ABSTRACT

JONATHAN NAIMON. A Case Study of the First Proposed Field Test of An Environmental Application of Biotechnology in the United States (Under the direction of DR. FRANCES LYNN).

This paper analyzes the processes by which three levels of government analyzed potential risks from a precedent-setting environmental application of biotechnology, Advanced Genetic Science's FROSTBAN product. The research is based on regulatory decision dockets, accounts of the case in scientific journals and newspapers, and personal interviews with key scientists, policy analysts, and senior decision makers. The 1.5 hour interviews employed both fixed choice and open-ended questions.

Four distinct conceptions of potential hazards arose in the AGS case: toxicity to humans, pathogenicity to plants, ecological risks to non target species, and climate changes. Worst case scenarios were devised in each organization to evaluate the application. The scientific assumptions of these analyses differed substantially. All three organizations requested additional technical data from AGS. Criteria for evaluating such data were not always prepared before performing experiments. Scientists believed the most critical uncertainties related to their individual discipline.

Many of the uncertainties identified in the AGS case could not be unambiguously resolved by provision of more data. A framework for interpreting information on potential ecological hazards of introduced organisms is not available from any one of the disciplines that contributed to the AGS review. Future risk analyses could be improved by developing explicit ecological goals and criteria for data interpretation. In the meantime, biological controls should be required for tests of engineered microorganisms to reduce many identified uncertainties.

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I. INTRODUCTION

This technical paper critically examines the risk assessment practices used by the U.S. EPA, California Department of Food and Agriculture (CDFA), and Monterey County to analyze a proposal to conduct a small scale field test of a genetically engineered microbial product. The proposed test involved spray application of a mist of two genetically engineered bacteria Pseudomonas syringae and Pseudomonas fluorescens on strawberry plants to retard frost formation. Advanced Genetic Sciences Inc. (AGS) planned to market a product based on engineered Pseudomonads throughout the United States as a cost effective and ecologically sound method of reducing frost damage.

This report analyzes:

1. the nature of the scientific issues and uncertainties identified in the initial government risk analyses of a proposed field test of an engineered microorganism by Advanced Genetic Sciences Inc. (AGS), and
2. the procedures used by three public organizations to resolve the scientific and technical uncertainties and make decisions on the field test proposal.

On the basis of an analysis of the issues that arose in evaluation of this precedent setting case, some

recommendations to facilitate risk management of future environmental biotechnology applications are presented.

Identifying and managing risks from proposed environmental applications of biotechnology is important for a number of reasons. Biotechnology is expected to become an engine of sustained economic growth in the USA. (OTA, 1981) Its ability to spur productivity improvements in a diverse range of outdoor human activities will be limited if hazards cannot be identified and controlled. Post World War II experience with organic pesticides, nuclear power, and other technologies suggests to many observers that unanticipated, detrimental effects on the environment and some human activities are common traits of powerful new technologies such as biotechnology. (Alexander, 1985)

A. Scientific Issues

There has been a polarized debate in scientific journals as to whether or not there is a need for specialized analysis of risks arising from environmental applications of biotechnology. Authors such as geneticist Winston Brill have argued that genetic engineering products are not likely to pose different classes of risk than existing agricultural products. He believes that genetically engineered products should be expected to pose less severe ecological risks than natural organisms introduced into new environments because the engineered organisms are not optimized for terrestrial environments by evolutionary processes. (Brill, 1985)

Ecologists such as Frances Sharpless (1987) have argued that the adaptation of genetically engineered organisms to new environments is unpredictable and has the potential to create substantial new risks to the viability of certain ecosystem processes and members. Among potential environmental products, genetically engineered microorganisms have generated more controversy than genetically engineered plants or animals. (Sharpless, 1987)

While there is no accepted scientific evidence that genetically engineered microorganisms (GEMs) as an entire class are dangerous, there are some scientific reasons for expecting different types of uncertainties with environmental applications of biotechnology than in environmental chemical applications. For example, viable microbes have the ability to reproduce and multiply rapidly in favorable environments. Industrial chemicals can never increase in quantity after environmental release. Exogenously introduced organisms can colonize new habitats, displace existing organisms, and thus may be able to affect underlying ecological processes such as nutrient cycling, animal behavior, and evolution. Non living chemical mixtures typically affect fewer environmental biochemical processes and cannot act as new competitors for resources in the environment. More than genetically engineered plants and animals, GEMs have the ability to transfer their genetic material to naturally occurring organisms and receive DNA from organisms in the target environment. This capability

can lead to changes in the functions that novel and natural organisms play in different ecosystems over time. Even if no genetic material is exchanged, the functional capabilities of an introduced organism can be expected to change as the organism adapts to its environment over the course of many generations. For these reasons, risk assessment of environmental biotechnology applications should involve different issues than risk assessments of chemicals used in the environment.

Environmental applications of genetically engineered organisms will also pose different scientific and technical questions for risk management than indoor biotechnology applications. Because of the variability and diversity of natural ecosystems, there are a wider number of opportunities for offsite transport by wind, insects, animals, and people. Technical control of environmental applications is therefore much more difficult. Perhaps most importantly, there is much less information available on the relevant parameters of multiorganism environmental systems than the single organism systems targeted in biomedical and chemical production applications. Thus, the task of assessing potential scientific risks from AGS proposed field test could be expected to involve different scientific issues, different types of evidence, and different scientific uncertainties than those associated with either outdoor chemical applications or indoor biotechnology applications. (Gillette, 1986)

In addition to these theoretical questions about the safety of environmental applications of biotechnology, practical limitations on available information make evaluation of potential risks difficult. Because deliberate environmental dispersal of GEMs has not been permitted by most developed countries at the time of the proposed AGS field test, there is only scanty, anecdotal data available on the behavior of a few viable, engineered organisms in natural environments.

The limits of existing disciplines may contribute to the difficulty in evaluating potential effects from applications of biotechnology. Environmental applications of biotechnology represent a hybrid field requiring inputs from molecular biology, cell biology, plant pathology, public health, microbial ecology, and systems ecology. During the last ten years, interaction between many of these fields has been infrequent if at all. Research activity is more concentrated in previously established disciplines with stable support. Few scientists have developed theories or conducted experiments linking molecular modifications and changes in ecosystem dynamics or function.

Despite these technical differences between environmental biotechnology applications and environmental chemical applications, statutes created for non living chemicals were used as the basis for regulation of the first genetically engineered products intended for environmental release. Under the "Coordinated Framework for Regulating

Biotechnology" published in the Federal Register (Office of Science and Technology Policy, 1984), the AGS field test was regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA was written in 1946, before DNA was even isolated, to limit acute health risks from ineffective and dangerous pesticides. While there is more diversity in state policies concerning environmental biotechnology , California also treated the AGS product as a new pesticide. (Jones, 1986) Laws created to regulate less subtle agricultural products could be expected to miss certain new effects of biotechnology products.

B. Information Processing by Regulatory Organizations

There are many lenses through which to view scientific policy analyses like the evaluation of the FROSTBAN field test. A popular approach to policy analysis has been to divide the process into a series of steps akin to scientific research. (Stokey and Zeckhauser, 1976) According to this model, public organizations need to undertake the following activities in doing policy analysis: problem definition, information research, information analysis, information preservation, and decision-making. A premise of this policy analysis model is that the information obtained and analyzed by an organization is critical to that organization's decision. Some alternative views of policy analysis focus on political pressures agencies face and the inadequacy of

certain disciplines to resolve complex policy issues. (Schrader-Frechette, 1980)

Perhaps because problem definition often has political inputs, this phase has received the least systematic treatment of these imputed phases. The literature suggests that it is crucial to determining the nature of subsequent activities including decision-making. Many authors suggest that problems be defined as broadly as possible. (Stokey and Zeckhauser, 1976)

The literature on information acquisition analyzes activities in terms of the actors involved, the content acquired, sources of the information, and the external constraints on the search process. In novel situations private sector research and development organization managers rely on individual "information stars" to tap extra-organizational information sources to support decisionmaking. (Fisher, 1984) When there is a high level of technical uncertainty, senior management in government research and development organizations use unstructured channels like telephone conversations that permit immediate feedback rather than formal sources like reference texts or databases. (Holland, 1984) The literature suggests that two distinct classes of information, technical and political, are acquired in the search phase of the analysis process. Non technical information includes:

1. the legal rules and regulations constraining its policy choices,

2. the past activities of the agency and its internal resources,

3. the preferences of important actors within the agency, its constituency groups, other agencies, and its executive, legislative, and judicial sovereigns, and

4. the probable reactions of important political actors to the substantive consequences of each policy alternative. (Sabatier,1978)

While scientific and technical information may seem less uncertain than political information, four types of technical uncertainty have been identified in the literature on regulatory activities: inadequate data, conflicting data, different interpretations of the same information, and uncertainty resulting from different models. (McLaughlin, 1987) The capacity of organizations and individual analysts to utilize new information is apparently reduced in crisis conditions. In crisis situations, managers tend to display a lower tolerance for ambiguities like the uncertainties mentioned above and a cognitive rigidity to alternative policies that have not been deployed before. (McLaughlin, 1987) The AGS case, since it developed over the course of a year, cannot be considered a crisis . However, the rapid technological change that precipitated the regulatory questions reduced the lead time available to government officials and could indirectly contribute to a crisis management syndrome. (Fischer, 1986)

C. Study Hypotheses

On the basis of the scientific questions raised by the advent of open environment applications of genetic engineering and the literature on processing of technical information by regulatory organizations, we developed a few working hypotheses to guide our research. These hypotheses were:

1. the non routine nature of the scientific questions that arose would compel each organization to use non routine decisionmaking processes. These processes could be expected to make extensive use of information sources that provide instant feedback and information about political factors.
2. the limits of existing disciplines would prevent organizations from fully evaluating scientific questions about the impact(s) of the introduction of GEMs into a natural environment. Organizations that devised procedures to include individuals with diverse backgrounds would be better equipped to evaluate potential impacts than organizations that employed routine processes and regular personnel used to traditional environmental problems.

D. Methods

The Advanced Genetic Sciences 1985 proposal to field test Pseudomonas syringae and Pseudomonas fluorescens was selected as a case study because it was the first proposal to deliberately release a genetically engineered microorganism analyzed by EPA after responsibility for

regulating environmental applications of biotechnology was shifted to EPA from the National Institutes of Health. As the first case of its type considered, the aforementioned scientific issues seemed likely to be explicitly treated in the process of making decisions on the proposal. We believed that analysis of the handling of the case could provide insight into the type of regulatory policy issues that are likely to recur in future evaluations of environmental products that utilize biotechnology.

The regulatory and legal background of the case was obtained by analyzing relevant notices in the Federal Register. A Freedom of Information Act request was filed with EPA in order to obtain the AGS Experimental Use Permit application, supporting AGS scientific data and correspondence, transcripts of the special Subpanel of the EPA FIFRA Scientific Advisory Panel convened to evaluate this application, comments of individual subpanel members on the test proposal, and comments of other agencies. Congressional hearing records were used to identify additional policy issues. Newspaper articles were used to identify key actors in California's and Monterey County's regulation of the AGS proposal. Public interest organizations were contacted by phone to obtain copies of lawsuits and correspondence with agency officials. All of these documents were analyzed to identify key individuals who were involved in the analysis of the case and who were responsible for regulatory decisions made by the US EPA, the

California Department of Food and Agriculture, and Monterey County. Additional documents used or prepared in each organization's decision-making processes were obtained during the in person interviews. These documents helped provide a basis for understanding the evolution of the consensus technical opinions in each organization.

AGS scientific personnel were asked to participate in this study. AGS representatives declined because of concurrent negotiations with EPA's Office of Special Counsel at the time of the interviews. (EPA Office of Compliance Enforcement, 1986) Dr. Stephen Lindow, the University of California at Berkeley scientist who elaborated the concept of a bacterial frost damage protection system, and Mr. Edward Lee Rogers, Foundation for Economic Trends legal counsel, were also interviewed in person to obtain historical information about issues surrounding the proposed field test.

One and a half hour in person interviews were conducted with both analysts and senior decision-makers to compare the types of information that were important to each in the decision-making process. The interviews were structured using the UNC Institute for Environmental Studies/School of Business Administration NSF project interview guide. This guide was designed to probe ways in which scientific and technical information is processed by federal agencies in non-routine situations. Interviewees were asked questions to examine the potential importance of individual and work

unit disciplinary background, time constraints, legal constraints, organizational uncertainties, and other suggested influences on the processes of problem formulation, information search behavior, information analysis, and decision-making. (Lynn, 1986) Interviewees were asked to characterize both the nature and sources of scientific uncertainty, and the quality of different types of information that were utilized in their analysis of the AGS proposal. The NSF interview guide used is given in Appendix 1.

In the next chapter, EPA's handling of the AGS proposal to field test genetically engineered bacteria is described. Readers interested in the technical basis for the AGS FROSTBAN product are referred to Appendix II, "Technical Background for the AGS Case."

II. DESCRIPTION OF RISK ASSESSMENT BY EPA

This chapter examines the process by which EPA defined the issues, acquired, analyzed, and presented scientific information to carry out its regulatory responsibility for an environmental biotechnology application. Background information on Advanced Genetic Sciences (AGS) and the policies that governed the review process are given in section A. The processes by which scientific information was obtained are described in Section B, Section C describes EPA's analysis of the scientific information it acquired. Section D discusses the way that scientific information was presented within EPA in the decision making process. The utility of the information acquisition and analysis process EPA used is evaluated in Section E.

A. Background

1. AGS Inc.

Advanced Genetic Sciences Inc. (AGS) is a medium sized biotechnology firm founded in 1980. AGS's focus is on products for the agricultural production and food processing markets. Like many biotechnology startup firms, international chemical companies are now major minority shareholders. Rohm & Haas, has a 12% of the public stock,

and Hillshoeg AB of Sweden owns 16% of AGS. AGS has manufacturing facilities in Canada and Sweden. Its American scientific and management operations are now based in Oakland, California in a building leased from the University of California at Berkeley. (Advanced Genetic Sciences, 1985)

In 1981, while AGS was based in Greenwich, Connecticut, Dr. Steven Lindow, then at the University of Wisconsin Department of Plant Pathology, approached AGS with an idea for a bacterial snowmaking product utilizing INA+ (Ice Nucleation Active) P. syringae. This product concept has been refined by AGS and a dehydrated concentrate of irradiated INA+ P. syringae is now marketed as SNOWMAX to ski resorts to increase the efficiency of artificial snowmaking at near freezing temperatures. (Harris, 1985) In 1982, AGS acquired an exclusive license from the University of California to commercially develop, produce, and market a genetically engineered (Ice Nucleation Inactive) INA- bacterial products to reduce agricultural frost damage. AGS retained Dr. Steven Lindow, who first proposed using INA- bacteria to retard frost formation and tissue damage on plant leaves, as a consultant. While the terms of individual licensing agreements are confidential, most University of California technology license agreements provide that 50% of all royalties the school receives from licensees is given to the inventor. (Strom, 1987)

2. Federal Policy

In 1982 Dr. Lindow and Dr. Panopoulos (both of the University of California at Berkeley) requested permission from the National Institutes of Health (NIH) to perform outdoor experiments to test the efficacy of this new frost control technology in the field. At this time, the Department of Health and Human Services (HHS) had jurisdiction over all recombinant DNA experiments in which researchers were supported by civilian federal agencies. This request was approved in a 7-5 vote (with two abstentions) by the NIH Recombinant DNA Advisory Committee (RAC). However, HHS and NIH withheld approval because of concerns raised in the RAC about: 1) the anticipated effects of tagging Pseudomonas strains with antibiotic resistance, and 2) potential climatic effects from non ice nucleating (INA-) genetically engineered microorganisms (GEMs) displacing INA+ bacteria that may play a role in ice nucleation in rainclouds. NIH invited the scientists to reapply and provide information to allay these two RAC concerns. (Milewski, 1983)

In early 1983 the two Berkeley professors resubmitted a revised application with additional information on the strains they planned to use, and arguments rebutting some of the RAC's concerns. On April 11, 1983 the NIH RAC approved this application 19-0. On June 1, 1983, following approval by the US Department of Agriculture Recombinant DNA Committee, NIH granted Drs. Panopoulos and Lindow permission

to proceed with the field test at a single site, the University of California Field Station at Tulelake, California. (Milewski, 1983) Immediately thereafter, a public interest group, the Foundation for Economic Trends (FET) sued in the DC Federal Court to block the test on the basis that an adequate environmental impact statement for the risks accruing from the proposed experiment was not performed. District Court Judge John Sirica agreed with the suit and issued an injunction blocking the proposed field test until an adequate environmental impact statement, filling the National Environmental Policy Act's substantive requirements, was made. (Foundation on Economic Trends v. Heckler, 1984)

The novel scientific nature of the regulatory decision on proposed field tests of engineered bacterial frost control strains was compounded by a shifting legal and regulatory framework for outdoor tests of engineered organisms. In late 1983 the White House Office of Science and Technology Policy (OSTP) formed a Biotechnology Coordinating Committee (BSCC) to analyze regulatory issues associated with commercialization of biotechnology. This committee had representation from the National Science Foundation, the Office of Science and Technology Policy, and the EPA. In 1984, this committee suggested that EPA be given lead responsibility for regulation of bacterial biotechnology products deployed in the open environment and USDA be given lead responsibility for regulation of animal

and plant biotechnology products. While EPA and USDA did not have NIH's experience as a major patron of modern biotechnology, their regulatory actions are interpreted by courts as providing the equivalent of the required National Environmental Policy Act environmental impact review. This proposal was implemented by courts in an Executive Order on the regulation of biotechnology products published in the Federal Register. (Office of Science and Technology Policy, 1984)

EPA has legal authority to regulate genetically engineered microorganisms (GEMs) under either the Toxic Substances Control Act of 1976 (TSCA) or the Federal Insecticide Rodenticide and Fungicide Act of 1946. Shortly after the Federal Register notice was published EPA Associate Counsel Abrahmson suggested that FIFRA was preferable for GEMs because of the similarities between conventionally obtained microbial pesticides and genetically engineered microbial products. Thirty one microbial pesticides were already registered for use in the U.S. in 1984. (Abrahmson, 1984)

In November 1984, AGS field engineer Steven Cull sent a letter to EPA indicating AGS's intent to conduct outdoor experiments with two genetically engineered strains of Pseudomonas. EPA Assistant Administrator for Pesticides and Toxic Programs Jack Moore determined that the proposal would be regulated under FIFRA.

The rationale for considering AGS' genetically engineered INA- bacterial preparation to reduce frost formation (FROSTBAN) as a pesticide is explained in a communications packet EPA released in November 1986. It states,

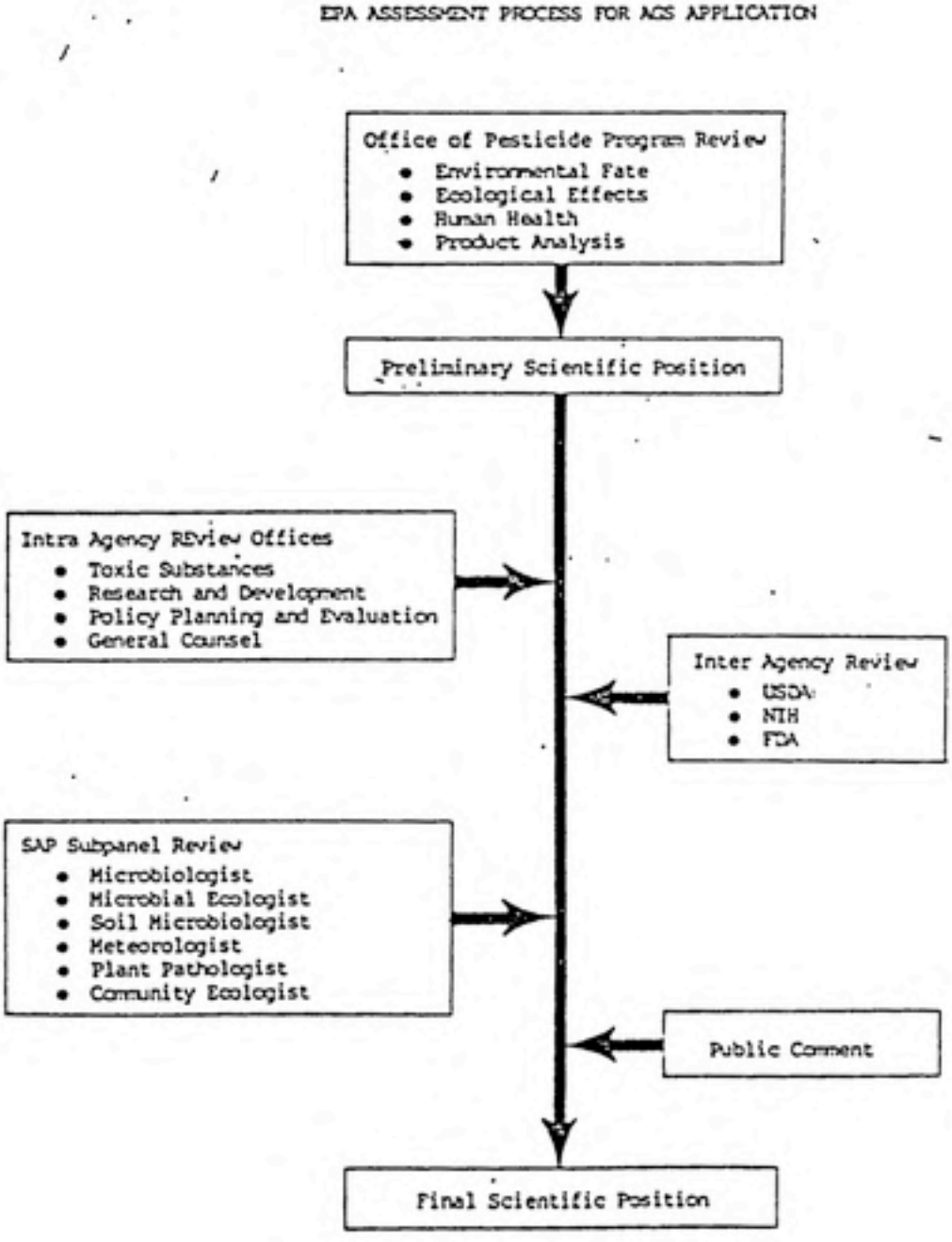
> "Under FIFRA, a pesticide is defined as any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. In this instance, the INA+ bacteria are the pests because they nucleate frost that in turn destroys or harms crops, and the INA- products are pesticides because they are intended to displace the INA+ bacteria and prevent or mitigate the harm (frost) caused by them.
>
> (EPA Office of Public Information, 1986)

FIFRA classifies new product proposals by the size of proposed field tests. EPA doesn't require an Experimental Use Permit (EUP) for all pesticide tests involving less than four acres. In 1984, EPA published an Interim Rule which gave it authority to require an EUP for small scale field tests of products that included genetically engineered organisms such as AGS' FROSTBAN.

The process by which different units in EPA contributed to the formulation of its scientific position on the AGS proposal is outlined in Table 1. The SAP is an acronym for EPA's FIFRA Scientific Advisory Panel, a panel of outside scientists selected to review problematic scientific questions that arise

under FIFRA. FDA is the acronym for the Food and Drug Administration. USDA is the acronym for the Department of Agriculture.

TABLE 1



The Office of Pesticide Programs (OPP) Review was delegated to the Hazard Evaluation Division. This division is principally responsible for assessing health and environmental risks from new chemicals. It was responsible for considering environmental fate, ecological effects, human health, and other potential impacts of the AGS product.

The subsequent review by the USDA, NIH, FDA and the Scientific Advisory Panel Subpanel is not required by FIFRA for regular EUPs. The additional input was required to improve the public credibility and legal defensibility of EPA's scientific review of the AGS product.

Assistant Administrator Moore said,

> "We knew that (Federal Judge) John Sirica found the NIH process not consistent with NEPA (National Environmental Policy Act)... The perception of credibility of the EPA process is essential. It seemed unlikely that the agency would have enough expertise on hand to deal with the AGS request. Therefore, we evolved a process with external peer review of EPA judgements. We used the SAP (FIFRA Scientific Advisory Panel) subpanel approach because the SAP is legally mandated to look at scientific questions related to FIFRA registrants, and the FIFRA SAP did not have any expertise in climatology." (Moore, 1986)

The SAP subpanel was chaired by Dr. Wendell Kilgore, a member of the regular FIFRA Scientific Advisory Panel and an environmental toxicologist from the University of California at Davis. The other members of the special subpanel created

for the AGS Case were: Dr. Susan Hirano (University of Wisconsin, microbial ecologist), Dr. Robert Colwell (University of California at Berkeley, zoologist and evolutionary biologist), Dr. Martin Alexander (Cornell University, soil scientist, microbial ecologist) Dr. Randy Borys, (Colorado State University, meteorologist), and Dr. James Tiedje (Michigan State University, soil scientist and microbiologist).

Dr.Moore suggested that the

> "SAP (Subpanel) would not just respond to questions identified by EPA staff but also be able to look at the raw data themselves and draw their own conclusions. Thus, the SAP subpanel could function as an educational tool for EPA (in the area of impacts of release of genetically engineered organisms) and provide the important imprimateur of scientific rigor on EPAs first case of a modified (genetically engineered) pesticide."
>
> (Moore, 1986)

Nonetheless, EPA's Hazard Evaluation Division (HED) was responsible for initially defining the scope of the analysis. Within HED, Fred Betz, an environmental engineer on the Science Integration Staff, was responsible for operationalizing EPA's policies on GEMs, managing the scientific review, and drafting consensus scientific positions.

B. Search

HED's first task was to determine whether EPA should require an EUP for AGS. Under the interim FIFRA policy, the statutory time frame for this decision was 90 days. Betz delegated the initial review of the scientific issues to ecologist Zigfridas Viatuzis, toxicologist Reto Engler, in the HED Human Health Effects Branch, chemical engineer Herbert Manning, in the HED Exposure Assessment Branch, and chemist William Hazel in the HED Product Residue Chemistry Branch.

These HED analysts began by carefully reading the formal AGS proposal and NIH RAC review of a similar experiment proposed by Lindow and Papadopolous. Second, the EPA scientific analysts had phone conversations with AGS scientific personnel. Written records of phone conversations were maintained for incorporation into HED records. Face to face meetings with AGS scientific management were held to clarify EPA's regulatory requirements rather than to answer scientific questions. Literature searches on naturally occurring P. syringae and P. fluorescens were also conducted by the EPA scientific analysts; however, the scientific information these searches yielded was not considered very useful.

The four HED reviewers submitted their initial, confidential analyses of the AGS test proposal to Betz within 30 days. These analyses apparently addressed two types of questions:

1. could the engineered bacteria persist in the natural environment?
2. could they cause any detrimental effects to humans, plants, or the weather?

The preliminary consensus was that it is possible both for the organisms to persist and to contribute to some adverse effects.

Mr. Betz sought to fill gaps in the information provided by his reviewers by undertaking a subsequent information search. In addition to using many of the same sources as the staff reviewers, Betz called additional scientific experts outside the EPA and AGS. Mr. Betz commented that while discussions with experts are useful for finding answers to specific questions he had, the scientific literature may be more useful because relevant articles can be more easily cited in subsequent decision support documents. (Betz, 1986)

C. Analysis

1. Worst Case Scenario

Using the initial confidential HED analyses and the information from his search, Mr. Betz devised a technically plausible worst case scenario for evaluation. First, the microbes are borne off site by water, wind or insects; second, the GEMs survive on related plants, multiply, third; the GEMs exclusively colonize plants in a nearby off site area, fourth, the GEMs are dispersed into the air, where

fifth, the INA- GEMs depress the rate of formation of ice droplets in clouds. This in turn could lead to an adverse effect "branch": changes in precipitation patterns in areas adjoining the test site(s).

The second "branch" of HED's qualitative adverse consequence tree concerned pathogenesis of commercial plant relatives of the strawberries on which the GEM would be applied. In this branch, the GEM would establish itself on neighboring fields and potentially cause a pathogenic infection in potential plant hosts. Like the precipitation modification possibility, this "branch" could only occur if the first contingency in the scenario occurred: INA- GEMs competing with naturally occurring INA+ bacteria and colonizing plants off site.

2. Information Exchange

On the basis of the hazards defined in this qualitative preliminary analysis, Mr. Betz determined that an Experimental Use Permit (EUP) should be required to conduct the test. On February 1, 1985 EPAs Office of Pesticide Programs (OPP) sent a letter to AGS advising that it had decided to require an EUP for the proposed test to resolve uncertainties that were identified by HED staff, and the public. In this letter, Office of Pesticide Programs Director Steven Shatzow formally requested AGS to submit additional experimental information to resolve many of the questions HED staff had.

Determining what information was needed to resolve the scientific questions it had was HED's second principal task. On February 10, 1985 EPA HED staff met with AGS scientific management to discuss experimental strategies to meet the identified concerns. AGS was given responsibility for devising experiments to satisfy EPA's general concerns. EPA indicated that the design and conduct of the AGS experiments would not be closely monitored. To analyze the likelihood of the two scenario branches described above, and meet separate FIFRA EUP information requirements, HED requested AGS to supply a wide range of scientific and technical information. Table 2 shows a sample of the types of information EPA asked AGS to supply.

Table 2

Scientific and Technical Information Requested by EPA to Evaluate the AGS EUP

- methods used to construct the INA- GEM
- purity of the INA- GEM preparation
- colonizing ability of Ice Nucleating Minus strains (INA-)
- genetic and biochemical characteristics of INA- P. syringae
- parental strain pathogenicity to crops and native plants (grown in the area of the proposed test site)
- methods for detection of INA- GEMS
- survival rates of INA- GEMS
- growth rates of INA- GEMS
- temperature range of INA- GEM relative to the parental strains
- site location and nearby crops
- plans for detecting possible off-site dissemination."

(Betz, 1985)

In April and June 1985, AGS submitted approximately 300 pages of results from experiments they had conducted and a footnoted narrative concerning the competitiveness issue. The bulk of AGS's EUP support materials covered three issues:

** toxicology of P. syringae and P. fluorescens
** pathogenicity of the organisms for different plants, and
** role of P. syringae effects on rainfall patterns

EPA staff did not use any formal techniques (e.g., statistical methods, sensitivity analysis, decision analysis) to analyze the voluminous data AGS supplied. Because experimental conditions were not uniformally supplied by AGS, EPA asked AGS for some specific protocols.

On the basis of this information and extensive discussions within HED, Mr. Betz drafted a preliminary scientific position based on information at hand and the potential risks from the test HED identified. When fundamental interpretative questions arose, Mr. Betz requested comments from the special SAP subpanel members at their quarterly meetings. SAP subpanel members based their comments on the entire AGS data package. A few additional experiments were requested by SAP Subpanel members. HED transmitted these requests to AGS. AGS executed some of new plant pathogenicity tests. It did not do any additional experiments suggested by the Subpanel after September, 1985.

EPA encountered varied uncertainties in evaluating the information AGS provided. Two questions that were pivotal to EPA's worst case scenario are the competitive fitness of FROSTBAN vis a vis native INA^+ microflora and the role of P. syringae in atmospheric precipitation processes. The nature of the uncertainties EPA faced are illustrated by EPA's treatment of these two scientific issues.

3. Competitiveness

In its initial application, AGS argued that the engineered INA- mutants would tend to be less evolutionary fit than naturally occurring microflora and therefore would not spread off site. EPA staff, with the advice of the SAP Subpanel, requested that AGS do experiments on young strawberry and other plants, pitting a mixture of the wild type INA+ and NA^- bacteria with the purely INA- FROSTBAN GEMs. The results of the experiment showed that the concentration of GEMs that colonized young, bacteria-free plants depended on the relative concentrations of INA- GEMs and INA+ bacteria that were applied initially. The wild type INA+ P. syringae did not reproduce more actively than the GEMs, nor did the GEMs outcompete the INA+ P. syringae on the experimental plants. (Advanced Genetic Sciences Experimental Use Permit application and support data, 1985)

This result could be interpreted in divergent ways. It could indicate that the AGS contention that GEMs were inherently less fit than wild type plants was erroneous. It

could reflect the similarity of the GEM to the wild type microbe, buttressing the AGS contention that genetically engineered FROSTBAN behaved identically to the parental microbes. The experiment itself could be criticized as irrelevant because the greenhouse test system didn't reflect fluctuations of moisture, temperature, and light that have been reported to dramatically effect colonization behavior of the parental strains. (Gross, 1984)

Adding complexity to AGS' greenhouse test system would not guarantee that natural ecosystem behavior would be well modeled. If the AGS test data is indicative of the behavior of INA- GEMs in field conditions, one could deduce that displacement of INA^+ organisms on uncolonized vegetation depends primarily on the concentration sprayed. This is consistent with an extrapolation that spraying a 100% INA^- P. syringae preparation on a plot of uncolonized vegetation would result in substantial displacement of natural INA^+ populations. This data is also consistent with an extrapolation that INA^- GEMs are unlikely to displace INA^+ P. syringae if a low concentration of FROSTBAN is sprayed on areas with normal concentrations of native INA^+ bacteria.

HED did not develop a testable standard by which to evaluate the competitive fitness experiments before they received the information. Faced with ambiguous data that could be interpreted in divergent ways, HED apparently used the following implicit criterion for evaluating the experiment:

> "If the INA^- GEM displaces the native INA^+ bacteria to the extent that there are no functional INA^+ bacteria, adverse effects can ensue.
>
> (Betz, 1985)

Embedded in this criterion is a concept of ecological functioning depending on a threshold level of INA^+ organisms present. Alternatively, intact ecosystem function could depend on the percentage of INA^+ bacteria available in a system. No information was presented by AGS to suggest the existence of thresholds for ecological functioning. Ecological function were not explicitly defined in the analysis.

It seems that the ecological function framework for interpreting the competitive fitness data was based on toxicology concepts or regulatory needs, rather than ecological data or theory. Use of alternative assumptions with the same data could have yielded a different interpretation of the AGS competitive fitness experiments.

4. Weather

As early as 1974, scientists suggested that ice nucleation could be induced by P. syringae. (Maki, 1974) By 1978, Lindow established that INA^+ P. syringae were present in a wide variety of agricultural crops and could provide nucleation sites to initiate frost damage. Maki and Willoughby extended this notion to atmospheric processes in an article "Bacteria as biogenic sources of freezing

Nuclei." (Maki, 1978) Since 1982 Dr. Russell Schnell has amplified the possibility that INA+ bacteria could be instrumental to natural atmospheric droplet formation in popular science magazines as well as in scientific journals. (Schnell, 1983, 1984) Dr. Schnell is consultant to the National Ocean and Atmosphere Administration (NOAA). His stated views on potential changes in precipitation from widespread application of INA^- P. syringae were a lynchpin in the FET's successful suit against the Department of Health and Human Services.

EPA staff contacted Schnell by phone to obtain his view on the AGS proposed EUP test.His reply suggested that there was no substantial risk of climatic modification from AGS' proposed test because of its small size (0.2 acres). He remained concerned about the potential impact of a wide scale commercial program to reduce INA^+ P. syringae on agricultural plants. Schnell discussed his scientific position in a Science article, "EPA Approves Field Test of Altered Microbes."

> "There is no proof that decreasing the population of (unaltered P. Syringae) on plants affects precipitation. There is substantial circumstantial evidence that such a relationship might exist, but the science "is very loose and very shaky right now." Schnell said that he has 'no concern' about this particular experiment given its small size. "What concerns me is spraying hundreds of square mile plots. We need to do some better modeling." (Schnell, 1985)

One reason Schnell may have suggested more modeling of precipitation processes could be his professional orientation as an atmospheric scientist. Another is the present unavailability of an instrument that can reliably detect small ice nuclei in clouds.

Schnell's proposal that modeling be done as a surrogate for experimentation to supply a theoretical answer runs contrary to time-honored experimentalist traditions in biological and physical sciences. Dr.Lindow, who also speculated on possible role of P. syringae in atmospheric precipitation formation, criticizes Schnell's concern because no experimental research has been done to support it. Lindow suggested that NOAA could try sampling in the atmosphere if there was sufficient scientific interest in the question of whether P. syringae were quantitatively involved in atmospheric ice nucleation and raindrop formation. (Lindow, 1986)

Rather than try to resolve the controversy on the necessity for experimental evidence to establish the role of bacteria in a physical process, EPA HED confined its attention to the question of risks of climate modification from the proposed 0.2 acre test. EPA did not request additional scientific data from AGS on this subject, only additional opinions from SAP Subpanel meteorologist Randolph Borys.

The use of sources of scientific information not subject to peer review surfaced briefly in EPA's consideration of

the AGS EUP. The FET had used AGS marketing publications and articles from popular publications such as Science News in its comments on the AGS EUP. AGS had already released SNOWMAX, a bacterial concentrate of conventionally selected INA + P. syringae sold to improve the efficiency with which artificial snow is made. AGS 1984 Annual Report states

> "SNOMAX works because the bacterium from which it is made, Pseudomonas syringae, is an extremely effective nucleator of ice crystal formation. When SNOMAX is added, water changes from the liquid to solid state more rapidly and at higher temperatures than non-nucleated water.
>
> (AGS, 1984)

It is ironic that the marketing literature for SNOMAX provides circumstantial supportive evidence for the FET's scientific contention that P. syringae can play an important role in ice crystal and raindrop formation in natural atmospheric settings.

EPA HED did not consider SNOMAX's properties as described in AGS' annual report to be as useful a source as the solicited opinions of Schnell and Borys. From the analysis of the weather issue, EPA concluded that there is no evidence that links potential decreases in terrestrial INAP+ P. syringae concentrations with decreases in natural rainfall. While inconclusive, the evidence from AGS' marketing literature suggests the plausibility of changes in atmospheric ice nucleation activity if ambient concentrations of INA+ bacteria are altered substantially.

D. Presentation

The preliminary HED analysts' reviews were done on FIFRA pesticide registration review forms. The composite scientific positions prepared by Betz were not based on standard EPA reporting formats, but organized around the worst case scenario. The comments from other offices in EPA and other agencies were in the form of half page letters, generally indicating support for HED's position.

In July 1985, EPA requested public comments on the AGS EUP in the Federal Register. Like other agencies, EPA had to note and respond to comments it received before arriving at its final decision. The views of groups holding alternative opinions in the issues in HED's scientific analysis (e.g. FET) were included in the form of questions directed to the specific SAP Subpanel and AGS.

E. Decision Process

In September, OPP Director Steven Shatzow asked the SAP to review the HED's scientific position on the case. Each SAP member submitted an independent written review of the HED position and the adequacy of AGS' supporting materials to the Subpanel chairman or Phillip Grey, the SAP Executive Director.

The tone of the reviews differed substantially between different reviewers. James Tiede offered praise for AGS and HED's analysis. Martin Alexander said that sections of the

AGS EUP "showed an inadequate understanding of ecology." (Alexander, 1985).

Entomologist Robert Colwell described additional concerns that had not been dealt with: potential dispersal by honeybees, and potential pathogenicity to the ancestral wild strawberry plants found only in Monterey County, California. Most of the reviewers supported doing the test. Two reviewers, Colwell and Alexander, said they did not think their remaining concerns (after EPA HED's review) warranted further delay of the field test.

In addition to these written opinions, SAP member Randolph Borys was called by OPP Director Shatzow to clarify his position on the FET's contention that P. syringae were involved in atmospheric precipitation. In October, Phillip Grey, Executive Secretary of the regular FIFRA SAP, compiled the responses and drafted a formal letter to OPP Director Shatzow indicating that the SAP Subpanel supported HED's position that the proposed field test was environmentally benign.

A formal decision memorandum suggesting approval of the AGS EUP was drafted by HED with assistance from EPA Office of General Counsel attorney Pat Roberts. This draft memorandum was transmitted from Betz through Amy Ripson, Chief of HED, to OPP Chief Steven Shatzow. Rather than presenting multiple decision options, the consensus recommendation of the staff and the SAP, approval of the

EUP, was presented in this memorandum along with arguments rebutting anticipated arguments.

On November 6, 1985, Steve Shatzow transmitted the 7 page decision memorandum to EPA Assistant Administrator for Pesticides and Toxic Substances Jack Moore. The thrust of the decision document sent from OPP Director Shatzow to Jack Moore was that because of the absence of clearly demonstrated weather modification, human pathogenicity, or plant pathogenicity hazards, EPA's SAP staff, other federal agencies and the special Subpanel all recommended approval of the AGS EUP application.

On November 8, 1985, Assistant Administrator Jack Moore approved the decision memorandum and the EPA granted permission to AGS to pursue the field test. In its letter to AGS, EPA recommended the test be conducted in a remote area and that AGS acquire the appropriate permits from the state government agency with responsibility for such tests in California, the California Department of Food and Agriculture.

EPA officials from HED and the Office of Research and Development visited the proposed test site on December 12, 1985 and approved its use by AGS. ORD was represented in order to ascertain requirements for the aerial monitoring program it had planned for the test. Apparently, the proposed test site was located on an inactive farm near a residential suburban area in the most densely populated quarter of an agricultural county (Monterey). An indirect

confirmation that the site was in a higher density area is found in subsequent EPA EUP requirements that AGS:

1) notify all contiguous property owners, and
2) obtain the approval of some adjacent property owners to monitor off site dispersal of the GEMs on their property.

F. Utility of Information Processing

1. Resolving Different Types of Uncertainty

The EPA review process used data from scientific experiments and expert opinion to resolve most of the scientific questions that arose in the case. The competition between INA^- and INA^+ bacteria question was resolved by interpreting greenhouse test data AGS provided. The weather modification uncertainties were resolved by using the expert opinions of the SAP member.

A third type of uncertainty arose in the course of EPA's analysis of the reliability of the information provided by the applicant. With regard to off site transport, there were discrepancies between the data and arguments AGS submitted and published scientific evidence on population dynamics of P. syringae.

Mr. Betz told the SAP:

> "So we don't see any compelling reason to expect that it would not survive and replicate. We are aware that AGS has submitted information showing a decline of the microorganisms after application....we don't think the data provides conclusive proof that all the organisms

> necessarily died. They do appear to have been reduced to lower levels but depending upon environmental conditions, it is conceivable that populations would rebound." (Betz, January 1985 SAP transcript)

Another indication of the potential for unreliable information was a subsequent enforcement action against AGS in which the company was fined for not accurately reporting experimental conditions. (EPA, 1986)

A fourth type of uncertainty raised in EPA's review is the potential for different interpretations of the same information based on different assumptions or scientific models. For example, EPA's treatment of the weather issue rested on current models of atmospheric precipitation formation as much as on empirical evidence.

Mr. Betz viewed the scientific questions of GEM identity, non target plant pathogenicity, and competitive relationships as being due to incomplete data, rather than a result of unreliable data, conflicting information, or the inadequacy of available scientific paradigms. Accordingly, provision of scientific data resolved the uncertainty he and other EPA staff identified. Had the HED analytic team determined that the scientific uncertainties were the result of unreliable information or inadequate scientific explanation, the provision of more data by the applicant would not have resolved the perceived uncertainties.

Within HED, differences of opinion were resolved through information consensus process among technical staff members. Differences of opinion among SAP members were not discussed or resolved. Members independently submitted their reviews of the adequacy of the AGS EUP to part of the decision memorandum Stapzow sent to Assistant Administrator Moore. The questions Colwell and Alexander had were "absorbed" but not explicitly resolved by the Chairman of the panel. This suggests that minority opinions, while solicited did not dominate EPA's analysis of scientific effects.

2. Importance of Scientific Information

From the start, it seems that the framing of scientific questions that were the basis for EPA's regulatory analysis of the AGS case reflected political and legal pressures on the agency from the FET. For example, the presence of a meteorologist on the SAP is an indication the importance of the weather modification scenario contained in the FET suit that blocked the proposed test by Steve Lindow. At least for potential ecological effects, legal pressure was important in gaining consideration in EPAs analysis. The analysis of acute toxic effects could be attributed to the orientation of FIFRA towards acute health effects on humans.

Matching the lists of items discussed by HED and the SAP with the initial list compiled by EPA HED shows small changes in identified uncertainties and issues following EPA's HED's initial information acquisition and analysis.

Mere inspection suggests that the mass of information obtained and processed by EPA did not substantially dispel many areas of scientific uncertainty. Presumably, the function of the information obtained was not limited to the reduction of scientific uncertainty. An additional function of the requested information could be to provide a public, "objective" basis for justifying regulatory decision-making.

EPA officials contacted in the course of this research contend that:

1) EPA has collected a vast amount of scientific information
2) the science is very well "pinned down", and
3) Public perception and politics are very important to determining whether the field test can be executed. (Betz, 1986)

Mr. Betz felt that the scientific and technological information was extremely influential in the final decision reached by EPA. By contrast, Moore viewed the final decision as in the court's and public's hands. Accordingly, he said that scientific and technical information was relatively unimportant in the final decision of society. This suggests that senior decision-makers have a different perspective on the role of scientific information in regulatory risk analysis than policy analysts.

Scientific and technical information are frequently lumped together by non-scientists. EPA's review focused on

scientific rather than technical issues. For example, EPA did not assess the techniques AGS devised to monitor off site dispersal worked. Engineering development needed to obtain scientific data on atmospheric ice nuclei components was not assessed by EPA. Finally, engineering controls of the Pseudomonas in the field during a test was not discussed by EPA -- only the scientific question of whether substantial off site colonization and weather modification could occur. In short, relevant technical information was not acquired, analyzed and presented as part of EPA's decision making for the AGS case.

In summary, it seems that neither scientific nor technical information obtained in EPA's analysis were critical to resolution of the uncertainties posed by the AGS EUP. EPA used the expert opinion of the SAP Subpanel but relid heavily on the consensus of its staff. Though the analysis had elements of worst case analysis, evidence was not always interpreted conservatively. While many profound scientific questions were asked, the criteria used to evaluate the available evidence were not clear and could be used to justify a prior outlook that the field test was benign.

In the next chapter, the issues raised and the processes used by California's state government to review the proposed AGS test will be detailed.

III. DESCRIPTION OF SCIENTIFIC AND TECHNICAL INFORMATION PROCESSING AT THE CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE

A. Background

This section reviews the approach utilized by the California State Departments of Food and Agriculture to assess the safety of the proposed AGS experiment. Special attention is given to the information sources used and how key risk assessment questions were framed, explored and resolved. In comparison with most state programs, California has an elaborate and well staffed environmental protection apparatus. The California Department of Food and Agriculture (CDFA) has the largest pesticide registration analysis staff of any state in the the United States. There are cases in which EPA has registered chemical pesticides that CDFA has not approved for use in California. The root of this independent capability is a close working relationship between CDFA and the substantial commercial agricultural constituency it serves.

Policy Development

In the summer of 1984, the California Assembly asked the Assembly Office of Research (analagous to the Congressional Research Service) to investigate the authority available to

California to regulate the emerging biotechnology industry. An interdepartmental state Biotechnology Working Group was formed to address any regulatory issues. This Working Group had representation from the public, industry, and state government. This Working Group decided that all agricultural biotechnology products, (including microbes, plants, and animals) would be regulated by CDFA either within the existing pesticide or "exotic species importation" framework. This regimen meant that the California Department of Food and Agriculture (CDFA), rather than the California Department of Environmental Quality would have regulatory authority for most ambient environment biotechnology applications. Applications outside CDFA's purview such as sewage treatment systems, oil and ore recovery applications, and artificial snowmaking could be regulated by California's Department of Environment Quality. Like EPA, CDFA decided to assess specific regulatory issues on a case by case basis rather than in advance. No staff additions were made to aid in biotechnology regulation. (Rosenburg, 1986)

Companies intending to test genetically engineered crops or microbes for agricultural purposes in California must first obtain federal approval from EPA. They must also obtain a research use and a transportation permit. The research use permit is a similar but less formal procedure than pesticide registration which governs wide scale commercial usage of new substances. (Goldberg, 1987) The

transportation permit is analagous to the USDA's Animal Plant Health Inspection Services (APHIS) permits required for importation of new pathogens into the United States.

B. Transportation Permit Analysis: What if the product is released en route to the test site?

Dr. Don Koehler, the individual who coordinated the research use permit review, was not available during the period in which the California interviews were conducted. Accordingly, CDFA's transportation permit review will be used to help illustrate the California's approach for analyzing risks for the proposed AGS field test of genetically engineered INA- bacteria.

1. Search Process

In mid- November, Dr. Conrad Krass, a senior member of the Division of Plant Industry Pesticide Registration Branch CDFA Analysis and Identification unit, was given the task of analyzing AGSs' request for permits to transport plant pathogens from AGS's lab facility in Oakland to a number of potential field test sites within the state. The Analysis and Identification unit has historically had two responsibilities: first, identifying organisms brought to the department by growers or county officials who fear them to be harmful. The second responsibility is to do assessments of impacts of potential new pests to California, and make recommendations on how to alleviate possible

problems. Thus there is a sense in which the regulatory questions posed in the AGS case were routine for the Analysis and Identification Unit. Formal CDFA transportation permit analyses typically entail:

1. a literature review.

2. an exotic pest profile covering its history, distribution, hosts, methods of detection, methods of control, and

3. making recommendations for CDFA action.

Dr. Crass's analysis of AGS EUP transportation safety was expected to take two weeks. He expected that the most questionable information would be which crops could be infected by pseudomonas syringae in each affected county. In contrast to the registration analysis which focussed on P. fluorescens, this analysis' focus was on P. syringae, a documented plant pathogen.

Sources of Information

The first information sources provided to the Analysis and Identification unit was the AGS EPA Experimental Use Permit (EUP) application. Second, Crass used the Pesticide Registration Branch's extensive in house files and library. The library was used extensively because there is a great deal of information in the plant pathology literature concerning P. syringae's interaction with commercial crops. Third, Crass used the Dialog computer-based information retrieval service to do an exhaustive literature search on

the organisms in question. The fourth source of information used was a group of University of California scientists. These were selected because they had expertise on certain plants' pathology These consultations were conducted by telephone; no written confirmation memos or letters were produced for inclusion in the CDFA records for the case. The last information source utilized was AGS. AGS provided additional experimental results to CDFA scientists to assess the pathogenicity of the genetically engineered INA- P. syringae on non target host plants of commercial importance.

In evaluating the usefulness of these information sources, Crass rated them as follows:

Table 3

In-house files	Very useful
Scientific Literature:	
Library-accessed	Very Useful
Dialog-accessed	Very Useful
AGS EUP Application	Somewhat useful
Univ. California experts discussion (phone accessed)	Somewhat useful

Crass reported that the AGS information search process followed his typical pattern with two exceptions. Dialog was consulted because needed information was unavailable through other sources (not because of possible time savings through use of the database service). The AGS experiments were analyzed because the scientific literature did not discuss AGS's engineered strain.

2. Analysis Processes

For the purpose of evaluating potential risks to commercial agriculture in California, an accidental transportation release of the entire quantity of AGS' product was considered. Since Crass assumed that standard transportation control practices would break down away from the proposed test site, Crass's analysis could be construed a worst case contingency analysis. Worst case was limited to the experimental P. syringae leaving the site, establishing colonies, and infecting various commercial plants. Crass did not consider possible effects on non commercial non target species of plants and animals, local ecoosystem function, ranges of temperature sensitive species, or precipitation. There was no attempt to quantify the risk assessment.

From a disciplinary perspective, the main information sources used by Dr. Conrad Krass were, in order of importance: plant pathology, microbiology, and the ecology literature for the two parent strains of AGS' test product. Crass viewed little of the information he obtained as uncertain. The greatest perceived uncertainty concerned the host plant range of the AGS P. syringae strains. To resolve these questions, Crass requested that AGS or the University of California at Davis perform additional host range studies in which the parent strain, the engineered INA- mutants, and a known pathogen of the same species are tested on different host trees. These experiments provided evidence that

alleviated Crass' perceived uncertainties. Other than scientific judgement in interpreting these tests, no special analytic procedures were used to evaluate risks covered by the California transportation permit. Crass assumed throughout his analysis that the behavior of the AGS products in the field should closely resemble the behavior of the parent strains.

3. Presentation of Scientific and Technical Information

The conclusion drawn by Crass were presented in a handwritten, half page memo to CDFA attorney Sharon Dobbins. In this memo, he suggested that the permits be approved. There was an understanding that decisionmakers wanted a single recommendation rather than a detailed presentation of different options. Crass does not believe that any techniques are more successful than any others in conveying scientific or technical information or uncertainty. He believes that prior attitudes color the reception of uncertain scientific information on pesticide risks. "How you say it doesn't matter. Some people are against all new pesticides." (Crass, 1986) In early December, Ms. Dobbins sent a letter to AGS formally approving permits to transport both AGS INA- species to twenty six counties in the northern and central parts of the state. (Dobbins, 1985)

C. CDFA's Experimental Use Permit Review

Scope of CDFA Review

Dr. Tobi Jones, Acting Branch Chief of the Pesticide Registration Branch, was responsible for managing the review of the AGS application for the experimental use permits. When the review process started, the three scientific and technical questions she identified as having the greatest uncertainty were:

1. how could quality control be maintained for the bacterial agents,
2. how could humans be monitored for whether any of the bacterial agents had infected themselves, and
3. what the main areas of scientific safety questions were for engineered microorganisms.

In accordance with CDFA's interim policy on regulating biotechnology products, Dr. Jones decided to spread the review of the application to a number of technical experts in CDFA and other departments. Three alternative definitions of the potential hazards from FROSTBAN were considered initially:

1. What is the human pathogenicity of the AGS strains?
2. What are the risks of environmental contamination?
3. What are the plant pathogenecity risks?

Rather than participate in the component analyses of the scientific and technical questions analyzed to assess the

safety of the proposed test, Dr. Jones reviewed its conclusions, concurred, and presented them to higher authorities in CDFA and outside groups. Dr. Jones designated DPRB staff member Don Koehler, a plant physiologist, to coordinate the technical review and develop a composite position and recommendation on the AGS application. (Jones, 1986)

1. Search Processes

The primary responsibility for developing coordinating the technical analysis of the safety of AGS' test product and developing a CDFA position fell on Dr. Don Koehler, a senior Plant Physiologist. Dr. Koehler requested comments on the EUP data package from a select group of individuals in CDFAs Division of Pest Management and the CDFA Biotechnology Working Group as well as representatives of the California Department of Health Services, and the State Water Resources Control Board. Koehler asked reviewers to address "Whether there will be environmental or health hazards presented by the proposed small-plot testing on strawberries, the significance of any such hazards, and whether they can be mitigated." (Koehler, 1985) Each of these groups were represented on the state Biotechnology Working Group. The disciplinary backgrounds of these reviewers included microbiology, toxicology, industrial hygiene, entomology, bacteriology, water pollution, and wildlife biology.

2. Analysis

Health Department Microbiologist Paul Duffey noted that P. syringae has never been a human pathogen and that P. fluorescens is only an opportunistic human pathogen. Opportunistic pathogens are microorganisms that can adversely effect certain hosts only when the hosts, e.g. humans, are in a weakened condition due to other infection, burns, or other trauma. Most reviewers concurred with this characterization of the test strain's parents.

Duffey surmised that a high but indeterminate dose of P. fluorescens was required to initiate human infection because few variants naturally grow at human body temperature. He suggested a set of chemical and physical controls to protect applicators from breathing in a potentially infectious dose of P. fluorescens. The recommendations for worker protection included use of a specific type of respirator, procedures for chemical decontamination of clothing and equipment, and a requirement for medical monitoring of the applicators. Harvard R. Fong, an Environmental Hazards Specialist in the Worker health and Safety Branch, amplified on Duffey's recommendations, suggesting specific coveralls, gloves, boots and goggles be used by applicators involved in the test. (Mengle, 1985)

Etymologist Arun Sen suggested the desirability of conducting experimental trials with beneficial insects to examine the effects of using the AGS product on insect pests. Microbiologist H. Daoud, and J.F. Remsen, a

toxicologist, requested that AGS do quality control tests to assure that the experimental innoculum is the one identified in the documentation and is viable. An Environmental Hazards Specialist in the Medical Toxicology Branch of CDFA, T.E. Esser, suggested that a contingency plan be developed for early termination of the experiment in the event that the organisms behave as pests. Lesser, Remen, and Daoud suggested AGS perform additional tests, that would be desirable but would not required. (Mengle, 1985)

In his review, Dr. Remsen noted "the question of environmental impact needs to be addressed by the appropriate evaluators." The California Fish and Wildlife reviewer, John Shelgan, felt that there would be no adverse effects on nontarget fish or wildlife from the test. (Shelgan, 1985) Division of Water Quality Pollutant Investigations Branch Chief Dr. David Cohen was concerned about possible drift or discharge of the test bacteria to the surrounding water bodies. He asked that aquatic toxicology tests be performed prior to large scale field testing. (Cohen, 1985)

3. Resolution of Ambiguity and Conflicting Scientific Interpretations

Dr. Koehler quickly developed a regulatory position on the test that integrated most of the reviewers' control suggestions but not the proposed experimental questions. On December 12, Koehler sent a memorandum supporting approval

of the EUP to Dr. Jones in which he responded to individual reviewer concerns. For example, in regard to two reviewers' questions about quality control, Koehler noted that "each batch of bacteria must be grown up fresh and used immediately, since it is not stable...There is no reason to expect that contamination would occur in this preparation, when it has never been seen to be a problem previously." Responding to the question about the test's effect on beneficial insects, Koehler said,

> "For the most part, these types of data (questions about beneficial insects) have to do with larger scale testing or a Section 3 registration of this product...Exposure to insects, wildlife, or bodies of water will be extremely small, since considerable precautions are being taken to prevent off-site movement, and monitoring will be conducted to check for this." (Koehler, 1985)

At the conclusion of the two page memorandum, Koehler recommended that the state EUP be approved with requirements for protective clothing for applicators, medical monitoring of applications, and development of a plan for early termination of the experiment. Koehler's resolution of the proposed experimental questions brought out in the review is consistent with the theory that policy analysts "absorb uncertainty."

4. Decision Outcomes: The CDFA EUP Paper Trace

On the same day (December 12), Koehler sent a letter to AGS Field Engineer Steven Cull approving California experimental use permits for the P. syringae and the P. fluorescens. The permits were subject to the following conditions:

1. Personnel from CDFA and the Monterey County Agricultural Commissioners Office were to be present as observers when the application of the bacteria is made.

2. A contingency plan for the termination of the experiment and destruction of the treated vegetation should symptoms of disease or toxicity attributable to the treatment occur be implemented.

3. Specific recommendations for worker protection developed by the department of health services for medical monitoring and protective clothing and equipment should be followed.

4. EPA EUP conditions be followed, and all reports sent to EPA concerning the results of the experiment be sent to CDFA.

5. The Monterey County Agricultural Commissioner, Dick Nutter shall be notified five days before the test and invited to be present at the test. (Nutter is an employee of CDFA, under the Division of Plant Industry, and not of the Monterey County to whom it also has responsibilities.) (Koehler, 1985)

The alacrity with which Koehler responded to the AGS request after he completed his analysis, usurping one of Jones' titular responsibilities, suggests that there may have been some undocumented pressure to render an expedited approval.

5. Organizational Factors that Influenced CDFA's Process

Dr. Jones indicated that what made the AGS EUP process organizationally atypical was the use of Koehler's special review committee with membership outside of CDFA. While there was no precedent for handling genetically engineered microbial pesticides, the CDFA had already developed a procedure for such situations. This protocol used existing legal standards and required solicitation of (but not adherence to) scientific judgments of extramural (out of CDFA) reviewers.

Senior management at CDFA did not intervene in the scientific information search process by working as team members, monitoring information gathering, or providing tips on possible sources. When the staff presented its findings to senior management, there was informal oral questioning. Despite interdepartmental communication at the higher "policy level" in developing the CDFA protocol for dealing with genetically engineered agricultural products, the in state transportation risk analysis was done by one person without input from other scientists in his unit or the health department. This type of relatively cursory review

is analagous to the type of review that USDA's APHIS does for transportation of exotic plant imports.

In contrast, the analysis in support of the California research use permit, analagous the federal EPA EUP, had input from four different departments who conducted independent analyses. This type of review can be characterized as a composite review. It was not truly interdisciplinary, because no attempt was made to facilitate two-way discussions between people in different fields. The paucity of consideration of broad environmental impact questions may stem from differences in public participation between the CDFA Research Use permit process and the EPA EUP process.

As senior decisionmaker on this issue, Dr. Jones indicated a detailed presentation of different options for modifications of the permit would be less useful to a single recommendation. No attempt was made to replicate EPA's time-consuming risk analysis review process. While EPA was a primary source of information, extramural scientific review by University of California scientists was used as a "reality check" on EPA's process outcome.

6. Evaluation of the Utility of Scientific and Technical Information

In terms of CDFA's decisions, Dr. Jones suggested that three pieces of scientific information had the most weight in the final CDFA decision to approve the permits: the

microbial competition data, the comparative plant pathogenicity data, and biochemical and taxonomic analyses that indicated the similarity between the AGS INA- bacteria and the parent strains of P. syringae and P. fluorescens. The scientific literature on the pathogenicity and toxicology of naturally occurring p. fluorescens was necessary, but not as important to her as these three sources. Scientific and technical information, in contrast to economic or political information, was described as between moderately and extremely influential in reaching CDFA's decisions by the CDFA personnel interviewed.

D. Comparison of CDFA with EPA

1. Comparison of Scientific Issues

CDFA, like EPA was concerned with risks from nontarget plant pathogenesis. CDFA's solicitation of extra experiments by AGS, monitored by the University of California at Davis, indicates that risks to commercial agriculture from nontarget plant pathogenesis were more important to its decision than at EPA. Individual EUP reviewers reiterated AGS arguments that its INA- strains were competitively inferior, although data submitted to EPA showed competitive equality. Nevertheless, CDFAs independent transportation permit review assumed local domination of INA- strains and found no adverse effect. While the absence of competitive domination by applied INA- strains was an important fact in EPAs decision to authorize its EUP, the

relative competitiveness was not critical to the state EUP authorization, with its more limited view of potential hazards.

EPA reviewers did not comment on the potential for changes in host ranges of beneficial insects, an indirect ecological balance issue. While a single CDFA reviewer brought up this issue, Koehler said that the small scale of the test obviated the need to assess it at this stage. Thus, the small scale of the test was important to the handling of different qualitative risk issues in the EPA and CDFA permit review processes.

AGS Strain Identity

The identity of the AGS strains posed a major question for the EPA reviewers. EPA reviewers tended to treat the AGS mutants as a new strain whose hazard they had to evaluate. In contrast, Dr. Jones was impressed by a high level of similarity between the AGS strains and the parental Pseudomonas strains shown by a set of bacterial physiology tests. Consequently, she felt justified in treating the AGS EUP as a routine case with a high level of scientific knowledge about the behavior of the bacteria. EPA HED personnel were not as comfortable with this qualitative measure of similarity; consequently, they perceived the scientific question of AGS organism identity as more non routine.

The greatest difference between scientific issues considered in the the EPA EUP review and the CDFA review concerned the issue of possible effects on precipitation. EPA recruited an individual with a background in atmospheric science to review the arguments. In CDFA, plant pathologists were responsible for obtaining information and resolving the associated uncertainties. Both EPA and CDFA contacted NOAA consultant Russell Schnell by telephone to solicit his views before rendering their final decisions.

CDFA required more controls than EPA to reduce potential risks of human infection from applying AGS' P. fluorescens strains. This may reflect the professional practices of industrial health specialists represented in California's review process, but not in EPA's. EPA's SAP suggested selection of a remote site, a physical control measure. By contrast, CDFA added no additional requirements for site selection. CDFA relied on chemical bacteriacides as a control measure to combat any untoward contingencies during the tests.

2. Comparison of EUP Review Processes

Despite the precedent-setting nature of the case, CDFA treated the case, with a few exceptions, in a generally routine fashion, employing common processes to search, analyze, and transmit scientific and technical information. By contrast, the EPA, which also used an existing legal framework designed for chemicals and conventionally selected

organisms, employed a more pluralistic organizational process to analyze scientific and technical information related to the test. Perhaps as a consequence of these organizational process differences, CDFAs analysis focussed on questions for which there was a high degree of perceived scientific certainty. EPAs analysis, by contrast, focussed on questions for which there was a high level of perceived uncertainty.

The process utilized by CDFA relied heavily on the separate, independent scientific judgement of in house experts. While there was a fairly broad disciplinary spread among CDFA technical staff, few had any direct experience with genetically engineered organisms, nor with the infant art of "predictive ecology." Technical staff at CDFA availed themselves of the resources of the University of California University system, which is strong in both plant ecology and genetic engineering. This reliance contrasts with EAA's more independent process.

Our review of the CDFA documents and the interviews with participants supports the view of a compartmentalized, independent scientific analysis process that followed a more political policy setting process. It is also plausible that the political policy process preceded the scientific approval process and merely waited long enough for validation of its prior decision to "fish" rather than cut bait.

CDFA considered the state Research Use Permit and transportation permit with less public knowledge and participation than the EPA. One rationale is that the EPA function of obtaining input from the public had already been sufficiently treated in the previous phase of the process. Perhaps as a result, CDFA's process operated much more quickly. Like EPA, CDFA required AGS to notify a public body in the component jurisdiction in which the test was proposed. Unlike EPA's requirement that AGS notify CDFS, CDFA's requirement to notify County Agricultural Commissioner Richard Nutter did not provide Monterey County with an opportunity to independently review and potentially reject the test proposal or site. As an Agricultural Commissioner, Nutter is an employee of the CDFA rather than of the County, potentially compromising his independence.

The most important difference between CDFA and EPA's policy regarding lower government levels is probably there there was no requirement that the County government be notified of the proposed test. The test could be legally conducted in secret under existing California law and regulations in February, 1986.

At this point we will turn our consideration to Monterey County, where the proposed test site was located.

IV. DESCRIPTION OF SCIENTIFIC AND TECHNICAL INFORMATION PROCESSING AT MONTEREY COUNTY

A. Background

The initial impetus for Monterey County's consideration of the proposed AGS INA- field test was a petition tree farmer Glenn Church filed with the Monterey County Board of Supervisors on January 6, 1986. The petition asked the County Board of Supervisors to look into the safety of the proposed test site and consider local regulation of the experiment because of various unanswered questions. Church and other county residents had been in contact with FET president Jeremy Rifkin, who served as an information source to the local group. Following CDFA's December approval of the California EUP and transportation permits, persistent rumors suggested that the site of the AGS test was the farm of AGS field engineer Steven Cull. Cull's property was located near Castroville in the northern part of the county. These reports were initially denied by AGS, CDFA, and EPA in newspaper accounts.

Mark Del Piero is the Supervisor elected who represents the northern district of Monterey County where Glenn Church lived and the test was expected to be performed. He suggested to Chairman Sam Karas that Monterey County find

out definitively what was being contemplated and what could be done about the situation. Karas called a meeting with County Environmental Health Director Walter Wong and Supervisor del Piero. Wong was asked to lead a special committee that would quickly define the extent of the problem, if any, and determine what options are available to the County to address it. The Supervisors requested a report as soon as possible, preferably within one week.

Walter Wong suggested that other county department heads be represented on the special committee. Members were: Agricultural Commissioner Richard Nutter (a CDFA employee), Director of Planning Robert Simmons, County Counsel Ralph Kuchler, and Air Pollution Control Officer Larry Odle, and Robert Melton, the Health Department Director and a medical doctor.

Organizational Factors that Influence Search Processes

As Environmental Health Director, Mr. Wong's primary duties relate to toxic materials, food sanitation, solid waste and sewage, vector control and other public health issues. While the bulk of his department's work is regulatory, special research projects are often undertaken by the County Health Department. Wong's time is split between administration, research and analysis and communication.

B. Search Processes

When he started his analysis of the situation, Wong had no trustworthy information available on the test site location, acute health, environmental, or long term ecological impacts from the proposed test. Because of the emotional impact of the topic in the County, Wong indicated that it was very important.

Mr. Wong was individually responsible for defining the issues posed by the experiment. He defined five classes of potential adverse effects to consider: agricultural impact from unanticipated pathogenesis of crops, (agriculture is very important to Monterey County, 90% of iceberg lettuce grown in the U.S. is from Monterey County), human health impacts, ecological impacts, financial liability for unanticipated effects, and the lack of local input to decision-making.

Prior to undertaking the process, Wong considered himself to be very knowledgable about pesticides and quite knowledgable about the field of genetic engineering. The press was a major source of information about the issues in the initial phase of the investigation before Monterey County's public hearing.

At the outset, the types of technical information that seemed to have the greatest potential for being uncertain or questionable for reasons of conflict of interest were the following:

- identity of bacteria being tested
- availability of assays for monitoring the field tests
- safety of tests
- bacterial pathogenicity (long term).

A number of organizational questions also seemed quite uncertain. These included:

- what organization would perform the tests;
- whether the federal government could regulate genetic engineering if it cannot adequately monitor the environment for the presence of the bacteria;
- whether the state needed information from AGS to do its monitoring;
- what the legal options of the county were and
- when the proposed test would begin.

Sources of Technical Information

The first organizations contacted by Wong in his effort to assess the significance of the proposed AGS experiments were the EPA and CDFA. These contacts were by telephone. The second source of information was published documents in peer reviewed science journals. Along with them, the Committee examined letters to editors in science journals commenting on the development of the field of recombinant DNA and the potential hazards associated with outdoor applications of biotechnology. Wong received initially unsolicited input from a loose knit network of private citizens in Monterey County who opposed the test. The last

source of information Wong tapped prior to the public hearing was the Foundation on Economic Trends.

The first information acquisition mode, phone interviews, was selected to save time and energy. Federal, state and industry sources were contacted. Initially, these sources refused to release information to the Health Department on the grounds that it was proprietary to AGS. In addition, EPA and the state of California were of the opinion that Monterey County had no legal interest in the case.

The second scientific and technical information source, the published literature, was considered "not very useful" because the Committee needed decision making criteria for evaluating environmental releases. Scientific articles did not deal with such regulatory questions. Wong suggested that one can only obtain opinions on decision making criteria in person and on the phone. The scientific literature did suggest that the bacteria could be transported off a test site. There was no time for in person visits to any information sources prior to the January 14 hearing.

The third source of information was the press. While the press did not provide technical information on the organisms, the press used its resources to corroborate previously unsupported rumors relevant to the test site and test date. For instance, an initial rumor, that the test was planned for the Castroville property of AGS Field Manager, Steven Cull, was corroborated by matching an EPA

map of the test site with Salinas, California obtained with an aerial photograph of the property. The expense involved in corroborating such useful information would have been prohibitive for the county Health Department.

An important contribution to the process of information acquisition was non scientific legal research on statutory regulations and legal precedents. The Board of Supervisors' attorney, Ralph Kuchler and Sam Karas, operated independently to examine these issues. Kuchler examined the interrelated legal requirements of federal, state, and local laws. Karas obtained a review of California's regulatory regimen for biotechnology from the California Assembly Office of Research. It was through the attorney's review of this document that the regulatory option of a land use moratorium was devised.

Additional Sources of Input

Many "organizational uncertainties" bore on process of gathering technical information. First, there were differences in the values and perspectives of the various groups in the county. In particular, there was a split between the ecologically minded Carmel coastal area citizens and the agriculturally minded residents of inland areas. Wong made a conscious attempt to contact leading agricultural powers in the county to assure that their interests were not being overlooked in the County's deliberations on the case. In addition, there was a split

between the less affluent, more remote southern two thirds of the county and the more populous, suburban communities in the northern third of the county. Wong, Karas, and del Piero touched base with political leaders in the different sections of the county to obtain their perspectives. The organizational uncertainty that most impressed the entire committee was the lack of precedent for handling such situations. To its collective knowledge, no local community in the world had dealt with a deliberate release of a genetically engineered microorganism in its jurisdiction yet.

In the face of these uncertainties, the full County Board of Supervisors met on January 14th. Wong presented two alternative recommendations to the Board of Supervisors: 1) that AGS be asked to find a site further away from residential areas or 2) conduct a public hearing in which testimony from AGS, EPA, CDFA, and citizens would be received. In an emotionally charged hearing room with over 150 opponents of the planned test, the Board of Supervisors decided to hold a formal hearing on January 27 in which testimony from AGS, EPA, CDFA, and citizens could be presented.

The level of external political pressure on the County Board of Supervisors started to rise. At this hearing they received a telegram from 27 Green party members of the West German parliament (Bundestag). The telegram said, " Our health and environment must not be sacrificed to the

commercial interests who are so eager to bring their new living engineered products to the marketplace." (San Francisco Chronicle, 1986) Shortly thereafter, Karas' and Wong's phone began to ring off the hook as representatives from CDPA, the California Department of Health, the California Commerce department, individual legislators, and EPA personnel called to suggest that local regulation of outdoor applications of biotechnology was inappropriate.

Karas insisted that all information be funnelled through Walter Wong so that he would have the broadest range of sources and serve as the County's primary scientific resource. Because of the high level of political pressures, and technical controversy and public relations experience involved in the case, Wong decided not to allocate any research tasks to junior people in his department, but rather to do the subsequent analysis personally.

C. Analysis Processes

In his review of the AGS EUP support data, Wong noted that one of seven rabbits treated with the bacterial preparation developed an infection. Although this infection cleared up with time, Wong was concerned that it could indicate possible toxicity to humans. He urged AGS and CDFA to repeat the dermal application test. Wong was also concerned with the toxicity test used because it was designed to test the acute toxicity of chemicals and not the pathogenicity or other chronic effects of bacteria. AGS,

EPA and CDFA did not agree to repeat any tests, asserting that Monterey County had no right to assess health issues where the federal government had preemptive authority.

The literature indicated that monitoring protocols for INA- bacteria test were readily available, although it was unclear whether genetic markers were present in the AGS formulation to permit distinguishing of genetically modified INA- bacteria form naturally occurring INA- strains. CDFA and EPA did not share this information AGS designated as "confidential business information" (CBI) with Wong.

The reputation of Pseudomonas aeroginosa as a human pathogen did impress Wong because of the differences between P. aeroginosa, P. syringae and P. fluorescens hosts. However, the ability to absorb antibiotic resistance bearing plasmids from other pseudomonads did suggest an additional risk factor to Wong. In the 14 days between the Jan 14 Supervisors' meeting and the Jan 27 hearing, Wong could only use a process of elimination to analyze questions concerning adverse effect scenarios EPA and CDFA hadn't explicitly dealt with.

Wong thought the risk with the greatest percentage of adverse effect was of pathogenesis to nontarget agricultural species by P. syringae, a known plant pathogen. Wong felt that the threat of climatic change resulting from the test was minimal. However, some offsite dispersal seemed inevitable, particularly if the test was executed (as

planned) in February, historically the rainiest month in Monterey County.

Accordingly, the site selection issue emerged as the most important county issue. Wong again requested that CDFA, EPA, or AGS definitively identify the location of the proposed test site. None of the organizations complied with the request, fueling both public and County staff suspicion that the test was slated for a property in the northern third of the county. Wong worked on the assumption that the test would be conducted in a mixed farming and residential area like the one in which Steve Cull's property was located. He noted that CDFA required protection of applicators, but residents were not provided with protective clothing and masks. This juxtaposition could make it look as if the County was not adequately protecting the health of its residents.

A related county responsibility issue concerned potential liability. The PET suggested that the County could be liable for possible adverse off site effects from the test even if such effects result from mistakes made by AGS . The County counsel reviewed this issue and supported the PET's interpretation. Potential county liability was perceived as another reason for having a say in the selection of a site for the test.

In conjunction with the rest of the special committee, Wong and Planning attorney Kuchler prepared a decision option for Monterey County based on its statutory power to

regulate land uses within the county. According to the committee's analysis, AGS' INA- GEMs are animals, and application of nonindigenous GEMs is a new land use in the county. AGS could be required to obtain a land use permit to assure that their field test is in concord with the county's land use zoning for that area.

The Public Hearing as an Analytic Process

On January 27, the Monterey County Board of Supervisors held a seven hour hearing on the test proposal. Representatives of AGS, CDFA, EPA, the FET, and independent scientists supporting and opposing the test testified in front of a packed auditorium. National and international news media reported on the event. At the hearing, the primary issues were: the organizational responsibilities, the selection of a remote site, and the potential for ecological disruption from competition between AGS'GEM and natural INA+ bacteria.

AGS Director of Marketing and Product Support Douglas Serojak began the meeting by offering to : postpone the test for 30 days to fully address local concerns, provide all information to the supervisors regarding the details of the test, and relocate the trial within Monterey County based on consultation from the appropriate local officials. Trevor Suslow, Director of Product Research, suggested that the proposed test is a small step on the road to responsible

development of environmentally sound commercial agriculture. He said that

> "These are not new issues, merely the same uncertainties now being discussed in a public forum... Those given the public responsiblity (EPA, CDFA) of evaluating the merits (of the AGS EUP data) have determined an absence of any real danger to humans, animals, plants, or the environment...Our shortcoming has been to wholly underestimate the abilities of anti-technologists to manipulate the fears of responsible concerned citizens and scientists who haven't had ready access to all the information."

AGS Project Director Julianne Lindemann (a former colleague of Steven Lindow at the University of Wisconsin) said that worst case analyses for the experiment had been evaluated. She used an elaborate analogy of senior, junior, and sophomore students piling into Volkswagons in a parking lot to describe the competition between INA+ and INA- bacteria on strawberry blossoms on which all the impact scenarios hinged. She suggested that because genetically engineered INA- bacteria have growth behavior like wild type INA+ parents in a variety of hostile laboratory environments (dessicated soil, freezing, heating), they should not be considered as essentially novel organisms. Accordingly, analogies using exotic species introductions such as the Kudzu vine or Dutch Elm Disease are "not appropriate or accurate." She ended AGS' presentation by saying " I ask you to please bear these facts in mind as you, listen to the hypothetical disaster scenarios, illogic, and misinformation

brought forward as fact by those who wish to stop this experiment." (Advanced Genetic Sciences, 1986)

Edward Lee Rogers, the Foundation on Economic Trends counsel, presented a prepared statement on behalf of FET president Jeremy Rifkin. In this statement, he outlined a set of scientific uncertainties that suggested shortcomings in the EPA process. He confined his comments to the precedent-setting nature of the test from a legal perspective and the uncertainties associated with P. syringae's atmospheric ice nucleation activity.

Acting CDFA Pesticide Registration Branch Chief Dr. Tobi Jones testified on behalf of CDFA. She emphasized the fact that the state of California and EPA were treating the Frostban product as a pesticide, and that an analysis of the parent bacteria strains shows that they are not hazardous to either humans or commercial crops.

EPA was represented by Fred Betz. He described the process by which HED and the SAP reviewed the AGS application and resolved uncertainties concerning possible risks from the experiment. EPA FIFRA SAP Subpanel reviewer and University of California at Berkeley biologist Robert Colwell indicated his support for the small scale test as approved in the EPA process; however, he said that he had reservations about widespread commercial use at this time. Sloan Kettering geneticist Liebe Cavalieri pointedly disagreed with AGS' scientists, saying that the test organisms were genetically different from the naturally

occurring INA- bacteria, and consequently their behavior could not be identical to the parents. He suggested the test could have "potentially catastrophic consequences." (Cavalier, 1986)

The majority of comments from members of the public unaffiliated with groups reflected a distrust of AGS and of the safety of the experiment. The question and answer period amplified this sentiment. In response to a questions, Douglass Serojak denied the Cull property in del Piero's district was the planned site of the test, although he offered to work with the supervisors to find another site. EPA biologist Fred Betz admitted "We used the description of the site and surrounding area provided by AGS. Our representatives should conduct on -site inspections, but we don't usually do it." Betz's comment prompted Supervisor Del Piero to comment, "That's a hell of a way to run any kind of agency." (Del Piero, 1986)

County Attorney Ralph Kuchler delivered an opinion on the ability of the County to regulate novel microorganisms. The thrust of his opinion was that while the federal and state governments have preemptive authority for chemical pesticides, a field test of the AGS product, a live bacterium, represented a novel land use and could be regulated as such by county zoning ordinances.

D. Decision Outcomes

On the basis of the received testimony and the assembled political pressures, the County Supervisors adopted a set of four motions culminating in a 45 day emergency moratorium on field tests of new genetically engineered biological materials in the county. The action called for :

1. a special committee to be appointed by the Board of Supervisors to learn more about the field test,
2. this committee shall cooperate with AGS in identifying an alternative, more remote site for the test, and
3. the committee should learn enough about the field test to assure that the Supervisors that the test will not present any significant risk to the community or the environment, and
4. a 45 day period commencing on January 27 in which AGS agrees to postpone conducting the proposed test.

AGS representatives agreed to the 45 day postponement at the hearing. The Board asked the committee to work with legislative staff in the county and state to draft an appropriate zoning ordinance for regulating such experiments in Monterey County by its Feb 11 meeting.

At the February 11 Board of Supervisors meeting, Mr. Wong presented a report by the same special committee that was convened earlier to define the problem at hand. Members were: Supervisor Sam Karas, Supervisor Mark Del Piero, Agricultural Commissioner Richard Nutter, Director of

Planning Robert Simmons, County Counsel Ralph Kuchler, and Air Pollution Control Officer Larry Odle. On the basis of testimony at the hearing and its subsequent review, the committee's principal findings were:

1. Federal and state procedures for granting AGS' EUP were deficient in:
    a. not requiring an independent risk assessment,
    b. not making an onsite inspection of proposed site,
    c. not responding to issues raised by the County Board,
    d. not providing detailed information on human health effects and not requiring follow-up tests.
2. The testing would have minimal impact on plant physiology.
3. Legal issues relating to the California Environmental Assessment Process, and the authority to regulate genetically engineered pesticides need to be reviewed. (Monterey County Investigative Committee, 1986)

The Committee unanimously voted to recommend an Interim Ordinance prohibiting "Experimental Field laboratories using experimental Genetically Altered Bacteria" for 45 days. This recommendation was unanimously adopted by the Board of Supervisors on February 11.

Soon afterwards, Karas and Wong were invited to testify before an Oversight and Investigation Subcommittee of the U.S. House Committee on Science and Technology. A former AGS employee, Dennis Botstein, disclosed that AGS had

illegally conducted plant pathogenicity tests on the roof top of its Oakland facility prior to receiving the EPA EUP. At this hearing, SAP member Robert Colwell reversed his support for the proposed February 1986 field test because EPA ignored his proposed recommendation that the test be conducted in a remote area. In light of these findings, Monterey County leaders felt vindicated in their decision to block the proposed February field test.

In March 16, 1986, with almost no debate, the Monterey County Board of Supervisors passed a temporary, one year moratorium on experiments involving genetically altered bacteria. At this point, Monterey County ceased active consideration of the safety of the AGS test proposal. Sam Karas and Walter Wong continued to press their views on the public participation and legal issues that arose in Monterey County in federal and state legislative forums, the media, and California state agencies during the balance of 1986.

E. Organizational Roles in Evaluation of the AGS EUP

In the Monterey COunty process, Health Department Director Walter Wong acted as both a risk analyst and as a risk manager, personally searching for scientific information, examining the data submitted (after the hearing) by AGS to EPA and CDPA, and maintaining liaison with major corporate and community agricultural interests in a highly agricultural county. Perhaps most importantly, the individual who undertook the analysis of risks posed by the

case was involved in upper level discussions of how to manage the situation. By contrast, the EPA and CDFA reviews of AGS EUP separated the risk management responsibility from the risk assessment functions so effectively that the individuals doing the analysis of the EUP did not report any political pressure in a major precedent-setting case.

One reason Wong may have assumed so much responsibility was the fact that Chairman Sam Karas, a businessman, did not have a formal background in the sciences like the senior decisionmakers in EPA and CDFA. Mr. Karas consulted two independent sources of scientific information in addition to Wong and the investigative committee. The first was a personal friend who was a science teacher at the local community college. He gave Karas, a former executive in the meat packing industry, a basic background on microbiology. The second source Karas consulted was Paul Berg, a Nobel Laureate, Professor of Biochemistry at nearby Stanford University, and a participant in the 1973 Asilomar Conference, at which biologists first considered the implications of the ability to artificially recombine genetic material from different organisms. Ironically, the Asilomar Conference Center is also in Monterey County.

F. Trust and the Burden of Proof

It seems that in Monterey County the burden of proof was shifted from the F.E.T. to AGS to prove the safety of the tests beyond a reasonable doubt. Monterey County accepted

circumstantial evidence in evaluating the merits of the AGS test proposal, for example, the resemblence between the EPA site map and the aerial photo of Cull's property published by the Salinas Californian. By contrast, EPA's scientific review panel didn't accept circumstantial evidence like INA+ P. syringae in raindrops as relevant to its consideration of "scientific risks" posed by the test. In the case of a reasonable doubt, EPA seemed to defer to a no significant risk interpretation. In contrast to both EPA and Monterey County, CDFA did not identify that many uncertainties in its analysis.

Underlying both the burden of proof and the trust questions are organizational questions of what bodies should society rely upon to do risk assessments for new technology products. In subsequent testimony to the House Science and Technology Subcommittee, Wong suggested that organizations with financial interests in the outcome, such as AGS, are inappropriate evaluators of risks from their projects. (Wong, 1986c)

The oft-mentioned specter of qualitatively different types of adverse effects resulting from field application of these INA- bacteria hung in the background of Monterey's considerations. However, that scientific issue did not seem to be as salient as the cavalier attitude with which CDFA and EPA brushed off Wong's requests for additional tests to assure safety of residents of the area adjoining the test site.

One question that had not arisen in the CDFA and EPA consideration was the rights and responsibilities of local communities vis a vis outdoor tests of biotechnology products. Glenn Church, the community leader who initiated Monterey County's consideration, said, "there's a lot of questions but the real question involves the right of the community to protect itself. No one asked county residents if they wanted to be the test site for the first microorganisms test in the whole world." (Church, 1986) Supervisor Karas echoed this sentiment in testimony before the House Science and Technology Committee . He said, "Failure on their (EPA and CDFA) part to notify us of an experiment of such national, if not worldwide significance, is unconscionable...no public official in the jurisdiction most effected was notified." (Karas, 1986b)

Finally, while risks and scientific uncertainties were given as the basis for decisions by Monterey County, press reports indicate that an informal cost benefit analysis weighed the potential benefits from this particular biotechnology application. Environmental Health Director Walter Wong said,

> "Local strawberry growers do not have a problem with frost." Monterey County is not the optimum site for the testing. The major reason for testing here is the proximity to Advanced Genetic Sciences' (Oakland laboratory facility)." (Wong, 1986)

V. CONCLUSIONS

Four distinct types of risk were identified in the problem definition phase of the analyses of the AGS field test proposal. These are human infection, plant pathogenesis, weather alteration, and ecosystem disruption. As Table 4 indicates, EPA, CDFA, and Monterey County focussed on different types of hazards. The lack of consensus between organizations could reflect differences in organizational responsibilities and environmental values as well as differences of opinion concerning the probability and undesirability of each risk from the proposed experiment.

Table 4

Four Types of Risks Identified in Analysis of AGS, Inc. Field Test Proposal

Principal Concern of Risk Analysis	Organization
A. Human Infection	Monterey County
B. Plant Pathogenesis	California
C. Weather Alteration	EPA
D. Ecosystem Disruption	None

Five sources of scientific and technical information were used by the organizations we surveyed. These sources were the scientific literature, individual scientists, expert panels, court cases, and new experiments. Three sources (individual scientists, expert panels, and court cases) can provide political or non technical information along with technical information.

EPA, CDFA, and Monterey County used a variety of information channels to access the technical information the aforementioned sources had. The agencies that utilized each channel are shown in Table 5.

Table 5

Information Channels used in Regulatory Analysis of AGS EUP

Channel	Agencies
A. Agency Libraries	CDFA
B. Online Catalog Services	CDFA
C. Formally Constituted Expert Panels	EPA
D. Informal Network of Experts	MC, CDFA
E. AGS Scientists	EPA, CDFA
F. University Scientists	CDFA
G. Public Hearings	MC

No organization used formal analytic techniques or statistical methods in the evaluation of the EUP or supporting data. All three organizations undertook some sort of worst case analysis. Each worst case analysis had

different assumptions that bore on the scientific conclusions that could be reached by risk analysts. A characterization of the key worst case analysis assumptions used in each organization is given in Table 6.

Table 6

Assumptions for Worst Case Scenario Evaluation

EPA assumed that the weather could change, but assumed substantial off site transport and colonization would not occur.

CDFA assumed that off site transport and colonization could occur, but assumed that changes in the weather could not occur as a result of changes in the distribution of INA+ P. syringae in the atmosphere.

MC assumed that off site transport and colonization could occur, but assumed that changes in the weather could not occur as a result of changes in the distribution of INA+ P. syringae in the atmosphere. MC also assumed that there was a possibility of human infection.

The scientific assumptions each organization made in order to undertake its risk analysis led to differences in the key parametric uncertainties in each analysis. Key parametric uncertainties are uncertainties in which experimental finding could lead to a reversal of a conclusion. A summary of these critical uncertain parameters is given in Table 7.

Table 7

Key Parameteric Uncertainty	Organization
Competition between INA- GEM and wild type INA+ bacteria	EPA
Pathogenicity of INA- GEM to Important Commercial Plant Families Grown near Test Site	CDFA
Human Infection Potential	MC

All three organizations requested that new experiments be performed to help resolve the uncertainties they considered critical. In evaluating the new experimental data requested, EPA, CDFA, and Monterey County seemed to use differing standards. Distillations of these de facto criteria are shown in Table 8.

Table 8

Implicit Criteria Used to Evaluate New Experimental Data Requested in Analysis of AGS Field Test Proposal

EPA	Will GEMs outcompete INA+ P. syringae to the extent that functional populations no longer exist (in clouds).
CDFA	If GEM response is identical to parental strains on a battery of microbial physiology tests, it is considered functionally equivalent to the parental. If GEM causes pathogenic change on a target plant that looks like changes caused by known pathogen, then GEM should be considered pathogenic for that plant.
MC	If there is any doubt as to human infectiousness of INA- product, do not accept presumption of safety.

With the exceptions of the criteria utilized by CDFA to analyze non target pathogenesis by the AGS GEM and the criteria proposed by Monterey to evaluate the chronic human pathogenicity, the organizations surveyed did not formulate criteria for evaluation of requested experimental data prior to receipt of this information. The absence of explicit prior criteria and operational hypotheses permitted organizations evaluating the safety of such experiments to use whatever data is received to justify a decision that is already favored by an organization.

In each organization, there were instances in which differences of opinion on the meaning of scientific and technical information arose. The three organizations relied on the judgement of individuals rather than analytic methods. However, different individuals were responsible for actually resolving identified uncertainties in the organizations. A characterization of the principal organizational processes used to resolve technical uncertainties is shown in Table 9.

Table 9

Processes for Resolving Identified Uncertainties

Consensus of Technical and Legal Staff:	EPA
Judgement of Individual Analyst:	CDFA
Collective Perception of Constituency: at Hearing	MC

On the basis of the analysis of the technical issues each organization pursued, it is possible to interpolate some of the underlying assumptions shared by the technical analysis teams in each organization. For the sake of brevity, I have divided organizational views on each environmental biotechnology risk topic into two opposing sides. Within two organizations, there were some discrepancies in the fundamental assumptions held by analysts. For example, a CDFA reviewer mentioned indirect effects on the ranges of beneficial insects, but the final agency position was that such changes were not possible from the AGS test. Similarly, an EPA SAP member mentioned the potential for changes of the ranges of insects from application of INA- GEMs, but EPA staff did not analyze such potential changes. These interpolated assumptions about GEM introduction are shown in Table 10.

Table 10

Risk Analysis Assumptions

Topic	Viewpoint	Organization
Identity of AGS test product	Novel Parental	EPA, MC CDFA,
Quantitative Effects Threshold	Yes No	EPA, MC CDFA
Indirect Ecosystem Effects (ranges of insects)	Possible Not Possible	CDFA, MC, EPA two reviewers
Horizontal Transfer of INA Trait	Considered Not Considered	-- EPA, CDFA, MC
Influence of Environmental Conditions on Growth	Important Unimportant	MC EPA, CDFA

Each organization had a requirement for presenting scientific and technical information to other analysts and to senior decisionmakers. All three organizations relied on verbal communication. The only graphics used were part of an EPA public information package prepared after a decision had been reached. All the reviewing organizations used textual descriptions rather than scales to characterize the level of uncertainty present in each issue. The primary difference concerned the length and mode of verbal communications. The principal information presentation vehicles used to communicate within the reviewing organizations are described in Table 11.

Table 11

Internal Information Presentation

Organization	Presentation Mode
	1) among field test analysts 2) to senior decision maker
EPA:	1) Primarily used exchange of 10+ page written drafts 2) Presentation to senior decision maker was a 7 page formal decision memorandum.
CDFA:	1) Primarily used 1-2 page interoffice mini-memos, 2) 2 page internal justification written prior to decision
MC:	1) Primarily oral interaction in meetings and on telephone. 2) Primarily oral, 2 page memos written prior to decision

Monterey County's extensive use of oral interaction could be due to the tighter time constraints in which it was was operating as well as underlying differences in legal requirements and management style.

The utility of the scientific and technical information acquisition and analysis process may be examined by looking at the evidence each organization had on the scientific issues it identified as most crucial to its decision. The reduction of uncertainty as a result of new information is hard to characterize. On the basis of the interviews with analysts and examination of the documents that were used, summary characterizations of the uncertainty reduction achieved by each organization on given issues are made. Table 12 shows some of the principal scientific issue the

reviewing organizations were concerned with and a composite characterization of the uncertainty reduction vis a vis that issue that was achieved.

Table 12

Did information acquisition actually reduce perceived uncertainties in analysis of AGS EUP?

Organization	Issue	Uncertainty Reduction
EPA	Weather Alteration	Partial
CDFA	Pathogenicity	Yes
MC	Toxicity in Humans	No

EPA was able to make a decision in the face of arguable scientific uncertainty concerning possible climatic involvement of P. syringae. CDFA was able to convincingly resolve its plant pathogenicity question with information it acquired. Monterey was unable to obtain new experimental information to reduce its uncertainty about the mammalian toxicity of the AGS GEM.

The salience of scientific and technical input in regulatory decisionmaking is difficult to assess for many reasons. Certainly, political factors are more important to the functions of senior decision makers than to staff analysts. The opinions of senior management and analysis staff in each organization that reviewed the AGS EUP on the relative importance of the scientific and technical information are displayed in Table 13.

Table 13

How important was scientific and technical information relative to political and organizational information in making the final decision?

EPA	Senior Management	Low
EPA	Staff	High
CDFA	Senior Management	High
CDFA	Staff	High
MC	Senior Management	Low
MC	Staff	Low

CDFA staff we interviewed apparently collectively viewed the AGS EUP decision as a scientific and technical decision with relatively unimportant political inputs. Monterey County viewed the scientific and technical information as relatively unimportant relative to organizational factors. At EPA, technical staff viewed the scientific and technical information as critical to the final EPA decision. In contrast, the senior decisionmaker for this case viewed the scientific and technical information as less important. The difference of opinion between the EPA officials could reflect the chasm between the concerns of senior management and staff personnel. Perhaps we can conclude that scientific and technical information was not necessarily critical to regulatory decisions concerned with the proposed AGS field test.

The processes employed by EPA, CDFA, and Monterey County to analyze the AGS EUP each had elements of routine processing and non routine information processing. It is

unclear whether the non routine nature of the scientific questions raised by the AGS EUP resulted in non routine information processing. Summary characterizations of the processes the three organizations employed are given in Table 14.

Table 14

Did the Non Routine Scientific Nature of AGS EUP Questions Result in Non Routine Information Processing

Organization	Characterization of Process
EPA	Non Routine but formal process oriented to resolving scientific uncertainties.
CDFA	Routine, compartmentalized process with some participation by other state agencies.
MC	Non Routine with representation of senior management in investigative team.

CDFA's analysis process was the most similar to the procedures used to handle routine, chemical EUPs. EPA treated the decision as non routine but not unprecedented. EPA's process was based on a time-honored way of handling non routine decisions in the government, using an expert panel. Perhaps because Monterey County viewed the case as unprecedented, it devised a special strategy just for this case. Monterey County's process most closely resembled the processes used by private organizations to handle non routine decisions, with closer collaboration of senior

management and technical staff. The hypothesis that the non routine scientific and technical aspects of the case would cause each organization to adopt non routine information processing procedures is not borne out by this research.

The notion that the AGS case would be treated like a crisis because the advent of environmental biotechnology decreased the effective lead times available to government personnel may be evaluated by seeing whether common characteristics of crisis management situations were present. Table 15 recaps five reported characteristics of crisis management situations and reviews the evidence for these characteristics in the AGS case.

Table 15

Crisis Management case studies suggest the following characteristics of crisis decisionmaking.

Characteristic	Evident in AGS Case
No Time to Do Analysis	no
Reliance on Past Search	no
Cognitive Rigidity	yes
Reduced Consideration of Alternatives	yes
Reduced Tolerance for Ambiguity	no

In the AGS case, most organizations had time to do analysis of the questions at hand. No organization relied on past searches, all undertook new searches. All three organization seemed to display cognitive rigidity in analyzing risks from the test. None of the three

organizations considered a cross section of risk management alternatives discussed in the literature on regulation of environmental biotechnology applications. Since only two of five characteristics of crisis management situations were evident in the AGS case, the crisis management literature does not seem to be a particularly apt analogy for the types of problems that arose in the AGS case.

The Importance of Disciplinary Background

The disciplinary background of the individuals and the orientation of the organizations that evaluated the AGS EUP are displayed in Table 16.

Table 16

Disciplinary Orientation of Organizations Surveyed

Organization	Disciplines Represented in AGS EUP Analysis	Dominant Disciplines in Organization
EPA	Microbiology Plant Pathology Atmospheric Science Microbial Ecology Environmental Toxicology Zoology Soil Science Chemistry (staff) Engineering (staff) Law	Chemistry Engineering
CDFA	Plant Pathology Microbiology Medical Toxicology Water Pollution Entymology Industrial Hygiene	Plant Pathology
MC	Public Health Planning Medicine Law	Public Health

At this point, it is not clear what disciplines are most relevant to the analysis of effects from introduction of GEMs into natural environments. Differences in the professions represented on teams analyzing the proposed test for the three organizations could account for differences in the foci of the analyses as well as the evaluation of information obtained in the analysis. The influence of disciplinary orientation on the identification of critical information by individuals involved in the AGS EUP analysis is explored in Table 17.

Table 17

Influence of Disciplinary Orientation in Problem Identification

Individual	Education	Most Important Information
Betz	Envr. Engr., MS	Competition, Scale of test
Moore	Vet. Toxicology, PhD	Pathologic host range of parent organism
Crass	Plant Pathology, PhD	Pathogenicity towards non target plants
Jones	Microbiology, PhD	Microbial physiology
Wong	Public Health, MS	Chronic Human pathogenesis
Karas	Business, High School	Organizational Issues
Rogers	Chemistry, Law JD	Ecosystem Impacts

The theory that individual analysts would focus their attention on components of the larger regulatory question that are part of their individual or institutional disciplinary heritage is strongly supported by the responses of Ph.D.'s interviewed in this case study. A slightly different picture, showing increasing importance of institutional affiliation, is suggested by the responses of interviewees without doctoral training. Wong's concern about the interpretation of acute mammallian toxicity tests is consistent with his departmental responsibilities that include analyzing acute effects of agricultural pesticides on applicators. Mr. Rogers' concern with ecosystem impacts is more resonant with his organizational role as PET counsel

than his background in law or chemistry. Mr. Betz's responses generally displayed less disciplinary direction of concern than other interviewees. Apparently, scientists we interviewed viewed the most critical questions raised in evaluation of the AGS EUP as questions relating to their individual academic background. Individuals without Ph.D.'s tended to reflect more concerns of their organization as well as their principal disciplinary background.

While a diverse interdisciplinary review panel was assembled by EPA, and CDFA invited reviewers with a wide variety of academic backgrounds, scientific concerns identified by individual team members were not synthesized by EPA or CDFA staff into adverse effect scenarios to be evaluated. For example, SAP member Martin Alexander's concerns about offsite transport were not linked with Colwell's concerns about potential ecosystem function impacts from wider scale tests. Likewise, CDFA's AGS EUP reviewers identified some ecological and safety concerns not addressed by EPA. These concerns were not linked together with EPA's analysis in CDFA's consideration of the EUP. The primary interdisciplinary scenario that was evaluated was synthesized not by agency staff, but by the F.E.T. This suggests a weakness in EPA's present capacity to analyze proposed environmental biotechnology applications by scenario analysis.

Lack of representation of the ecology discipline at a staff level has been suggested by some observers as one

reason for inadequate consideration of ecological effects of engineered organism introduction. The presence of ecologists and entymologists as reviewers in the AGS case suggests that disciplinary representation is not sufficient to guarantee consideration of potential risks to ecosystems.

Public Participation in the Analysis of Scientific and Technical Information

Differences in the decision criteria used by government bodies in the absence of definitive data could be related to the active public participation. EPA formally encouraged participation but did not include the public in its internal decisionmaking process. CDFA did not encourage any public participation. Monterey County encouraged participation formally, and included members of the public in their open, hearing-centered decisionmaking process. This process for including the public in deliberations on the proposed AGS field test could have contributed to Monterey County's greater acceptance of circumstantial data from non-scientific sources, and its more stringent decision criteria on risk questions for which definitive scientific information was not available.

Behind the rubric of public participation in the AGS case is the work of an organized, public interest group whose attention is directed almost soley to biotechnology applications: the FET. The everpresent FET instigated the development of the very Interim Policy under which the

proposal was regulated by EPA, identified key scientific issues, encouraged the communication of members of the West German Bundestag opposed to the proposed AGS test (and most deliberate environmental releases of engineered microbes) with the Monterey County Board of Supervisors, provided information to the public and Monterey County, and eventually uncovered evidence leading to EPA's Compliance action against AGS. More than the general public, the FET defined the interdisciplinary scientific issues, and directed EPA's action, as an antagonist in a chess match. Through its actions, the FET directed the media's treatment of the AGS field test application, and focussed the public's attention on weak points in the EUP.

FET's apparent success in temporarily blocking the AGS field test could not have occurred without the public support of Concerned Citizens of Monterey County, the informal coalition tree farmer Glenn Church founded following CDFA's approval of the test proposal. One reason for Church's success in blocking the test was the assistance of his politically savvy father, a former County Supervisor. A second reason may be Monterey County's position as an unofficial seat of New Age consciousness. (Santa Cruz Express, 1986) According to Fritjof Capra, a Monterey county resident and author of <u>The Tao of Physics</u>, New Age politics involves a reevaluation of the role of man in the ecosystem and a respect for nature's balance. This perspective may have contributed to a distrust, at least

among the liberal Monterey county populace, of EPA judgement vis a vis protection of ecosystem integrity as well as human safety. Unlike the 1983 NIH University of California INA-field test proposal case, FET's legal challenge to the AGS EUP was unsuccessful. This juxtaposition suggests that FET's importance is primarily as an issue and information source, powerful only when it has public support, rather than as a powerful litigant without any constituency, as some observers have contended. (Wall Street Journal, 1986)

In a sense, the public, invited by Monterey County government, acted as a science court. Like a court, it rendered a decision with the advice of experts but independently, on the basis of classes of risks identified in popular magazines, speculations by non-scientists, the use of P. syringae to enhance artificial snowmaking operations, and other evidence that was inadmissable in more august forums that considered only existing scientific information. Much like traditional juries, the apparent forthrightness and trustworthiness of witnesses was weighed heavily in the public's evaluation of their input. AGS was not viewed as trustworthy because it was not forthright in disclosing information about the test to the public. In addition, AGS's apparently contradictory testimony on the complex question of the identity of the genetically engineered strains debased the currency of its other arguments. Many Monterey County opponents of the test did not share the FET's moral opposition to genetic engineering

or even environmental applications of biotechnology. For example, Monterey County journalist Jonathan Drake says,

> "I think the use of genetic engineering will be a boon to chemical manufacturing and biomedicine...But I think that the AGS application is potentially dangerous to the ecology and is unnecessary. Frost damage is not a significant problem in the U.S." (Drake, 1986)

Monterey County's decision prevailed despite the opposition of an influential, well supported industry, and federal and state agencies who felt their authority could not be preempted by any county. One interpretation of this unlikely outcome is that Monterey County and the general public acted to assure that due process was taken in regard to the evaluation of the risks from the first environmental test of a viable GEM in the U.S. While FIFRA analysis fulfills the legal requirement for an environmental impact statement or equivalent review to comply with NEPA (that sunk the 1983 proposed Lindow and Panopolous experiment in District Court Judge Sirica's court), it does not necessarily fill society's expectation for a robust environmental impact statement to support the first deliberate application of viable, genetically engineered microbes in the USA. This argument is buttressed by the fact that neither CDFA nor the US EPA has sued Monterey County over its position on this case, despite the fact that representatives of both EPA and CDFA publicly challenge Monterey County's right to regulate tests of GEMs.

EPA did not obtain the public approval of their process and support of their position that Assistant Administrator Moore identified as "crucial" to the success of the EPA biotechnolgy regulation program. CDFA has subsequently altered its process for analyzing genetically engineered pesticides to provide for special public notice in potential host counties prior to issuance of future EUPs. Local approval of field tests is not required by CDFA.

Potential Conflict of Interest

In February 1986, on the basis of a hand typed communication from a digruntled employee and at the instigation of the FET, EPA began investigating the conduct of AGS experiments in support of its EUP. EPAs subsequent evaluation of AGS experimental data revealed that relevant experimental conditions were not accurately reported by AGS. The verified allegation was that EUP support tests EPA believed were conducted in indoor greenhouses were actually conducted on the rooftop of AGS Oakland facility. (EPA Compliance Enforcement, 1986) AGS was initially fined $20,000. Following an invited negotiation with EPAs Office of Special Counsel, the fine was reduced to $13,000 and the charge of "falsification of data" was tempered.

AGS asserted that the level of containment of GEMs injected in trees is higher than the containment achieved in spraying GEMs inside a conventional greenhouse without negative pressure or other controls. Many scientists agree

with this contention, although the practice of not reporting the experimental site fully was deplored. An important technical problem with using trees on the rooftop is that many experimental conditions relevant to the outcome of colonization tests, such as level of moisture available, can be substantially different from the inside of a moist greenhouse.

This enforcement action brought the potential for conflicts of interest in doing experiments used in risk assessments for environmental applications of biotechnology to the fore. While this enforcement action occurred after EPA's first EUP decision, it suggests that alternative institutional sources of experimental information may be needed to avoid conflicts of interest in risk assessment data reporting in the future.

VI. RECOMMENDATIONS

To resolve difficult new environmental conflicts, the USA has frequently sought legislative solutions. Many issues raised in the AGS case are not amenable to solution by legislative fiat. Due to the diversity of environmental biotechnology products and conditions, a unitary legislative framework for environmental applications may not make sense. As FDA Special Assistant Henry Miller noted in a letter to Science, a single enzyme produced by a single organism to perform two applications in different environments requires review by individuals or organizations with substantially different expertise. (Miller, 1986)

Legislation can provide new standards for balancing the risks and benefits of environmental applications of biotechnology. A broad public debate is needed to develop a set of policy goals for environmental biotechnology development. Policy endpoints, identified in additional legislation administered by different agencies, could provide criteria for regulators to use in evaluating the various impacts of diverse environmental biotechnology applications on the environment. Such legislation will not reduce the magnitude of the uncertainties faced in ecosystem function assessment nor the difficulties in determining the

scientific significance of possible changes. However, legislation designed for environmental applications of biotechnology could reflect the potential for impacts that could not arise from historical environmental chemical release.

Legislation can also vacate the present EPA policy of separating risk management from risk assessment. Cogent regulation of future environmental applications of biotechnology should more closely relate management practices that are adopted for specific tests to the risks that are identified and analyzed. While legislation cannot mandate management styles, this review of the AGS case suggests that, at least for environmental applications of GEMs, special care should be taken to manage risks that are analyzed.

While the use of external data sources is suggested for non routine decisions, special care should be taken to assure the comprehensiveness and credibility of sources of information used in evaluating environmental applications of biotechnology. Legislation could provide guidelines for the use of corporate, university, and anecdotal sources of information to evaluate new applications of biotechnology for which there will probably be little information published in peer reviewed journals.

A second recommendation is the development of a new, biology-based conceptual framework for analyzing effects of environmental applications of biotechnology. The AGS case showed that two of the three government organizations relied

on chemical hazard assessment assumptions. The use of interdisciplinary panels like the EPA FIFRA SAP Subpanel is an important first step towards the goal of developing an capability to analyze biological impacts of environmental applications of biotechnology. However, this case study showed that existing boundaries of relevant academic disciplines do not extend to cover many of the transdisciplinary issues that emerged. The development of a hybrid science like predictive ecology, to supplement the contributions of existing disciplines, is needed to address issues that seem likely to recur in future environmental biotechnology applications. The development of this new discipline, like the development of fields such as neurolinguistics, may involve changes in both the types of research questions asked and types of answers obtained. Sustained financial and institutional support is needed to obtain the participation of creative academics in addition to the environmental consulting organizations that have been responsible for much of the extant analysis of risks from genetic engineered microorganisms. In the long run, developing a new conceptual scientific framework for environmental biotechnology analysis may be more important than new legislative criteria for decisionmaking, for this framework will be used to frame the very questions that are assessed in any review.

The task of risk analysis is a technical endeavor which shares conceptual components with academic research, but has

different requirements. In the analysis of the AGS EUP, scenarios were developed and evaluated. The role of scenario generation is too important to current analysis of environmental applications of biotechnology to be left to litigants like the PET. Regulatory agencies should be responsible for the task of weaving together physically and biologically plausible scenarios for each proposed application. Evaluation of such scenarios cannot rely on expert opinion indefinitely; protocols for systematically analyzing biological scenarios need to be developed. (See Appendix III for a discussion of requirements for usable intermediate testing protocols.) Whatever approach is used to evaluate adverse effect scenarios, technical risk analysts should define decision criteria for evaluation prior to undertaking experiments. Based on the AGS case analysis, it seems possible that this framework will be based on qualitative characteristics of organisms and ecosystems rather than quantitative parameters. This could have important implications for future risk management practices.

The third recommendation is the support of research elaborating biology based risk management practices for environmental application of biotechnology. In the AGS case, Monterey County and the EPA only required the most rudimentary physical control: siting. CDFA required chemical biocontrol methods that have clear limitations in uncontrolled environments. If the test was executed on schedule and the product colonized a substantial area off

site, (the first step in EPAs adverse effect scenario) neither physical or chemical control method would suffice. Successful control of the risks identified in risk analysis is a logical requirement for management of future environmental biotechnology applications.

Rather than relying on the accuracy of scientific prediction at the frontiers of science, the engineering principle of using conservative design to achieve safety could be applied to environmental applications of biotechnology. As Kenneth Drexler points out in The Engines of Creation, risks from new applications of molecular biology are unlikely to be reduced by attempts to slow down technological development because of the types of benefits that are likely to accrue to society from certain applications of biotechnology. The design process, applied to biotechnology products, would be a more appropriate phase in which to incorporate concerns about ecosystem interaction than the outdoor testing phase. Potential risks from eventual widespread deployment of environmental biotechnology applications may be reduced by many orders of magnitude by applying conservative judgement and combinations of appropriately selected biological control mechanisms. The hierarchy of biocontrol mechanisms can be integrated into plans for staged testing of enviornmental applications of biotechnology. Such an approach of course depends on the willingness of both proposing and regulatory organizations to use these to avoid future potential risks

and liabilities. On the basis of the uncertainties identified in this report, the use of biology based control regimens seem to provide the best technique for ameliorating the unique risks of environmental applications of biotechnology.

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APPENDIX I

QUESTIONNAIRE FOR GOVERNMENT POLICY ANALYSTS

QUESTIONNAIRE FOR GOVERNMENT POLICY ANALYSTS

Interviewer #_____

Interview # _____

Institution: (1) Govt. _____ (2) Industry _____

(3) Trade Assoc. _____ (4) Public Int./Union __

Position (1) Policy Analyst ____ (2) Sr. Decision Maker ____

Type of company (1) Pharmaceutical ___

(2) Processing natural resources or agricultural products ___

(3) Manufacturing products ___

(4) Public utility ___ (5) Other ___

INTRODUCTION:

As the letter and previous phone calls mentioned, the University of North Carolina's Institute for Environmental Studies and the School of Business Administration are conducting a comparative study of the use of scientific and technological information in making decisions in the federal government and private industry. The focus of the study is on non-routine situations in which definitive scientific and technical information is not available and there isn't enough time to use the normal procedures for gathering and analyzing data. The interview contains both closed and open-ended questions with possibilities for comments throughout. Please don't hesitate to give your opinion. Everything you say will be held in strict confidence. Results of the survey will be reported in aggregate form and no identification of individuals will be made.

We have organized the interview questions into three sections:

First, the methods used for searching and gathering information,

Second, the processes used to analyze or synthesize information and

Third, the techniques used to present the analysis and recommendations to senior decisionmakers.

SECTION I: BACKGROUND ON AGENCY AND ORGANIZATIONAL UNIT

Before we start, I would like to get some information on the agency and organizational unit in which you work. If it is available I would like to get a copy of the organizational chart of your agency.

Q. B 1 When was the [INSERT AGENCY NAME] formed? _____

HAND RESPONDENT THE INDEX CARD PACKET WITH CARD 'A' ON TOP AND EXPLAIN:

I am giving you a set of index cards which will be used in answering some of the fixed choice questions. Please use the first card marked "A" to respond to the next question.

Q. B 2 How would you describe the primary role of the agency?*

			RANKING IN TERMS OF IMPORTANCE IF MORE THAN ONE CATEGORY SELECTED
(1)	administrative	_____	_____
(2)	regulatory	_____	_____
(3)	research	_____	_____
(4)	oversight	_____	_____
(5)	consultative	_____	_____

*IF MORE THAN ONE CATEGORY, ASK:

How would you rank the categories you selected in terms of importance?

ENTER RANKING IN SPACE PROVIDED TO THE RIGHT OF THE CATEGORIES

Q. B 3 When was the [INSERT NAME OF DEPARTMENT OR DIVISION] organized?

_____

Q. B 4 How many people work in your unit? _____

(1) 1-5 _____
(2) 5-10 _____
(3) 11-20 _____
(4) 21-50 _____
(5) 51-100 _____
(6) over 100 _____

Q. B 5 What is the primary academic background of people who work in your unit?

_____

_____

_____

_____

Q. B 6 How would you describe the mission and the key responsibilities of your unit?

Q. B 7 How would you describe <u>your</u> responsibilities in the unit?

<u>PROBE</u>: Could you please flip to index card "B." If you had to categorize your work, would you say the majority of your time is spent in:

		%
(1)	administration	_____
(2)	research	_____
(3)	analysis	_____
(4)	communication	_____

If the respondent suggests another category, please ask them to specify their other categories.

(5) other (specify) _____

Q. B 8 Whom does your unit primarily serve?

PROBE: Who else does it serve?

Q. B 9 When a decision has to be made what is the normal chain of command? [HAVE RESPONDENT DRAW DIAGRAM, IF NECESSARY].

Q. B 10 Who is the usual senior decision maker?

Name _____

Title _____

SECTION II: DECISION BACKGROUND AND CONTEXT

Now I'd like you to select the most recent issue you analyzed which you would characterize as involving a non-routine decision, one that had to be made in a relatively short time period and in which definitive scientific and technological information was not available. The issue you select will be used as the basis for subsequent questions. The time frame in which a decision had to be made should be 3 to 6 months or less.

Q. C 1 Could you please briefly describe the issue/situation?

PROBE: Could you give the decision a label?

_____

Q. C 2 At the start, how long were you given to do the analysis?

_____ days

_____ months

Q. C 3 How long did it actually take to complete the analysis?

_____ days

_____ months

PROBE: What were the key dates in terms of the start and finish of the process?

STARTING DATE _____
ENDING DATE _____

Q. C 4 What was the stimulus for deciding to tackle the particular issue (i.e. how did the issue come to be perceived as warranting analysis, what were the main forces that brought it to decisionmakers attention and the need for resolution)?

(1) Press _____
(2) Congress _____
(3) From within agency _____
(4) From within unit _____
(5) Interest group _____
(6) Other (specify) _____

Q. C 5 Please flip to index card "C." How important do you think was the resolution of this issue to your agency (company)? [READ POSSIBLE ANSWERS TO RESPONDENT]

(1) not at all important
(2) not very important
(3) important
(4) very important

Q. C 6 Who was the person or persons who defined the issue?

Q. C 7 Were alternative definitions of the issue considered?

*(1) yes ____
(2) no ____

*IF "YES": What alternatives were considered?

Q. C 8 Did others from your agency work with you on this assignment?

*1. Yes ____
2. No ____

*IF "YES": How did you organize internally to accomplish the work?

Q. C 9 Were other organizations involved in working on the same issue?

*(1) yes ____
(2) no ____

*IF "YES": Which were the other organizations?

Q. C 10 Could you please describe the chain of command for making the final policy decision? ASK PERSON TO DRAW A DIAGRAM IF THIS SEEMS HELPFUL

Q C 11 Who was the senior decisionmaker on this issue?

Name _____

Title _____

Q. C 12 Please flip to index card "D." How knowledgeable did you consider yourself on this issue prior to this analysis? [READ POSSIBLE ANSWERS TO RESPONDENT]

(1) not knowledgeable at all
(2) slightly knowledgeable
(3) knowledgeable
(4) very knowledgeable
(5) expert

Q. C 13 Did you have information on hand when you started to do the analysis?

*(1) yes ____

(2) no ____

[*IF "YES":] Could you please describe what the information was?

Q. C 14 At the start of the process what types of information appeared to have the most potential for being questionable?

II. SEARCH

Now I'm going to ask you questions on how you conducted your search for the scientific and technological information that you used in your policy analysis, focusing both on the source or sources of information and the form in which you gathered the information.

THE NEXT THREE QUESTIONS (S1, S2, S3) ARE TO BE RECORDED ON THE CHART BELOW. THE QUESTIONS ARE TO BE REPEATED UNTIL YOU EXHAUST THE SEARCH PROCESS. AFTER YOU HAVE ASKED ABOUT THE 'FIRST' SOURCE THEY TURNED TO, THE FORM IN WHICH THE INFORMATION CAME AND THE REASON FOR CHOOSING THAT PARTICULAR SOURCE, PROCEDE TO ASK ABOUT THE SECOND SOURCE THEY TURNED TO, THE FORM, REASON, THEN GO TO THE THIRD SOURCE ETC.

ASK RESPONDENT TO FLIP TO CARD E AND TELL THEM THEY WILL USE IT TO ANSWER A QUESTION ABOUT THE FORM IN WHICH THE INFORMATION WAS OBTAINED.

Q. S1 Where did you turn to first in your search for the necessary scientific and technological information?

Q. S2 How did you obtain the information? (Remind them to look on CARD E)

1. Face-to-face
2. Telephone
3. Personal documents such as letters or memos
4. Formal written documents
5. Numeric documents
6. Other (please specify)

Q. S3 Why did you turn to _____ (name source S1, S2, etc.)?

Source (Q.S1)	Form (Q.S2)	Reason Selected (Q.S3)	Usefulness (Q.S4)
1.			
2.			
3.			

Source (O.S1)	Form (O.S2)	Reason Selected (O.S3)	Usefulness (O.S4)
4.			
5.			

O. S4 Would you please turn to Card F. I would like you to describe the usefulness of each source of information you used. [GO THROUGH THE LIST OF SOURCES AND WRITE THE RANKING IN THE LAST COLUMN ON THE ABOVE CHART.] Did you find very useful somewhat useful not very useful. not useful at all?

1. Very useful
2 Somewhat useful
3 Not very useful
4. Not useful at all
9. D.K.. N R (this is not on their card)

O. S5 Could you please flip to Card G. [ASK:] What was the extent of involvement of the senior decisionmaker in the search process?

1 Worked as team member
2 Monitored information gathering
3 Provided tips on possible sources
4. Not involved
5 Other

O S6 What other sources of S&T information would you anticipate that your decisionmaker "client" would consult or would gain access to him or her?

O. S7 Did the educational background or personal characteristics of the persons who would be making the decision influence where you went for information?

*1. Yes
2 No

*IF "YES": How did the decisionmaker's background influence where you went for S&T information?

O. S8 Were there statutory or legal requirements that you had to meet in acquiring information?

*1. Yes
2 No

*IF "YES": What were the statutory or legal requirements?

O. S9 Was the gathering of information influenced by organizational uncertainties such as (Please flip to CARD H)?

1. Differences in values and perspectives
2 Conflicts over who would make important decisions
3 Uncertainty over the willingness of actors to cooperate
4 Lack of precedent for handling such situations
5. Ambiguity in mission or objectives
6 Other

O. S10 Were there political pressures that influenced the gathering of information?

*1 Yes
2 No

*IF "YES": What were the pressures?

O. S11 Is this the typical search pattern that you use in situations when time is short and data unavailable?

1 Yes
*2 No

*IF "NO": What made it atypical?

III. ANALYSIS

Using the same case as before, I'd like to focus how you analyzed the information you gathered and how you drew conclusions.

Q. A1 In the process of gathering the information did you encounter information which could be characterized as being uncertain?

*1. Yes ____
2. No ____

[*IF "YES":] Please flip to Card I [ASK:] What was the nature of the uncertainty? Was it due to

1. Uncertainty resulting from different assumptions____
2. Uncertainty resulting from conflicting data_____
3. Uncertainty resulting from different models_____
4. Uncertainty resulting from different interpretations of the same information ____
5. Other _____
_____

[RESPONDENT MAY PICK MORE THAN ONE ANSWER]

PROBE: How did you resolve the questions of uncertainty?

Q. A2 In the process of conducting your analysis did you use any formal analytic techniques?

*Yes _____
No _____

[*IF "YES":] What techniques did you use?

[*IF "YES":] In retrospect how effective were these techniques?

[*IF "YES":] Did you use any particular computer software?

1. Yes _____
2. No _____

[*IF "YES":] What software did you use?

Q. A4 How many professionals worked on the analysis?

[IF MORE THAN ONE, ASK:]
Were any from outside your shop?

*Yes _____
No _____

[*IF "YES":] Where were they from?

Q. A5 [IF MORE THAN ONE PERSON WORKED ON THE ANALYSIS ASK RESPONDENT TO FLIP TO CARD J, ASK:]
How were differences among the team members resolved in preparing the report?

1. Consensus _____
2. Majority rule without vote _____
3. Majority vote _____
4. Dominant individual _____
5. Referred to supervisor(s) _____
6. other _____ Specify _____

Q. A6 Were differing opinions of other groups who were not included on the team represented in the analysis presentation?

*1. Yes ____
2. No ____

[*IF "YES":] How were they included?

Q. A7 Who or what groups reviewed the analysis and its recommendations before they were presented to the senior decisionmaker?

Q. A8 Could you please flip to Card K. What was the extent of involvement the senior decisionmaker in the analysis and drawing of conclusions?

1. Worked as part of the team ____
2. Reviewed the analysis and conclusions ____
3. Not Involved ____

Q. A9 Were there political pressures from any other group that influenced the drawing of conclusions?

*1) Yes ____
2) No ____

[*IF "YES":] What were the political pressures and from whom?

Q. A10 Is this the typical pattern of analysis you would use in other non-routine decisions?

1. Yes ____
*2. No ____

[*IF "NO":] What made it atypical?

IV. PRESENTATION

NOW I'D LIKE TO ASK YOU QUESTIONS WHICH FOCUS ON THE ACTUAL PRESENTATION OF S&T INFORMATION TO THE SENIOR DECISIONMAKER(S).

Q. P1 How did you present the information to the senior decisionmaker?

Q. P2 Do you have a standard reporting format that you use?

*1. Yes ____
2. No ____

[*IF "YES":] What is your standard reporting format?

Q. P3 Have you found any one method of presenting S&T information more successful than others?

Q. P4 How did the educational background and the preferences of decision maker influence the way you presented the S&T information?

Q. P5 Did the senior decisionmaker want a detailed presentation of different options or a single recommendation?

1. Different options _____
2. Single Recommendation _____

Q. P6 How did you present scenarios which had elements of uncertainty?

1. Worst case? ___
2. Most likely? ___
3. Best estimates? ___
4. other ___

PROBE: Have you found any technique more successful than others in conveying the type and extent of uncertainty in scientific and technological information?

Q. P7 How did you present decision options? (CARD L)

1. Consensus recommendation of the staff ___
2. Alternative interpretations with arguments for and against each ___
3. Majority recommendation, with minority views noted ___
4. Majority recommendation, with formal minority report ___
5. Other, specify ___

Q. P8 Did you use computer graphics?

*1. Yes ____
2. No ____

*If "yes": Were they color?
*If "yes": How effective are they in communicating?

Q.P 9 How influential do you feel that the scientific and technological information was in the final decision? Please flip to CARD M. Was it:

1. Extremely influential
2. Moderately influential
3. Slightly influential
4. Not influential at all
9. D.K., N.R.

[PROBE REASONS FOR ANSWER]

V. GENERAL QUESTIONS

I am going to ask you a few general questions.

G1 In general, do you feel that science or technological information changes policy makers minds?

1. Yes _____
2. No _____
3. Mixed _____
9. D.K., N.R.

G2 In your experience, do the senior decisionmakers understand the science or technical information that underpins policy? Please look at Card N. Would you say that most senior decisionmakers,

1. a good understanding
2. a basic understanding
3. a minimal understanding
4. don't really understand scientific and technological information

G3 If you were to advise a young new policy analyst of the skills they need to deal with non-routine policy decisions with scientific and technological components, what skills would you recommend they learn?

VI. BIOGRAPHICAL

I'D LIKE TO END THE INTERVIEW BY ASKING YOU SOME BACKGOUND QUESTIONS.

V1. Could you sketch your education for me, including college majors and degrees

FOR UNDERGRADUATE DEGREES: IF ANSWERED WITH A UNIVERSITY BE SURE TO ASK WHICH COLLEGE

College	Dates	Degree	Major

V2. How long have your worked at your current job? _____

V3. Could you please sketch your previous employment history, including where you worked, for how long and a general idea of what your job entailed?

Employer	Dates	Job Responsibilities

V4. Do you consider yourself a federal career employee?

1. Yes ___
2. No ___

V5. In what year were you born? _____

V6. What is your GS level? _____

APPENDIX II

TECHNICAL BACKGROUND FOR THE AGS CASE

Technology

In addition to catalyzing to a quantum leap in man's qualitative understanding of biological systems, modern biotechnology permits exponential quantitative decreases in the time it takes to accomplish tasks of conventional applied genetics. Not only a new research tool, modern biotechnology can also be viewed as an extension of historical methods of genetic control and selection used in many commercial processes like fermentation and animal breeding. Striking success in bacterial genetics research suggests that some genes with special properties can now be added to the normal coterie of functions to add special functionality to bacteria for ambient environment applications. (Office of Technology Assessment, 1981)

As a result of both scientific and technological advances, many companies have been formed to commercialize new processes for making existing products and to develop entirely new products for many industries. Diverse environmental applications targeted by US biotechnology companies include plants breeding, microbial pesticides, microbial fertilizers, metal mining enhancers, waste

processing, artificial snowmaking, silvaculture, and polymers materials.

While many product concepts have emerged since the advent of biotechnology, substantially more effort is needed to produce a commercially viable product than simple introduction of a viable gene for the functional product into a convenient vector. The challenge of obtaining overexpression of introduced genes in new organisms has revealed a variety of organismal control mechanisms. In many cases, years of research are needed to determine what factors are responsible for controlling functional expression of new genes.

B. The Technical Basis for the AGS FROSTBAN Product: Pseudomonas fluorescens and Pseudomonas syringae

Pseudomonas fluorescens and Psueodmonas syringae are two of over fifty distinct strains of the diverse bacterial genus Pseudomonas. Members of this genus are found in the air, water, as well as on plants and animals. Pseudomonads are 1.5 to 4 micrometers long and 0.5 to 1.0 micrometers wide, and appear to be shaped like slightly curved rods under the microscope. (Clarke, 1980) Pseudomonas as a genus are most notable for their ability to utilize a wide variety of substances (including nitrate and hydrogen gas) as energy sources. Some individual strains that live in human, animal, or plant hosts can cause the hosts some deleterious effects. Accordingly, these have been

classified as opportunistic human pathogens and as specific plant pathogens.

Historically, pseudomonas have not received the rich attention that model species such as Escherichia coli and Sacchromyces yeast have received. This is in part due to the arbitrary choice of certain species for the first rigorous molecular analysis in the early 1970s. Also, many methods for studying bacterial genetics require cloning experiments that were only permitted in specially constructed "safe" E. coli systems in the mid 1970s. One strain of Pseudomonas has received a good deal of attention because of its apparent clinical importance: Pseudomonas aeroginosa. This strain is an opportunistic pathogen that is often isolated from secondary infections of burn victims in hospitals. It is particularly bothersome because it has or can acquire resistance to most therapeutic antibiotics available. (Clarke, 1980)

In the 1980s, psuedomonads have received much more attention for a variety of reasons. First, their ubiquity in soil, water, and air, has made them candidates for environmental application products that can now be envisioned. Zaugg and Swarz (1982) suggest that Pseudomonas, Acinetobactor, and Flavobacteria will be the most used genera in the chemical industry, while Thiobacillus, Leptospirillum, and Sulfolobus may be used by the mining industry to promote leaching of valuable minerals. (OTA, 1981) The NIH restrictions on use of

naturally occurring bacterial hosts for recombinant DNA experiments were lifted in the revised 1978 NIH Points to Consider Notice. (Milewski, 1985) Finally, biochemists and molecular biologists have become interested in expanding the knowledge of non fermentative, aerobic metabolism and multi-substrate catabolism that many Pseudomonads perform. (Clarke, 1980)

The AGS FROSTBAN product is a mixture of deletion mutants of two bacteria, Pseudomonas syringae and Pseudomonas fluorescens). In temperate climates, Pseudomonas syringae and Erwina herbicola are two of the leading bacteria that inhabit the leaves of plants. Pseudomonas fluorescens is primarily found in the soil associated with plants. Pseudomonas syringae is not considered a human pathogen. Plant pathologists have described pathogenic relationships that some strains of P. syringae has with certain types of fruit trees. Phytopathogenic pseudomonads such as P. syringae generally have relatively narrow host ranges. The appearance of Pseudomonas infections varies depending on the host tree and bacterial strain. They often have the appearance of dark, inploded soft spots on bark tissue. (Mount, 1980)

Apparently, P. fluorescens, P. syringae, Erwina herbicola and perhaps other bacteria secrete a lipoprotein from their cell wall onto the surfaces of plants. Lipoproteins are protein molecules with a hydrophobic lipid component. Lipids are the basis of fats, which naturally

repel water. Groups of water molecules on the plant surface are induced to align themselves with one another in a crystalline formation in the presence of this protein. This induced alignment of water molecules can drastically reduce the time necessary for a given amount of water to turn to ice at a given temperature. Without sites that catalyze nucleation, water can exist at temperatures below 0 degrees Celsius in a supercooled state for a long time. In addition to bacteria that secrete lipoproteins, other agents including chemicals, dust, and pollen can act as ice nucleation centers. However, the rate at which ice is formed on a given surface seems to depends on the ice nucleating (INA+) agent that is active at the highest temperature. The most efficient ice nucleating agents at temperatures just below thermodynamic freezing (0 degrees celsius) known are strains of P. syringae such as P. syringae pathovar syringae.

A certain percentage of naturally occurring Pseudomonads do not secrete this ice-nucleating (INA+) protein. (Lindow, 1979) The temperature at which frost forms on outdoor plant leaves with a given ambient concentration of water vapor depends on the number of nuclei that are formed by E. herbicola and P. syringae and secreting that protein on the leaf surfaces.

Lindow hypothesized that application of a mist of bacteria that are selected for their ability to secrete the INA protein would increase the rate at which ice crystals

are formed on plants. Conversely, the highest temperature at which frost forms on the leaf surface could be lowered if INA+ bacteria were killed or displaced by a mist of INA- bacteria sprayed on the plant. Subsequent experiments using E. herbicola isolates on corn in growth chambers and in the field bore out this hypothesis. (Lindow 1978)

Lindow, the son of an Oregon farmer, realized the potential capability of this experimental technique to provide frost protection for growing plants. Subsequently, using a simple bacterial screening technique, Lindow prepared a mist of INA- pseudomonas syringae and P. fluorsescens and sprayed it on corn plants to test its ability to control frost formation outdoors. The INA- strains colonized the surface of the plant leaves and lowered the de facto frost formation temperature by 2-3 degrees centigrade. (Lindow, 1984)

Subsequent research by Lindow's colleagues at the University of California at Berkeley established that a small, 256 base pair gene codes for the INA protein. Disruption of the ice nucleation (INA) protein gene results in INA- Pseudomonads. It is not clear whether naturally occurring INA- bacteria do not produce the INA protein, form an inactive ice nucleation lipoprotein, or simply fail to secrete it onto plant surfaces where it can provide a nucleus for frost formation. (Orser, 1980)

Established genetic engineering techniques permitted this gene to be deleted from the genome of the INA+ P.

syringae. When the 266 base pair gene is deleted, the potential for the bacteria to revert is reduced dramatically. Instead of requiring a mere single base pair change to stop secretion of an active INA protein, a more unlikely simultaneous change of thousands of base pairs would have to occur to cause phenotypic reversion to INA+ now. Since the daughters of engineered INA- cells would not have the genetic material that codes for this protein, its recurrence would be extremely unlikely. Rather than arising from background rates of random mutation, functional INA reversion with the genetically engineered INA- deletion mutant would now be virtually impossible without entrance of exogenous viral or bacterial DNA containing a gene for a similar protein, or strong selection pressures over a number of generations. (Colwell, 1985)

Since the genetic modification is a deletion of a unitary segment of bacterial DNA, the product is much simpler to construct than many genetically engineered organisms. Because no extracellular genetic material is incorporated into the Pseudomonads' genome, the likelihood of the manipulation resulting in a completely dysfunctional bacteria is low. In contrast to most biotechnology products, FROSTBAN requires that the gene of interest, the gene that codes for the ice nucleation lipoprotein, not be expressed for the application. Accordingly, the technical barriers to producing it seem quite modest.

Application of FROSTBAN is intended to reduce frost damage in annual commercial agricultural plants. The most widely used current method of preventing frost damage are relatively ineffective smudge pots that burn at night to raise the temperature of fields at marginal frost temperatures. Since FROSTBAN does not rely on changing the ambient temperature but rather on displacing plant surface microflora that serve as nuclei for ice nuclei formation at near freezing temperatures, FROSTBAN would represent a novel technological approach to agricultural frost protection.

While there are some conventionally selected bacterial preparations used to kill other plant pests, FROSTBAN would be among the first agricultural product intended to extinguish a nonpathogenic functions of native bacteria. For this reason, FROSTBAN's method of action can be considered novel. While there are a host of companies that provide inputs to the plant agricultural process, this application is not a cultivar nor a pesticide, nor a chemical fertilizer. As such, it is an early example of a potential biotechnology product that provides a new commercial function in an existing market sector.

From the successful production of INA^- clones on, work on the FROSTBAN product can be considered development rather than research on a technical activity spectrum ranging from basic research to applied research to development, to pilot scale demonstration to commercial scale demonstration to to commercial use. In the US, there is a tradition of

companies picking up product ideas after the universities have shown the feasibility of a product concept in research situations. It is in the context of development and pilot scale demonstration activities, rather than as either pure or applied research, that the AGS proposal to field test genetically engineered INA- P. syringae should be considered.

Appendix III

Underlying Scientific and Technical Issues that Arose in Evaluation of the AGS EUP

The AGS EUP review process may be viewed as a window on both scientific and technical issues that are likely to recur in future analyses of environmental biotechnology applications. Some of these scientific and technical issues are discussed below.

A. Are Impacts Dependent on the Initial Dose?

As suggested earlier, the threshold dose concept that is central to toxicological risk analysis of chemical hazards was assumed in EPA's analysis. In contrast, CDFA seemed to generally assume a digital, threat/no threat concept that is characteristic of microbiological analysis. In its analysis of the AGS transportation permits, CDFA did not assume any adverse effects would exhibit quantitative, dose-related thresholds. Monterey County seemed to assume a threshold based concept of risks from the test, albeit with a different decision point on the theoretical dose response curve than EPA apparently had. Accordingly, the Monterey County Board of Supervisors initially indicated to AGS that a mutually defined test site remote from the population centers of the county could be acceptable. Apart from the

potential merits of utilizing a quantitative threshold assumption in specific atmospheric or plant pathogenesis contexts, the assumption that risk can be limited by the absolute quantity of the organisms that are applied is oblivious to the reported capacity of bacteria and viruses to reproduce exponentially from literally undetectable numbers if conditions become favorable for their growth. (Alexander, 1985)

B. Will horizontal transfer of genetic material alter environmental function of GEM or native organisms?

None of the regulatory arms of the organizations we surveyed considered possible impacts resulting from uncontrolled, probabilistic transfer of genetic material from the GEM to naturally occurring microflora or from related bacterial taxa to the GEM population. The ability of living organisms to transfer genetic material also confers the potential for an organisms functional properties to change substantially. The rates of transfer of genetic material from one species to another are quite low but quantitatively estimated for many types of possible crosses. (Strauss) As long as there are no limitations on the time that the GEMs will remain in the environment, risk assessments should assume some genetic transfer will take place as a result of the reproductive capabilities of normal microorganisms. Potential hazards could result from incorporation of elements of extant environmental genes or

from contribution of introduced genes into existing ecosystems that can alter the functional abilities of the introduced GEM in a new environment.

Identity of Genetically Engineered Microorganisms

The relationship between the identity of the AGS INA- GEM, its parents, and naturally occurring INA- bacteria is somewhat more subtle than the summaries of each reviewing organization given in Table 11 suggest. In an SAP Subpanel meeting, Robert Colwell noted,

> "the chemical mutagens (INA- bacteria obtained by a process of chemical mutagenesis of INA+ parents and selection for INA- daughters) are not as effective at repressing the nucleation of ice as the (genetically engineered) deletion mutants. They are not in other words identical in their phenotype even regarding the ice-minus characteristic (for which they were selected)." (Colwell, 1985)

Historically, bacteria have been identified and classified on the basis of their observable characteristics, or phenotype. More recently, molecular biology has developed techniques for experimentally, directly assessing the genetic content of bacteria. As a result, another basis for determining the identify and classifying bacteria is available. Some traditional classifications of bacteria have been thrown in disarray by the use of modern genetic analysis. Moreover, the relative importance of genetic composition in relation to observable, functional

characteristics of bacteria is a matter of controversy among bacteriologists.

An alternative to using the visible INA function as an indicator of the identity of AGS' GEM is the use physiological comparison tests such as those requested by CDFA to compare biochemical functions of GEMs and parents. There was no imputed relationship between INA function and these biochemical functions. In the AGS case, CDFA reported that the GEM had the same response pattern to a battery of biochemical and physiological tests as the INA+ parents of AGS' GEM. A potential problem with using physiology tests as an indicator of similarity of GEMs to their parents is the question of how to evaluate the significance of differences that are found between responses of other GEMs and their parents to physiological test batteries. The implicit criterion used in the AGS case by CDFA, that the more similar the GEM is to the parent, the better its behavior can be modelled by the parent, may not be useful if the genetically engineered trait's are novel or independent of the functions assessed in the physiological test battery. These problem will be exacerbated when organisms that are more different from predecessors than AGS' bacteria are from wild type P. fluorescens and syringae.

C. Competition and Ecosystem Function Evaluation

SAP Subpanel member Susan Hirano suggested that the question of whether the AGS organism is considered novel or

natural may not make a difference in evaluating the potential risks posed by its introduction into given ecosystems. The question of how to evaluate risks from new organisms in a given ecosystem, whether genetically engineered, the result of naturally occurring recombinatory processes, or physical transport, is affected by the other participants in a target ecosystem as much as by the identity of introduced organisms of any sort. (Hirano, 1985)

Competition between AGS' INA- GEM and natural microflora was a key issue in EPA and Monterey County analyses. As noted previously, a variety of alternative and alterable competitive balances can be expected to result from future GEM introductions. Evaluating the likelihood of these outcome profiles on the basis of indoor greenhouse tests and current theory is problematic.

Current theory suggests that microbial competition is affected by a variety of environmental conditions including the presence of water, heat stress, organic molecules, other microbes, and many other factors. The competitive balance between microbes may be drastically different on two sides of a 1 cm^2 soil sample. Accordingly, knowledge of environmental conditions seems critical to any effort to predict microbial competition.

Determining what events would constitute an ecological dislocation if offsite colonization occurs is a thorny question that was not explicitly tackled in any evaluation of the AGS field test. For example, changes in

precipitation patterns were viewed as an adverse effect, but no standard was developed to determine when the atmospheric ecology was substantially changed, or changed enough to cause a terrestrial ecological dislocation. An illustrative standard could be, "a dislocation occurs if the percentage of INA+ bacteria in low lying rainclouds would be reduced by a factor of 5 or more following application of an INA- mist on 100 acres of fields underneath the atmospheric experimental area." Determining ecological dislocation with such criteria requires development of goals for ecosystem integrity. These goals in turn depend on current knowledge about ecosystem function and current thought about the role of man in ecosystems.

The National Environmental Policy Act (NEPA) set one legal standard for ecological dislocation: prevention of species extinction. The ecology literature has recently provided suggestions that intact ecosystem function can be evaluated in terms of continuance of microbial nutrient cycling processes, community membership stability, and impact on higher trophic levels. (Cairns, 1986)

Ecological risk assessment for future environmental applications of biotechnology will require the refinement and comparison of ecosystem integrity indicators from these alternate conceptions of intact ecosystem function. Evaluating the significance of disruptions to existing ecosystems is likely to remain a perplexing problem because some elements of natural environments and human society are

likely to gain and others to lose from different types of environmental biotechnology mediated ecosystem alteration.

Two competing lenses through which to view the ecological consequences of EBA introduction have been introduced in the scientific literature. Winston Brill, Director of Research for Agracetus, has suggested that the most appropriate lens through which to view the introduction of environmental applications of biotechnology is the lens of commercial agriculture. For hundreds of years, man's knowledge of genetics has been harnessed to introduce literally thousands of new varieties of plants and animals. These changes have been accomplished, with isolated exceptions, without wreaking wholesale ecological damage. Thus, the introduction of genetically engineered microbial pesticides can be modelled by examining the impact of introducing large quantities of conventionally selected microbial pesticides into agricultural environments. In the absence of reports of significant ecological disruption from such analagous introductions of new species into a variety of man made environments, one could conclude that similar introductions of genetically engineered microbes, plants, or animals would not present a threat to continued ecosystem function.

Frances Sharpless, an ecologist at Oak Ridge National Laboratory, suggests that a better lens through which to view the ecological consequences of environmental biotechnology introductions is the history of the

inadvertant spread of natural organisms brought to new environments. She notes that man has served an unwitting vector for many pests that have hurt economically important plants (e.g., chestnut blight) and created ecological nuisances (e.g., the gypsy moth, Kudzu vine, and cockroach). While she agrees that only a fraction of immigrating species produce ecological dislocation, she does not believe that available ecological theory permits prediction of what new species or new traits are most likely to penetrate existing biotic assemblages and cause ecological dislocation. She suggests that "stressed or simplified environments (such as commercial monoculture agriculture) are more vulnerable to successful invasion."(Sharpless, 1982)

D. Technical Requirements for Monitoring and Control

EPA required AGS to monitor the soil, insects and plants in the vicinity of the test site for the presence of GEMs. In order to develop its capabilities for aerial monitoring, EPA's ORD planned to conduct aerial monitoring during the field test. In the AGS case, Steven Lindow had already developed a simple, efficient protocol for determining the level of INA+ bacteria on natural surfaces. The development of equally sensitive assays for presence of GEMs on the basis of their genetic content is a current EPA research priority. The utility of monitoring GEM presence in the environment for scientific research in early field tests like the AGS proposal is obvious. However, the regulatory

utility of a well developed monitoring capability without a concomitant ability to control the environmental behavior of the GEM and/or its genes seems questionable. Control technology options received less attention in EPA and Monterey than in CDFA.

In contrast to EPA, CDFA did not require monitoring but did require simple physical and chemical controls. The physical controls included respirators and personal protective equipment to prevent overexposure to the AGS technicians during application. The chemical controls were antibacterial chemicals designed to kill bacteria on equipment used in the field test and on the test plot in the event an unanticipated outcome occurred. The requirement of personal protective equipment for applicators was cited as a cause of concern by both Monterey County citizens and Monterey County decisionmakers.

Technical controls for GEMs can be profitably divided into three classes with different properties: physical, chemical, and biological. Physical controls range from selection of sites remote from major population centers to use of negative pressure greenhouses or tents to contain GEMs. EPAs site selection requirement was a physical control, though it was not closely tied to its scientific risk analysis. CDFAs personal protective equipment requirement was also a physical control. CDFA's proposed use of chemical bactericides to control possible offsite colonization is an example of chemical controls. Biological

controls for GEMs range from the presence of competing naturally occurring organisms to the selection of organisms with temperature ranges that restrict their growth potential in a given environment to the engineering of test organisms. For plants, biological controls include excision or covering of sexual parts of plants, and the use of species that do not cross pollinate. AGS said that competition with wild type Pseudomonads was a natural biological control on the proposed FROSTBAN experiment. No other biological controls were mentioned in the analyses of the AGS case. The types of controls required in the AGS case are shown in Table 18.

Table 18

Controls Required for Execution of AGS Field Test

Organization	Type of Control Required		
	Physical	Chemical	Biological
EPA	Siting	---	---
CDFA -	Protective Gear	Bactericides	---
MC	Siting	---	---

Physical controls were the preeminent class of control in regulatory decisions on the AGS field test proposal. Chemical controls were only detailed by one organization. Biological controls, except for natural competition with native microflora, were not required by any of the three organizations.

Physical controls seem best suited to control of large animals and plants. The use of any chemical control for controlling microbial reproduction seems less likely to provide long term protection from novel bacterial strains than animals or plants because of the adaptive ability and rapid reproductive rates of bacteria. Biological controls, including genetic engineering seem to have the greatest potential for controlling undesired GEM activity.

The engineering principle of minimizing risks through design conservatism could be applied to both environmental biotechnology experiments and commercial applications. Even if certain risks cannot be quantitatively analyzed in advance of a field test, they may be reduced by application of appropriate control technologies. (Drexler, 1986) Artificial biological controls were used in conjunction with both chemical and physical controls to ameliorate unknown potential risks from escape of errant genetic engineering projects from labs in the mid 1970s.

A strategy for minimizing risks from early environmental applications of biotechnology could employ a variety of biological controls to reduce the potential risk of such applications by many orders of magnitude. A first tier control could involve selection of test organisms. Early experiments could use animals that have extensive physical barriers to extra-species gene transfer to examine impacts of new genes on ecosystem dynamics. Plants have a lower level of genetic stability than animals, however, they are

still orders of magnitude more stable than bacteria. Among bacteria, certain genera have shared fewer genes with other species over the eons. Transposable elements of DNA called plasmids are necessary for much interspecies bacterial sex. Certain species bear less mobile plasmids or none at all under most conditions. Pseudomonads bear plasmids and chemical antibiotic resistance has been demonstrated to be borne on plasmids for one species of Pseudomonas. Use of this tier of biocontrol would have eliminated the AGS strain from consideration and prioritized other genera for early deliberate environmental experiments with GEMs.

A second tier of control of environmental applications of biotechnology could involve the growth requirements for GEMs. GEMs could be developed from species with narrower, more specific growth requirements, so that the likelihood of their colonization in a given set of environmental conditions would be lower than a generalist organism more suited to those conditions. One analogy for this type of control is the introduction of tropical plants into temperate agriculture. These plants, because they could not survive the temperature fluctuations of temperate climates, should be more controllable as a result of their higher temperature requirement. (Pinmental, 1987)

A third tier of biological control could feature modifications of the GEMs themselves including use of genetic engineering techniques. Genetic engineering can be used to locate potentially deleterious genes on stable parts

of the nuclear genome rather than on more mobile plasmids. Genes for both sexual and asexual genetic transfer can be removed from GEMs, thus decreasing the probability of transmission of genetic material from the GEM to other organisms. Unique physical or nutritional requirements can be given to GEMs designed for field use. For example, the provision of an synthetic organic chemical without many natural structural analogs could be required for an environmental GEM to function. The extent of the GEM application could then be limited by the extent of the provision of the special chemical nutrient. Finally, irradiation of bacteria can prevent them from reproducing. While it seems impractical to irradiate a field of indeterminate size to control reproduction of GEMs, prior irradiation of bacteria to prevent reproductive explosion on release could work for some applications if the function is not debilitated by this process. AGS irradiates its conventionally selected INA+ P. syringae SNOMAX product to control offsite replication. While most of these third tier control mechanisms would reduce the viability of the GEM in natural ecosystems, they could provide additional assurance that risks are controllable in the early years of environmental biotechnology. (Strauss, 1985)

While biological controls have the promise of mitigating some ecological risks of proposed environmental biotechnology applications, complex problems relating to the integration of such controls with the functional and market

needs of environmental biotechnology applications need to be resolved for this approach to be used widely by commercial entities.