The Journal of the Iowa Academy of Science: JIAS

Volume 96 | Number 			Article 13

1989

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Jour. Iowa Acad. Sci. 96(2):74-77, 1989

Public Policy on the Introduction of Genetically Engineered Microorganisms

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This presentation raises questions of research needs and issues. Underlying assumptions are that only beneficial or useful microorganisms will be "released"; that extensive laboratory and contained experiments will have been done prior to introduction and live microorganisms can be confined within the areas of introduction. Evidence to support these assertions will be presented. Critical needs for progress in this area include: 1) Recognition that the nature of the product introduced into the environment is of primary significance, not how the organism was genetically altered or modified. 2) Recognition that microorganisms are introduced into the environment as part of our daily lives. 3) Classification of microorganisms into categories, include a GRACE (Generally Regarded as Compatible with the Environment) list. For example, most microorganisms used by humans in food and agriculture would be on such a list. 4) Categorization of "new" traits transferred to microorganisms: all are not equal. 5) Revision of the Plant Pest Act. Interpretation by the USDA is now so broad that almost any microorganisms may be a "plant pest". 6) Development of the means to enable continuarion of basic research in small-scale traditional tests with GEMs. 7) Recognition of the adequacy of the methods used for mitigation and decontamination of microorganisms. 8) Development and use of selective, narrow spectrum chemicals and biologicals. 9) Critical evaluation of appropriate regulations and attendant costs for research on GEMs in the environment. These issues need recognition and wide-spread support among scientists, policy-makers and the public if the potential uses for microorganisms in the environment are to be realized.
INDEX DESCRIPTORS: bioethics, biotechnology, genetic engineering, microorganisms, public policy

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As the last speaker, I am going to talk about some more general areas of biotechnology, genetically engineered microorganisms and genetically modified organisms. I was specifically asked to discuss some critical questions regarding the introduction of genetically altered microorganisms into the environment, and, to me, genetically engineered microorganisms are a subset of that category.

I want to give you the take-home message first, because that will give you something to ponder as I make my presentation. My take-home message is essentially that with respect to the introduction of genetically engineered microorganisms into the environment, I think we are at a critical phase in this country. I think we either have to have reasonable guidelines and regulations within the next 12 to 18 months, or, in my opinion, we jeopardize the whole area of academic research and ultimately agricultural competitiveness. My reason for emphasizing academic research is I think that most people in this audience and others as well would agree that academic research provides the foundation for commercial and public development and use of science, including these types of microorganisms.

Let me begin by defining what I'm talking about. First, when we are talking about genetics, which we have been doing, we are talking about the hereditary properties of microorganisms (Fig. 1). By convention we talk about any microorganism as well as other types of organisms (plants or animals) that are in the environment as so-called "wild-type", but I wish to emphasize for those who don't think about it, that these populations are highly variable to begin with. Then we have a variety of changes that occur, and the changes that we are most familiar with in history are those that are labeled spontaneous. That simply means we don't know enough to be able to explain what has happened, but we obviously have those changes.

In commerce and industry, we have used physical and chemical agents to provide those changes and ultimately end up with genetically altered or modified microorganisms. Where we have a new technology is in being able to use specific enzymes in recombinant DNA technology to provide genetically engineered microorganisms (GEMs), but what we end up with is, again, a genetically altered or modified microorganism. It is simply different in kind.

Now, many people think that genetically altered products are something alien, but I would like to remind people that we are familiar with and comfortable with genetically altered products in public use. Very quickly, because time is short, I will indicate that all of our domesticated animals are essentially genetically altered products. We have our beef coming from very genetically altered cattle. We are not eating wild cattle, at least as far as I know. Similarly, with domesticated plants, Pioneer would not be in business if we were not dealing with domesticated plants.

We are familiar with microorganisms on a daily basis. Some of you are going to have yogurt for lunch, for example. Those are live microorganisms in there, and if you eat different brands of yogurt, you will realize that each one has a slightly different taste. That is because you have a different organism in each one of those brands. In agriculture, many of you are familiar with the legume inoculants that provide nitrogen fixation for those crops, and so on.

We have a history of using genetically altered products in our collective experience, and we also have a history of using genetically altered microorganisms in research. We are asking all kinds of questions about how these microorganisms behave and function. In legume inoculants, for example, we are interested in competition in nitrogen fixation, one aspect of those microorganisms.

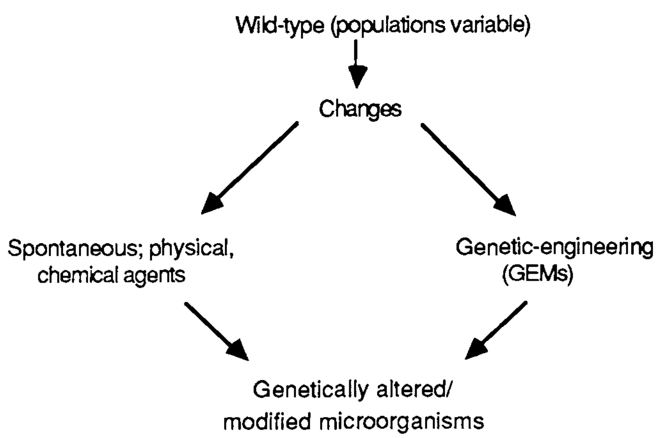

Fig. 1. Genetic (hereditary) properties of microorganisms.

Similarly, with silage inoculants, there is interest in how to make them function better in terms of providing nutrition for the animals that eat them, how to preserve the materials longer, and so on. And then, in terms of bacteria that could promote intensive growth of plants, or at least healthier growth of plants, many people have found such types of microorganisms. There also are organisms that can be used in animals and organisms that can be used as biological control agents. There are many different kinds of organisms that can be used in this fashion, some of which are useful in weed control (e.g., mycoherbicides) and the microbial pesticides which you have heard about. People modify them in standard ways, mostly to put in what we call markers to identify them, or to put in genetic material or modify them so that we can determine by reference to the original organism just what it is that the modified organism actually does.

When we consider genetically engineered microorganisms, we have a lot of laboratory experience, but when we come to the question of what has actually gone into the environment, at the present time we really have only three examples, one of which is yet to go in this spring. *Rhizobium meliloti* is a legume inoculant of alfalfa which presumably will be more efficient in nitrogen fixation. The only way to find that out is to actually do the experiment. Again, we are talking about very minor modification in a wild-type organism. The *Pseudomonas fluorescens* is simply a test organism that can live on roots, and that is the one that is publicized through the experiments being done at Clemson University, sponsored by Monsanto. Then you have Steve Lindow's experiment being done with *Pseudomonas syringae.*

What we have now is, I think, a situation where only these very minor tests are going into the environment, but they get a lot of publicity. I think it is unfortunate in the extreme that except for Steve's experiment, from the academic community, as far as I can determine, we will not have a single experiment that goes out into the environment this year. Now, as he has indicated, it is extremely difficult, tedious, and time-consuming, and he didn't even mention money — something that I will discuss in a moment.

I think we have to distinguish in these categories fear *vs.* risk, and I think that is something that we all tend to forget. For example, we all fear food poisoning, but when you go to the grocery store and buy some yogurt, you know that there is a very low probability, practically zero, that it is going to make you sick. We have no fear of getting up in the morning, at least I don't think we do, although we know by all the figures that our households are very risky. There are more dangers in our homes than virtually anywhere else, at least if we believe some of these statistics. So we need to distinguish fear *vs.* risk. An example of what fear has generated in terms of genetically engineered microorganisms is illustrated in several cartoons. They make for good show, but indicate the anxiety of some people with respect to microorganisms, and of course, I'm taking the prejudiced view that this is fear and not warranted by risk. It is fear, in my view, and hypothetical risk that is driving the regulatory policies, not only in this country but throughout the world. This is illustrated by a very recent issue of *Biotechnology* which indicates the world regulatory patchwork with respect to the regulation of biotechnology and, under this, the subset of microorganisms. This has generated not only a large bureaucracy which is beginning to emerge, but the bureaucracy has, in my view, conflicting and overlapping jurisdictions. As I have indicated, I think these are having very deleterious effects, not always based on science.

One of the questions that was raised for us to consider was dissemination of microorganisms. Plant pathologists have been working with actually harmful organisms scientifically for at least 150 years. We know a great deal about quite a few microorganisms, even bad ones. I want to illustrate with this slide that you can see the location of microorganisms right down to the row. The plants on the right which had a fungus infection are stunted and not very healthy. In the middle, the row of plants which were treated with a biological control agent (a soil microorganism) essentially resemble the untreated controls that are on the left. In many cases we can predict very well the dissemination of microorganisms very, very precisely, and that applies above ground as well as below. We are down to one row of bean plants that have been inoculated by a plant breeder *vs* an adjacent row of bean plants that have not been treated. This is done routinely. The inoculated plants are sick after a while, which is what we expected, and the untreated, control plants do not get sick even though they may be there the whole season. Sometimes there is some cross-over, but basically those plants are contained.

We have a long history, going back over 150 years, and I estimate approximately 100,000 tests in the environment, in which these tests have been done with harmful, known organisms. What is dramatic and is not recognized by the public, much less the press, is that we have not had any documented evidence that such tests have created an epidemic. They have not created any harm, therefore they don't make the news. But I think we have to take those kinds of situations into account as we are talking about realistic policy with respect to genetically engineered microorganisms.

So we have, in my view, a high degree of safety built into these kinds of experiments in the environment. To relate it to something that perhaps many of you are familiar with, it isn't just scientists who are involved with the dissemination of microorganisms. I presume that most of you in the audience have seen some of the tulips around. None of those tulips have come from Iowa. All of those tulips, to my knowledge, have come from the Netherlands and each one of those, when it is planted, has at least a million associated organisms about which we know nothing. Now, if you take 100 of those tulips and make a nice little bed, you've got approximately 100 million microorganisms in your yard, and we collectively have the experience that nothing happens. The world is still here after we have planted all those tulips all over the world. That's from the public.

From the agricultural sector, we also have the experience collectively of many farmers throughout the world using legume inoculants, particularly *Rhizobium* and now *Bradyrhizobium,* to inoculate such crops as alfalfa and soybeans. Again, those organisms have gone all over the world. There is, to my knowledge, no documented case that in spreading all those bacteria all over the world for at least a quarter-century there has been any harm to the crops. On the contrary, they are considered to be beneficial and sometimes essential to get that crop established.

I want to illustrate another facet of microorganisms that I am interested in besides the pathogens; these are organisms that live inside plants. Simply, I am calling them endophytic bacteria. We take them out of stalks of corn and sorghum. This material is perfectly healthy in appearance. You don't see any visible microorganisms, and yet by techniques that are customary in microbiology, we can find a whole array of microorganisms. I'm particularly interested in bacteria. Plants that are perfectly healthy, even inside, harbor many kinds of microorganisms. What I am particularly interested and intrigued by is that the populations roughly divide into two: the population that, when you inoculate plants, will die after some period of time (those aren't particularly interesting) and the ones that, after you inoculate, will either maintain themselves or grow. Then my question is how to capitalize on such organisms in ways that you have heard already from earlier speakers, and that includes such properties as whether or not they can produce something beneficial (e.g., antimicrobial against a deleterious organism), whether or not they themselves could be insecticidal or you could put the Bt toxin gene into one of these bacteria, whether or not they would produce plant growth regulators, whether indeed they could also provide herbicide resistance to the plants or such genetic material could be inserted into one or more of them, or whether or not they could improve the nutritional qualities of plants, such as lysine in corn. These are all speculative, and the prospects of doing any one of them is very small, but not zero. This is something that we would be aiming towards, but my guess is that it would take us at least a decade or more, if in fact we even succeed to a limited degree.

That brings me to considering some of the strategies and attributes of chemicals and microorganisms that are used in plant health and protection (Table 1). I think most of us would agree that we would like to diminish the use of chemicals as far as possible, but I think that means you can't have it both ways. That is, if we are talking about plant health and protection, if we don't have chemicals, what else are we going to do? One answer, and by no means a panacea, is to use microorganisms. As indicated earlier, one of the questions and concerns is whether or not these microorganisms multiply. Chemicals, of course, don't multiply; microorganisms can, but in most cases they are very limited. As you have seen, they die out for the most part. There are some exceptions, but the idea of their taking over the world, which is in some scenarios, is in my view not scientifically tenable.

Shelf life is a commercial concern, and that's actually where microorganisms are at a disadvantage because their shelf life is virtually minuscule compared to the majority of chemicals.

The cost of production for chemicals, all the way from the research to the manufacture to the consumer price, is usually quite high, and the prediction is that these costs are going to go higher because of the many variables that are involved. We can talk about those if time permits. To me, the irony with biologicals is that in many cases the cost, all the way from the research to the consumer, could be very low, but as you have seen, the costs are likely to be very high, and perhaps in many cases, higher than many chemicals, because of what I consider undue stringency at the present time in requirements for getting these products into the marketplace.

In terms of persistence, chemicals, of course, are highly variable, and as we have indicated, microorganisms rarely persist. In pollution potential, again, chemicals are variable. The pollution potential of microorganisms is very low, and I don't know of any case where this has been an issue. In terms of commerce, what companies wish to do in regard to specificity, of course, is to have something that will take care of all your problems — one pass-through and everything you don't like will be taken care of. That, of course, is an ideal, but then what you end up with is the concern with destroying or harming non-target organisms. Whereas, with biologicals, you have almost the teverse situation where you very commonly have the specificity actually being a deterrent to the commetcialization. It is a very difficult issue.

Safety with chemicals is extremely variable, as you know. I was trying to find a case where any of the microorganisms we have used in the environment, either for biological control or plant pathogens, had any documented adverse effect, and I couldn't find any. That doesn't mean it can't exist, but it means we have a very large database to show that we do not have a problem with the organisms that we are presently using, and that is basically ignored by the public press.

That brings me to the last point. In assessing the critical needs for planned introduction of genetically engineered microorganisms (Table 2), I put down a statement of our present situation which is not all-encompassing but just some items so that I wouldn't forget to comment on them. One of these is that the chemicals that we are using in agriculture are being de-registered. I'm not quarreling with that, but it means that we have few to no alternatives to several agricultural chemicals and that is going to come home to roost in approximately 3 to 5 years in my estimation. There are legitimate concerns about pesticides and their costs, and we can certainly discuss those.

Table 1. Strategies and Attributes of Chemicals and Microorganisms Used in Plant Health and Protection

Strategy/Attribute	Chemicals	Microorganisms
Replication	No	Yes (limited)
Shelf-life	Long	Short
Cost	High	Low to Very High
Persistence	Variable	Rare
Pollution potential	Variable	Low
Specificity	Rare	Common
Safety	Variable	Absolute (?); No known adverse effects

Table 2. Critical Needs for Planned Introductions of GEMS

Situation: Agrichemicals being deregistered; few to no alternatives; pesticide concerns and costs: new product potential. GEMs: one alternative.

1. Public differentiation between fears and risks.
2. Public media role: history and use of microorganisms.
3. Differentiation between research and commercial development.
4. Reasonable guidelines, regulations based on science.
5. GRACE classification: (Generally Regarded as Compatible with the Environment).
6. Categorization of 'new' traits transferred to microorganisms.
7. Revision of Plant Pest Act.

The new product potential for chemicals is essentially limited to herbicides and a few pesticides, but there is a new product potential for genetically engineered microorganisms if, in fact, we want to use them. Genetically engineered microorganisms, in my view, are simply one alternative; they are not a panacea. As I have indicated, we have to differentiate between fears and risks, and this is not always done. We need to have public media play a more active role in demonstrating that microorganisms have been used in the envitonment for various purposes, both by the public and by scientists, for a long period of time, and that the world is still here and is likely to remain so.

We need, in my view, a differentiation between research and commercial development. For example, Dr. Dean talked about the requirements for registration of a microbial pesticide. This is fine when you are talking about a product, but if you are just starting out and are trying to determine whether or not that microorganism actually does something, you have to be able to do the preliminary work to determine whether or not it is even worth bothering to go ahead, and that distinction is blurred in my mind at the present time. We need, in my view, reasonable guidelines and regulations that are based on science and not on fear. In my judgment, it is scientifically bordering on fraud to have had the investigators monitoring Steve Lindow's field test put on special suits. It implies that those organisms are dangerous to work with. We have worked with those organisms for nearly 100 years in various environments. They pose no danger, and it is unfortunate that that perception is put forth.

We have to have recognition that not all microorganisms are the same, and I am suggesting that we have to have something like a GRACE (Generally Regarded as Compatible with the Environment) classification. There clearly are microorganisms that are generally regarded as compatible with the environment, and the chief illustration is *Rhizobium.* We have been working with that organism for over a hundred years with no problem. We need to recognize that that is not the same thing as something that is going to kill a corn plant. Likewise we need categorization of new traits that are transferred to microorganisms. They are not all the same. Something that is going to provide a nutritional base to a plant that it did not have before is not going to be the same thing as a vertebrate toxin that has a potential to harm a human being.

Then finally, one of my pet concerns is revision of the Plant Pest Act, with which most of you probably are not familiar. The Plant Pest Act is now being interpreted by the USDA so broadly that virtually any microorganism that affects a plant or even a plant derivative and its products can be considered to be a plant pest. One of the primary illustrations that I think demonstrates there is a problem here is *Rhizobium* which now falls in that category. Farmers probably do not know that the USDA now considers *Rhizobium* a plant pest and yet recommends it as a legume inoculant — a logical inconsistency to me.

I think that I have raised a number of issues here. It comes down to this: if we are going to be competitive and if we are going to realize the benefits, particularly of genetically engineered microorganisms, we need public support, and we need a reasonable public policy. In my view, we have a long road ahead.

Questions and Discussion

ARTHUR WEISSINGER, Moderator

(Weissinger) Thank you, Dr. Vidaver. That gave us a lot to think about. Now I'd like to move on to a couple of people who have agreed to serve as our representatives to ask questions of these biologists. The first will be Dr. Donald Huffman who is Chair of the Department of Biology at Central College in Pella, where there probably are many hundreds of millions of microorganisms residing on tulips. Dr. Huffman comes from a biological background, trained as a plant pathologist, and is, I think, an excellent person to ask questions from a biological perspective, but as a person who is not directly involved in this kind of work.

(Huffman) I don't think that most of you expect nor would you appreciate a lot of comments of my own. Instead, I would like to move directly to some questions that I would like to have addressed. I do thank our speakers for a very fine coverage of the topic. There is one question I would like to address to all three individuals.

Do we have good information on the extent to which altered genes can be transferred to other organisms besides the target organism of *Bacillus* or other genera? In other words, what is the likelihood of transfer of these genes to other natural ecosystem bacteria?

(Dean) In many cases we know that mechanisms exist, but we have no examples in the case of *Bacillus thuringiensis*, which is the major experiment I mentioned that has been conducted, of genes being transferred out of or into this organism. I might say that the genes that encode the toxins for insect toxicity are borne upon plasmids, which would make them excellent candidates for transfer into other organisms and some other bacilli which exist in nature that couldn't possibly transfer their genes, if they would be harmful, into this massive inoculum of *Bacillus thuringiensis*. I think that since we have no examples of this, we could ask, "Have we done all the experiments we need to do to find cases?" I think certainly not. The field of microbial ecology has been compared to microbiologists attempting to study their subject without microscopes. That should have caused a roar of laughter, but it didn't. At any rate, this area of microbiology has been, in fact, the least funded and most ignored, and now at least it's coming into its own light as many other subjects do in the evolution of time.

Nevertheless, scientifically we know that if genes are to be transferred and persist, there must be some selective advantage for the recipient organism to receive these genes. It is simply not a scientific response to say yes, the mechanism is known, and therefore make up your own answer. We have to perceive that there would be some selective advantage in the case of the microorganism to have the genes to open up a new niche for itself, and if this is to be the case, we have to imagine what those selective advantages might be.

(Huffman) I could speculate on what it might be if you had, let's say, endophytic organisms such as were mentioned here, and you could alter those endophytic organisms, that could presumably be an advantage to the organism harboring them.

(Dean) Which way would you alter them?

(Huffman) If you were able to take, let's say, insect resistance conferred by *Bacillus thuringiensis* and to incorporate that into one of these endophytic organisms, surely that would be of some advantage to the host plant harboring the endophytic organisms.

(Dean) Well, there would have to be an advantage to the endophyte. It would have to create a new niche for insect pathogenesis, and that involves a number of steps. It involves the fact that the microorganism would be able to maintain itself in a pathogenic interaction with that insect and detailed, subtle, and multifaceted interactions. It could not be assumed that now I have a gene and can be king of the world. The development of a pathogenic situation is very fine tuned, and I think most of us are working in this area of microbial genetics have a great sense of *deja vu*. We are asking ourselves, "Didn't we discuss these things ten years ago when recombinant DNA first come out?" When epidemiologists first indicated that *E. coli*, the gut microorganism of humans, happens to be the major experimental tool we are using in the laboratory, the reaction was, "Wow, you stick things in there and they happen to get out, and there are going to be some pathogens to humans." The epidemiologists have spoken on this more than ten years ago and have said that it was a ludicrous assumption. What is necessary is for the public to be cognizant of the terms of which they speak when they make that decision.

(Vidaver) I will comment just briefly on that endophytic question. It turns out there is a company using a similar approach that wants to put out an endophytic bacterium similar to mine with precisely that toxin in it. The proposal is being evaluated by the EPA. Experimentally the difficulty with that organism is to have that toxin expressed long enough for it to be effective. The probability of transfer is extremely low, even in experimental situations. People who have not worked with microbes might need to know that you need literally millions and sometimes billions of cells in order to find a single transfer. You have to recognize also that there are probably at least a million microorganisms catalogued throughout the world, and we think that we don't even know about half of them yet. They are all distinct, and they remain distinct. Obviously if we had easy genetic transfer from one microorganism to another, we would have only one or two of them. So, it isn't easy,but that does not mean it can't work.

(Huffman) To me, this represents a very good situation in which one cannot extrapolate, let's say, from antibiotic resistance which does appear to be of some concern, to a situation like this.

(Vidaver) That is correct, and the common thing about that is, that typically that works under selective conditions.

(Lindow) I was going to add that we can basically assume that some transfer would almost inevitably occur in almost all organisms. This can't be demonstrated in natural environments. Some transfer does