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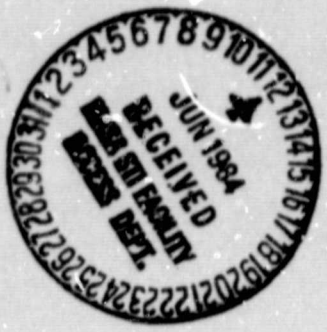

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UC-S1a & UC-61d

ECUT
ENERGY CONVERSION AND UTILIZATION TECHNOLOGIES PROGRAM

Industry, University, and Research Institute Interest in the U.S. Department of Energy ECUT Biocatalysis Research Activity

R.E. Wilcox

November 1, 1983

Sponsored by:
Energy Conversion and Utilization Technologies Division
Office of Energy Systems Research
U.S. Department of Energy

Through an Agreement with
National Aeronautics and Space Administration

Prepared by:
Jet Propulsion Laboratory
California Institute of Technology
Pasadena, California 91109

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The Biocatalysis Research Activity is managed by the Jet Propulsion Laboratory, California Institute of Technology, for the United States Department of Energy through an agreement with the National Aeronautics and Space Administration (NASA Task RE-152, Amendment 307; DOE Interagency Agreement DE-AI01-81CS66001).

The Biocatalysis Research Activity focuses on resolving the major technical barriers that impede the potential use of biologically-facilitated continuous chemical production processes.

ABSTRACT

This report presents the results of a Research Opportunity Notice (RON) disseminated by the Jet Propulsion Laboratory for the U.S. Department of Energy (DOE) Energy Conversion and Utilization Technologies (ECUT) Program's Biocatalysis Research Activity. The RON was issued in late April of 1983 and solicited expressions of interest from petrochemical and chemical companies, bioengineering firms, biochemical engineering consultants, private research laboratories, and universities for participating in a federal research program to investigate potential applications of biotechnology in producing chemicals.

The RON results indicate that broad interest exists within the nation's industry, universities, and research institutes for the Activity and its planned research and development program. Both large firms (e.g., Allied, American Cyanamid, Bechtel, Celanese, Genentech, Genex, Martin Marietta, and UOP) and small firms expressed interest in responding to future Request for Proposals (RFPs) issued by the Activity. The specific interest areas of the RON respondents varied widely. For example, biotechnology firms and firms specializing in contracted research seem to have a distinct preference for investigating the technical issues most relevant to near-term (high-value/low-volume) biocatalysis applications. Conversely, the engineering firms that design and build chemical plants expressed strongest interest in the issues most relevant to the longer-term, low-value/high-volume applications of biocatalysis. The various respondents' distinct research preferences emphasize the need for the Activity's mission-oriented strategy that coordinates research and researchers to achieve the technical feasibility of biocatalyzed continuous chemical production processes.

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SECTION I

INTRODUCTION

A. BACKGROUND

In November 1982, the Guidance and Evaluation Panel for the U.S. Department of Energy's Energy Conversion and Utilization Technologies (ECUT) Program's Biocatalysis Research Activity recommended that the Activity solicit interest from private-sector firms and universities for investigating potential applications of biotechnology in producing chemicals. In response to this recommendation, the California Institute of Technology's Jet Propulsion Laboratory (JPL), the managing center for the Biocatalysis Research Activity, drafted a Research Opportunity Notice (RON). After a review by the Guidance and Evaluation Panel, the RON was published in the Commerce Business Daily (CBD) on April 27, 1983. (See Appendix A.) Additionally, JPL sent copies of the RON to two groups of potential respondents: (1) over 60 U.S. companies currently involved in both biotechnology research and chemical markets (as listed in the November/December 1982 issue of Genetic Engineering News) and (2) U.S. universities with established reputations in technical areas relevant to the Biocatalysis Research Activity. This report summarizes and discusses the response to the RON.

B. PURPOSE OF THE RON

The RON has served three purposes for the Biocatalysis Research Activity. First, it has provided a means for identifying the subset of technical issues that potential researchers currently have the greatest interest in and capability of addressing. Second, it has stimulated broad interest throughout industry, academia, and research institutions in proposing innovative research activities in response to forthcoming Requests for Proposals (RFPs). Third, it has helped the Activity in generating a source list of potential researchers.

C. PREPARATION OF THE RON

The major effort in drafting the RON was definition of the generic technical issues associated with producing chemicals biocatalytically. A list of issues generated by the Activity's Guidance and Evaluation Panel at their November 1982 meeting was used as the starting point. Through a series of in-house and panel member reviews, JPL condensed the original list to nine technical issues (Table 1-1). A tenth issue covering "other research areas of interest" was added.

These technical issues encompass the four major categories of applied research and exploratory development under the purview of the Biocatalysis Research Activity: (1) biocatalysis by genetically-improved live organisms, (2) catalysis by biologically and chemically derived molecules, (3) process and reactor vessel design, and (4) product separation.

Table 1-1. RON Technical Issues

(1)	Approaches for product release, separation, and recovery.
(2)	Advances in microbiology and recombinant DNA techniques for genomic stability, resistance to harsh environmental conditions, and enhanced productivity.
(3)	Significance of feedstock selection in process performance.
(4)	Combining productivity/efficiency improvements from biological and chemical catalytic processes.
(5)	New processes involving multiple species.
(6)	Advanced concepts for control and regulation of biological processes.
(7)	Methods to extend the useful life of enzymes.
(8)	Control of secondary metabolite production and continuous fermentations.
(9)	Process and reactor design and its relationship to productivity and energy efficiency.
(10)	Other research areas consistent with the approach of the Activity.

SECTION II

RON RESULTS

A. FINDINGS

1. Respondent Categories and Overall Geographical Distribution

The 67 responses to the RON demonstrated a broad interest in the Biocatalysis Research Activity, both in terms of the industry/academia mix and the geographical distribution of responses.[1]

Responses were separated into five categories: (1) Research and Development (R&D) Industry (e.g., biotechnology companies and firms specializing in contracted R&D); (2) Chemical Processing Industry (CPI) (e.g., producers of commodity, specialty, and fine chemicals); (3) Engineering Firms (e.g., firms providing architectural and engineering services to the CPI); (4) Universities; and (5) Research Institutes (e.g., large non-profit research laboratories). As shown in Table 2-1, R&D Industry firms formed the single largest group (43%) of respondents, followed by universities (25%), CPI firms (12%), research institutes (10%), and engineering firms (9%). Overall, private-sector firms constituted the majority of responses with 64%, while universities and research institutes accounted for the remaining 36%.

As shown in Figure 2-1, responses came from 25 different states. All regions of the country are represented, except the northern Rocky Mountain and northern Great Plains states, Alaska, and Hawaii. In terms of the location of the U.S. chemical industry, all the states with major centers that produce both basic and intermediate chemicals (Ref. 1) had respondents. Additionally, 20 of the 27 states that shipped more than $500 million worth of chemicals in 1975 (Ref. 2) had respondents.

2. Overview of Interest in Technical Issues

In general, respondents indicated broad interest in all ten technical issues. As shown in Table 2-2, 34% to 55% of all respondents expressed interest in each issue. The three technical issues Advanced control and regulation concepts, Product release, separation and recovery, and Advances in microbiology and recombinant DNA (rDNA) techniques received the highest proportion (55%) of respondents' expressions of interest (Table 2-3). Four other issues received indications of interest from roughly 50% of the respondents: Process and reactor design (52%), Secondary metabolite and continuous fermentation control (51%), New processes (49%), and Hybrid chemical/biological processes (48%). The remaining technical issues received

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[1] As discussed more fully in Section III, the results discussed in this report indicate the interests of only the RON respondents. A more concerted effort (i.e., survey) would be required to extend the results to the nation's entire industry.

Table 2-1. Categories of RON Respondents

Category	Number of Responses	% of All Responses
R&D Industry	29	43
Universities	17[a]	25
CPI Firms	8[b]	12
Research Institutes	7	10
Engineering Firms	6	9
Total	67	100[c]

[a] Fifteen universities responded. Two different departments within each of two universities responded.

[b] Seven CPI firms responded. Two different subsidiaries of the same company responded.

[c] Column entries do not total 100 because of rounding error.

fewer indications of interest, primarily from the R&D Industry category: Methods to extend enzyme life (39%), Feedstock impacts (37%), and Other (34%).

The overall interest of respondents in the set of technical issues varied across respondent categories. Research Institutes had the broadest interest, with an average of 73% of the respondents expressing interest in each technical issue. The remaining categories, as shown in Table 2-4, had lower average expressions of interest, ranging from 54% for CPI firms to 35% for universities.

Of all the respondent categories, the "issues of interest" of R&D Industry firms and universities most closely paralleled each other. (The correlation coefficient between the two groups' expressions of interest equaled 0.48 -- statistically significant at the 0.10 level.) This may reflect the close ties between the two groups, which have formed as university researchers join or establish R&D Industry-type firms.

CPI firms and Engineering firms tended to have opposing levels of interest in the same technical issues. Specifically, Engineering firms expressed no interest in the two issues that received the highest level of interest from CPI firms: Advances in microbiology and rDNA techniques and Methods to extend enzyme life. (The correlation coefficient between the two groups' expressions of interest equals -0.50 -- statistically significant at the 0.10 level.) This apparent inverse relationship may indicate that Engineering firms' and CPI firms' R&D interests complement each other.

Total = 67

Figure 2-1. Geographical Distribution of RON Responses

Table 2-2. RON Technical Issues of Interest[a]

Technical Issues	R&D Industry	Universities	CPI	Research Institutes	Engineering Firms	TOTAL (% of all responses)
(1) Product release, separation, and recovery	18	6	5	5	3	37 (55)
(2) Advances in microbiology and rDNA techniques	18	7	6	6	0	37 (55)
(3) Feedstock impacts	9	3	3	7	3	25 (37)
(4) Hybrid chemical/ biological processes	16	5	3	5	3	32 (48)
(5) New processes	18	6	3	6	0	33 (49)
(6) Advanced control and regulation concepts	17	7	5	5	3	37 (55)
(7) Methods to extend enzyme life	11	5	6	4	0	26 (39)
(8) Secondary metabolite and continuous fermentation control	15	7	4	6	2	34 (51)
(9) Process and reactor design	13	9	3	4	6	35 (52)
(10) Other	8	5	5	3	2	23 (34)

[a]See Table 1-1 for complete definition of technical issues.

Table 2-3. Ranking of RON Technical Issues[a]

Proportion of Responses, %	Rank	Issue
55	1	Advanced control and regulation concepts
55	2	Product release, separation, and recovery
55	3	Advances in microbiology and rDNA techniques
52	4	Process and reactor design
51	5	Secondary metabolite and continuous fermentation control
49	6	New processes
48	7	Hybrid chemical/biological processes
39	8	Methods to extend enzyme life
37	9	Feedstock impacts
34	10	Other

[a]Rankings were based on the proportion of all respondents expressing interest in each issue. Issues with equal proportions of respondents were ranked according to a measure of broad-based interest (i.e., the standard deviation of the proportion of respondents in each category expressing interest in each issue -- level of "broad-based interest" being inversely related to the standard deviation). For example, 55% of all respondents expressed interest in issues 1, 2, and 6 in Table 1-2; however, in terms of broad-based interest across categories, these three issues were ranked 6, 1, and 2.

3. Detailed Description of Responses

a. R&D Industry. With 43% of all responses, R&D Industry firms constituted the largest group of RON respondents. Table 2-5 lists the respondents in this category. As shown in Figure 2-2, the geographical distribution of R&D Industry firms paralleled the overall distribution of RON responses except that no R&D Industry responses came from any Gulf Coast state.

R&D Industry expressions of interest in the various technical issues ranged from 28% to 62% of respondents (Table 2-6). Four issues received

Table 2-4. Average Interest in Technical Issues

Respondent Category	Average Proportion of Respondents Expressing Interest, %
Research Institutes	73
CPI Firms	54
R&D Industry	50
Engineering Firms	37
Universities	35

Table 2-5. R&D Industry Respondents to the RON

Advanced Mineral Technologies
Albany International Research Company
AMGen
Atlantic Research Corporation
Bend Research, Incorporated
Bethesda Research Laboratories
Bioassay Systems Corporation
BioChem Technology, Incorporated
BioInformation Associates
BioTechnica International, Incorporated
Chemapec Incorporated
Codon
Covalent Associates, Incorporated
CPAC, Incorporated
EIC Laboratories, Incorporated
Dynatech R/D Corporation
Film Tec Corporation
Genentech, Incorporated
General Environmental Science
Genetics Diagnostics Corporation
Genex Corporation
Incell Corporation
Ingene, Incorporated
IPRI, Incorporated
Lee Biomolecular Research Laboratories
Native Plants, Incorporated
Polybac Corporation
Synergen
Syntro Corporation

Total = 29

Figure 2-2. Geographical Distribution of R&D Industry Responses

Table 2-6. R&D Industry RON Respondents' Level of Interest in Technical Issues

Proportion of Respondents Indicating Interest, %	Rank	Technical Issue
62	Group 1 (highest)	- Product release, separation, and recovery
62		- Advances in microbiology and rDNA techniques
62		- New processes
62		- Advanced control and regulation concepts
55	Group 2	- Hybrid chemical/biological processes
55		- Secondary metabolite and continuous fermentation control
45		- Process and reactor design
38	Group 3 (lowest)	- Methods to extend enzyme life
31		- Feedstock impacts
28		- Other

the highest level of interest: Product release, separation, and recovery, Advances in microbiology and rDNA techniques, New processes, and Advanced control and regulation concepts. Significantly, Feedstock impacts received the lowest level of interest, which may suggest that a majority of the R&D Industry respondents may want to focus their attention on high-value/low-volume specialty chemicals where feedstock cost and impact on process performance will not significantly influence product profitability in the near term.

b. Universities. Universities made up the second largest group of RON respondents with 25% of all responses. As shown in Table 2-7, various types of academic departments constituted the group of respondents in this category. The geographical distribution of University respondents resembles that of the R&D Industry category, except that Universities had fewer southwestern state respondents and more south Atlantic state respondents. (See Figure 2-3.)

Universities' level of interest in any given technical issue fell below the average level expressed by RON respondents overall. Also, unlike any of the other respondent categories, Universities had only one technical issue (Process reactor design) designated an area of interest by 50% or more of its respondents. (See Table 2-8.) These results suggest that Universities

Table 2-7. University Respondents to the RON

Cornell University - School of Chemical Engineering
Duke University - Department of Chemistry
University of California, Berkeley - Department of Chemical Engineering
University of Florida - Institute of Food and Agricultural Science
University of Iowa - College of Pharmacy
University of Iowa - Department of Microbiology
Lehigh University - Biotechnology Research Center
Massachusetts Institute of Technology - Department of Chemical Engineering
Massachusetts Institute of Technology - Dept. of Nutrition and Food Service
Michigan State University - Department of Chemical Engineering
University of Minnesota - Department of Microbiology
North Carolina State University - Department of Food Science
University of Rochester - Department of Microbiology
Rutgers University - Department of Chemical and Biochemical Engineering
University of South Carolina, Columbia - Department of Biology
University of Southern California - Department of Biological Sciences
University of Virginia - Department of Chemical Engineering

(consistent with their variety of academic departments) are both more diversified as a group and more selective individually than the other RON respondents.

c. CPI. As shown in Table 2-9, three of the United States' largest chemical producers (Allied, American Cyanamid, and Celanese) responded to the RON. In just the first quarter of 1983, the combined sales of these three corporations exceeded $4 billion (Ref. 3). The geographical location of these firms and the other CPI RON respondents centered on the midwestern and northeastern states (Figure 2-4). These states, as mentioned earlier, include some of the country's leading chemical production centers.

Second only to Research Institute respondents, CPI firms expressed the broadest interest in the various technical issues. Advances in microbiology and rDNA techniques and Methods to extend enzyme life received CPI firms' highest level of interest (Table 2-10). Four issues received this group's lowest level of interest: Feedstock impacts, Hybrid chemical/biological processes, New processes, and Process reactor design. Similar to other RON respondents, the CPI respondents' high level of interest in advanced microbiology coupled with their lower level of interest in feedstock impacts suggests a possible bias towards investigating high-value/low-volume products.

Total = 17

Figure 2-3. Geographical Distribution of University Responses

Table 2-8. University RON Respondents' Level of Interest in Technical Issues

Proportion of Respondents Indicating Interest, %	Rank	Technical Issue
53	Group 1 (highest)	- Process and reactor design
41	Group 2	- Advances in microbiology and rDNA techniques
41		- Advanced control and regulation concepts
41		- Secondary metabolite and continuous fermentation control
35		- Product release, separation, and recovery
35		- New processes
29		- Hybrid chemical/biological processes
29		- Methods to extend enzyme life
29		- Other
18	Group 3 (lowest)	- Feedstock impacts

d. Research Institutes. Seven of the United States' major non-profit research institutes responded to the RON. (See Table 2-11.) As shown in Figure 2-5, the geographical location of these respondents parallels the overall distribution of RON responses fairly closely.

Research Institute respondents had the broadest level of interest in the various technical issues (Table 2-12). With the exception of Other, all the technical issues received expressions of interest from 57% or more of these respondents. In stark contrast to all the other categories of RON respondents, 100% of the Research Institute respondents expressed interest in Feedstock impacts. They also expressed high interest in Advances in microbiology and rDNA techniques, New processes, and Secondary metabolite and continuous fermentation control. Methods to extend enzyme life, Process and reactor design, and Other received the lowest relative level of interest.

e. Engineering Firms. Six Engineering firms, located primarily in the Northeast, responded to the RON. (See Table 2-13 and Figure 2-6.)

Figure 2-4. Geographical Distribution of CPI Firms' Responses

Table 2-9. CPI Respondents to the RON

Allied Corporation
American Cyanamid Company - Stamford Research Laboratories
American Cyanamid Company - Medical Research Division
Celanese Research Company
Martin Marietta Laboratories
Lifeline Biologicals, Incorporated
Owens-Illinois
UOP, Incorporated

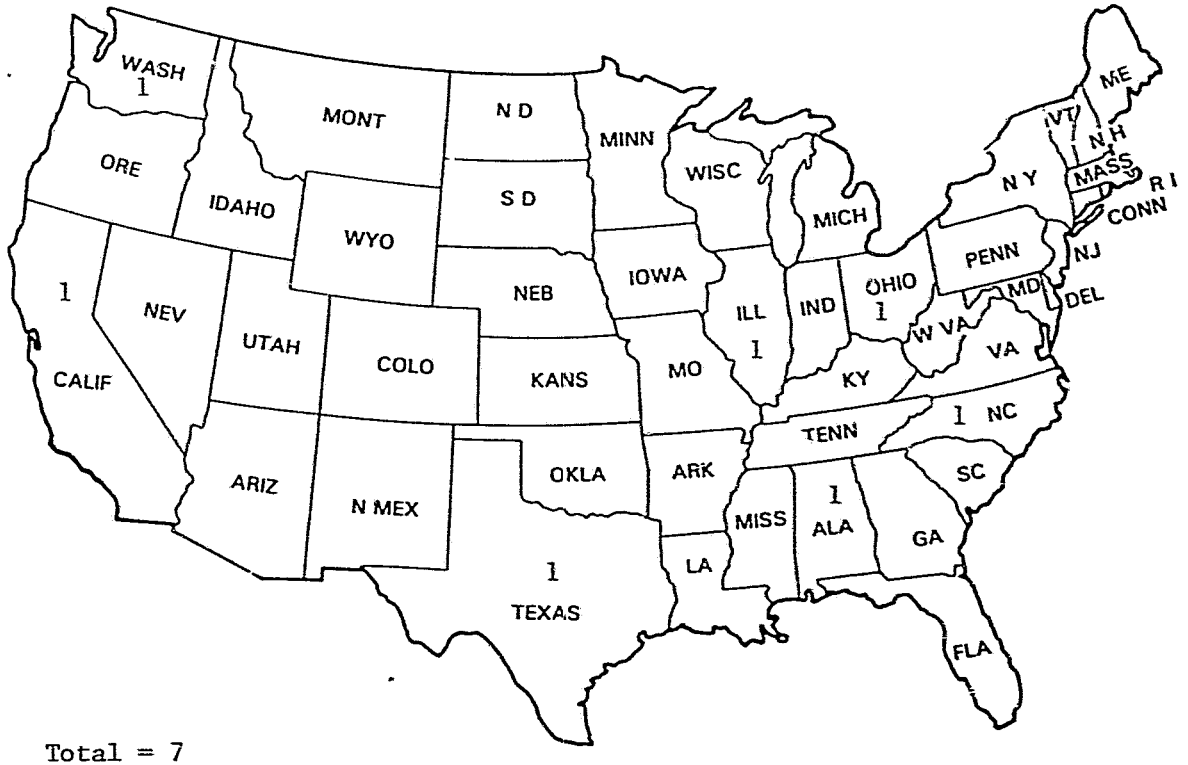
Table 2-10. CPI Industry RON Respondents' Level of Interest in Technical Issues

Proportion of Respondents Indicating Interest, %	Rank	Technical Issue
75	Group 1 (highest)	- Advances in microbiology and rDNA technology
75		- Methods to extend enzyme life
63	Group 2	- Product release, separation, and recovery
63		- Advanced control and regulation concepts
63		- Other
50		- Secondary metabolite and continuous fermentation control
38	Group 3 (lowest)	- Feedstock impacts
38		- Hybrid chemical/biological processes
38		- New processes
38		- Process and reactor design

Table 2-11. Research Institute Respondents to the RON

Battelle Columbus Laboratories
Battelle Pacific Northwest Laboratories
Institute of Gas Technology
Research Triangle Institute
Southern Research Institute
Southwest Research Institute
SRI International

Engineering firm respondents did not express broad interest in the technical issues. Uniformly, they all indicated interest in Process and reactor design while expressing no interest in Advances in microbiology and rDNA techniques, New processes, and Methods to extend enzyme life (Table 2-14. This dichotomy suggests that engineering firms' interests may focus on applying their conventional chemical processes background to new biocatalyzed processes. Similarly, this may also indicate an interest in investigating low-value/high-volume biocatalyzed chemicals.



Total = 7

Figure 2-5. Geographical Distribution of Research Institutes' Responses

Table 2-12. Research Institute RON Respondents' Level of Interest in Technical Issues

Proportion of Respondents Indicating Interest, %	Rank	Technical Issue
100	Group 1 (highest)	- Feedstock impacts
86		- Advances in microbiology and rDNA techniques
86		- New processes
86		- Secondary metabolite and continuous fermentation control
71	Group 2	- Product release, separation, and recovery
71		- Hybrid chemical/biological processes
71		- Advanced control and regulation concepts
57	Group 3 (lowest)	- Methods to extend enzyme life
57		- Process and reactor designs
43		- Other

Table 2-13. Engineering Firm Respondents to the RON

Bechtel Group, Incorporated
Carltech Associates, Incorporated
Crawford and Russel, Incorporated
Foster-Miller, Incorporated
Randers Engineering, Incorporated
Sysochem Engineering

Figure 2-6. Geographical Distribution of Engineering Firms' Responses

Table 2-14. Engineering Firm RON Respondents' Level of Interest in Technical Issues

Proportion of Respondents Indicating Interest, %	Rank	Technical Issue
100	Group 1 (highest)	- Process and reactor design
50	Group 2	- Product release, separation, and recovery
50		- Feedstock impacts
50		- Hybrid chemical/biological processes
50		- Advanced control and regulation concepts
33		- Secondary metabolite and continuous fermentation control
33		- Other
0	Group 3 (lowest)	- Advances in microbiology and rDNA techniques
0		- New processes
0		- Methods to extend enzyme life

SECTION III

POLICY IMPLICATIONS

The RON responses provide some useful information for developing programmatic and procurement strategies for the Biocatalysis Research Activity. This section presents the conclusions drawn from the analysis of RON results in Section II and discusses their ramifications for defining the "mix" of research subcontractors and the types and time-phasing of research supported by the Activity.

A. CONCLUSIONS OF THE RON IMPLEMENTATION

1. Scope of Ron Technical Issues

The technical issues contained in the RON appear to have covered the range of respondents' research interests. As evidence for this, the issue Other areas of research relevant to the Biocatalysis Research Activity received the lowest level of interest from respondents. This suggests that the major research areas of interest were subsumed by the nine RON technical issues.

2. Value of Direct Solicitation of Responses

As mentioned in Section I, JPL's active solicitation of interest from R&D Industry firms and Universities did increase the RON responses from this group. The fact that JPL directly invited responses probably had less to do with the eventual increased level of responses than the fact that many firms and universities do not regularly review CBD notices. In any case, because some CPI and Engineering firms with capabilities relevant to the Biocatalysis Research Activity also may not regularly consult the CBD, the Activity should identify and then send copies of forthcoming RFPs to these firms. Alternatively, the Activity could send copies of the RON to these firms prior to release of an RFP, and on the basis of responses received decide which firms would want to receive the RFP. Awareness of the Activity and interest in submitting proposals might also be increased by advertising the pending release of an RFP in Chemical and Engineering News.

3. Validity and Reliability of RON Results

The results and conclusions drawn from the RON responses might be criticized on the basis that they did not come from either a random selection or a complete survey of potential respondents. However, the fact that the RON was published in the CBD mitigates this potential criticism.

The CBD is one of the primary and most widely known publications for federal government advertising for research and development sources. Because of this, the firms and institutions that subscribe to the CBD represent a close proxy for the population of likely near-term participants in a federal

program. Because near-term competitive government R&D procurements will most likely go to this group, DOE/ECUT should pay close attention to the perspectives and interest expressed by this group -- especially if DOE/ECUT wants both to encourage R&D cost-sharing and to build interest in the long-term objectives of the Activity.

B. IMPLICATIONS OF THE RON RESULTS FOR DEVELOPING PROGRAMMATIC STRATEGY

1. Comparisons with the National Science Foundation

The RON results highlight the need for the DOE/ECUT Biocatalysis Research Activity. The ten technical issues used in the RON comprise the scope of work for the Activity. However, research interest in the various technical issues varies both within and between different respondent categories. Only by following a mission-oriented strategy that coordinates research and researchers in these ten areas can the Activity establish the technical feasibility of biocatalyzed chemical production processes in a continuous mode.

A comparison of the programmatic approaches of the Activity and the National Science Foundation helps explain why the Activity must stress an integrated effort to accomplish this objective.

The National Science Foundation (NSF), because of its focus on basic research, does not follow detailed mission objectives in deciding whether to fund research proposals. NSF also does not attempt to coordinate its ongoing research to meet specific technical objectives. Besides the Division of Industrial Science and Technological Innovation (where biotechnology is not a major focus), NSF does not actively involve or encourage industry participation in its funded research. While it fosters technology transfer from universities to industry in a broad sense, it does not focus on transferring specific research results to specific industries. These attributes do not constitute an indictment of NSF but instead describe the strategy NSF follows in encouraging a broad range of scientific breakthroughs at the nation's universities.

Conversely, the Biocatalysis Research Activity emphasizes integrating NSF-supported and other basic research findings into a coordinated industrial applied research/exploratory development program to accomplish two specific objectives: (1) establish the technical feasibility of biocatalyzed continuous chemical production processes by 1990 and (2) establish the technical feasibility for theoretically-based design, optimization, and control of both biocatalyzed and hybrid chemically/biologically catalyzed processes for chemical production by 1997.

If the Activity emulated NSF by focusing on universities for its research, a large number of universities would be required to adequately address all the various issues. (The RON results demonstrated that universities are both more diversified as a group and more selective individually than CPI firms, R&D industry firms, research institutes or engineering firms.) Also, it is highly unlikely that universities will significantly cost share federal research; they are least able to take a process beyond "technical feasibility" to actual commercial application.

While the Biocatalysis Research Activity requires university participation in its program (for generating innovative technological solutions and translating basic research findings into fruitful areas of applied research), unlike NSF, the Activity must stress industrial participation to (1) leverage scarce federal research funding, (2) achieve technology transfer, and (3) maintain a manageable program focused on accomplishing specific technical objectives.

2. Research for High-Value/Low-Volume versus Low-Value/High-Volume Chemicals

RON respondents' interests appear biased towards the issues most pertinent for investigating high-value/low-volume chemicals.[2] As shown in Table 2-6, respondents indicated their highest interest in issues most pertinent to existing and near-term applications of biocatalysis. On the other hand, issues relevant to the longer-term application of producing low-value/high-volume chemicals (e.g., Feedstock impacts and Methods to extend enzyme life) received the lowest level of interest.

This distinct bias likely reflects industry's understandable interest in applications that potentially have shorter-term research payoffs. However, the Biocatalysis Research Activity exists to overcome the barriers to long-term biocatalysis applications that may both significantly reduce the demand for nonrenewable petroleum feedstocks and greatly improve the international competitiveness of the U.S. chemical processing industry.

Because the level of cost-sharing will depend on industry's interest in proposed research projects, the Activity will likely need to stress early research that addresses both near-term and long-term applications. Because biocatalysis research is at an early stage, this approach will not compromise the government's research and development policy. (For example, certain types of research, such as techniques for maintaining plasmid replication stability, advance the potential for both near- and long-term biocatalysis applications.) However, the Activity should differentiate between research that advances both near- and long-term applications as opposed to just long-term applications. Cost sharing should be emphasized for the former so that sufficient funding exists for the latter -- research that industry/universities will be unwilling/unable to cost share. As time progresses, the Activity will be able to cost share a much larger portion of "long-term" research.

3. Balancing the Mix of Research and Research Contractors

As mentioned above, to accomplish its objectives the Activity must both address the range of technical issues and involve the various groups of RON respondents. However, the RON results suggest that satisfying both these

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[2]Some commercial respondents who have not yet decided to pursue biocatalysis research may view participation in the Activity as a means for staying abreast of potentially profitable applications. However, even these firms likely define the areas to investigate as those currently being looked at by competitors or those projected to have near-term market potentials.

requirements simultaneously may be complicated. The level and differences of interest expressed in the technical issues across the respondent categories present three potential areas of difficulty.

First, the two respondent categories that currently represent the primary target industry for the Biocatalysis Research Activity (i.e., CPI and engineering firms) included less than 25% of all respondents. On the average, they comprised 21% of the indications of interest in any given technical issue. Unless the Activity actively solicits participation by these firms, a strong possibility exists that universities and R&D Industry firms -- the two largest respondent groups and also the two groups with the most similar interests in the technical issues -- will dominate near-term involvement in the Activity's research. Limited funding for competitive procurements will exacerbate this problem in two ways: (1) by limiting the number of research contracts the Activity can award and (2) by increasing the incentive to build a "broad-based" program by funding low-budget, unsolicited proposals from universities. While a "large business set-aside" procurement provision would be improbable, the Activity could make a concerted effort to define and then cost share research projects of particular interest to CPI and engineering firms. This would both help build a broad-based program and add to the legitimacy of the Activity and its objectives.

A second difficulty alluded to above is the probable unbalancing influence that R&D industry firms and universities will exert on the mix of research necessary for accomplishing the Activity's objectives because of their predominant number of responses to an RFP. For example, research institutes and engineering firms were the only two groups whose responses indicated a major interest in the technical issues most relevant to "low-value/high-volume" applications of biocatalysis. Because of this, the Activity should have less difficulty encouraging these two groups to focus on "longer-term" applications. However, these two groups represented only 22% of all responses. Therefore, the Activity may want to purposely pursue some research issues that do not have industry's overall highest interest so that the groups representing the main stream interest of the Activity will be involved in the program's research. Similar to the "first difficulty" discussed above, the second difficulty will become less important as the Activity's budget increases.

A third area of concern for maintaining the balance of research and research contractors in the Activity arises from the opposing interest of CPI and engineering firms. Because the overall research and development of these two groups may be complementary in developing new chemical processes or products, the activity may want to coordinate research conducted by these two groups. For example, if the activity funded a multi-year research effort with a CPI firm focused on hybrid chemically/biologically catalyzed processes, it might also be appropriate to fund an effort with an engineering firm to investigate feedstock selection or downstream processing relevant to hybrid processes. As the activity grows and generates more detailed information about the interactions between and differences in research perspectives of firms involved in chemical markets, other significant relationships may become evident. Programmatic strategies similar to the one recommended here should be developed and integrated into the Activity's research policy.

4. Building Broadly Based Participation and Interest in the Activity

As long as the Activity has sufficient funding to issue a range of competitive research procurements, it will be able to generate widespread involvement and interest in its research program. The responses to the RON came from every portion of the country except the northern Rocky Mountain and northern Great Plains states, Alaska, and Hawaii. As mentioned in Section II, all the states with major chemical industry centers responded to the RON. Because both R&D industry firms and universities -- the two groups comprising the majority of respondents -- closely paralleled the distribution of all responses, the Activity should have no concerns about achieving a broadly based and decentralized research effort.

In terms of building a broadly based research program in industry, the Activity (as mentioned above) must make a concerted effort to involve CPI firms, engineering firms, and research institutes in the near term, especially if program funds are scarce. The activity should pursue a variety of options including but not limited to industrial cost sharing. For example, close coordination with DOE's Office of Industrial Programs (OIP) may represent a means for building chemical industry participation in the Activity without obligating a significant portion of program funds. Additionally, the activity should attempt to achieve the widest possible distribution of its technical reports. The DOE Technical Information Center and journal publications already are widely used and represent a baseline for technology transfer. However, direct mailings of reports to selected individuals in industry (especially if accompanied by brief progress updates or fact sheets on the Activity) and industrial project review meetings (e.g., Project Integration Meetings, or PIMs) represent more direct and active means for raising industry's awareness of and interest in the program.

C. IMPLICATIONS OF THE RON RESULTS FOR DRAFTING RFPs

Most of the implications of the RON results for developing programmatic strategy apply to drafting Requests for Proposals (RFPs). The discussion presented here, while similar to subsection B above, focuses on near-term RFPs (i.e., RFPs issued by the Activity in the next one to two years).

1. The Mission Model Perspective

The Biocatalysis Research Activity, as discussed earlier, differs from NSF in that it has an applied research/exploratory development program with specific objectives focused on transferring a specific type of technology to the chemical industry. This structured definition of the activity extends beyond the description of the program's charter and pervades the decision-making process that the program uses in funding research proposals.

For example, the activity is in the process of developing quantitative models for evaluating the impact of particular technological advances on the cost/effectiveness and efficiency of hypothetical biocatalyzed chemical production processes. These models will help the Activity's managers identify the research areas that may lead to the highest potential improvement in future biocatalyzed chemical production processes.

While these quantitative models help identify high potential research areas, the RON results help identify the areas in which industry, universities, and research institutes have the greatest interest. The intersection of the information provided by these two planning "tools" help define the RFPs eventually released by the Activity. The information on potential contractor capabilities contained in the responses to the RFPs will provide the basis for funding specific research activities, and represents a final component of the Activity's "mission model" (i.e., the systematic approach the Activity follows in planning and implementing its research program).

2. Contractor Characteristics and their Relationship to Program Budget Levels

As mentioned throughout this section, because the interest in the various technical issues differed across the various RON respondent catagories, the Activity will need to determine the likely mix of research contractors that will respond to any given RFP topic. Because the Activity has a small research budget, it should generally emphasize RFP topics that will encourage responses from potential contractors who have the following characteristics:

(1) Broad-based interest in and capability to address a wide range of technical issues.

(2) Capable of and/or willing to cost share.

(3) Genuinely interested in the long-term objectives of these activities.

(4) Able to transfer research findings to industry for further development beyond the scope of the activity.

(5) Able to provide self-sustaining support for the research after the Activity has provided initial funding.

Only CPI firms and perhaps a few R&D industry firms and engineering firms will likely possess all these characteristics. Therefore, to involve universities, research institutes, and most R&D industry firms, the activity cannot exclusively use these characteristics as requirements. However, without growing program budgets, the Activity may have no recourse but to impose such requirements if it is to move towards accomplishing its objectives.

3. The Relationship Between RFP Topics, Industrial Interest, and Budget Levels

The selection of RFP topics will influence the level of industrial interest in the Activity. Similarly, the Activity's budget will determine the number of RFPs and associated contracts that can be released and awarded, respectively. With larger budgets, the importance of these relationships

diminishes. However, because the near-term budget for the Activity is small, the Activity must consider the inherent trade-offs indicated by the RON results.

For example (based on the RON results), if the Activity releases RFPs for CPI Firms' two issues of highest interest (i.e., Advances in microbiology and rDNA technology and Methods to extend enzyme life) the ratio of combined R&D industry firms and university proposals to CPI proposals would approximate 3.4:1. In addition, no engineering firms would respond. In other words, even by focusing on CPI firms' major research interests, non-CPI proposals would swamp the Activity's "target" industry. A small number of contract awards (i.e., a small budget) would only compound this problem by lowering the probability that a proposal from a CPI firm would be funded. Unless proposal evaluation criteria include measures that give some level of preference to the characteristics discussed in subsection C.2 above, the Activity would likely have trouble fostering research of low-value/high-volume biocatalyzed production processes in the CPI.

From a strategic point of view, the existence of small budgets also dictates that the Activity avoid releasing RFPs that address broad research areas. For example, if an RFP was released for Advances in microbiology and rDNA technology, potentially 37 proposals might be received. If only two contracts were awarded, there would be 35 disappointed and potentially disinterested respondents. A potential remedy to this problem would be to more narrowly define the RFP subject research area with the "hope" that fewer proposals would be submitted; however, with this approach the Activity may discourage innovative technological solutions to generic problems.

In general, small budgets restrict the Activity in using RFPs to address the generic problems associated with biocatalysis. This in turn limits the Activity in building an industrial technology base and in having the capability for developing biocatalyzed and hybrid chemically/biologically catalyzed continuous chemical production processes.

SECTION IV

FINDINGS AND RECOMMENDATIONS

A. FINDINGS

The major findings and recommendations of this repport are:

(1) Broad interest exists within the nation's industry, universities, and research institutes for a federally supported program for investigating potential applications of biotechnology in producing chemicals.

(2) Some of the country's large chemical companies, including Allied Chemical, American Cyanamid, Celanese, Martin Marietta, and UOP, have expressed interest in responding to Request for Proposals (RFPs) released by the ECUT Biocatalysis Research Activity.

(3) Interest in the Activity has also been expressed by a number of the nation's emerging leaders in biotechnology, such as AMGen, Genentech, and Genex.

(4) Research institutes expressed the broadest interest in the various Research Opportunity Notice (RON) technical issues. In other words, the typical research institute expressed interest in a larger portion of the technical issues than any other type of respondent.

(5) The expressions of interest from universities and R&D Industry firms (i.e., biotechnology companies and/or firms that perform contracted R&D) most closely paralleled each other. This likely reflects the close ties that have formed between these two types of respondents.

(6) Chemical companies expressed levels of interest in the technical issues that opposed those expressed by the engineering firms designing and building chemical plants. This result likely reflects the complementary relationship that exists between these two types of respondents.

(7) R&D Industry firms are primarily interested in the technical issues most relevant to near-term applications of biocatalysis.

(8) Chemical industry firms also appear to be more interested in the technical issues most relevant to near-term applications; however, their apparent bias is weaker than that exhibited by the R&D industry firms.

(9) Engineering firms were the only respondents to express strong interest in the issues most relevant to the longer-term, low-value/high-volume applications of biocatalysis.

B. RECOMMENDATIONS

(1) Prior to release of any RFPs, the Activity should identify those firms that may want to participate in the program but did not receive a copy of the RON.

(2) The Activity must stress industrial participation in the program in order to: leverage scarce federal research fundings, achieve technology transfer, and maintain a mission-oriented program.

(3) The Activity's early RFPs should stress research topics that address both near-term and long-term biocatalysis applications.

(4) Cost sharing should be emphasized for research that advances near-term applications, or both near-term and long-term applications.

(5) To build a broad-based program, the Activity should make a concerted effort to define, cost-share, and coordinate research projects of particular interest to chemical companies and engineering firms.

SECTION V

REFERENCES

1. Ruben, B. G., and Burstall, M. L., The Chemical Economy, published by William Clowes and Sons, Limited, 1973, p 125.

2. Charles H. Kline & Co., Inc., The Kline Guide to the Chemical Industry, 3rd Edition, 1977, p 44.

3. "Corporate Scoreboard: First Quarter Profits of 875 Companies," Business Week, May 16, 1983, p. 60.

APPENDIX A

RON CBD NOTICE[3]

Attn: Karl W. Koch, M/S 511-303, 213/577-9268

APPLIED RESEARCH FOR ADDRESSING THE TECHNICAL BARRIERS IMPEDING THE USE OF BIOLOGICALLY-FACILITATED CHEMICAL PRODUCTION PROCESSES. Responses of interest are invited from petrochemical and chemical companies, bioengineering firms, biochemical engineering consultants, private research laboratories and universities to participate in a research program to investigate potential applications of biotechnology in producing specialty chemicals, value-added chemicals, and simple chemicals. The Div. of Energy Conversion and Utilization Technologies (ECUT) of the Dept. of Energy (DOE) has designated the California Institute of Technology's Jet Propulsion Laboratory (JPL) operating under a prime contract with the National Aeronautics and Space Administration (NASA), as manager of the Biocatalysis Research Activity. This R&D effort sponsored by the DOE through an interagency agreement with NASA is an essential step in building a strong technology base for the chemical processes industry to increase the utilization of non-critical resources. The objective of this effort is to establish the technical feasibility of producing chemicals in bulk using microorganisms or their products by 1997. JPL has identified several major technical barriers impeding the use of biologically-facilitated chemical production processes. These technical barriers will help define research activities for the program. The ultimate result of this work is expected to be the definition of the laboratory-scale chemical production processes that suggest that production of chemicals using enzymatic catalysts is feasible at the pilot-plant scale. The Biocatalysis Research Activity supports applied research and exploratory development that builds on basic research findings. The Activity stresses an interdisciplinary approach involving experts in biology, chemistry, and engineering. Funded research uses innovative approaches to address the generic technical issues of producing chemicals biocatalytically. These issues fall into four categories: (1) biocatalysis by genetically-improved live organisms, (2) catalysis by biologically and chemically derived molecules, (3) process and reactor vessel design, and (4) product separation. Technical issues to be addressed by the biocatalysis research activity include: (1) Approaches for product release, separation, and recovery, including strategies for reducing the water content of bioreactor streams for organics conversions; (2) Advances in microbiology and recombinant DNA techniques for genomic stability, resistance to harsh environmental conditions, and enhanced productivity under reaction conditions; (3) Significance of feedstock selection on process performance; (4) Combining productivity/efficiency improvements from biological and chemical catalytic processes; (5) New processes involving multiple species, either as separate organisms or as newly constructed, recombinant organisms; (6) Advanced concepts for control and regulation of biological processes; (7) Methods to extend the useful life of enzymes; (8) Control of secondary metabolite pro-

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[3]Published in the Commerce Business Daily, Issue No. PSA-8322, April 27, 1983, p 24.

duction and continuous fermentations; (9) Process and reactor design and its relationship to productivity and energy efficiency; (10) Other research areas consistent with the approach of the Biocatalysis Research Activity. JPL requests that interested respondents, which have the capability to fulfill the requirements synopsized herein, provide a written expression of interest to JPL by NLT 20 days from date of publication of this synopsis. Respondents shall indicate specifically which of the 10 technical issues listed above are of particular interest. Telephone inquiries will not be honored. This is not an RFP. It is anticipated one or more RFPs will be issued in September 1983. No additional info is available at this time. (112)