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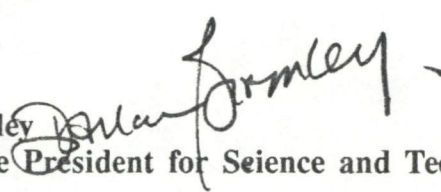
THE WHITE HOUSE

WASHINGTON

March 22, 1990

MEMORANDUM TO LARRY LINDSEY

FROM:

D. Allan Bromley 
Assistant to the President for Science and Technology

SUBJECT:

Draft Proposal on Scope of Organisms Subject to Oversight in
Field Release

Dr. Luther Williams, Chairman of the Biotechnology Science Coordinating Committee (BSCC), has sent me the enclosed draft Federal Register notice announcing a proposed definition for scope of organisms to be included in oversight for planned introductions of organisms into the environment. The background of this issue is described beginning on page 5. The thinking process of the subcommittee is described beginning on page 8. The arguments for oversight based on estimate of risk, the characteristics of the organism and the environment into which it is introduced, and the familiarity with both, then proceed for several pages, but the proposed definition for inclusion in oversight, pages 13-15, is essentially that of deliberate genetic modification. Thus, given the expectations raised by the preceding discussion, the impression is created that such organisms satisfy the presumption of risk warranting special oversight.

The BSCC discussed this definition at several meetings. Approximately one-half of the members of the BSCC felt that in spite of the disclaimers, the definition was essentially process based. Many attempts were made to develop alternative strategies, for example to establish an oversight inclusion definition by a statement the obverse of that on page 27, number (2), as follows, "that oversight would be required for organisms for which there was insufficient familiarity to foresee environmental effects equivalent to past safe introductions of similar organisms in similar targets/test environments." Representatives of the regulatory agencies found those terms lacking in sufficient definition or precision to serve as a screening discriminant. However, not all members of the BSCC were persuaded that familiarity could serve as a basis for exclusion (page 27) but not for inclusion. All other proposed alternative definitions also were unacceptable to USDA and EPA, as impractical for regulatory use.

Finally, the compromise represented by this document was adopted, namely to go forward with the publication of the proposal in the Federal Register, but specifically to request public comment on the definition and to invite alternative language from commenters who might have a better idea of how to avoid the term genetically modified organism.

Because this proposal has important policy implications, and may well set an important precedent not only for regulatory agencies in the U.S. but throughout the world, I believe it should be discussed by the Competitiveness Council, perhaps after preliminary assignment to the Working Group on Biotechnology, perhaps even to its subgroup on Science and Technology. A position statement from the Working Group to the Competitiveness Council could form the basis for further discussion and approval, modification, or rejection of the proposal as received from the BSCC.

Enclosure

March 20, 1990

MEMORANDUM FOR LAWRENCE B. LINDSEY

FROM: ~~/s/~~ James B. Wyngaarden
James B. Wyngaarden, M.D.
Associate Director for Life Sciences

SUBJECT: BSCC Scope Paper

Dr. Bromley has asked me to respond to your March 16 memorandum concerning the scope of oversight of small scale field trials.

I thought it might be useful for me to paint a little background so that your concerns, which I agree are valid, are placed in the proper context. The BSCC is, as you know, a science review and coordinating committee. Both the biotechnology community and the Congress have anticipated that the BSCC would provide a set of definitions for use in regulation. This has proved extremely difficult, and perplexingly so in the minds of the Congress. But even such an apparently straight forward term as "pathogen" is defined quite differently by scientists interested in human infection, and by regulators in protection of human, animal, plant, and environmental health.

Last fall the BSCC appointed a Subcommittee on Scope of Oversight for planned introduction of organisms into the environment, to distinguish those organisms for which a certain level of review is indicated from those for which it is not. It is important to state clearly that the report of the committee deals only with that limited subject, not with the entire scope of regulation of everything in biotechnology. The Committee was appointed in anticipation of implementing the recommendations of the National Research Council (NRC) committee that had been commissioned by the BSCC to examine the scientific basis of oversight of microorganisms and plants in limited field trials. The NRC issued a useful report which stressed that oversight should be based on risk assessment of the organism, on the extent to which scientists and agencies were familiar with its characteristics,

and with the nature of the environment into which the test organism was to be introduced. While stressing that the process should not be the primary basis of oversight, the report does point out that knowledge of the process involved in production of test organisms could contribute valuable information on quality and risk potential, thus could not be ignored. The report also stressed that there was nothing inherently more risky in an organism made with the newer techniques of biotechnology, including recombinant DNA technology, than with those produced under traditional methods. But the report does acknowledge that there are scientific uncertainties associated with recombinant DNA technologies, and indeed incorporated the term "genetically modified organisms" into its title. (Full title: Field Testing Genetically Modified Organisms: Framework for Decisions.)

The Committee on Definition of Scope found it very difficult to use the concepts of familiarity with respect to plant or microorganism, and the characteristics of the environment, in a manner that would be useful for regulators. They did not want to include organisms that had been exempt from oversight because of historic familiarity and unblemished record, especially organisms made by traditional techniques of modification. The gate, or trigger, for initial inclusion in the proposed oversight process was "genetically modified organism," followed by a series of exemptions, which admittedly are largely process-based exclusions. One is left chiefly with recombinant DNA modified organisms, but even here there are some exemptions, such as those based on transfer of well characterized non-coding regions.

This approach to scope definition was presented to scientific advisory committees of both USDA and EPA, and approved by them, following open discussions which involved participation by the biotechnology community as well as the ecology societies and members of the National Research Council committee. Thus considerable public and industrial support has been developed for this approach. This despite reservations similar to yours on the part of some members of industry who, nevertheless, feel this definition of scope is workable, and sufficiently unambiguous, to give the industry the direction that it has been seeking. As stressed in our committee discussions, regulatory uncertainty is viewed as a serious problem by the industry.

Had a vote been taken by the BSCC on philosophical grounds it would probably have ended up 4 to 4 with the two representatives each from EPA and USDA favoring the present version of the draft and the 4 representatives from the research agencies (NIH and NSF), FDA and OSTP opposing this version of the draft. But after several months of effort, and an apparent inability of the critics of this approach to propose suitable and acceptable

substitute language, the compromise suggested by EPA was accepted, namely to proceed with publication in the Federal Register, but simultaneously to request special attention to the definition by public commentators, and provision of substitute language of practical utility in oversight, by those who are critical of the approach taken. A copy of the proposed notice is appended to this letter.

Immediately following the special meeting of the BSCC on March 9 at which this action was recommended, I reviewed these matters with Dr. Bromley, because the course recommended by the BSCC clearly had policy implications. He agreed that another level of review was indicated. As you know, we now have an established process for this. The BSCC is a Subcommittee of FCCSET, which is chaired by Dr. Bromley. It was Dr. Bromley's opinion that he should consult with a few members of the FCCSET Committee about this matter, and with their agreement request the Council on Competitiveness to address the issue, probably by referring it to the Working Group on Biotechnology which has both policy and scientific representation. Thus, the result of OSTP initiatives would be similar to those that you propose, but procedurally preferable.

By following the reporting procedure presented to the Council on Competitiveness, we can avoid the likely public criticism that the White House is arbitrarily overruling its scientific advisory mechanism. Instead we will be able to report quite accurately that we are following the procedure established for reviewing policy issues, or for resolving differences of opinion within the BSCC.

Please let Dr. Bromley know if you do not agree with this manner of proceeding.

Attachment

OSTP/DLS:JBWyngaarden/mcq:3/20/90

DRAFT

FR Notice: Scope of Organisms to be Included in Oversight for
Planned Introductions into the Environment

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

AGENCY: Office of Science and Technology Policy,
Executive Office of the President

ACTION: Notice: Announcement of Proposed Definition,
Request for Public Comment, and
Announcement of Open Meeting

SUMMARY: This FEDERAL REGISTER notice announces a proposed definition describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment. The Biotechnology Science Coordinating Committee (BSCC) is seeking comment on the proposed definition. This document also gives notice of an open BSCC meeting to discuss the proposed definition.

DATES: Comments must be received on or before (insert date 30 days after receipt at FEDERAL REGISTER). An open meeting of the BSCC will be held on May 2, 1990 at 3 p.m. (tentative).

ADDRESSES: Comments specific to the BSCC proposed definition should be addressed to:

Biotechnology Science Coordinating Committee

Docket # NSF 0001

National Science Foundation Library

Room 248

1800 G Street, N.W.

Washington, D.C. 20550

The BSCC open meeting will be held at the:

Jefferson Auditorium

U.S. Department of Agriculture

14th St. and Independence Ave., N.W.

Washington, D.C. 20250

FOR FURTHER INFORMATION CONTACT: Dr. Luther S. Williams, Senior Science Advisor, National Science Foundation, Room 520, 1800 G Street, N.W., Washington, D.C. 20550, (202-357-9447).

SUPPLEMENTARY INFORMATION: This notice announces a proposed definition describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment. It has been developed by the Biotechnology Science Coordinating Committee (BSCC) for interagency science policy coordination and guidance. As such, the proposed definition addresses science issues. Each agency will use the definition as appropriate within its oversight structure. Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

The proposed definition is intended to apply to all kingdoms of organisms used in planned introductions into the environment for field testing. It is not intended to address all of the issues associated with large-scale applications or the scientific, ethical and societal issues that may be associated with large-scale

applications. However, the principles applied in developing this definition may be extrapolated, as appropriate, to other uses of organisms such as large scale environmental applications.

The proposed definition is intended to identify those organisms to be screened before they are introduced into the environment for field testing. That an organism is covered by the definition does not imply a priori that a risk is associated with that organism or its use. The definition simply circumscribes a group of organisms to be evaluated to determine whether a risk exists in the test situation.

The definition is intended to complement, not supercede existing oversight mechanisms for the planned introductions of organisms. Organisms excluded from the scope definition would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight.

An open public meeting of the BSCC will be held to take comment on the proposed scope for planned introduction to the environment for field testing. Time will be allocated for public comments on the scope definition. Attendance by the public will be limited to available space. Priority will be given to commenters who have provided written comments in advance of the meeting.

D. Allan Bromley
Assistant to the President for
Science and Technology and
Director, Office of Science
and Technology Policy

BACKGROUND: In the June 26, 1986 Federal Register, the U.S. government described its comprehensive regulatory policy for ensuring the safety of research and products produced through the use of biotechnology (51 FR 23302, 1986). This comprehensive policy document is entitled the "Coordinated Framework for Regulation of Biotechnology", referred to in this notice as simply the "Coordinated Framework".

In creating the Coordinated Framework, the underlying question addressed by the U.S. government was whether the existing regulatory structure pertaining to products, including products developed by traditional genetic modification techniques¹, was adequate for products obtained with the new techniques of biotechnology (e.g., recombinant DNA, recombinant RNA, and cell fusion). A similar question arose regarding sufficiency of the review process for research conducted for agricultural and environmental applications.

In the U.S., the oversight structure is based upon laws which seek to ensure that products and research pose no unreasonable risk. A concise index of these U.S. laws was published in the Federal Register of November 14, 1985 (50 FR 47174).

¹"Traditional genetic modification techniques" refers to controlled mating (breeding) of plants and animals through the sexual process and the selection of spontaneous mutations in plants, animals, and microorganisms, or mutations induced by chemical and ultraviolet means. The application of traditional genetic modification techniques is relied upon broadly to enhance characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (treatment of sewage with bacteria), medicines (e.g., hormones, vaccines), pesticides (e.g., Bacillus thuringiensis), etc.

Upon examination of the existing laws, it was determined that, for the most part, these laws as currently implemented would adequately address products produced by use of the new techniques. It was recognized that for certain products, regulatory requirements, available under existing statutory authority, needed to be established. No need for new legislation was identified.

In addition to discussing the laws which support regulations within the Coordinated Framework, the June 26, 1986 Federal Register also described how guidelines for biomedical research would be used and announced proposed guidelines for agricultural research. These guidelines address requirements for the conduct of research funded by the Federal government in the biomedical and agricultural areas.

The June 26, 1986 Coordinated Framework announcement, in addition to describing how the framework would provide jurisdiction over both research and products, spelled out a basic philosophy for oversight of biotechnology. First, the approach should be "product/organism directed", in keeping with the product and organism-specific nature of the Coordinated Framework.² Second, where oversight is adequate no new requirements would be imposed. Third, duplicative reviews are to be avoided where possible. Fourth, a distinction should be made between organisms which

²The Coordinated Framework is product and organism specific because the laws supporting it focus on the product or test organism in question. These laws are used to regulate individual products/test organisms on the basis of the characteristics of a particular product/test organism or its intended use.

require a certain level of Federal review and those which do not. Fifth, agencies should seek to adopt consistent definitions.

A number of the commenters on the June 26, 1986 Federal Register addressed the issue of consistency of definitions among the agencies. All commenters who addressed the relationship between the definitions and the Coordinated Framework recognized the importance of definitions that were consistent among the agencies. A number of public commenters expressed concern that inconsistencies existed between the agencies in terms of definitions. Other commenters urged that definitions consistent among the agencies be developed.

Commenters also addressed the issue of whether the definitions discussed in the Coordinated Framework policy statements were appropriate for distinguishing between those organisms for which a certain level of review may be indicated and those for which it is not.

The agencies contributing to the Coordinated Framework have, since 1986, been evaluating how to best distinguish between those organisms for which a certain level of review may be indicated and those for which it is not. An underlying question has been the need for a definition, consistent among the agencies, describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment.

This current notice describes, in light of experience accumulated in the years since the 1986 publication of the Coordinated Framework, the BSCC attempt to address the issue of a

consistent definition describing the scope of organisms to be included in oversight for planned introductions into the environment. This definition (hereafter referred to as the "scope definition") would distinguish those organisms for which a certain level of review is indicated from those for which it is not. The assessment³ which would then be performed on these organisms would be conducted through consideration of the characteristics of the product/test organism and the environment in which the product/organism is to be used or tested.

In order to address the issue of a consistent scope definition, the BSCC formed a Subcommittee on Scope ("the Subcommittee") and charged it with developing such a definition.

In its work, the Subcommittee chose to focus on several science concepts articulated in reports^{4,5} by the U.S. National Academy of Sciences (NAS). These are:

- "...assessment of an organism should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was produced."

³The Federal agencies of the Coordinated Framework have performed a number of assessments since 1986 using a product and organism specific approach. A number of field trials have occurred and a number of products produced by the new techniques of biotechnology have come to market.

⁴Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues, National Academy of Sciences, 1987.

⁵Field Testing Genetically Modified Organisms: Framework for Decisions, National Research Council, National Academy Press, 1989.

- "... although genetic modification by molecular methods may be more powerful and capable of producing a wider range of phenotypes, no conceptual distinction exists between genetic modification by classical methods or by molecular methods that modify DNA and transfer genes."
- "Are we familiar⁶ with the properties of the organism and the environment into which it may be introduced?"

As it proceeded with its work, the Subcommittee was guided by several other important concepts:

- A scope definition should be consistent with the basic philosophy of oversight spelled out in the Coordinated Framework (i.e., the approach should be product and organism specific; an oversight structure is, for the most part in place; a distinction should be posed between organisms which require a certain level of review and those which do not).

⁶The familiarity criterion is central to the NAS' suggested framework for evaluation. "Familiarity" is based on past experience with the introduction of plants and microorganisms into the environment. The NAS report notes that "[f]amiliar does not mean safe. Rather, to be familiar with the elements of an introduction means to have enough information to be able to judge the introduction's safety or risk."

- In keeping with the basic philosophy of the Coordinated Framework it can be inferred that oversight requirements would be imposed only where human health or environmental concerns or uncertainties may be raised which differ from, or are in addition to, those issues addressed in assessing "familiar" organisms.
- Oversight of a product/test organism should be commensurate with the risk from a product/organism, or with uncertainty about risk because of "newness" or "unfamiliarity."
- While the process by which an organism is modified is not a determinant of risk, information on how a specific organism is modified can be valuable in assessing the characteristics of the modified organism and its potential effect on human health and the environment. "Knowledge of the method used . . . yield[s] useful information concerning the precision of the genetic characterization of the [organism] which in turn may be relevant for assessment. . . ." ⁷

The Subcommittee addressed the following issues: What are the assessment issues which would be used to determine the level of risk when the organism is not one with which we have familiarity?

⁷Field Testing Genetically Modified Organisms: Framework for Descisions, National Research Council, National Academy Press, 1989.

The Subcommittee began its work by attempting to describe assessment issues which might exist in addition to, or different from, those encountered with the introduction of organisms with which we have familiarity.

Based on these discussions, the Subcommittee identified the following questions:

- What genetic material has been added to the construct and what is the function of that material; particularly if the material is not naturally part of the organism's known gene pool⁸ and its addition may result in an organism whose characteristics are unfamiliar and the risks not well understood?
- What modifications have been made in regulatory sequences; particularly with regard to changes which allow genetic material not known to be available in the organism's gene pool to be expressed?
- What is the potential for exchange of the introduced genetic function to other organisms?

⁸In addition to the ability to move genetic material among distantly related organisms, molecular genetic techniques permit the incorporation of sequences that code for completely novel proteins designed by the researcher. For example, such synthetic sequences have been designed to supplement the overall production of essential amino acids in potatoes.

The Subcommittee then sought to circumscribe those organisms for which these questions can be posed. The strategy initially adopted by the Subcommittee to create such a definition was to develop and examine the advantages and disadvantages of several potential approaches. The Subcommittee first evaluated three major options for capturing within the scope organisms for which the new or different assessment issues can be posed: circumscribing the relevant organisms by capturing under the scope all organisms (Option 1); organisms formed by deliberate combination of genetic material from sources in different genera (intergeneric, Option 2); or organisms modified through the use of recombinant DNA (Option 3).

The Subcommittee concluded that none of these approaches would serve as an appropriate scope definition. It was the sense of the Subcommittee that Option 1 could be further refined to incorporate the concepts of the NAS study and a growing body of scientific information to develop broad categories of exclusions. The approach of focusing scope on "intergeneric" organisms would capture for review organisms for which the three assessment issues identified should be posed. However, its heavy reliance on taxonomy is problematic, particularly for microorganisms. The approach of focusing on organisms modified by recombinant DNA techniques would subject to review organisms for which the three additional safety issues should generally be posed. However, the process by which an organism is modified is not necessarily a determinant of risk. As with the approaches based on

"intergeneric" and "all organisms," an approach based on recombinant DNA would capture within the scope some organisms for which the new or different assessment issues identified by the Subcommittee would not be posed.

The Subcommittee then developed a preliminary draft definition. The preliminary draft scope definition was: "Organisms deliberately modified by the introduction into or the manipulation of genetic material in their genome." "Genome" was defined as "the sum total of genetic material of a genotype."

Six exclusions from the preliminary draft scope definition were identified. These were: (1) "Plants and animals that result from natural reproduction or from the use of familiar, traditional breeding techniques such as hand pollination of plants, and artificial insemination, superovulation, and transfer of embryos in animals." (2) "Microorganisms that result solely from chemical and physical mutagenesis, transduction, transformation or conjugation by known physiological processes." (3) "Plants regenerated from tissue culture, including those produced through selection of somaclonal variants or use of embryo rescue in plants." (4) "Vascular plants that were developed from protoplast fusion of cells from vascular plants." (5) "Organisms which have been modified by the introduction of non-coding nucleotide sequences and which serve only to mark the organism." This exclusion was to apply to "'trademark' sequences and linker sequences." The exclusion did not apply, for example, to the use of "'marker' genes associated with resistance to clinically

valuable antibiotics or genes associated with pesticidal activity useful in management of the organism in the environment or management of pest organisms with which it shares a gene pool."

(6) "Organisms resulting from the use of new techniques of biotechnology (modification by the use of recombinant DNA or similar techniques) when the person responsible for the planned introduction into the environment can demonstrate that the resulting genotype could readily be produced or selected through the techniques listed in 1-4 above, and that there is sufficient familiarity with the genotype to predict no adverse effects on human health or the environment."

The advice of two science advisory committees, the EPA Biotechnology Science Advisory Committee (BSAC) and the USDA Agricultural Biotechnology Science Research Committee (ABRAC) was sought. The BSAC met on December 20, 1989. The ABRAC met on January 10-13, 1990. These meetings were open to the public and a number of written comments were received from the public. Materials from those meetings can be found in the docket established for this notice.

The science advisory committees generally supported the approach; suggestions were made, however, to clarify or improve the draft definition. These suggestions were addressed and a proposed definition developed. The next section of this notice describes the definition on which the BSCC is requesting comments, and offers rationales for the language of the definition and its exclusions.

PROPOSED DEFINITION*

The proposed scope definition is "Organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes."

The term "organisms" is intended to be inclusive and encompass the organisms of all kingdoms, including viruses. It is not intended to cover, however, organisms that result from natural reproduction.

The definition includes organisms whose genetic make-up has intentionally been modified by human intervention. However, "modification by the introduction of genetic material into, or manipulation of genetic material within" organisms should not be construed to apply to organisms which have only been "selected." Selection is the isolation of a desired organism from natural sources.

In the context of the definition, "genomes" refers "to the sum total of chromosomal and extrachromosomal genetic material of an organism." This would include the DNA and RNA of the chromosome, DNA or RNA in organelles, and DNA and RNA in the cytoplasm of an organism.

This definition identifies a very broad group of modified organisms. The inclusion of an organism within this scope does not imply that it is dangerous or that it has any additional intrinsic risk as compared with naturally occurring organisms. The scope

*Please refer to the request for comments at the end of this document.

definition was intended to set the boundary around all organisms for which questions might be raised about whether new or unfamiliar safety assessment issues exist. This has been accomplished by including all modified organisms within the scope.

The very breadth of the definition, however, encompasses many organisms for which we have considerable evidence that sufficient oversight⁹ mechanisms already exist. For several groups of organisms that fall within the scope, there is a long history of introduction into the environment. For those groups, the assessment issues are known, and there is a "familiarity" with the behavior of the organisms in the environment. In addition, there is sufficient familiarity with the range of phenotypic expression associated with these organisms in the environment to predict probable behavior and to assess its safety or risk when introduced into the environment. Any risks posed by their planned introduction into the environment are addressed by current oversight mechanisms. Five specific exclusions to the scope definition have, therefore, been developed to ensure that such organisms are not subjected to additional review and oversight.

Organisms excluded from the scope by any of the exclusions would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter

⁹Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight.

The first exclusion from the scope definition addresses "plants and animals that result from natural reproduction or the use of traditional breeding techniques. These include, for example, for vascular plants, mutagenesis and hand pollination, and for vertebrate animals, artificial insemination, superovulation, and transfer of embryos." This first exclusion encompasses many of the organisms which humans have cultivated, bred, and raised over the centuries as the science of agriculture has developed.

Vascular plants encompass those plants which contain small vessels that conduct fluid throughout the plant. Vascular plants are higher plants marked by the differentiation of tissues into organs such as roots, stems, leaves, and flowers. Crop plants, trees, and bushes are all vascular plants.

Many of the plants which are now major food crops were originally wild. Humans noted certain desirable qualities in these plants and began to aid the plant to propagate, for example, by hand pollination. Over the millennia, humans have selected plant species with desirable traits, taking advantage of the natural variation in plants. Through thousands of years, these practices termed "traditional breeding techniques," have led to crop plants that are "domesticated" and may be very different from their wild ancestors.

Domesticated crop plants generally will not survive without human intervention. These crop plants have been selected by humans to possess certain desirable characteristics (e.g., larger grain heads, easier harvesting). Frequently, qualities which a breeder prizes are not those which would ensure survival in the wild. Humans, therefore, have provided "managed-ecosystems" with attendant conditions (e.g., irrigation, protection from insects, propagation measures) that are favorable to the plant's survival. The ability of these types of plants to survive without human intervention in natural environments is often limited.

Depending on the crop species, practices to confine the experimental crosses have been developed, and there is greater certainty about the efficacy of practices that are routinely followed to confine plants in an experimental field situation. Such practices have proved effective over the decades of crop breeding. Familiarity with the plants' life cycle, system of reproduction, and growth requirements has allowed for greater certainty about the probable behavior of the organism in the environment. Moreover, this familiarity leads to a knowledge of the range of potential phenotypic expression of the species in the environment.

Plants modified by traditional techniques are judged safe for field testing based on experience with hundreds of millions of crosses that have been field tested. Current oversight mechanisms are adequate to address any risks that might be posed by their planned introduction into the environment.

Vertebrate animals refers to those animals with a backbone. The term vertebrate is used in this notice to identify those animals specifically, since the animal kingdom encompasses many life forms that may not readily come to mind as animals, such as insects, worms, or mollusks.

As with plants, humans have selected vertebrate animals through "traditional breeding techniques." These breeding techniques allow humans to enhance characteristics humans find desirable, (e.g., docility, ratio of body fat, feed efficiency). Such modifications of vertebrate animals have been conducted for centuries. As with plants, those qualities humans find desirable are generally not those which ensure survival of an animal in the wild. The domestication of animals has generally made them less able to survive in the natural ecosystem and more dependant on human intervention for survival. These animals are, therefore, bred and raised in management environments such as barns or open range.

Animal breeding has become more sophisticated through use of modern medical techniques such as artificial insemination, superovulation, and embryo transfer. These techniques are employed to increase the frequency of desired traits in a domesticated animal population. These breeding techniques are generally applied only to animals being raised in a setting where the population is routinely confined and managed to ensure survival.

As with plants, familiarity with the animal's life cycle, system of reproduction, and range of phenotypic expression in the

environment allows us to predict probable behavior. In general, existing oversight mechanisms address any risks that might be associated with planned introduction into the environment of domesticated animals.

The above discussion utilizes vascular crop plants and domesticated vertebrate animals to elucidate how familiarity with the organism and with the range of phenotypes likely to result when the organism has been modified through traditional breeding techniques can be used to justify excluding these organisms from the scope definition. If similar degrees of familiarity exist for other plants and animals modified through traditional breeding techniques, these organisms would also be excluded.

The second exclusion from the scope definition addresses "microorganisms that are modified solely: (a) through chemical or physical mutagenesis; (b) by the movement of nucleic acids through physiological processes including, but not limited to transduction, transformation, or conjugation; or (c) by plasmid loss or spontaneous deletion. If nucleic acid molecules produced using in vitro manipulation are transferred using any of the techniques listed in (a) through (c), the resulting organisms do not fall under this exclusion."

This exclusion applies to a class of organisms, microorganisms, which differ in several respects from the organisms described in the first exclusion. First, the term "microorganism" covers a wide range of types of organisms; viruses, bacteria, fungi, algae, etc. The life cycles, reproductive behaviors and

adaptive strategies of these different types of microorganisms can vary enormously.

The most important difference between microorganisms and other organisms for the purposes of this discussion is that while some classes of microorganisms do not possess an ability to exchange genetic material through the types of sexual processes associated with plants and animals, they do possess various mechanisms to exchange genetic material in pseudosexual ways.¹⁰

Microorganisms engage in such exchanges through: (1) transduction, a process in which a virus can pick up nucleic acid from one host and transfer it to a subsequent host; (2) transformation, a process in which the microorganism takes up DNA from the environment (perhaps released into the environment by the death of another microorganism) and incorporates the DNA into its genome; and (3) conjugation, a process in which genetic material is transferred from one microorganism to another through physical contact.

We are familiar with these processes and know that they occur in nature. One can argue, therefore, that when a microorganism is modified by recreating in the laboratory conditions under which these types of genetic exchanges can occur, it is likely that the resulting organism is a variant that exists in nature. The

¹⁰Some classes of microorganisms possess mechanisms for asexual propagation, such as binary fission, budding, and asexual spore formation. The proposed definition is not intended to cover organisms that result from asexual reproduction.

conditions for exchange may have been optimized in the laboratory for efficiency, but the exchange is not qualitatively different.

Microorganisms, as are other organisms, are often exposed in the natural environment to chemical substances called mutagens, or physical agents such as ultraviolet light or X-rays which cause modifications in genetic material. Treatment of organisms with chemical or physical mutagens in the laboratory only accelerates natural phenomena. Here again one can argue that when an organism is modified by recreating in the laboratory conditions which occur in nature, the result will likely be organisms not significantly different from those found in nature. Another means by which genetic changes take place in nature is through loss of genetic material. Genetic material can be spontaneously deleted from chromosomal and extrachromosomal elements. In some cases, large segments of genetic material, e.g., plasmids, may be lost. Similar types of changes brought about in the laboratory would result in organisms that are variants likely to exist in nature.

This is not to say that because an organism occurs in nature it is safe. Rather, if the organism occurs naturally in the environment we are more likely to have observed its interaction with the environment, and better understand the risks that it might pose. It is also more likely that existing oversight mechanisms are adequate to address any risks that might be posed by these organisms.

Microorganisms modified by the introduction of in vitro manipulated nucleic acids are not covered by this exclusion

(although the fifth exclusion may apply). In vitro modifications to nucleic acids include in vitro treatment with enzymes and in vitro joining of nucleic acid sequences. They would also include the application of chemical or physical techniques to enrich for particular nucleic acid sequences, for example, use of the polymerase chain reaction, and the use of sequence-specific DNA affinity columns. These are powerful techniques that can be used to change organism sufficiently that we might not be familiar with the resulting phenotype and their potential range of interactions in nature.

The third exclusion from the scope definition addresses "vascular plants regenerated from tissue culture, including those produced through selection of somaclonal variants, embryo rescue, protoplast fusion, or treatments that cause changes in chromosome number."

Tissue culture involves growing plant cells in a culture or medium that will support them and keep them viable. The culture can be started with plant organs (e.g., leaves or roots), tissues (e.g., epidermal cells of a leaf), and with single cells. In culture, isolated plant cells can be induced to undergo repeated cell division and growth. If culture conditions are adjusted, the cells will differentiate and grow into a plant. Tissue culture, then, is a process in which plant tissue is isolated from an adult plant and placed in special media for the purpose of regenerating an adult plant without having to go through a normal reproductive cycle.

Embryo rescue is a process wherein embryos that would otherwise probably die are treated to special culture conditions to increase their likelihood of survival. Generally, the type of embryo that would not survive is that which exhibits a basic incompatibility between the embryo and the maternal plant. Such a situation might arise, for example, when plants from different genera are crossed.

In protoplast fusion, cells are treated to remove their rigid outer walls and placed in conditions which permit the combining or melding (fusion) of two individual cells (sometimes from different species) into one cell. The fusion cell is then used to produce an adult, hybrid plant, via tissue culture. Thus, the restrictions imposed by natural breeding barriers can be circumvented, and the resulting plant would contain genetic material from both progenitor plant cells. There are still many limitations on the types or plants which can be produced through protoplast fusion, mainly due to the instability of chromosome pairing. Usually, most of the genetic information in the regenerated plant is from one of the parental cells.

Variants can be produced from a single parental plant when somatic cells of that plant are treated so that they form protoplasts and then plants are subsequently regenerated from those protoplasts. These variants are called "somaclonal variants." They are thought to result from mutations, deletions or rearrangements of the parental genetic material. Somaclonal

variation can be used to generate plants from somatic tissue of the parent, thus by-passing the sexual process.

Vascular plants developed through regeneration in tissue culture are excluded from oversight because there is a long history of familiarity and safety with introductions of vascular plants per se. There is also a considerable body of experience that demonstrates safety and familiarity with the behavior of vascular plants treated with these techniques and regenerated through tissue culture techniques. For several decades, plant varieties have been developed through these techniques which generally supplement traditional breeding techniques. Existing oversight mechanisms are adequate to address any risks that might be posed by the planned introduction of such plants developed through the use of these techniques.

Exclusion three does not address nonvascular plants. These plants lack the extensive history of safety and familiarity that is available for vascular plants. Furthermore, adequate containment for some non-vascular plants may be problematic (e.g., with certain marine algae); and non-vascular plants often are found in non-managed, fragile, or threatened ecosystems.

The fourth exclusion from the scope definition addresses "organisms which have been modified by the introduction of non-coding, non-expressing nucleotide sequences that cause no phenotypic or physiological changes in the parental organism."

This exclusion applies to organisms that have been modified by introduction of in vitro manipulated nucleotide sequences that

serve only to identify the organism's genome. The exclusion also includes organisms that have been modified by the addition of short nucleotide sequences whose sole function is to facilitate subsequent in vitro genetic manipulations, or so-called "linker" sequences. To qualify for this exclusion, it should be demonstrated that the inserted nucleotide sequences are non-coding and non-expressing and no change in phenotype will occur due to the insertion.

These non-coding, non-expressing sequences should be well-characterized, including knowledge of the nucleotide sequence, of the site of insertion, and the effects of inserting material in that site. The exclusion does not apply to organisms modified by the introduction or manipulation of non-coding nucleotide sequences that function in gene regulation.

When these conditions are met, no "new" or unfamiliar safety assessment issues pertaining to introduction into the environment of these organisms would exist compared to the parental organisms that have not been modified in this manner.

This policy notice does not address who determines whether the nucleotide sequence is non-coding, non-expressing and causes no phenotypic change within the organism because the definition with its exclusions is intended to serve as guidance to the agencies. Each agency would, within its oversight structure, address the issue of who makes the determination.

The fifth exclusion from the scope definition addresses "organisms other than those exempted in 1-4 above, if it can be

demonstrated that: (1) they could be readily produced by the techniques listed above; and (2) there is sufficient familiarity with the organisms to foresee environmental effects equivalent to past safe introductions of similar organisms in similar target/test environments."

This exclusion recognizes that a specific genetic modification can be made in a specific organism by a number of different techniques. What is important in assessing the resulting organism is not the method by which the modification was made, but the phenotype resulting from that specific modification. For example, chemical and physical mutagenesis techniques can be used to modify an organism. Selective techniques can then be used to isolate from among its descendants, organisms modified in a particular phenotypic trait. An organism modified in that same phenotypic trait can, however, also be made by use of other genetic modification techniques, including procedures such as recombinant DNA.

The first four exclusions describe both categories of organisms and techniques of genetic modification. This approach is employed because: (1) for the most part the categories named in the exclusion consist of organisms with which we are familiar; and (2) information on the process by which a specific organism is modified can be valuable in predicting the probable characteristics of the organism and its potential effect on human health and the environment. When we know, for example, that a plant is to be modified by a traditional breeding technique, we have sufficient

familiarity with the parental plants, including their range of potential phenotypic expression, to predict probable behavior of the hybrid off-spring in the environment.

While the proposed exclusions include elements of technique, the scope definition with its exclusions is not a process based definition. It is, therefore, necessary to create a fifth exclusion. This fifth exclusion removes from the scope definition organisms that fall into the categories of excluded organisms listed in exclusion one through three, but are generated through techniques other than those listed in exclusions one through three, if two conditions are met.

First, they could be readily produced by the techniques listed in exclusions one through three. Second, there is sufficient familiarity with the organism and their descendants to foresee environmental effects comparable to past safe introductions of similar organisms in similar target/test environments.

When these requirements are met the resulting modified organism should possess a phenotype which falls within the range of phenotypic expression of the species. No new or additional assessment issues would be raised when such an organism is introduced to the environment, and existing oversight mechanisms should be adequate.

This policy notice does not address to whom or when it would be demonstrated that the organisms could "be readily produced by the techniques listed above;" and that "there is sufficient familiarity with the organisms to foresee environmental effects

comparable to past safe introductions of similar organisms in similar target/test environments." The scope definition and its exclusions are intended to serve as guidance to the agencies. Each agency would address this issue in terms of its oversight structure.

Organisms excluded from the scope definition would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight. Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

The BSCC is therefore requesting comment on the following proposed definition:

" Organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes.*

"The following organisms are excluded:

- "1. Plants and animals that result from natural reproduction or the use of traditional breeding techniques. These

*"Genomes refers to the sum total of chromosomal and extra-chromosomal genetic material of an organism.

include, for example, for vascular plants, mutagenesis and hand pollination, and for vertebrate animals, artificial insemination, superovulation, and transfer of embryos.

- "2. Microorganisms modified solely: (a) through chemical or physical mutagenesis; (b) by the movement of nucleic acids using physiological processes including, but not limited to transduction, transformation, or conjugation; or (c) by plasmid loss or spontaneous deletion. If nucleic acid molecules produced using in vitro manipulation** are transferred using any of the techniques listed in (a) through (c), the resulting organisms do not fall under this exclusion.
- "3. Vascular plants regenerated from tissue culture, including those produced through selection of somaclonal variants, embryo rescue, protoplast fusion, or treatments that cause changes in chromosome number.
- "4. Organisms which have been modified by the introduction of non-coding, non-expressed nucleotide sequences that cause no phenotypic or physiological changes in the parental organism.
- "5. Organisms other than those exempted in 1-4 above, if it can be demonstrated that: (1) they could be readily produced by the techniques listed above; and (2) there is sufficient

**"In vitro manipulation includes: the directed addition to, rearrangement of, or removal of nucleotide sequences from the genetic material that is introduced; or, the use of chemical or physical techniques to enrich for a specific sequence."

familiarity^{***} with the organism to foresee environmental effects equivalent to those associated with past safe introductions of similar organisms in similar target/test environments.

The BSCC acknowledges that this definition is based upon the concept of deliberate modification of the characteristics of an organism. In addition to other issues, the Committee requests public comment on the definition and substitute language that is more risk-oriented. Substitute language should take into account the practical needs of Federal agencies responsible for oversight of biotechnology.

The BSCC recognizes the need for regulatory flexibility in order to respond to the experiences of the industry and the agencies and to rapid changes in the science base. Therefore, as stated in the Coordinated Framework, it is recommended that this definition be reexamined periodically for its relevance to the current state of scientific knowledge and modified as appropriate.

^{***}"Familiarity does not necessarily imply safety. Rather, to be familiar with the elements of an introduction means to have enough information to be able to judge the introduction's safety or risk."

NATIONAL SCIENCE FOUNDATION

WASHINGTON, D.C. 20550



OFFICE OF THE
DIRECTOR

March 20, 1990

Dr. D. Allan Bromley
Assistant to the President for
Science and Technology
Room 358, Old Executive Office Building
Washington, DC 20506

Dear Dr. Bromley:

At its March 9, 1990 meeting, the Biotechnology Science Coordinating Committee (BSCC) approved the attached document, which describes the organisms for inclusion in oversight for planned introductions of organisms into the environment.

Accordingly, I am submitting this paper for your consideration for its publication in the FEDERAL REGISTER for solicitation of comments on the proposed definitions. Importantly for the proposed definition of scope, specific attention is directed to the following footnote. "The BSCC acknowledges that this definition is based upon the concept of deliberate modification of the characteristics of an organism. In addition, to other issues, the Committee requests public comment on the definition and substitute language that is more risk-oriented. Substitute language should take into account the practical needs of Federal agencies responsible for oversight of biotechnology."

Moreover, subsequent to the aforementioned BSCC meeting, I have added the following statement as an address to the sunset for the proposed definition. "The BSCC recognizes the need for regulatory flexibility in order to respond to the experiences of the industry and the agencies and to rapid changes in the science base. Therefore, as stated in the Coordinated Framework, it is recommended that this definition be reexamined periodically for its relevance to the current state of scientific knowledge and modified as appropriate."

Thanks for your attention to the submission and I look forward to notice its disposition.

Sincerely,

Luther S. Williams
Luther S. Williams
Chairman, BSCC

cc: Dr. James Wyngaarden

THE WHITE HOUSE
WASHINGTON

Date: March 19, 1990

TO: Jim Wyngaarden

FROM: KENNETH P. YALE
Special Assistant to the President
Domestic Policy Council

Attached is a thought piece on the current status of the scope proposal. I thought we might discuss this further.

Thank you.

SCOPE OF REGULATIONS

Issue: The appropriate organisms to be included in Federal oversight of planned introductions of biotechnology-related organisms into the environment.

Background: The 1986 Coordinated Framework for the Regulation of Biotechnology compiled the existing regulations affecting biotechnology products and provided the basis for further clarification and implementation of regulations.

The Coordinated Framework determined that existing laws were sufficient to regulate biotechnology, but further regulatory requirements would be needed for certain products. It is felt that such regulations should be scientifically based, and reflect a careful balance between health and environmental safety on the one hand and flexibility on the other. This will ensure public safety without unnecessarily hindering the growth of this new industry. Proper oversight of environmental release is also important to improve public perception of biotechnology.

Regulations for the environmental release of organisms have been considered by EPA (Federal Insecticide, Fungicide, and Rodenticide Act and Toxic Substance Control Act), and USDA. One basic issue is the kinds of organisms that should be subject to additional regulatory oversight, and hence which releases to oversee. Both Federal and state agencies are considering the scope of organisms appropriate for oversight.

Four reports have been developed on appropriate oversight considerations. These include: Introduction of Recombinant DNA-engineered Organisms into the Environment: Key Issues, National Academy of Sciences, 1987 (white paper); New Developments in Biotechnology-Field Testing Engineered Organisms: Genetic and Ecological Issues, Office of Technology Assessment, 1988; The Planned Introduction of Genetically Engineered Organisms: Ecological Considerations and Recommendations, Ecological Society of America, 1989; Field Testing Genetically Modified Organisms: Framework for Decisions, National Research Council (NRC), 1989.

These reports generally conclude that new organisms produced by biotechnology have no unique hazards that distinguish them from organisms produced by conventional breeding techniques. Thus, regulation should be based on the characteristics of the organisms and the environment into which they will be released (product-based) -- not on the basis of how they were made (process-based). This is a significant distinction as some believe process-based regulation could single out biotechnology products for special treatment and might foster the perception that such products are different and have unique hazards.

Discussion: The Biotechnology Science Coordinating Committee (BSCC) has developed a draft scope proposal in an attempt to provide an overall approach. It begins by covering all genetically modified organisms. Categories of exemptions are then applied to drop from additional oversight organisms with which there is sufficient "familiarity" to predict their probable behavior in the environment (ie., the safety or risk of a planned introduction can be determined). In predicting the behavior of an organism in the environment, the process by which an organism is modified is specifically considered. This approach has been criticized both for singling out genetically modified organisms and as process-based. In addition, it does not distinguish between plants and microorganisms. The latter arguably pose different problems of control and environmental effect.

A product-based regulatory approach that prohibits any consideration of process, however, is not without problems. It would avoid using any biotechnology-based process as the primary trigger for regulatory oversight, and thereby reduce the concern that biotechnology might be perceived as having unique hazards. It could, however, result in overly broad regulation, by requiring new or additional oversight of all organisms (even those naturally grown) released into any environment.

There may be a middle ground between these viewpoints. The familiarity standard was outlined in the 1989 NRC report. It is based upon past experience with environmental introductions, and could be used to develop exemptions to regulatory oversight. In addition, it is flexible enough to incorporate new scientific information in the future. It is not totally process-based, although the NRC concluded that in determining familiarity, information about the process used to create an organism can assist in understanding its characteristics. Thus, the inquiry does not focus on unique hazards of a process, but process is one criteria in assessing familiarity.

More problematic is the starting point of the BSCC inquiry - genetically modified organisms (GMO). Arguably, this narrows the scope of inquiry and avoids overly broad regulation. Nevertheless, there is little scientific basis for singling out GMOs, and there may be greater harm in implying they impose unique risks. A different starting point may be required.

Implications: A policy decision must be made on the general direction and appropriate starting point for Federal oversight of planned introductions of biotechnology-related organisms into the environment. Once that decision is made, scientifically based exemptions could be crafted. Regulations have been under development for over three years. Industry has become uncertain about their eventual direction, and may be willing to begin with any formulation, just to see movement. In addition, states are beginning to develop their own regulations, and there are indications of more state action.

THE WHITE HOUSE

WASHINGTON

March 16, 1990

MEMORANDUM FOR D. ALLAN BROMLEY

FROM: LAWRENCE B. LINDSEY

SUBJECT: BSCC Scope Paper

At the first meeting of the Competitiveness Council dealing with biotechnology issues, the Vice President opposed having the issue of scope decided formally at the BSCC level. It has now come to my attention that the BSCC has chosen to proceed with publication for public comment of its scope paper.

I am particularly distressed that the definition of scope adopted in that paper is based on process, not product. The paper defines the scope as being any genetically modified organism with several specified exceptions.

If this were the only plausible scientific definition of the scope of biotechnology regulation, then there would be no reason for policy level review. However, the National Academy of Sciences has proposed a regulatory mechanism based on the "familiarity" of the resulting product. While this alternative no doubt has problems, it is at least a product based approach; an approach to which the Administration is committed.

I urge you to delay publication of the BSCC report and any related regulations until it has been reviewed by the Working Group. I suggest that the report and attendant regulations be first sent to the Science and Technology sub-group, and then forwarded to the full Working Group. I do not believe that this will necessitate any undue delays.

cc: The Vice President
Boyden Gray, Counsel to the President

FR Notice: Scope of Organisms to be Included in Oversight for
Planned Introductions into the Environment

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

4/4/90
version

AGENCY: Office of Science and Technology Policy,

ACTION: Notice: Announcement of Proposed Definition,
Request for Public Comment, and
Announcement of Open Meeting

SUMMARY: This FEDERAL REGISTER notice announces a proposed definition describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment. The Biotechnology Science Coordinating Committee (BSCC) is seeking comment on the proposed definition. This document also gives notice of an open BSCC meeting to discuss the proposed definition.

DATES: Comments must be received on or before (insert date 30 days after receipt at FEDERAL REGISTER). An open meeting of the BSCC will be held on May 2, 1990 at 3 p.m. (tentative). *No longer possible.*

ADDRESSES: Comments specific to the BSCC proposed definition should be addressed to:

Biotechnology Science Coordinating Committee

Docket # NSF 0001

National Science Foundation Library

Room 248

1800 G Street, N.W.

Washington, D.C. 20550

The BSCC open meeting will be held at the:

Jefferson Auditorium

U.S. Department of Agriculture

14th St. and Independence Ave., N.W.

Washington, D.C. 20250

FOR FURTHER INFORMATION CONTACT: Dr. Luther S. Williams, Senior Science Advisor, National Science Foundation, Room 520, 1800 G Street, N.W., Washington, D.C. 20550, (202-357-9447).

SUPPLEMENTARY INFORMATION: This notice announces a proposed definition describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment. It has been developed by the Biotechnology Science Coordinating Committee (BSCC) for interagency science policy coordination and guidance. As such, the proposed definition addresses science issues. Each agency will use the definition as appropriate within its oversight structure. Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

The proposed definition is intended to apply to all kingdoms of organisms used in planned introductions into the environment for field testing. It is not intended to address all of the issues associated with large-scale applications or the scientific, ethical and societal issues that may be associated with large-scale applications. However, the principles applied in developing this

definition may be extrapolated, as appropriate, to other uses of organisms such as large scale environmental applications.

The proposed definition is intended to identify those organisms to be screened before they are introduced into the environment for field testing. That an organism is covered by the definition does not imply a priori that a risk is associated with that organism or its use. The definition simply circumscribes a group of organisms to be evaluated to determine whether a risk exists in the test situation.

The definition is intended to complement, not supercede existing oversight mechanisms for the planned introductions of organisms. Organisms excluded from the scope definition would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight.

An open public meeting of the BSCC will be held to take comment on the proposed scope for planned introduction to the environment for field testing. Time will be allocated for public comments on the scope definition. Attendance by the public will be limited to available space. Priority will be given to commenters who have provided written comments in advance of the meeting.

D. Allan Bromley

Assistant to the President for
Science and Technology and
Director, Office of Science
and Technology Policy

BACKGROUND: In the June 26, 1986 Federal Register, the U.S. government described its comprehensive regulatory policy for ensuring the safety of research and products produced through the use of biotechnology (51 FR 23302, 1986). This comprehensive policy document is entitled the "Coordinated Framework for Regulation of Biotechnology," referred to in this notice as simply the "Coordinated Framework."

In creating the Coordinated Framework, the underlying question addressed by the U.S. government was whether the existing regulatory structure pertaining to products, including products developed by traditional genetic modification techniques¹, was adequate for products obtained with the new techniques of biotechnology (e.g., recombinant DNA and cell fusion). A similar question arose regarding sufficiency of the review process for research conducted for agricultural and environmental applications.

In the U.S., the oversight structure is based upon laws which seek to ensure that products and research pose no unreasonable risk. A concise index of these U.S. laws was published in the Federal Register of November 14, 1985 (50 FR 47174).

¹"Traditional genetic modification techniques" refers to controlled mating (breeding) of plants and animals through the sexual process and the selection of spontaneous mutations in plants, animals, and microorganisms, or mutations induced by chemical and ultraviolet means. The application of traditional genetic modification techniques is relied upon broadly to enhance characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (treatment of sewage with bacteria), medicines (e.g., hormones, vaccines), pesticides (e.g., Bacillus thuringiensis), etc.

Upon examination of the existing laws, it was determined that, for the most part, these laws as currently implemented would adequately address products produced by use of the new techniques. It was recognized that for certain products, regulatory requirements, available under existing statutory authority, needed to be established. No need for new legislation was identified.

In addition to discussing the laws which support regulations within the Coordinated Framework, the June 26, 1986 Federal Register also described how guidelines for biomedical research would be used and announced proposed guidelines for agricultural research. These guidelines address requirements for the conduct of research funded by the Federal government in the biomedical and agricultural areas.

The June 26, 1986 Coordinated Framework announcement, in addition to describing how the framework would provide jurisdiction over both research and products, spelled out a basic philosophy for oversight of biotechnology. First, the approach should be "product/organism directed," in keeping with the product and organism-specific nature of the Coordinated Framework.² Second, where oversight is adequate no new requirements would be imposed. Third, duplicative reviews are to be avoided where possible. Fourth, a distinction should be made between organisms which

²The Coordinated Framework is product and organism specific because the laws supporting it focus on the product or test organism in question. These laws are used to regulate individual products/test organisms on the basis of the characteristics of a particular product/test organism or its intended use.

require a certain level of Federal review and those which do not. Fifth, agencies should seek to adopt consistent definitions.

A number of the commenters on the June 26, 1986 Federal Register addressed the issue of consistency of definitions among the agencies. All commenters who addressed the relationship between the definitions and the Coordinated Framework recognized the importance of definitions that were consistent among the agencies. A number of public commenters expressed concern that inconsistencies existed between the agencies in terms of definitions. Other commenters urged that definitions consistent among the agencies be developed.

Commenters also addressed the issue of whether the definitions discussed in the Coordinated Framework policy statements were appropriate for distinguishing between those organisms for which a certain level of review may be indicated and those for which it is not.

The agencies contributing to the Coordinated Framework have, since 1986, been evaluating how to best distinguish between those organisms for which a certain level of review may be indicated and those for which it is not. An underlying question has been the need for a definition, consistent among the agencies, describing the scope of organisms to be included in oversight for planned introductions of organisms into the environment.

This current notice describes, in light of experience accumulated in the years since the 1986 publication of the Coordinated Framework, the BSCC attempt to address the issue of a

consistent definition describing the scope of organisms to be included in oversight for planned introductions into the environment. This definition (hereafter referred to as the "scope definition") would distinguish those organisms for which a certain level of review is indicated from those for which it is not. The assessment³ which would then be performed on these organisms would be conducted through consideration of the characteristics of the product/test organism and the environment in which the product/organism is to be used or tested.

In order to address the issue of a consistent scope definition, the BSCC formed a Subcommittee on Scope ("the Subcommittee") and charged it with developing such a definition.

In its work, the Subcommittee chose to focus on several science concepts articulated in reports^{4,5} by the U.S. National Academy of Sciences (NAS). These are:

- "...assessment of an organism should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was produced."

³The Federal agencies of the Coordinated Framework have performed a number of assessments since 1986 using a product and organism specific approach. A number of field trials have occurred and a number of products produced by the new techniques of biotechnology have come to market.

⁴Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues, National Academy of Sciences, 1987.

⁵Field Testing Genetically Modified Organisms: Framework for Decisions, National Research Council, National Academy Press, 1989.

- "... although genetic modification by molecular methods may be more powerful and capable of producing a wider range of phenotypes, no conceptual distinction exists between genetic modification by classical methods or by molecular methods that modify DNA and transfer genes."
- "Are we familiar⁶ with the properties of the organism and the environment into which it may be introduced?"

As it proceeded with its work, the Subcommittee was guided by several other important concepts:

- A scope definition should be consistent with the basic philosophy of oversight spelled out in the Coordinated Framework (i.e., the approach should be product and organism specific; an oversight structure is, for the most part in place; a distinction should be posed between organisms which require a certain level of review and those which do not).

⁶The familiarity criterion is central to the NAS' suggested framework for evaluation. "Familiarity" is based on past experience with the introduction of plants and microorganisms into the environment. The NAS report notes that "[f]amiliar does not mean safe. Rather, to be familiar with the elements of an introduction means to have enough information to be able to judge the introduction's safety or risk."

- In keeping with the basic philosophy of the Coordinated Framework it can be inferred that oversight requirements would be imposed only where human health or environmental concerns or uncertainties may be raised which differ from, or are in addition to, those issues addressed in assessing "familiar" organisms.
- Oversight of a product/test organism should be commensurate with the risk from a product/organism, or with uncertainty about risk because of "newness" or "unfamiliarity."
- While the process by which an organism is modified is not a determinant of risk, information on how a specific organism is modified can be valuable in assessing the characteristics of the modified organism and its potential effect on human health and the environment. "Knowledge of the method used . . . yield[s] useful information concerning the precision of the genetic characterization of the [organism] which in turn may be relevant for assessment. . . ." ⁷

The Subcommittee addressed the following issues: What are the assessment issues which would be used to determine the level of risk when the organism is not one with which we have familiarity?

⁷Field Testing Genetically Modified Organisms: Framework for Descisions, National Research Council, National Academy Press, 1989.

The Subcommittee began its work by attempting to describe assessment issues which might exist in addition to, or different from, those encountered with the introduction of organisms with which we have familiarity.

Based on these discussions, the Subcommittee identified the following questions:

- What genetic material has been added to the construct and what is the function of that material; particularly if the material is not naturally part of the organism's known gene pool⁸ and its addition may result in an organism whose characteristics are unfamiliar and the risks not well understood?
- What modifications have been made in regulatory sequences; particularly with regard to changes which allow genetic material not known to be available in the organism's gene pool to be expressed?
- What is the potential for exchange of the introduced genetic function to other organisms?

⁸In addition to the ability to move genetic material among distantly related organisms, molecular genetic techniques permit the incorporation of sequences that code for completely novel proteins designed by the researcher. For example, such synthetic sequences have been designed to supplement the overall production of essential amino acids in potatoes.

The Subcommittee then sought to circumscribe those organisms for which these questions can be posed. The strategy initially adopted by the Subcommittee to create such a definition was to develop and examine the advantages and disadvantages of several potential approaches. The Subcommittee first evaluated three major options for capturing within the scope organisms for which the new or different assessment issues can be posed: circumscribing the relevant organisms by capturing under the scope all organisms (Option 1); organisms formed by deliberate combination of genetic material from sources in different genera (intergeneric, Option 2); or organisms modified through the use of recombinant DNA (Option 3).

The Subcommittee concluded that none of these approaches would serve as an appropriate scope definition. It was the sense of the Subcommittee that Option 1 could be further refined to incorporate the concepts of the NAS study and a growing body of scientific information to develop broad categories of exclusions. The approach of focusing scope on "intergeneric" organisms would capture for review organisms for which the three assessment issues identified should be posed. However, its heavy reliance on taxonomy is problematic, particularly for microorganisms. The approach of focusing on organisms modified by recombinant DNA techniques would subject to review organisms for which the three additional safety issues should generally be posed. However, the process by which an organism is modified is not necessarily a determinant of risk. As with the approaches based on

"intergeneric" and "all organisms," an approach based on recombinant DNA would capture within the scope some organisms for which the new or different assessment issues identified by the Subcommittee would not be posed.

The Subcommittee then developed a preliminary draft definition. The preliminary draft scope definition was: "Organisms deliberately modified by the introduction into or the manipulation of genetic material in their genome." "Genome" was defined as "the sum total of genetic material of a genotype."

Six exclusions from the preliminary draft scope definition were identified. These were: (1) "Plants and animals that result from natural reproduction or from the use of familiar, traditional breeding techniques such as hand pollination of plants, and artificial insemination, superovulation, and transfer of embryos in animals." (2) "Microorganisms that result solely from chemical and physical mutagenesis, transduction, transformation or conjugation by known physiological processes." (3) "Plants regenerated from tissue culture, including those produced through selection of somaclonal variants or use of embryo rescue in plants." (4) "Vascular plants that were developed from protoplast fusion of cells from vascular plants." (5) "Organisms which have been modified by the introduction of non-coding nucleotide sequences and which serve only to mark the organism." This exclusion was to apply to "'trademark' sequences and linker sequences." The exclusion did not apply, for example, to the use of "'marker' genes associated with resistance to clinically

valuable antibiotics or genes associated with pesticidal activity useful in management of the organism in the environment or management of pest organisms with which it shares a gene pool."

(6) "Organisms resulting from the use of new techniques of biotechnology (modification by the use of recombinant DNA or similar techniques) when the person responsible for the planned introduction into the environment can demonstrate that the resulting genotype could readily be produced or selected through the techniques listed in 1-4 above, and that there is sufficient familiarity with the genotype to predict no adverse effects on human health or the environment."

The advice of two science advisory committees, the EPA Biotechnology Science Advisory Committee (BSAC) and the USDA Agricultural Biotechnology Science Research Committee (ABRAC) was sought. The BSAC met on December 20, 1989. The ABRAC met on January 10-13, 1990. These meetings were open to the public and a number of written comments were received from the public. Materials from those meetings can be found in the docket established for this notice.

The science advisory committees generally supported the approach; suggestions were made, however, to clarify or improve the draft definition. These suggestions were addressed and a proposed definition developed. The next section of this notice describes the definition on which the BSCC is requesting comments, and offers rationales for the language of the definition and its exclusions.

PROPOSED DEFINITION*

The proposed scope definition is "Organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes."

The term "organisms" is intended to be inclusive and encompass the organisms of all kingdoms, including viruses. It is not intended to cover, however, organisms that result from natural reproduction.

The definition includes organisms whose genetic make-up has intentionally been modified by human intervention. However, "modification by the introduction of genetic material into, or manipulation of genetic material within" organisms should not be construed to apply to organisms which have only been "selected." Selection is the isolation of a desired organism from natural sources.

In the context of the definition, "genomes" refers "to the sum total of chromosomal and extrachromosomal genetic material of an organism." This would include the DNA and RNA of the chromosome, DNA or RNA in organelles, and DNA and RNA in the cytoplasm of an organism.

This definition identifies a very broad group of modified organisms. The inclusion of an organism within this scope does not imply that it is dangerous or that it has any additional intrinsic risk as compared with naturally occurring organisms. The scope

*Please refer to the request for comments at the end of this document.

definition was intended to set the boundary around all organisms for which questions might be raised about whether new or unfamiliar safety assessment issues exist. This has been accomplished by including all modified organisms within the scope.

The very breadth of the definition, however, encompasses many organisms for which we have considerable evidence that sufficient oversight⁹ mechanisms already exist. For several groups of organisms that fall within the scope, there is a long history of introduction into the environment. For those groups, the assessment issues are known, and there is a "familiarity" with the behavior of the organisms in the environment. In addition, there is sufficient familiarity with the range of phenotypic expression associated with these organisms in the environment to predict probable behavior and to assess its safety or risk when introduced into the environment. Any risks posed by their planned introduction into the environment are addressed by current oversight mechanisms. Five specific exclusions to the scope definition have, therefore, been developed to ensure that such organisms are not subjected to additional review and oversight.

Organisms excluded from the scope by any of the exclusions would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter

⁹Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight.

The first exclusion from the scope definition addresses "plants and animals that result from natural reproduction or the use of traditional breeding techniques. These include, for example, for vascular plants, mutagenesis and hand pollination, and for vertebrate animals, artificial insemination, superovulation, and transfer of embryos." This first exclusion encompasses many of the organisms which humans have cultivated, bred, and raised over the centuries as the science of agriculture has developed.

Vascular plants encompass those plants which contain small vessels that conduct fluid throughout the plant. Vascular plants are higher plants marked by the differentiation of tissues into organs such as roots, stems, leaves, and flowers. Crop plants, trees, and bushes are all vascular plants.

Many of the plants which are now major food crops were originally wild. Humans noted certain desirable qualities in these plants and began to aid the plant to propagate, for example, by hand pollination. Over the millennia, humans have selected plant species with desirable traits, taking advantage of the natural variation in plants. Through thousands of years, these practices termed "traditional breeding techniques," have led to crop plants that are "domesticated" and may be very different from their wild ancestors.

Domesticated crop plants generally will not survive without human intervention. These crop plants have been selected by humans

to possess certain desirable characteristics (e.g., larger grain heads, easier harvesting). Frequently, qualities which a breeder prizes are not those which would ensure survival in the wild. Humans, therefore, have provided "managed-ecosystems" with attendant conditions (e.g., irrigation, protection from insects, propagation measures) that are favorable to the plant's survival. The ability of these types of plants to survive without human intervention in natural environments is often limited.

Depending on the crop species, practices to confine the experimental crosses have been developed, and there is greater certainty about the efficacy of practices that are routinely followed to confine plants in an experimental field situation. Such practices have proved effective over the decades of crop breeding. Familiarity with the plants' life cycle, system of reproduction, and growth requirements has allowed for greater certainty about the probable behavior of the organism in the environment. Moreover, this familiarity leads to a knowledge of the range of potential phenotypic expression of the species in the environment.

Plants modified by traditional techniques are judged safe for field testing based on experience with hundreds of millions of crosses that have been field tested. Current oversight mechanisms are adequate to address any risks that might be posed by their planned introduction into the environment.

Vertebrate animals refers to those animals with a backbone. The term vertebrate is used in this notice to identify those

animals specifically, since the animal kingdom encompasses many life forms that may not readily come to mind as animals, such as insects, worms, or mollusks.

As with plants, humans have selected vertebrate animals through "traditional breeding techniques." These breeding techniques allow humans to enhance characteristics humans find desirable, (e.g., docility, percent body fat, feed efficiency). Such modifications of vertebrate animals have been conducted for centuries. As with plants, those qualities humans find desirable are generally not those which ensure survival of an animal in the wild. The domestication of animals has generally made them less able to survive in the natural ecosystem and more dependant on human intervention for survival. These animals are, therefore, bred and raised in management environments such as barns or open range.

Animal breeding has become more sophisticated through use of modern medical techniques such as artificial insemination, superovulation, and embryo transfer. These techniques are employed to increase the frequency of desired traits in a domesticated animal population. These breeding techniques are generally applied only to animals being raised in a setting where the population is routinely confined and managed to ensure survival.

As with plants, familiarity with the animal's life cycle, system of reproduction, and range of phenotypic expression in the environment allows us to predict probable behavior. In general, existing oversight mechanisms address any risks that might be

associated with planned introduction into the environment of domesticated animals.

The above discussion utilizes vascular crop plants and domesticated vertebrate animals to elucidate how familiarity with the organism and with the range of phenotypes likely to result when the organism has been modified through traditional breeding techniques can be used to justify excluding these organisms from the scope definition. If similar degrees of familiarity exist for other plants and animals modified through traditional breeding techniques, these organisms would also be excluded.

The second exclusion from the scope definition addresses "microorganisms that are modified solely: (a) through chemical or physical mutagenesis; (b) by the movement of nucleic acids through physiological processes including, but not limited to transduction, transformation, or conjugation; or (c) by plasmid loss or spontaneous deletion. If nucleic acid molecules manipulated in vitro are transferred using any of the techniques listed in (a) through (c), the resulting organisms do not fall under this exclusion."

This exclusion applies to a class of organisms, microorganisms, which differ in several respects from the organisms described in the first exclusion. First, the term "microorganism" covers a wide range of types of organisms; viruses, bacteria, fungi, algae, etc. The life cycles, reproductive behaviors and adaptive strategies of these different types of microorganisms can vary enormously.

The most important difference between microorganisms and other organisms for the purposes of this discussion is that while some classes of microorganisms do not possess an ability to exchange genetic material through the types of sexual processes associated with plants and animals, they do possess various mechanisms to exchange genetic material in pseudosexual ways.¹⁰

Microorganisms engage in such exchanges through: (1) transduction, a process in which a virus can pick up nucleic acid from one host and transfer it to a subsequent host; (2) transformation, a process in which the microorganism takes up DNA from the environment (perhaps released into the environment by the death of another microorganism) and incorporates the DNA into its genome; and (3) conjugation, a process in which genetic material is transferred from one microorganism to another through physical contact.

We are familiar with these processes and know that they occur in nature. One can argue, therefore, that when a microorganism is modified by recreating in the laboratory conditions under which these types of genetic exchanges can occur, it is likely that the resulting organism is a variant that exists in nature. The conditions for exchange may have been optimized in the laboratory for efficiency, but the exchange is not qualitatively different.

¹⁰Some classes of microorganisms possess mechanisms for asexual propagation, such as binary fission, budding, and asexual spore formation. The proposed definition is not intended to cover organisms that result from asexual reproduction.

Microorganisms, as are other organisms, are often exposed in the natural environment to chemical substances called mutagens, or physical agents such as ultraviolet light or X-rays which cause modifications in genetic material. Treatment of organisms with chemical or physical mutagens in the laboratory only accelerates natural phenomena. Here again one can argue that when an organism is modified by recreating in the laboratory conditions which occur in nature, the result will likely be organisms not significantly different from those found in nature. Another means by which genetic changes take place in nature is through loss of genetic material. Genetic material can be spontaneously deleted from chromosomal and extrachromosomal elements. In some cases, large segments of genetic material, e.g., plasmids, may be lost. Similar types of changes brought about in the laboratory would result in organisms that are variants likely to exist in nature.

This is not to say that because an organism occurs in nature it is safe. Rather, if the organism occurs naturally in the environment we are more likely to have observed its interaction with the environment, and better understand the risks that it might pose. It is also more likely that existing oversight mechanisms are adequate to address any risks that might be posed by these organisms.

Microorganisms modified by the introduction of nucleic acids manipulated in vitro are not covered by this exclusion (although the fifth exclusion may apply). Nucleic acid modifications in vitro include treatment in vitro with enzymes and joining in vitro

of nucleic acid sequences. They would also include the application of chemical or physical techniques to enrich for particular nucleic acid sequences, for example, use of the polymerase chain reaction, and the use of sequence-specific DNA affinity columns. These are powerful techniques that can be used to change the organism sufficiently that we might not be familiar with the resulting phenotype and their potential range of interactions in nature.

The third exclusion from the scope definition addresses "vascular plants regenerated from tissue culture, including those produced through selection of somaclonal variants, embryo rescue, protoplast fusion, or treatments that cause changes in chromosome number."

Tissue culture involves growing plant cells in a culture or medium that will support them and keep them viable. The culture can be started with plant organs (e.g., leaves or roots), tissues (e.g., epidermal cells of a leaf), and with single cells. In culture, isolated plant cells can be induced to undergo repeated cell division and growth. If culture conditions are adjusted, the cells will differentiate and grow into a plant. Tissue culture, then, is a process in which plant tissue is isolated from an adult plant and placed in special media for the purpose of regenerating an adult plant without having to go through a normal reproductive cycle.

Embryo rescue is a process wherein embryos that would otherwise probably die are treated to special culture conditions to increase their likelihood of survival. Generally, the type of

embryo that would not survive is that which exhibits a basic incompatibility between the embryo and the maternal plant. Such a situation might arise, for example, when plants from different genera are crossed.

In protoplast fusion, cells are treated to remove their rigid outer walls and placed in conditions which permit the combining or melding (fusion) of two individual cells (sometimes from different species) into one cell. The fusion cell is then used to produce an adult, hybrid plant, via tissue culture. Thus, the restrictions imposed by natural breeding barriers can be circumvented, and the resulting plant would contain genetic material from both progenitor plant cells. There are still many limitations on the types or plants which can be produced through protoplast fusion, mainly due to the instability of chromosome pairing. Usually, most of the genetic information in the regenerated plant is from one of the parental cells.

Variants can be produced from a single parental plant when somatic cells of that plant are treated so that they form protoplasts and then plants are subsequently regenerated from those protoplasts. These variants are called "somaclonal variants." They are thought to result from mutations, deletions or rearrangements of the parental genetic material. Somaclonal variation can be used to generate plants from somatic tissue of the parent, thus by-passing the sexual process.

Vascular plants developed through regeneration in tissue culture are excluded from oversight because there is a long history

of familiarity and safety with introductions of vascular plants per se. There is also a considerable body of experience that demonstrates safety and familiarity with the behavior of vascular plants treated with these techniques and regenerated through tissue culture techniques. For several decades, plant varieties have been developed through these techniques which generally supplement traditional breeding techniques. Existing oversight mechanisms are adequate to address any risks that might be posed by the planned introduction of such plants developed through the use of these techniques.

Exclusion three does not address nonvascular plants. These plants lack the extensive history of safety and familiarity that is available for vascular plants. Furthermore, adequate containment for some non-vascular plants may be problematic (e.g., with certain marine algae); and non-vascular plants often are found in non-managed, fragile, or threatened ecosystems.

The fourth exclusion from the scope definition addresses "organisms which have been modified by the introduction of non-coding, non-expressing nucleotide sequences that cause no phenotypic or physiological changes in the parental organism."

This exclusion applies to organisms that have been modified by introduction of nucleotide sequences manipulated in vitro that serve only to identify the organism's genome. The exclusion also includes organisms that have been modified by the addition of short nucleotide sequences whose sole function is to facilitate subsequent genetic manipulations in vitro, or so-called "linker"

sequences. To qualify for this exclusion, it should be demonstrated that the inserted nucleotide sequences are non-coding and non-expressing and no change in phenotype will occur due to the insertion.

These non-coding, non-expressing sequences should be well-characterized, including knowledge of the nucleotide sequence, of the site of insertion, and the effects of inserting material in that site. The exclusion does not apply to organisms modified by the introduction or manipulation of non-coding nucleotide sequences that function in gene regulation.

When these conditions are met, no "new" or unfamiliar safety assessment issues pertaining to introduction into the environment of these organisms would exist compared to the parental organisms that have not been modified in this manner.

This policy notice does not address who determines whether the nucleotide sequence is non-coding, non-expressing and causes no phenotypic change within the organism because the definition with its exclusions is intended to serve as guidance to the agencies. Each agency would, within its oversight structure, address the issue of who makes the determination.

The fifth exclusion from the scope definition addresses "organisms other than those exempted in 1-4 above, if it can be demonstrated that: (1) they could be readily produced by the techniques listed above; and (2) there is sufficient familiarity with the organisms to foresee environmental effects equivalent to

past safe introductions of similar organisms in similar target/test environments."

This exclusion recognizes that a specific genetic modification can be made in a specific organism by a number of different techniques. What is important in assessing the resulting organism is not the method by which the modification was made, but the phenotype resulting from that specific modification. For example, chemical and physical mutagenesis techniques can be used to modify an organism. Selective techniques can then be used to isolate from among its descendants, organisms modified in a particular phenotypic trait. An organism modified in that same phenotypic trait can, however, also be made by use of other genetic modification techniques, including procedures such as recombinant DNA.

The first four exclusions describe both categories of organisms and techniques of genetic modification. This approach is employed because: (1) for the most part the categories named in the exclusion consist of organisms with which we are familiar; and (2) information on the process by which a specific organism is modified can be valuable in predicting the probable characteristics of the organism and its potential effect on human health and the environment. When we know, for example, that a plant is to be modified by a traditional breeding technique, we have sufficient familiarity with the parental plants, including their range of potential phenotypic expression, to predict probable behavior of the hybrid off-spring in the environment.

While the proposed exclusions include elements of technique, the scope definition with its exclusions is not a process based definition. It is, therefore, necessary to create a fifth exclusion. This fifth exclusion removes from the scope definition organisms that fall into the categories of excluded organisms listed in exclusion one through three, but are generated through techniques other than those listed in exclusions one through three, if two conditions are met.

First, they could be readily produced by the techniques listed in exclusions one through three. Second, there is sufficient familiarity with the organism and their descendants to foresee environmental effects comparable to past safe introductions of similar organisms in similar target/test environments.

When these requirements are met the resulting modified organism should possess a phenotype which falls within the range of phenotypic expression of the species. No new or additional assessment issues would be raised when such an organism is introduced to the environment, and existing oversight mechanisms should be adequate.

This policy notice does not address to whom or when it would be demonstrated that the organisms could "be readily produced by the techniques listed above;" and that "there is sufficient familiarity with the organisms to foresee environmental effects comparable to past safe introductions of similar organisms in similar target/test environments." The scope definition and its exclusions are intended to serve as guidance to the agencies. Each

agency would address this issue in terms of its oversight structure.

Organisms excluded from the scope definition would still be subject to existing jurisdictional oversight where applicable. For example, if a pesticidal, plant pest, or food product property was associated with the organism, no matter whether that was the property modified or not, it would be subject to the appropriate jurisdictional oversight. Oversight refers to the application of appropriate laws, regulations, guidelines, or accepted standards of practice to control the use of an organism based on the degree of risk or uncertainty associated with that organism.

The BSCC is therefore requesting comment on the following proposed definition:

"Organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes.*

"The following organisms are excluded:

- "1. Plants and animals that result from natural reproduction or the use of traditional breeding techniques. These include, for example, for vascular plants, mutagenesis and hand pollination, and for vertebrate animals, artificial insemination, superovulation, and transfer of embryos.

*"Genomes refers to the sum total of chromosomal and extra-chromosomal genetic material of an organism.

- "2. Microorganisms modified solely: (a) through chemical or physical mutagenesis; (b) by the movement of nucleic acids using physiological processes including, but not limited to transduction, transformation, or conjugation; or (c) by plasmid loss or spontaneous deletion. If nucleic acid molecules manipulated in vitro** are transferred using any of the techniques listed in (a) through (c), the resulting organisms do not fall under this exclusion.
- "3. Vascular plants regenerated from tissue culture, including those produced through selection of somaclonal variants, embryo rescue, protoplast fusion, or treatments that cause changes in chromosome number.
- "4. Organisms that have been modified by the introduction of non-coding, non-expressed nucleotide sequences that cause no phenotypic or physiological changes in the parental organism.
- "5. Organisms other than those exempted in 1-4 above, if it can be demonstrated that: (1) they could be readily produced by the techniques listed above; and (2) there is sufficient familiarity*** with the organism to foresee environmental effects equivalent to those associated with past safe

**"Manipulation in vitro includes: the directed addition to, rearrangement of, or removal of nucleotide sequences from the genetic material that is introduced; or, the use of chemical or physical techniques to enrich for a specific sequence."

***"Familiarity does not necessarily imply safety. Rather, to be familiar with the elements of an introduction means to have enough information to be able to judge the introduction's safety or risk."

introductions of similar organisms in similar target/test environments.

The BSCC acknowledges that this definition is based upon the concept of deliberate modification of the characteristics of an organism. In addition to other issues, the Committee requests public comment on the definition and substitute language that is more risk-oriented. Substitute language should take into account the practical needs of Federal agencies responsible for oversight of biotechnology.

The BSCC recognizes the need for regulatory flexibility in order to respond to the experiences of the industry and the agencies and to rapid changes in the science base. Therefore, as stated in the Coordinated Framework, it is recommended that this definition be reexamined periodically for its relevance to the current state of scientific knowledge and modified as appropriate.