Pharming in crop commodities

To the editor:

On October 6th, the US Department of Agriculture (USDA) proposed new rules governing the regulations and oversight of genetically engineered crops[1]. Although some of the changes represent steps in the right direction by making regulatory oversight more coherent, the new biotech regulations would allow the outdoor cultivation of pharma food crops, in stark contrast to the editorial stance of your journal, which calls for food plants to no longer be used for producing drugs[2]. Indeed, Jane Rissler, senior scientist & deputy director, Food & Environment Program at the Union of Concerned Scientists (Washington, DC) has denounced the proposed USDA changes, saying, "If these proposals are enacted into law, American consumers must accept the possibility of drugs in their breakfast cereal or other common foods. Moreover, these rules likely will lead to contamination scares, which will hurt the food industry."

History has repeated itself several times when it comes to adventitious presence of transgenes in crop commodities. Adventitious presence or admixture refers to the accidental mixing of transgenic plants or plant parts in nontransgenics. Thus far, admixture has resulted in no documented negative health effects, but is that situation due to change as more and more therapeutic proteins are 'pharmed' in recombinant grain crop commodities? Corn, wheat, rice and soybean are four of the largest crop commodities that are shipped by the boxcar load from farms hundreds of kilometers to massive processors, and three of these, especially corn, rice and soybeans, have fallen prey to admixtures. The adventitious presence in most cases has involved transgenes coding for agronomic traits, such as a *Bacillus thuringiensis* (*Bt*) toxin transgene for insect control (e.g., StarLink event in 2000 in corn) or glufosinate-resistance gene encoding better weed control in rice[3]. The transgenes and proteins underlying these traits are undoubtedly safe for consumption as food and feed, but the transgenic events in question were not deregulated for human consumption at the time of admixture. These events might be construed as an unfortunate mistake of little practical consequence that was blown out of context.

One can argue, as Henry Miller of the Hoover Institute (Stanford, CA, USA) has done so eloquently, that overly cautious food manufacturers and regulators have fallen into the hands of Luddites in that insignificant amounts of DNA and protein 'contaminants' could not have any biological effects—that is, no harm, no foul[4]. But I do not see Miller changing many minds in food industry and regulation. Thus, we are left with the brute fact that transgenic pharma seeds of commodities will inevitably get mixed unless extreme measures are taken to segregate types. Even then, there is the issue of biosafety of ingestion by wildlife and accidental bulk ingestion by humans. In many ways, pharming in food and feed commodities are bad company.

Interspecific mixing has occurred already with a pharmaceutical transgene—the Prodigene (College Station, TX, USA) debacle of 2001–2002, in which volunteer transgenic corn was found growing in a soybean field[3]. Now, SemBioSys (Calgary, Alberta, Canada) is growing safflower in Washington state to produce a carp growth hormone and Ventria is planting hundreds of hectares of rice around Junction City, Kansas, for the production of several human proteins[3].

Transgene adventitious presence can occur by pollination of nontransgenic plants by transgenic plants resulting in seeds with the transgene in the hemizygous state, or from inadvertent seeding. Pollination can be averted by physical isolation and using crops that do not have sexually compatible relatives nearby. Limiting seed flow is more problematic because it can occur by movement of seeds from adjacent fields by wildlife and farm machinery or further afield by transportation of seeds that escape from containers. Of course, exposure is only half of the risk equation. The other half is hazard. What would be the effects of miniscule amounts of transgenic pharma product in food or feed? What about nontarget exposure and hazards to arthropods and vertebrates in the field? The questions of biosafety and risks are handled by regulators on a case-by-case basis. Toxicology from various exposure rates to appropriate organisms are done for each overexpressed protein or metabolite of interest. This procedure is no different from that for dozens of transgenic events deregulated in the United States and has proven to be effective because no negative human health or environmental effects have been noted as trillions of transgenic plants have been grown in the United States[5].

Pharming crosses paradigms of agriculture and pharmaceutical production, yielding economies of scale, and also transcends the nature of agriculture[6]. Even proponents of agbiotech like me are cautious about pharming applications, especially in commodities. Why? The issue is not that risk assessments are not performed or performed improperly. As noted above, US regulators have performed admirably in protecting the environment and food supply in the past 13 years of commercial transgenic crop production in the United States. The USDA Animal and Plant Health Inspection Service (APHIS) risk assessment concluded that the lysozyme, lactoferrin and human serum albumin being produced by Ventria rice are not toxic to nontarget organisms[7].

The main issue here is not about pharmaceutical or food purity. Transgenic DNA or proteins are the only 'contaminant' I am aware of where the adventitious presence doctrine is invoked at all—Miller is correct about misplaced fears[4]. The determination of adventitious presence is basically a product of the sensitivity of detection equipment and frightened people. Quantitative PCR can detect transgene presence in very low titers[8] and with immediate potential of detecting transgenes in the range of 1:50,000–1:200,000 genomic equivalent range (Yuan, J. & Stewart C.N.; unpublished data) with robust statistical procedures[9]. The issue of concern is one of perception. Reports of adventitious presence, no matter how benign, are bad publicity for plant biotech as a whole. Not only will biotechnologists suffer from guilt by association, but farmers and other agriculturalists are hurt when their state or region is found to have adventitious presence of transgenes.

That said, Ventria, at least, seems to have learned from the mistakes of others. They are now growing transgenic pharma rice in a state (Kansas) where little-to-no rice is produced, which is also outside its traditional production area. No other rice is grown within nearly 500 km of their fields[7]. They use dedicated farm machinery and take inordinate care in transporting their transgenic rice to processing. Processing and storage of rice is in a dedicated facility as well. Weedy red rice is the same species as cultivated rice, but it has not been reported to grow in the area of cultivation, therefore hybridization and introgression is not of concern and introgression rates are very low anyway in this species[10].

So why worry? Scientifically, I have very few worries with regards to biosafety in this particular case. Ventria is indeed taking extraordinary measures to ensure transgene containment. USDA APHIS continues to evolve and has improved inspection frequency and procedures. I do worry that, until we devalue the doctrine of adventitious presence, any slight detection of transgenes outside of their intended locales will be overblown beyond reason. In spite of Ventria's care, there is still a chance that vigilant people with advanced detection procedures will find something to report—regardless of real biosafety issues. Therefore, if we believe this to be true, Ventria (and any other company cultivating pharma crops in open fields) must perform perfectly year after year to avoid admixtures. In spite of the odds and current climate, I am cautiously optimistic that pharming rice in Kansas could be a model for other companies to follow.

But would they, and what issues lie beyond admixture? There are two absolute conditions to assure biosafety when pharming crop commodities (not counting Murphy's Law). The first requirement is extraordinary physical isolation and dedicated equipment. Still, there are limited numbers of suitably isolated sites that are available and conducive for rice production in the United States. Second, the pharma products must be safe for accidental consumption in bulk by wildlife and humans. For the latter, accidental bulk ingestion should be part of the standard regulatory package.

The bottom line for most people is a level of discomfort with open-air pharma production of any sort, and especially when it is in a grain crop that has been bred for palatability and nutrition (that is, begging to be eaten by humans and wildlife). It is hard to predict when and if this circumstance will change. In the meantime, the proposed rules are available for public comment for 45 days until November 24.

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Coexistence in the EU—return of the moratorium on GM crops?

To the editor:

The decision of European Union (EU; Brussels) commissioner for environment, Stavros Dimas, to defer market approvals of maize Bt11 and 1507 against the recommendation of his scientific advisers is an indication that Europe remains in a state of quasi-moratorium regarding the cultivation of genetically modified (GM) crops. Here, we outline another challenge that threatens to paralyze the cultivation of GM crops in Europe: regulations on the coexistence of GM and non-GM crops.

As a last building stone of the restyled EU legal framework, the adopted coexistence policy aims to ensure that different cropping systems develop side by side without excluding any agricultural option. Because of the heterogeneity in farm structures, crop patterns and legal environments among member states, the European Commission (EC; Brussels) follows the subsidiarity principle for the implementation of legal coexistence frames[1]. According to this principle, coexistence should be handled by the lowest authority possible. In the following text, we use the example of *Bt* maize, a crop that expresses the insecticidal protein Cry1Ab from *Bacillus thuringiensis* in its tissues, to explore how national and/or regional coexistence regulations might affect the future adoption of *Bt* maize. At present, *Bt* maize is the only GM crop planted over a significant area in the EU (**Fig. 1**).

To ensure coexistence between cropping systems, member states are currently implementing or developing *ex ante* coexistence regulations and *ex post* liability schemes. In *ex ante* coexistence regulations, preventive on-farm measures are prescribed

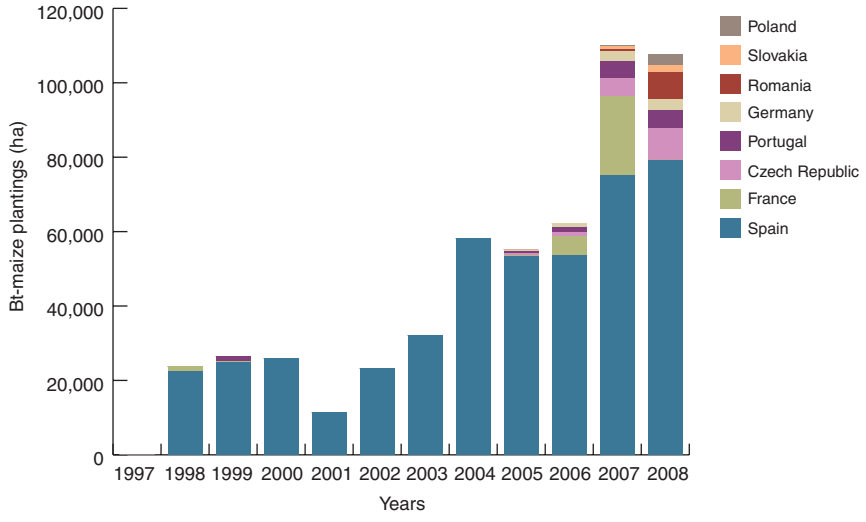

Figure 1 Cumulative *Bt* maize plantings (ha) per member state in the EU (1997–2008). In 2008, France banned the cultivation of maize MON810 on its territory.