



## Growing Nonfood Products in Transgenic Plants

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Plants have been a source of industrial and pharmaceutical products for centuries. Transgenically altered plants can be more efficient at producing these products and hence represent a logical advance in technology. However, the public has concerns that plant-made nonfood products, known as plant-made pharmaceuticals (PMPs) and plant-made industrial compounds (PMICs), may inadvertently mix with the food supply. To provide for food safety and gain public confidence, the USDA has adopted stringent guidelines<sup>1</sup> for PMPs and PMICs, distinct from those used for other transgenic crops intended to enter the food supply. The cost of containing PMPs and PMICs, however, can make production of many of these products unfeasible. Moreover, the public's understanding of nonfood production methods is generally intertwined with the standard practices of food production, leading to the perception of increased risk. A recent paper describes an alternative model for growing PMPs and PMICs<sup>2</sup> and addresses safety and economic concerns as well as some public perception issues. This review summarizes how these new products can be produced in plants comparably to other transgenic production systems, using a strategy that also creates a clearer distinction between food and nonfood products.

### Safety

Safety concerns about transgenic nonfood products can be divided into three categories. The first concern relates to the inherent toxicity of the molecule itself, whether exposure is from direct consumption of a pharmaceutical product or from indirect contact with a substance intended for an industrial use. Science-based models can predict the toxicity of any substance based on dosage. Such models are used by the Food and Drug Administration (FDA) and the USDA to evaluate pharmaceutical or food compounds. These evaluations are uniformly applied to all production systems to provide a baseline safety assessment of the compound.

The second safety aspect pertains to any unintended compounds that may be introduced into the final product during the purification or production process, including toxins, allergens, or pathogens, as well as inadvertent host proteins. These compounds are host specific and dependant on the level of purification of the final product. It has been argued that production hosts that are already in the food chain (e.g., eggs, yeast, food crops) have a distinct safety advantage because they are already generally regarded as safe (GRAS). In general, there can be significant differences in product safety depending on the specific organism and purification procedures used and whether or not the product is produced in plants.

The third safety consideration is for the environmental and health consequences of inadvertent exposure to these nonfood compounds. Plants used to make pharmaceutical or industrial compounds differ significantly from other transgenic platforms (e.g., microbial and cell cultures) in this regard, because of the concern that an industrial- or pharmaceutical-producing plant will cross pollinate or intermix with food crops nearby. Consequently, current regulations are written to restrict the movement of transgenic products and to confine the host plant in a way that will limit its ability to reproduce and generate transgenic products independently.

Yet despite science-based safety analyses and reasonable regulation, the perception persists that these products may inadvertently end up in the food supply, most likely because of the similarity between their production in plants and food production practices. Currently, any level of contamination of food products is considered unsafe. Biosafety models for regulated articles are based on tolerances or action levels, which allow regulators to set the maximum level of a product below which there is no cause for concern<sup>3,4</sup>. However, this type of model has not yet been applied to plants producing pharmaceutical or industrial products.

Plant production systems that can be contained inside a dedicated facility include plant cell cultures, aquacultures, greenhouse grown plants, and the use of underground caves. Each of these options is viable for certain products, though all have a substantial cost premium over field grown material and have a limited scale of production. Consequently, there is a need for field grown material. It is because plant-based systems are grown in fields outside a dedicated production facility, unlike these other types of transgenic production systems, that confinement measures have received by far the most regulatory attention.

There are differences of opinion about how best to achieve confinement, but methods generally include genetic, temporal, physical and/or geographic barriers to limit the host's reproduction outside the production site. An example of physical separation is used when the cultivation of sexually compatible crops is limited within a prescribed distance of regulated transgenic crops, as well as the use of border rows. The USDA guidelines are written with the assumption that in any given season or location, plants that are intended for food, feed, and industrial applications may potentially



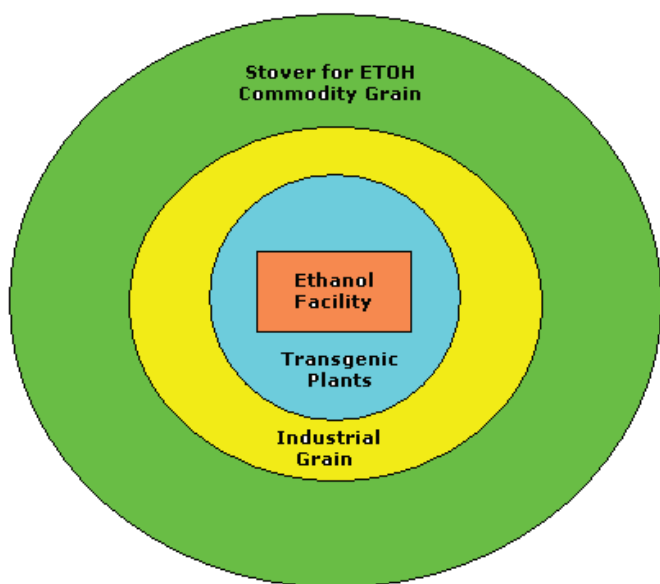
commingle. These strict guidelines may increase the fear that PMPs or PMICs will easily intermix with food crops.

### An Alternative Model for Growing Transgenic Nonfood Products in Plants

It is quite costly for producers to adhere to guidelines when using the same land to grow regulated products one year and commodity crops in subsequent years. An alternative to using crop land flexibly to grow all types of products is to dedicate the land solely for the production of industrial products. The detailed specifics of this approach, with underlying assumptions, can be found elsewhere<sup>2</sup>, but in general, a single location is employed for growing selected industrial products every year. In addition, all of the equipment, personnel, and practices are dedicated solely for this purpose as well. This model is similar in concept to that used with microbial and cell culture systems in that the location is not used interchangeably for the production of food and nonfood transgenic products. The only significant difference in this case is that the dedicated location includes the field as well as the building where the product is manufactured.

A transgenic crop can be grown amidst an industrial crop and thereby provide additional segregation and buffer zones from food crops at no additional cost. In most cases the transgenic crop, which requires a very small percentage of the total acreage, allows for a greater separation from potential food crops. A larger separation distance from food crops permits a greater distinction for the dedicated material and equipment, and thereby decreases public perception of risk. It also reduces fears of seeds inadvertently entering the food supply by spilling on the land and germinating the following season.

While this approach has advantages for pharmaceutical proteins, field grown production is also suitable for making industrial products that can only be produced economically in large volumes. Furthermore, this model integrates the transgenically produced products with the industrial crop. An example is given in **Figure 1**, which depicts the production of transgenic enzymes for the conversion of ethanol from corn stover. In this case, the transgenic enzyme is collected only from the germ fraction of plants harvested from the most central growing area and is in turn used for ethanol conversion with the stover that is growing in the surrounding locations.



**Figure 1:** Ethanol Production Field. All of the material inside the yellow grain circle would be harvested solely for industrial applications. Grain from the green circle can be used for industrial, food or feed applications. The transgenic plants in the center could be used for producing enzymes as well as grain and stover to make ethanol.

In this model, grain and stover, plus the enzymes needed to process them into ethanol, are all produced from the same acreage. This design allows for synergies in transportation and coordination, as well as for efficient utilization of natural resources. The system is self-contained, having all the necessary components to produce ethanol; there is no additional input required to provide the raw materials for stover ethanol over that which is needed to grow corn for grain ethanol. The benefits in this example go beyond the savings obtained when planting a field that otherwise would remain fallow and include: 1) more efficient utilization of raw materials without additional inputs, reducing the environmental



impact of growing separate crops for grain ethanol, lignocellulosic ethanol, and enzyme; 2) savings from the elimination of the highly capital intensive fermentation equipment traditionally used for making the vast quantities of enzyme required for biomass conversion into ethanol; 3) increased revenue for growers; 4) reduced transportation cost because the grain, stover, and enzymes required for ethanol production are supplied in one central location; and 5) lowered unit cost of the enzymes since all unit operations are similar to existing practices for growing commodity crops, except mixing the enzyme fraction with the stover. These economic benefits are realized in tandem with the additional benefit of being able to make the clear distinction that, in practice, the industrial product (enzyme) is clearly separated from those practices, locations, and fields used for food production.

### Conclusions

Transgenic plants used to produce biopharmaceuticals and bioindustrial products have great potential, but current production practices limit their cost effectiveness in some cases and raise concerns that the use of food organisms as hosts for nonfood products increases the potential for inadvertent exposure. This concept, however, is in direct conflict with other current production practices that use yeast and eggs (food sources) to produce products such as industrial enzymes, vaccines, and pharmaceuticals. The food - host argument diverts attention from the real issue, which is to ensure that transgenic nonfood products remain outside the food system, rather than which host is used for production.

The proposed model discussed above for production of nonfood products in transgenic plants may potentially alleviate associated cost constraints and public concerns. The practice of using a dedicated area for nonfood production would draw a clear distinction between plants used to produce food and nonfood applications. This should help put plant-based production on par with other non-plant production systems used for transgenic products.

### References

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