# *The Role for Edible Vaccines*

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For centuries, plants have been used as sources of pharmaceuticals. Since the advent of recombinant-DNA technology, however, there has been a dramatic shift to microbial and animal cell-culture production systems. *Escherichia coli* was the first *in-vitro* system employed because of technical feasibility. Yeast, fungal, mammalian, and other bacterial cells are now used. Each has its advantages; bacteria provide systems of low cost and animal cell cultures are able to process eukaryotic proteins. For the first few decades of rDNA protein production, plants were not considered a viable option, primarily because the technology was not fully developed. In addition, plant biotechnology was focused on crop improvement.

Several groups are now exploring plants as "bio-factories." The production of the first commercial recombinant products from plants has already been achieved for the diagnostic proteins, avidin and β-glucuronidase (Hood *et al.*, 1997; Witcher *et al.*, 1998). While these were proof-of-principle products and are used only in small quantities, they illustrate the advantages of plant-production systems for pharmaceuticals. These include up to a 100-fold reduction in raw-material costs and a ten-fold decrease in biomass needed for extraction and purification, which translates into savings for downstream processing. In addition, the risk of salmonella infection, which occurs when using chicken eggs for the production of avidin, is eliminated since plants do not harbor human pathogens.

Recently, the enzyme, trypsin, was produced from plants (Hood, 2002). The commercial quantities needed are more typical of pharmaceutical proteins. Therefore, commercialization of this third product addresses the practical issues of scaling up that most pharmaceutical manufacturing will face, including not only economic concerns but also the achievement of segregation from other crops.

The commercialization of these three sets the stage for the production of many new pharmaceuticals from plants, including therapeutic antibodies

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(Daniell *et al.*, 2001). One that we have worked on is aprotinin, which is effective in reducing blood loss in surgical procedures, but is costly based on its current supply from bovine lungs. Plants offer a low-cost production system, but it is critical that the protein is identical to bovine-produced material. We have been able to demonstrate chemical and functional equivalence *in vitro* (Zhong *et al.*, 1999) and are now preparing to show *in-vivo* equivalence.

These current and upcoming products demonstrate the role of plants as sources of materials free of animal pathogens and at lower cost. Plants, however, may provide additional benefits for the production of vaccines. This is being studied by a number of groups (Daniell *et al.*, 2001), and I will discuss our work in some detail. The basic question is: what are the benefits of using plants in contrast to other systems to produce vaccines? This can be summarized as safety, cost, and convenience, which extrapolate to greater accessibility worldwide.

## Advantages of Edible Plant-Based Vaccines

*Safety* Although they have been used for decades, and benefits have far outweighed risks, there have been some problems with vaccines based on killed or attenuated viruses. With the advent of rDNA, however, safer vaccines called "subunit vaccines" have been the preferred choice. The protein from the viral capsid is used to produce the vaccine, and this protein alone cannot cause infection. In theory, these viral proteins could be produced in any of the current production systems, but plants offer particular advantages. First, some eukaryotic proteins do not express well in prokaryotic systems, possibly due to cellular processing requirements that are present only in eukaryotic cells. Therefore, many of these proteins are expressed in animal systems. However, animal systems can harbor human pathogens and must be screened to ensure that such are not part of the subunit-vaccine product. Plants, in contrast, are inherently safe since they do not harbor human pathogens (or prions, the agent responsible for mad cow disease). In addition, if we choose a food-based crop, there is added safety. Maize, for example, has been a source of food for humans for centuries and its safety is thus proven. There is no added risk from the production system or the delivery system. Furthermore, agronomic and food-processing aspects have been extensively studied; one can argue that we know more about the production of maize than of any other crop in North America.

*Cost of Goods* The cost of a vaccine includes the expenditures involved in producing the raw material, and purification and formulation. Raw-material costs are shown in Table 1. Best-case scenarios are shown for each of the systems, illustrating the advantage of using plants. Production of pharmaceutical proteins from maize is at least an order of magnitude less costly than from other systems. Compared to mammalian cell-culture systems, plants are several orders of magnitude more economical.

**TABLE 1. APPROXIMATE RAW-MATERIAL COSTS FOR PHARMACEUTICAL MATERIAL.**

| System | $/g |
|---|---|
| Chinese hamster ovary (CHO) cells | 100 |
| Transgenic chickens/eggs | 1 |
| Transgenic goats/milk | 1 |
| Microbial fermentation | 1 |
| Plants | 0.1 |

*Rapid Scale-Up* Rapid scale-up of production is of particular importance to make vaccines available during epidemics. Table 2 compares time requirements for scaling-up for several different production systems. In this comparison, we assume that we have identified the vaccine product, and are limited only by our ability to increase production. Because of the rapid turn-around time for maize and the large multiplication factor for each generation (~200-fold increase every four months), we can go from 1 g to 8,000 kg in less than a year, a scale-up not achievable with non-plant systems.

**TABLE 2. RAW-MATERIAL SCALE-UP STARTING WITH 1 G OF RECOMBINANT PROTEIN.**

| System | 200 g | 40 kg | 8,000 kg |
|---|---|---|---|
| ProdiGene's | 4 months | 8 months | 12 months |
| Transgenic animals | 6 months | 5 years | Not practical |
| Fermentation | 4 months | 3 years | 3 years |
| CHO cells | 18 months | 3 years | Not practical |

*Direct Delivery* The greatest benefit of plants such as maize is that they can be used as an edible product for the oral delivery of vaccines. Clearly, oral delivery has a tremendous advantage in convenience. The elimination of shots and need for medical assistance, with the formulated dose of medication as, say, a wafer, would be a leap forward in vaccine delivery. This also translates into reduced dependence on refrigeration. Since corn-grain proteins are stable, recombinant proteins could be stored (for years) and transported at ambient temperatures. This would promote vaccine use in developing countries that are in greatest need but are inadequately equipped with large-scale refrigerated storage and transportation facilities.

Another aspect of direct delivery relates to greater reduction of cost of goods. As stated above, the raw-material cost for pharmaceuticals can be reduced with plants, but, in addition, the cost of goods for the administration of the vaccine is reduced, as a result of elimination of needles, syringes, and medical assistance. Figure 1 represents an approximation of the overall costs of a vaccine. The raw-material expenditure represents a small percentage of the total cost of the delivery system. Edible vaccines in corn could reduce the overall cost to the patient by over 90% compared to injectables, by reducing the need for purification, needles and syringes, and medical assistance.

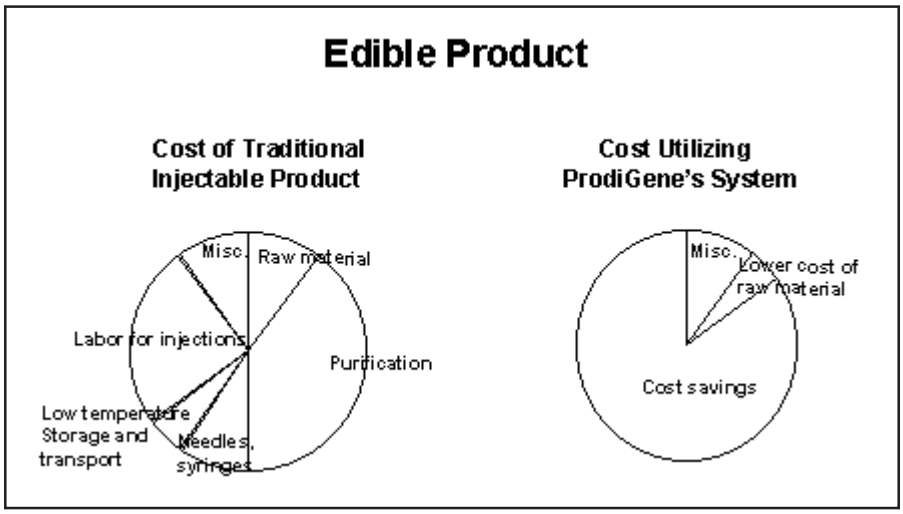


**Figure 1. Cost comparison: injectable vaccine *vs.* ProdiGene's.**

To appreciate the potential, let's consider a hypothetical example: the production cost of a purified vaccine is $1 per dose, and a dose contains 10 μg of protein. We assume that it will take a thousand times more protein for an edible vaccine than for an injectable product. With current systems, this translates the cost of an oral dose to $1,000. Of course, this would be unacceptable for most people in the developed world and impossible for those in developing countries. Using the same assumptions, however, the cost of a corn vaccine to give a 1,000-fold increase per dose could be as low as $0.01. This translates not only into cost reduction, but, in many cases, the difference between obtaining a vaccine or not.

The next advantage of using corn as the delivery system relates to compliance with vaccination regimes. Having patients take booster applications would be much more realistic if they could take an oral vaccine instead of having to go to medical facilities for secondary injections months or even years later. This translates into a much more effective vaccine.

The advantages of convenience and cost will translate into vaccines being available in parts of the world where none were available before. This brings the potential for global vaccination, with the possibility of eliminating certain diseases. In addition, these vaccines may be added to feed to prevent infectious diseases for animals and to address food-safety issues where animal pathogens would put humans at risk (*e.g. Salmonella* spp*., E. coli* O157:H7).

## Technical Challenges

While edible plant vaccines have tremendous theoretical advantages, none are on the market today. A series of hurdles must be overcome. The technical challenges can be divided into categories: the vaccine must survive the gut, must elicit an immune response, and, finally, must provide protection. Here are some examples to illustrate progress in these areas.

The first technical challenge for a potential edible vaccine is to keep the protein from being degraded upon ingestion long enough to have immunogenic activity. Current dogma predicts that proteins taken orally will be completely degraded in the digestive tract, with insufficient time to elicit an immune response. We tested this theory using avidin, as an example of a typical antigenic protein, by administering it to mice and looking for intact avidin in fecal material. When produced in transgenic maize and fed to mice in cornmeal, intact avidin, as well as major degradation products, was detected in fecal extracts (Bailey, 2001). However, when fed orally to mice in liquid form, fecal extracts contained no avidin or partial breakdown products. This "bio-encapsulation" could be the consequence of several factors, including higher degree of stability of the protein in corn or slow release of avidin from the corn granules. Current micro-encapsulation techniques for slow release of orally-fed protein products frequently include a carbohydrate matrix and protease inhibitors, components that exist naturally in maize kernels.

The next technical question beyond survivability in the digestive system is: can the protein produce an immune response? To test this, we cloned the gene for the S-protein from transmissible gastroenteritis virus (TGEV) and produced TGEV-S corn. Swine were then fed either control or transgenic corn prior to exposing them to live virus. The TGEV-S-fed swine demonstrated large increases in antibodies to the virus (Lamphear *et al*., 2002). No significant response was seen with control corn. This illustrates that immune responses are obtainable via the oral route.

The next question was whether this immune response would provide protection. Animals were fed TGEV-S corn or given the commercial TGEV vaccine by injection. The results showed that treatment with TGEV-S corn was successful in protecting animals from disease symptoms with results similar to those obtained with the commercial vaccine (Streatfield *et al*., 2001; Lamphear *et al*., 2002).

This practical example clearly shows that technical challenges can be overcome to provide an effective vaccine. Since the vaccine is in feed-grade material, not only are costs lowered but there is added flexibility and convenience in delivery.

The fact that edible corn vaccines can be practical for animals leads to the next question: will they work in humans? To address this, we examined traveler's disease which is caused by a strain of *E. coli* that produces heat-labile enterotoxin. This molecule consists of one A subunit and five B. The B subunit (Lt-B) does not possess toxin activity, but can induce an immune response. We, and others (Haq *et al*., 1995; Streatfield *et al*., 2001), examined Lt-B first in mice to see if it would induce an immune response when produced in plants and given orally. When challenged with the heat-labile toxin, the mice were protected from its effects after being fed Lt-B transgenic corn (Streatfield *et al*., 2001).

With efficacy demonstrated, our attention turned to how to make a practical version of a corn vaccine for humans. In is preparation, we examined homogeneity of the starting material, stability, processing requirements, and any adverse effects on the health of the animals.

The first practical question was: is the gene stable in maize? The examination of several corn lines revealed no indication of instability. In addition, the expression product was also found to be consistent in these seed lines and homogeneous in bulk grain samples (Streatfield *et al*., 2002).

By fractionating the grain, enrichment in Lt-B is possible. The mechanical process routinely performed on corn seed increases the concentration of Lt-B in the germ more than 5-fold when compared to the whole seed. This results in much lower amounts needed to feed patients, which is critical to achieving a manageable dose (Lamphear *et al*., 2002).

Palatability is also critical. Although eating whole kernels is conceivable, processed corn—as puffs, flakes, wafers, *etc*.—is more appetizing. Processing is typically done at high temperatures, which could result in loss of activity. As an example, Lt-B exists as pentamers that have high immunogenicity, but heat denaturation produces monomers with reduced activity. However, processing conditions have been modified to produce the Lt-B pentamers in corn puffs (Streatfield *et al*., 2002).

The last parameter we examined was whether this material would have any adverse effects on the health of the mice. There is no reason to suspect health problems, and, indeed, we observed no differences in any way in a comparison with mice fed control corn, including no changes in weight gain and no signs of diarrhea associated with the disease (Lamphear *et al*., 2002).

In conclusion, the edible Lt-B-corn vaccine has been shown to be efficacious in mice. We can process the corn into a palatable form for human consumption. The product is stable and safe. We are now preparing for human clinical studies, which are expected to begin shortly.

Traveler's disease is an excellent example of how edible vaccines can work, and we are now focusing on two other vaccines. The first is hepatitis B. We have already expressed the surface antigen in corn and have preliminary evidence of immune responses in animals. (B.J. Lamphear, personal communication). Hepatitis B is a major infectious disease with 300 million carriers worldwide. Symptoms include cancer, sclerosis of the liver, and, in some cases, death. It is the most common sexually transmitted disease. While an injectable vaccine exists, the availability of an edible vaccination would be a vast improvement, allowing its use in inaccessible areas and with better compliance.

The second major target is an AIDS vaccine. Many groups are developing injectable subunit vaccines for this disease. Although injections work well in some countries, this method of delivery will be difficult, if not impossible, in Africa and Asia because of cost and transportation and refrigeration requirements. Early results indicate that this type of subunit vaccine can be expressed in maize (M.E. Horn, personal communication).

## Safety Assessment of the Food Chain

Although subunit vaccines in maize promise to provide a safe product with great advantages, there are concerns. In particular: can these products inadvertently enter the food chain and what preventative measures are in place?

In an attempt to address these questions, we have developed a general model for assessment. This is similar to other models used for a variety of non-food products that have the potential to enter the food chain. It is based on the fact that the risk is proportional to the inherent toxicity or activity of the molecule and the exposure.

$$\text{Risk} \propto (\text{inherent activity}) \times (\text{exposure})$$

The risk is zero if either the activity or exposure goes to zero. While this is the over-simplified version that the general public likes to hear, it is, in fact, a myth. Absolute zero cannot be achieved with any current food-safety concern, and this applies to rDNA technology. This is not to say, however, that our food is unsafe, rather that all compounds have the potential for detrimental activity when taken at high enough doses. The corollary is also true; all compounds will show no activity when given at low enough doses. This is true for commonly eaten items such as table salt, nutrients such as fats, and drugs. None of these have effects at low doses, all are beneficial at moderate doses, and, in extremely high doses, can be detrimental.

What is critical is the exposure to these compounds in relation to their inherent activity.

$$\text{Exposure} \propto (\text{concentration}) \times (\text{time})$$

The concern over food safety then is: what is the level of our exposure? It is impossible to prove that exposure is zero. It can be proven only to be below a certain limit. As an example, if we test for 1 part in 100, we can say our exposure is below 1 in a 100. If we set this for 1 part per 1,000, likewise, this will be our exposure limit. Therefore, the question arises of how do we set the limit: should it be based on safety or detectibility?

We advocate that the unintentional exposure limits for edible vaccines be based on safety considerations. The first question then is, what kind of toxicity do subunit vaccines have? Generally these molecules are considered to be non-toxic. Primarily they are structural proteins for the virus. Although they may have some detrimental effects at high concentrations, it has not yet been observed. Furthermore, subunit vaccines have been injected into humans for decades without any known adverse effects. This is in contrast to pesticides, for example, which are known to be detrimental at low concentrations. Therefore, we would not expect any detrimental activity due to subunit vaccines unless one is exposed to much higher concentrations than known poisons. However, a true risk assessment cannot be done since we do not know the hazard. While we do not propose to keep giving higher doses until we see a hazard, we can use what is known about levels that have been shown to be safe and compare tolerances to other compounds. Regulatory agencies have examined exposure limits for pesticides, as an example, to determine the safe limit of exposure. Table 3 lists exposure limits for some compounds commonly present in corn. These limits have been set with the assumption of presence in our commodity-corn supply. Regulatory agencies have determined that these compounds show no effects when below the set tolerances.

**TABLE 3. FOOD TOLERANCES FOR KNOWN HAZARDS.**

| Compound | ppm |
|---|---|
| 2,4-D | 0.5 |
| Nicotine | 2.0 |
| Malathion | 8.0 |
| Paraquat | 0.05 |
| Glyphosate | 1.0 |
| Hexane | 25 |

In comparison to vaccines, which have not shown any toxic activity, these compounds have known detrimental effects at low concentrations. They also have other characteristics that create concerns, warranting lower exposure limits. As an example, pesticides are typically heat-stable, whereas proteins are readily degraded by heat. Pesticides are normally stable in the digestive system, whereas proteins are normally degraded in the digestive tract. In the environ-

ment, pesticides are relatively stable whereas proteins are usually degraded. Even though, in our system, the proteins are more stable than in solution, their instability is still high compared to other synthetic compounds. Many pesticides are halogenated hydrocarbons and, therefore, some of their breakdown products are toxic; proteins break down to amino acids, which are common nutrients. Therefore, logic dictates that the limits of exposure for vaccines are much higher than those for known toxins.

While subunit-vaccine toxicity seems unlikely, another concern is that a vaccine may evoke an unintentional immune response. What problems could this cause? At ProdiGene, we have spent the past five years and millions of dollars trying to evoke an immune response in animals utilizing oral delivery. We have found that high concentrations with repeated exposures are needed. It is illogical to argue from an efficacy position that oral vaccines will not work unless repeated high doses are given, and at the same time, argue that a one-time low dose entering the food chain would cause great danger. The answer to this dilemma is that we must address it in a quantitative manner to determine where the limits of exposure are set to see no effect or to see an immunogenic effect. A quantitative model can take into account the specifics of this system, including antigenicity of the vaccine, to set a limit of exposure that would be far below any concentration that would give the slightest effect. Containment systems can then be designed around the safety criteria. The containment system must include a series of steps to cover the growing, harvesting, transporting, storage, and processing of the grain. Because of recent fears of contamination, resulting largely from the StarLink™ story, the public has focused on corn pollen and there is confusion over the systems under which maize is grown.

Basically, there are three types of growing system. The first is for commodity grain. You can grow what you want, where you want, and however you wish to grow it. This system is used for producing most corn in the United States. The second system, identity preservation, allows you to grow when and how you like, however, there are specifications concerning the type of corn produced, and economic incentives exist to prevent commodity corn from mixing with the segregated product. The third system is the Identity Containment System, which specifies what crop is grown where, and how. These parameters are directed by companies such as ProdiGene, and include regulatory oversight.

ProdiGene's Identity Containment System includes many procedures that differ from those used to grow commodity food crops, and are summarized in Table 4. Included are a set of written standard-operating procedures for all steps in the process, and legal contracts between the grower and the company.

There are economic incentives for identity containment such that the grower will want to comply. The typical area requirement is around 1,000 acres for identity-contained crops—with which the extra steps must be taken—whereas 75 million acres of commodity corn are grown annually in the United States.

**TABLE 4. COMPARISON OF SYSTEMS FOR GROWING MAIZE.**

| Component | Commodity | Identity preserved | Prodigene's ICS$_{SM}$ |
|---|---|---|---|
| | Objective | | |
| | Maximize grain yield | Prevent exposure FROM commodity corn | Prevent exposure TO or FROM commodity corn |
| GENERAL | | | |
| SOPs | None | None | Required |
| Legal contracts | None | Optional | Required |
| Economic incentives above commodity | N/A | $.15–.35/bushel | $.50–1.00/bushel |
| Typical acreage | 75,000,000 | 1,000,000 | 1,000 |
| GROWING | | | |
| Grower's seed | Purchased | Purchased | Licensed |
| Location of plots | No restrictions | No restrictions | Pre-approved locations |
| Containment required | None | None | Regulated |
| Regulatory approval | None | None | Required |
| Regular field inspections | None | None | Required |
| HARVESTING | | | |
| Equipment | No special requirements | No special requirements | Dedicated equipment or standardized clean-out required |
| Transport | No special requirements | Segregated from commodity corn | ProdiGene or its designee must handle |
| Storage | No special requirements | Segregated from commodity corn | Dedicated storage containers/facilities |
| PROCESSING | | | |
| Requirements beyond minimum specifications | None | None | Regulated by FDA |
| Waste or by-products | Not regulated | Not regulated | Regulated by USDA |

In addition to these general considerations, other conditions vary with the different systems. Identity containment requires approval for where the seed is grown. Agronomic support is also provided by the company and regulatory approval with field inspections is required. Harvesting of the grain also requires special consideration. Commodity corn cannot be mixed with the contained crop. Therefore, dedicated harvesting equipment or thorough cleanout procedures are necessary. The company dictates the transportation requirements of the harvested crop. It is segregated and stored separately, requiring special storage arrangements and facilities.

When the grain has met the specifications of the regulatory agencies and of the company, it can be processed. The FDA sets processing requirements, which are similar to manufacturing requirements for vaccines from other production systems. Any by-products are regulated by the USDA if they are to go into the food or feed stream. The system for keeping these products out of the food chain thus is highly redundant.

The qualitative description for keeping edible vaccines out of the food chain is useful, but a quantitative assessment is needed. In order to propose a model, we must take into account other parameters. Several characteristics of plants need to be considered, including the following.

- The potential for out-crossing. In the case of maize, there are no weedy relatives in the United States, therefore, out-crossing is not possible.
- If farmers save their seed for future crops, "contamination" could accumulate, carrying the foreign gene. Since corn growers buy new seed each year to capitalize on hybrid vigor, such enrichment of vaccine corn is unlikely.
- What systems are already in place to keep harvested seed segregated? Commercial systems exist for special food and feed corn. These systems have been used for years to grow millions of acres of corn and keep it segregated. Therefore, additional requirements for containment would be a direct offshoot of systems that are already in place.
- The potential for pollen drift differs with different crops. Maize pollen is heavy compared with that of other species. The majority falls within several feet of the parent plant. Also, the pollen has a short half-life, and can lose viability within minutes after it is shed. In addition, many factors are known to reduce pollen flow such as isolation distances, vegetative barriers, and genetic male sterility.
- There is a broad and long-term experience-base. Professional growers and processors have been working with maize for many years.

Using this information, we can construct a model to show the limits of exposure that are possible in the food chain. Some key assumptions are needed for quantitation. The first is that the transgenic crop is grown immediately adjacent to a corn crop with no isolation, and no temporal or genetic barriers utilized. We also assume a high rate of expression for the vaccines, 1% of the total soluble protein in seed. In addition, we assume that the vaccine-synthesizing corn is grown on 1,000 acres or less, typical acreage for most pharmaceutical products. Each year approximately 75 million acres of commodity corn is grown in North America. Therefore, our product represents approximately 0.001% of the total acreage. Any contaminated material entering the food chain would be spread over the total corn acreage if it were to be available to everyone. Alternatively, we could assume that the farmer adjacent to the transgenic crop also segregates that field and collects 1,000 acres, which

goes specifically into food applications. This latter case poses a situation to give the highest concentration of vaccine but least availability to the population at large. These two scenarios represent the extremes. Most situations will fall between these two cases. The last assumption is in terms of how much cross-pollination will occur. We have estimated this on the bases on our own experience and data available in the literature, for contained and non-contained growing conditions.

With these assumptions we can model the amount of antigen or subunit vaccine present in food corn (Table 5). The highest concentration is shown when the adjacent grower segregates her/his field, with no containment. In this worst case, the vaccine could be as high as 0.1 part per million. If this were mixed with all corn grown in a year in the United States, it would represent 0.000001 parts per million, again assuming no containment parameters. In either case, these amounts are well below levels that are accepted for most known toxins. Clearly, this model predicts that vaccines will not present any toxicity danger, even without containment. Toxicity then becomes a non-issue for vaccines, as well as for most other proteins that we produce.

**TABLE 5. THEORETICAL CONTAMINATION RATES IN FOOD CORN.**

| Condition | ppm in grain of commodity corn | |
|---|---|---|
| | Segregated field | All corn in the United States |
| No pollen control measures | 0.1 | 0.000001 |
| 660-ft isolation | 0.004 | 0.00000004 |
| 1,320-ft isolation | 0.00004 | 0.0000000004 |
| Planting delay with border rows | 0.0000005 | 0.000000000005 |

The next question is: would these levels produce an immune response? We explored the possibility that low exposures could induce an unintentional antigenic response. Based on our experience with antigens such as HepBS and avidin, as well as utilizing data in the literature, an antigenic response requires several doses of 1 mg each in humans. To obtain a 1-mg dose with corn grown without pollination control would require 20 lbs of unprocessed corn. This translates into eating the equivalent of 320 bowls of cereal or 320 tacos in one sitting just to receive the minimal dose for a one-time exposure. If we now factor in that corn for human consumption is processed between 100 and 200°C, it is likely that the protein will be denatured and generate a much-reduced exposure. If we grow the vaccine crop under containment procedures using physical isolation, temporal isolation, and planting border rows, this reduces adventitious presence by an additional factor of a million.

Models such as this can differentiate between real and perceived risks. They provide an excellent starting point and can be challenged and revised when new information becomes available. They can be used with large safety margins when we have not fully tested products for toxicity. They can address the concerns of how to keep safe vaccine products on the market and, at the same time, keep the food chain safe.

## Summary

Edible vaccines represent a quantum leap forward in the ability to produce safe, efficacious vaccines for worldwide use. This quantum leap could make available vaccinations in developing countries where none exist today, and with greater ease and compliance in North America and Europe. These products have already shown efficacy in limited trials with oral delivery, for humans and animals. We believe that they will be instrumental in eliminating major diseases, such as hepatitis B and AIDS.

A perceived safety concern has been raised about unintended entry to the food chain. Containment procedures are in place to provide an extra buffer of safety while we obtain more information about these procedures. However, our model predicts no effect on food safety even without containment procedures. We need to treat corn as a valuable production factory for vaccines and other pharmaceutical products as we have done for other food-producing organisms. Yeast, for example, is used to produce pharmaceuticals and vaccines, as well as bread and beer. In this way, we will bring beneficial products to the marketplace, to save lives without unnecessary risk.

## References


Bailey MR (2000) A Model System for Edible Vaccination Using Recombinant Avidin Produced in Corn Seed, Thesis, Texas A&M University.

Daniell H *et al.* (2001) Medical molecular farming: production of antibodies, biopharmaceuticals and edible vaccines in plants. Trends in Plant Science 6 219–226.

Haq TJ *et al.* (1995) Oral immunization with a recombinant bacterial antigen produced in transgenic plants. Science 268 714–716.

Hood EE (2002) From green plants to industrial enzymes. Enzyme and Microbial Technology 30 279–283

Hood EE *et al.* (1997) Commercial production of avidin from transgenic maize: characterization of transformant, production, processing, extraction and purification. Molecular Breeding 3 291–306.

Lamphear BJ *et al.* (2002) Delivery of subunit vaccines in maize seed. J. Control Release 85 169–180.

Streatfield SJ *et al.* (2001) Plant-based vaccines: unique advantages. Vaccine 19 2742–2748

Streatfield SJ *et al.* (2002) Development of an edible subunit vaccine in corn against enterotoxigenic strains of *Escherichia coli*. In Vitro Cellular Development and Biology–Plant 38 11–17.
Witcher DR *et al.* (1998) Commercial production of β-glucuronidase (GUS): a model system for the production of proteins in plants. Molecular Breeding 4 301–312
Zhong GY *et al.* (1999) Commercial production of aprotinin in transgenic maize seeds. Molecular Breeding 5 345–356.