. Robert Wellek of the National Science Foundation to speak briefly about his impressions of the workshop and the extent to which it had achieved the organizers' goals.

Dr. Wellek began by noting that, like most of those present, he had participated in quite a large number of workshops during his career. This workshop, he said, was certainly among the most important, in that it represented an attempt to actually build some of the partnerships among government, industry, and academia that people so often talk about but so seldom actually achieve.

Dr. Wellek commended workshop participants for the seriousness with which they had addressed the issues before them, and he noted that the Proceedings of the workshop would be very valuable to him and others at NSF. He described the current environment for research as the best and worst of times – the best of times in the sense that the Administration is focusing more on civilian technologies, but the worst of times in the sense that limited resources demand difficult tradeoffs among competing research needs. Dr. Wellek said that the justifications for federal funding provided by this workshop would give NSF and others important leads in preparing environmental research budgets for 1996 and 1997. He noted that the workshop had also provided him with contacts that would be useful farther down the line, as some of the suggested programs began to reach fruition.

Dr. Sikdar thanked Dr. Wellek for his Agency's support of the workshop and said that he, too, had been very impressed by the seriousness with which

participants had approached the task at hand. He noted that the Proceedings would also be useful to EPA as the Agency begins to move more fully into the area of environmental R&D in support of benign syntheses and manufacturing. Following a few announcements regarding the review process for the Proceedings document, the workshop was adjourned.

U.S. Environmental Protection Agency and
The National Science Foundation

Workshop on Green Syntheses and Processing in Chemical Manufacturing

Omni Netherland Plaza
Cincinnati, OH
July 12-13, 1994

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U.S. Environmental Protection Agency and
The National Science Foundation

Workshop on Green Syntheses and Processing in Chemical Manufacturing

Omni Netherland Plaza
Cincinnati, OH
July 12-13, 1994

Agenda

TUESDAY	JULY 12	
12:00 Noon	**Registration**	
1:00PM	**Welcome**	*Dr. Subhas Sikdar, U.S. EPA*
1:15PM	**Advanced Manufacturing**	*Dr. Joe Bordogna, National Science Foundation*
1:30PM	**Benign Organic Synthesis**	*Dr. James Bashkin, Washington University*
2:15PM	**Benign Biosynthesis**	*Dr. Jerome Schultz, University of Pittsburgh*
3:00PM	BREAK	
3:15PM	**Benign Engineering Approaches**	*Dr. Tom Sciance, DuPont*
4:00PM	**Computer-Based Methods**	*Dr. Peter Radecki, Michigan Technological University*
4:45PM	**Guidance on Workgroups**	*Ms. Trisha Hasch, Eastern Research Group, Inc.*
5:00PM	ADJOURN	

WEDNESDAY	JULY 13
8:00AM	**Concurrent Breakout Sessions**
10:00AM	BREAK
10:15AM	**Concurrent Breakout Sessions (continued)**
11:45AM	LUNCH
1:00PM	**Concurrent Breakout Sessions (continued)**
2:30PM	BREAK
2:45PM	**Review and Wrap-up Session**
4:30PM	ADJOURN

APPENDIX C

MINUTES OF INDIVIDUAL BREAKOUT GROUPS

Minutes of the Workgroup on Benign Organic Synthesis
Minutes of the Workgroup on Benign Biosynthesis
Minutes of the Workgroup on Benign Engineering Approaches
Minutes of the Workgroup on Computer-Based Methods

MINUTES OF THE
WORKGROUP ON BENIGN ORGANIC SYNTHESIS

The Workgroup on Benign Organic Synthesis was facilitated by P. Anastas of the U.S. EPA. T. Hasch of Eastern Research Group served as Chart Writer for the workgroup, while J. Glaser served as EPA Writer. Other members of the workgroup were:

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C. Burns
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M. Chu
U.S. EPA

T. Collins
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S. DeVito
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F. Stevenson
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To begin the session, the group agreed on a general process for identifying areas in which research to promote green synthesis is needed. During the first stage of discussion, it was agreed that participants would raise as many issues as occurred to them, including both very broad and very narrow topics. To promote consideration of research in both organic and inorganic processes, the workgroup elected to change its name to the Workgroup on Environmentally Benign Synthesis. Following a brainstorming session during which individual group members offered their suggestions for needed research, the group agreed to the following master list of recommendations:

- Provide academic scientists with a list of 250 chemical processes for which alternatives are needed from the perspective of pollution prevention and encourage academic scientists to identify additional opportunities for pollution prevention

- Expose students to the ideas that chemistry is not only a source of pollution but a source of pollution prevention and that responsible chemistry is creative chemistry; incorporate benign chemistry as a core tenet of academic curricula

- Develop robust homogeneous transition metal oxidants

- Clearly state a stable commitment to long-term research in synthetic chemistry

- Develop safer solvents to replace those currently used, or develop solventless systems

- Encourage selective clean oxidation based on molecular oxygen in bond-making processes in order to reduce the use of substitution reactions

- Investigate novel media and/or reaction systems to enhance the selectivity of chemical reactions

- Develop and promote solid-acid catalysts (heterogenizing processes)

- Develop new separation techniques aimed toward enhanced recovery of products

- Develop educational approaches to familiarize chemists with separations and processes of physical/chemical isolation

- Develop evaluative tools to assess the environmental/economic impact of synthetic methods at the bench and process scale

- Develop a means of long-term funding for programs in which scientists from different disciplines can collaborate to address key issues in research and education

- Develop databases or an information network on benign synthesis and develop indexing techniques that are user-friendly

- Conduct research on the synthesis of oxide-based catalysts for lean burn processes (automotive emissions)

- Promote special issues of journals to disseminate information about benign synthesis; promote the use of benign synthesis as a key word, and work with editorial boards to promote publication in this area

- Promote research on small-molecule biomimetic catalysts

- Provide a venue that fosters communication among scientists from different disciplines (e.g., societies, research-oriented workshops, sessions at ACS meetings, etc.)

- Develop catalysts capable of carrying out difficult reactions by employing multiple steps at a single site

- Develop functional models of enzymes

- Investigate methods of improving enantioselective synthetic methods, especially in the area of catalysis

- Investigate biocatalysis, including the mechanisms of enzymatic and microbiological transformations

- Promote the use of photochemistry and electrochemistry for benign synthesis

- Investigate the use of supercritical fluids for chemical and biocatalytic transformations

- Promote efforts in molecular design for advanced separation systems

- Design target molecules to preserve desired functions while mitigating toxicity through structural modifications or modification of physical/chemical properties

- Develop a functional-group understanding of health and environmental hazards

- Develop *in situ* or more benign analytic sensors/monitors
- Promote the implementation of benign methods in industry

- Educate the general public about environmentally benign chemistry and the importance of chemistry in solving environmental problems

- Promote benign reactor designs
- Promote environmentally benign synthesis
- Learn more about industrial synthetic processes
- Gain a better understanding of industrial processes that could benefit from environmentally benign alternatives
- Develop generic reagent-based benign strategies
- Use renewable feedstocks in place of non-renewable feedstocks
- Identify barriers to implementing environmentally benign processes

Once the master list of topics had been generated, workgroup members were asked to vote for the topics they thought should be given highest priority. Each workgroup member was given a total of 10 votes to spread among the nominated research topics as he or she saw fit. The group was not satisfied with the voting procedure, noting that some categories overlapped with one another and others could easily be broken into two or more subcategories. One workgroup member abstained from the voting process entirely, indicating that he thought these issues deserved more thoughtful deliberation than such a voting process could possibly allow.

Following this discussion, the group decided to divide its recommendations into several general categories. All recommendations regarding specific reaction steps or process improvements were grouped under the general category of Benign Reaction Design. Two other general categories were established for topics related to Education and Implementation. Two items that didn't seem to fit into any of these categories were given a category of their own (Benign Products).

A voting procedure was used to develop priority rankings for the topics in each of these four categories. For topics in the Benign Reaction Design category, workgroup members also discussed the timeframe for the proposed research, who should conduct the research, and whether federal funding is needed in each area. The group felt that all of the recommendations regarding Education and Implementation had significant potential for short-term returns. The two items in the Benign Products category were designated as medium-term undertakings.

At the conclusion of their deliberations, the group selected T. Collins of Carnegie Mellon University to present their findings to the workshop as a whole.

MINUTES OF THE WORKGROUP ON BENIGN BIOSYNTHESIS

The Workgroup on Benign Biosynthesis was co-facilitated by J. Frost of Michigan State University and P. Elankovan of the Michigan Biotechnology Institute. R. Brenner of the U.S. EPA served as Chart Writer for the workgroup, while C. Potter served as EPA Writer. Other members of the workgroup were:

S. Barnett
University of Rhode Island

D. Bishop
U.S. EPA

M. Bradford
AE Staley Manufacturing Company

D. Cameron
University of Wisconsin at Madison

R. Dobbs
U.S. EPA

D. Kompala
University of Colorado at Boulder

T. Leib
General Electric Research and Development

J. Schultz
University of Pittsburgh

M. Seibert
National Renewable Energy Laboratory

V. Vilker
National Institute of Standards and Technology

L. Webster
U.S. EPA

To begin the workgroup meeting, each member of the group introduced him- or herself and offered a brief description the area of his or her primary interest. Following a brainstorming session during which individual group members expressed their general views regarding areas of needed research, the group agreed to focus on research needs in four major areas:

- Feedstocks
- Pathway Engineering

- Reaction Engineering
- Processing

As the group discussed each of these areas, there was a great deal of attention to semantics; in general, group members wanted to identify as many options as possible without giving the impression that their list of topics was an exhaustive one. In addition, the group thought it important to provide specific examples for each general research need they had identified.

Under the general category of Feedstocks, the group developed the following recommendations:

- Research is needed on the use of renewable feedstocks for the production of chemicals. Feedstocks that might be explored in this regard include carbon dioxide and methane, lignin, carbohydrates, mixed organic wastes, industrial and municipal sludge, and lipids.
- Research is needed on customizing feedstocks to produce chemicals. In this context, customization includes genetic as well as chemical/physical manipulation of feedstock-producing lifeforms.
- Research is needed to explore the use of non-carbon-based feedstocks in biosynthesis. Non-carbon-based feedstocks might include nitrogen-based compounds (fertilizer, nitrogen-containing chemicals), minerals (ceramics, metals), non-metals (sulfur- and phosphorus-containing chemicals), and water (hydrogen and oxygen).

Under the general category of Pathway Engineering, the group developed the following recommendations:

- Research is needed in the genetic modification of lifeforms to produce chemicals. Attributes that might be candidates for such modification include selectivity, yield, tolerance, productivity, titer, and robustness.

- Research is needed to expand and utilize biocatalyst diversity. Among the different types of biocatalysts that could be investigated are organisms, enzymes, catalytic antibodies, genes, and ribozymes.

- Research is needed to develop tools for pathway engineering. Examples of needed tools include pathway modeling programs, databases (gene pool, sequence, thermodynamics), and tools that allow an integration of thermodynamic, kinetic, stoichiometric, and molecular biological information.

Under the general category of Reaction Engineering, the group developed the following recommendations:

- Research is needed in stabilization of enzymes. In this context, factors that contribute to enzyme stability are temperature, solvents, pH, pressure, and electrolytes.

- Research is needed in electron transfer methods. Examples of such methods include cofactor regeneration, photochemistry, and electrochemistry.

- Research is needed in improving the productivity and selectivity of biocatalytic conversions. Approaches that might prove to be of benefit in this regard include phase-transfer catalysis, non-aqueous media, supercritical fluids, biocatalyst immobilization, post-translational biocatalyst modification, and substrate/product transport.

Under the general category of Processing, the group developed the following recommendations:

- Databases need to be established. Examples include databases dealing with the physical/chemical properties of aqueous and aqueous/ organic systems and databases dealing with process alternatives.

- Research is needed on methods of improved separation and purification of chemicals from biosynthetic processes. Problems that need to be addressed in this area include dilute solutions, aqueous solutions, trace contaminants, multi-phase systems, and waste (salts, solvents, adsorbants).

- Research is needed on reactor design and modelling. Examples of needed work in this area include process synthesis/integration, process design and modelling, integration of biocatalytic and abiotic catalytic methodologies, databases for process alternatives, and sensors/controls.

When the group completed its recommendations in each of these four areas, there was not time for discussion of the relative priority, timeframe, research sponsor, or need for federal funding for individual research initiatives. The group agreed to complete this portion of its work by fax polling after the workshop was over. The group selected D. Cameron of the University of Wisconsin at Madison to present their findings to the workshop as a whole.

MINUTES OF THE
WORKGROUP ON BENIGN ENGINEERING APPROACHES

The Workgroup on Benign Engineering Approaches was facilitated by A. Ford of Lamar University. Ford had to leave the meeting for approximately an hour, during which time C. Sciance of the DuPont Experimental Station served as facilitator. J. Hermann of EPA served as Chart Writer for the workgroup, while T. Harten served as EPA Writer. Other members of the workgroup were:

M. Anand
Air Products & Chemicals, Inc.

P. Biswas
University of Cincinnati

G. Brown
Union Carbide

T. Evans
The Dow Chemical Company

R. Fisher
Cargill, Inc.

T. Foust
U.S. Department of Energy

G. Howell
U.S. EPA

J. Hunt
National Science Foundation

K. Kar
U.S. EPA

P. Kokitkar
Michigan State University

A. Lee
Naional Institute of Standards and Technology

R. Mather
Hoechst Celanese Corporation

H. McGee
Virginia Commonwealth University

C. Nassaralla
Michigan Technological University

E. Nauman
Rensselaer Polytechnic Institute

W. Schmeal
Electric Power Research Institute

K. Schultz
Sandia National Laboratories

J. Watson
Oak Ridge National Laboratory

R. Wellek
National Science Foundation

To begin the session, Ford suggested that the group go once around the table, allowing each workgroup member to propose a research topic. Because of the large size of the group, it was agreed that going once around the table would be all that time allowed. Following discussion of each issue as it was raised, the group agreed to the following distillation of the topics that had been discussed:

- Enzymatic catalysts (including the use of catalysts to obtain higher product concentrations, issues related to catalyst attrition, the use of catalysts in separation processes, and the development of non-toxic catalysts)
- Freezing processes and melt crystallizations, particularly as they relate to organic separations
- Separation processes that avoid phase changes
- Reaction design to minimize the need for separations
- Microwave- or radiation-enhanced reactions
- Confinement techniques
- Control of abnormal processes
- Redesign of valves and fittings
- Remote sensors (especially as related to reducing the cost of monitoring critical emissions and to increasing the use of area-wide monitoring strategies)
- Unit operations (including physical separations, better modeling of unit operations, and methods for separating materials of value from wastes)
- Methods of water removal (especially as they relate to the dilute systems characteristic of biotechnologic processes)
- Membrane technology (including the development of new polymers)
- Hybrid unit operations

- Application of pinch technology to environmental aspects of process development and evaluation
- Gas phase/aerosol processing
- Disposal of bioprocess wastes (including both genetic and non-genetic techniques)
- Fluidized bed combustors
- Better understanding of emissions
- High-temperature combustion chemistry
- Adding value to solid wastes (i.e., fruitful use versus disposal)
- Non-chemical sources for electron exchange
- Supercritical fluids as solvents
- Renewable feedstocks (including methane coupling)
- Partial oxidation of wastes to syngas
- New technology approaches that start from the ground up

Just before the lunch break, workgroup members were asked to vote for those topics they considered of highest priority. Each workgroup member was given a total of five votes to spread among the nominated research topics as he or she saw fit.

After the lunch break, one person suggested that, in addition to the technology issues the group had identified, it might be good to try to capture the part of the morning discussion that had had to do with what he described as "front-end" issues cutting across all of the various technology areas. As examples of such issues, he listed the following:

- Defining exactly what is meant by benign technology
- Developing life cycle tools that could be used in making and defending process decisions
- Expanding efforts in benign synthesis to involve additional players, such as small companies, companies with related processes, and suppliers
- Promoting effective cooperative efforts
- Promoting the concept of benign chemistry as part of the professional education of chemists and chemical engineers

Other group members agreed that these issues were important and should be part of the workgroup's recommendations.

Following the voting on individual research topics, some members of the workgroup expressed concern about the extent to which overlaps among the topics might obfuscate the results of the voting process. To organize the topics in a more manageable form, the workgroup developed seven general categories, as follows:

- Unit Operations
- Sensors
- Containment
- Catalysis
- Process Synthesis
- Combustion
- By-Products

To develop proactive statements about the research recommended in each of these general areas, the workgroup broke into smaller teams, one addressing each of these seven areas and one to formulate the group's recommendations regarding front-end issues. One member from each team was selected to present that team's findings to the workshop as a whole.

MINUTES OF THE
WORKGROUP ON COMPUTER-BASED METHODS

The Workgroup on Computer-Based Methods was facilitated by C. Brunner of the U.S. EPA. D. Timberlake of EPA served as Chart Writer for the workgroup, while J. Spooner served as EPA Writer. Other members of the workgroup were:

H. Bostian
U.S. EPA

S. Ford
U.S. EPA

D. Meyer
The C.W. Nofsinger Company

P. Radecki
Michigan Technological University

G. Rosasco
National Institute of Standards and Technology

To set a framework for the group's discussion, Bostian described several past efforts related to process simulation that had been jointly sponsored by EPA and other federal agencies. Workgroup participants were given copies of the report of a December, 1992, Workshop on Environmental Considerations in Process Design and Simulation, as well as the minutes of meetings of a Process Simulation Workgroup that had grown out of that workshop. To the extent possible, it would be good to avoid duplicating these earlier efforts.

Brunner presented a brief outline of the procedure that would be followed by the workgroup. He indicated that he would go around the table twice, soliciting ideas from workgroup members, after which the floor would be opened for additional discussion or recommendations. Regarding the issue of whether to focus on broader or more specific recommendations for research, the group decided that it would probably be best to keep their recommendations relatively broad.

During the first round of suggestions, the following issues were raised for consideration:

- Maintenance of software and databases
- Integration of energy and mass transfer networks
- Process design, especially from the perspective of retrofitting
- Methods for addressing environmental concerns at the design concept stage
- Artificial intelligence for process simulation
- Methods for overcoming obstacles to information transfer and assuring that the information engineers need for process design is available to them
- Guidelines for making process design decisions

During the second round, the following issues were raised:

- Methods for performing environmental impact evaluation
- Development of dynamic process simulators to deal with start-ups, shutdowns, upsets, etc.
- Regulatory forecasting
- Small-customer modules

Brunner noted that a number of issues had been suggested on the cards submitted by workshop participants serving on other workgroups. Among these, he listed the following:

- Reaction path synthesis
- Surrogate selection

- Total cost assessment
- The tendency for new development to focus on user interface features rather than more robust modelling
- Improved optimization
- The observation that simulators tend to be good accounting devices but not good predictors, and that the better reactor models are proprietary systems not included in commercially available simulators
- Methods to address the formidable chemical engineering problems that often occur during process scale-up
- Methods of predicting the formation of trace contaminants
- Expert guidance/heuristics for pollution prevention design
- Catalyst design
- Aqueous systems/electrolytes

Following the morning break, workgroup members offered additional topics for research:

- Uncertainty analysis guidance similar to expert guidance in flowsheet building
- Stochastic modeling
- Data acquisition/predictions in a laboratory setting
- Data retrieval from proprietary sources (e.g., vendors, operating companies)
- Chemical structure-based data prediction
- Incorporation of life cycle assessment (which may be a long-term need)
- Toxicity data retrieval and prediction

- Integration of product-based methods (e.g., solvent substitution, materials selection)
- Application of industrial ecology analysis

To facilitate consideration of this broad range of topics, the workgroup attempted to devise categories that would subsume multiple research topics. Although there was some difficulty in coming up with names for these categories, the group eventually settled on the following six categories:

- Integrating Activities
- Decision-Making Tools
- Expanded Process Simulation
- Decision Support
- Reaction Engineering
- Data and Characterization

Regarding the timeframe within which a significant impact of the recommended research could be expected, the group agreed that all of the items they had discussed were ones that had the potential to produce such an impact in the short-term (i.e., within 5 years). There was a reluctance among some group members to place a specific timeframe on each item, since there was some fear that items identified as longer-term needs might be put off.

The group also had some difficulty in assigning the various tasks to industry, government, and/or academia. In general, however, they felt that industry and academia should be involved in all of these efforts, while government should only be involved in some. Government participation was considered especially important for topics like regulatory forecasting, which involve issues

where the government clearly plays an important if not determinative role. Bostian made a plea that the group not suggest that government funding is needed for all of its recommendations, and Brunner suggested that government funding be requested only where it is definitely needed.

Following the lunch break, a voting procedure was used to rank the topics in each category in terms of their relative priority. In this procedure, each workgroup member was allotted 10 votes per category, no more than 6 of which could be allocated to a single research topic. One workgroup member abstained from the voting due to a lack of adequate background in computer-based methods.

When the voting was complete, P. Radecki was selected to present the workgroup's recommendations to the workshop as a whole.

*U.S. GOVERNMENT PRINTING OFFICE:1994-550-001/00173