Comments to the U.S. Food and Drug Administration re:

Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use

FDA Docket No. 2004D-0369

by

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for

Friends of the Earth U.S.

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Summary Recommendations:

1) The US government should subject all genetically modified crops to a mandatory and rigorous review to detect any human health or environmental impacts they may have before any outdoor planting is allowed.

2) In the meantime, the US government should strengthen its regulation of GM crop trials to prevent contamination of neighboring fields with the pertinent GM trait. To this end, the government should acquire the means to test for such contamination, conduct regular testing, and improve compliance with gene containment protocols.

3) This FDA guidance should be scrapped since it lacks any scientific basis, has nothing to do with enhancing food safety, and is designed primarily to assist agribusinesses in avoiding liability for contamination of commercial food, feed and seed with experimental GE crop material.

4) If the guidance is adopted, at the very least seedstocks should be excluded from its purview

5) The US government is urged to establish clear rules placing liability for contamination of conventional and organic crops with genetically engineered crop material on the pertinent crop developer.

6) The US government should follow the lead of European countries, Japan, South Korea, and many other nations in establishing mandatory labeling of food products for ingredients derived from genetically engineered plants.

7) We urge the US government to cease its harrassment of the European Union and other countries for their sensible policies with respect to genetically engineered foods.

This guidance document is the FDA's attempt to implement the directive issued by the White House Office of Science and Technology Policy (OSTP) in August of 2002, the stated purposes of which are "further reducing in commercial seed lots, bulk commodities, and processed food and feed the likelihood of the occurrence of intermittent, low levels of biotechnology-derived genes and gene products from crops under development for food or feed until all appropriate safety standards have been met," "protection of public health and the environment," and "to enhance public confidence in the regulatory oversight of biotechnology-derived food crops and foods/feeds derived from such crops."[1] In short, OSTP's directive and FDA's draft guidance have the ostensible goals of reducing contamination, increasing food safety and enhancing public confidence in genetically engineered foods. As argued below, the guidance does not accomplish any of these goals, and in fact will have precisely the opposite effect in each case.

Our comments will address the guidance document as it relates to:

I. Frequency and magnitude of contamination
II. The "early food safety assessment" is inadequate and will not ensure safe food
III. The "early food safety assessment" is unscientific and fosters "regulatory junk science"
IV. The true purpose of the guidance and its likely impacts

I. Contamination

1) The frequency and level of contamination have generally been increasing since 1987 and will continue to rise with increases in the number and acreage of GE crop field tests

As both the FDA guidance and the OSTP directive upon which it is based admit, the ***number*** and ***acreage*** of GE crop field trials, and hence the ***likelihood*** of contamination, are ***on the rise***:

> *"As the number and diversity of field tests increase, the likelihood that cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced under field tests with commercial seeds or grain may also increase. This could* ***result*** *in* ***intermittent, low-levels*** *of biotechnology-derived genes, and gene products*

[1] "Proposed federal actions to update field test requirements for biotechnology derived plants and to establish early food safety assessments for new proteins produced by such plants," Notice, Office of Science and Technology Policy, *Federal Register*, Vol. 67, No. 149, p. 50578.

occurring in commerce that have not gone through all applicable regulatory reviews." (my emphasis)

Yet the logical "result" or consequence of a causal chain comparing present and future states (the ***increasing*** likelihood of contamination entailed by the ***rising*** number and acreage of GE crop field trials) must also be comparative in nature. That is, the "result" in the quote cited above cannot, logically speaking, be a static "intermittent" or "low-level" contamination, but rather must be comparative, that is, "more frequent, higher-level" contamination. Thus, we can say that if the number and acreage of field trials continues to rise, as assumed by OSTP & FDA, contamination will become more likely, more frequent, and at higher levels, than at present. This corrected formulation brings out the unspoken truth that, of course, contamination is occurring now, albeit at lower levels and less frequently than can be expected in the future. Likewise, we must assume that what is true of present and future is also true of the past. Contamination has been occurring ever since outdoor field trials of GE crops began in 1987. Only now, 17 years later, have OSTP and FDA decided to address this steadily growing problem (see Appendix 1 for a partial list of contamination episodes that were covered in the press.)

2) "Intermittent" and "low-level" are meaningless without quantification

"Intermittent" and "low-level" are terms that beg for quantification, yet FDA/OSTP fail to offer any numerical definitions anywhere in either document. Does "intermittent" contamination mean contamination episodes that occur once a month, once a week, daily or hourly per field trial? Does "low-level" mean that 0.1%, 1% or 10% of the commercial food, feed or seed is comprised of contaminating GE crop material? Without numerical specification (i.e. a "tolerance"), these terms mean absolutely nothing. In other words, FDA's "early food safety assessment" must be interpreted as applying to essentially ***unlimited*** levels of GE crop contaminant, up to and including 100% (i.e. the experimental GE crop at issue unmixed with any commercially approved variety). The implications this has for food safety will discussed in section III.

3) Persistence/increase of GE traits invalidate concept of "adventitious presence"

Unlike inert contaminants, the adventitious presence of transgenic traits could increase in frequency and amount over time under a variety of conditions. According to the principles of population biology, the fate of a (trans)gene that introgresses into compatible conventional cultivars or weed species is significantly influenced by:

i) the frequency of the introgression event; and

ii) whether the trait engendered by the transgene confers a selective advantage or disadvantage or is neutral.

With single transgene-flow events, detrimental traits diminish in frequency over time, neutral traits tend to persist, and beneficial traits may increase to fixation. With recurrent transgene flow, even detrimental traits may persist, while both beneficial and neutral traits will tend to increase to fixation (see table). Therefore, it is not only beneficial traits, but also neutral and in the extreme case of regular introgression even detrimental traits that may persist in the environment.[2] This potential for initially "intermittent" and "low-level" transgenic crop contaminants to become ***amplified over time*** is extremely troubling and confronts the FDA with a risk that is completely unaddressed in the guidance: a self-propagating contaminant that may not be controllable once released. In some cases, an initially low-level and intermittent presence (however that is defined) that causes no significant food safety problems may, through amplification, cross the threshold of human health impact years later. This is still another reason NOT to issue a blanket exemption of adventitious presence from regulation – it may amplify and cause unexpected impacts that would not occur at initially lower levels.

Change in Frequency of Escaped Transgene in Environment Over Time Based on Frequency of Transgene Flow and Fitness Effect of the Trait[3]

Fitness effect of trait:	**Frequency of Transgene Flow (to compatible weeds/crops):**	
	Single gene flow event	Recurrent gene flow
Detrimental	Decrease to extinction	Persist at intermediate frequency
Neutral	Persist at intermediate frequency	Increase to fixation
Beneficial	Increase to fixation	Increase to fixation

[2] The older view that natural selection always acts to eliminate neutral traits is based on the outdated notion that even the often low metabolic cost associated with expression of a trait/protein that offers no survival benefit *necessarily* represents a disadvantage large enough to be selected against. For our purposes, the potential for neutral and even detrimental traits to persist (versus beneficial only) greatly expands the universe of genetic modifications whose adventitious presence poses potential environmental concerns that must be addressed.

[3] Adapted from: "Mindful management of genes that produce industrial biochemicals in plants," presentation of Norman C. Ellstrand, geneticist, U of CA Riverside, at the Pew "Pharming the Field" Conference, Washington, DC, July 17 & 18, 2002.

There is a growing body of research on crop-to-wild gene flow which demonstrates that hybridization occurs more often than once thought and often has adverse consequences, but as of yet very little on transgenic crops, especially transgenic-to-conventional crop.[4] One reason is the environmental rather than agricultural focus of ecologists and geneticists who study gene flow phenomena, another is the relative novelty of this concern. Most important, however, is probably the assumption that conventional cultivars do not represent a viable population in which a GE trait could persist, much less increase in frequency, because crops are subject to control by agricultural practices rather than natural selection. That this assumption can be false is demonstrated by the case of herbicide-resistant canola.

a) ***Stacking of herbicide resistance traits in canola and related weed species:***
Volunteer canola plants resistant to one, two and even three herbicides are emerging as a serious weed problem in the Prairie Provinces of Canada.[5] These plants are generated by crosses between canola plants resistant to either glyphosate, glufosinate or imidazolinone (the former two generated by rDNA, the latter by mutagenesis). A 1999 study by Agriculture Canada recorded stacking of herbicide-resistance (HR) genes in volunteers in all 11 locations studied where Roundup Ready and Liberty Link crops were grown in adjoining fields.[6] According to plant scientist Martin Entz, "The GM canola has, in fact, spread much more rapidly than we thought it could." [7]

HR trait stacking can occur through cross-pollination between crop-crop, crop-volunteer, or even volunteer-volunteer, which occurs at large distances with canola via wind and insect. Canola gene flow is exacerbated by seed dispersal. Seeds are not only left in the field after harvest, they can be accidentally spread on farm machinery, through seed spillage, and perhaps even inside animals that consume them (i.e. undigested seeds excreted in cattle manure (Ibid)).

Related weed species provide another avenue for gene flow. In one study, field mustard (***B. rapa*** L.) was planted adjacent to three HR resistant canola varieties.[8] Seed from the field mustard plots were collected and planted. After one year, 5.9%,

[4] Ellstrand, N.C. (2001). "When Transgenes Wander, Should We Worry," *Plant Physiology*, Vol. 125, pp. 1543-45. www.plantphysiol.org/cgi/content/full/125/4/1543.
[5] "Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada," An Expert Panel Report on the Future of Food Biotechnology, The Royal Society of Canada, p. 122. www.rsc.ca/foodbiotechnology/indexEN.html.
[6] Beckie, H.J., Hall, L.M., Warwick, S.I. (2001). "Impact of herbicide-resistant crops as weeds in Canada," *Proceedings of the Brighton Crop Protection Conference – Weeds*, pp. 135-42.
[7] "Genetically modified canola becoming a weed," CBC News Online, June 22, 2002.
[8] Reddy, S. (2002). "Gene Flow and Accumulation Between Herbicide Resistant Canola (Brassica napus L.) and a Related Weed Species (B. rapa L.).

7.6% and 17.2% of the morphologically identified canola-mustard hybrids were resistant to glufosinate, glyphosate and imazamox, respectively. Fifteen percent of the resistant hybrids were self-compatible. When these single-herbicide resistant hybrids were each backcrossed to canola resistant to a different herbicide, 11.9% of the resulting seeds, on average, were resistant to two herbicides. This demonstrates the potential for related weed species to act as a "genetic bridge" or reservoir for subsequent passage of a transgenic trait back to cultivars, resulting in transgene stacking.

b) Gene flow from experimental GE crops could become significant

While the canola example above involves gene flow from commercial GE crops, the conditions that facilitate persistence or amplification of an escaped transgene beyond intermittent and low-level "adventitious presence" might be met in the experimental situation as well. Several of these conditions are:

i) **Sexually compatible cultivars/weeds in vicinity**

ii) **Recurrence:** Any given GE crop may undergo many (e.g. 5-10 years) of outdoor field testing; if conducted in the same area, as is common, introgression of the GE trait into sexually compatible commercial crops or weeds may be recurrent;

iii) **Gene flow increases with scale:** Field trial size often increases to hundreds or thousands of acres in the latter stages of testing, so field trial populations can be large enough to be significant sources of transgene outflow.

iv) **Gene confinement & regulation less effective at larger scale:** Gene confinement measures (e.g. spatial and temporal isolation) become much less effective with larger plantings. Inspections for regulatory compliance (e.g. for volunteers) necessarily become much less thorough at increased scale due to personnel limitations. It should be noted that the ProdiGene biopharm corn trial which left volunteers that eventually contaminated half-a-million bushels of soybeans in Nebraska in 2002 was reportedly only a single acre. Animal (especially bird) dispersal of viable seed also becomes a more significant issue with increasing scale (though APHIS field trial standards generally completely disregard this mode of transgene flow). Sexually-compatible wild relatives of the GE cultivar can act as "genetic reservoirs" for persistence/amplification of the transgenic trait.

v) **Beneficial traits increase chances of persistence/amplification:** While even neutral or in some cases detrimental transgenic traits may persist in the

environment (see above), the chances of this increase with traits that confer a selective advantage.

c) Case study of Ventria Bioscience's pharmaceutical or "value-added" rice[9]

Several rice varieties developed by Ventria Bioscience appear to meet four and in some cases all five of these conditions favoring the persistence/amplification of experimental GE traits. These rice varieties produce specialty compounds that are properly called "pharmaceutical proteins," but more recently have been re-christened "value-added proteins for human consumption."[10] This terminological confusion makes it unclear whether the FDA's guidance, which does not apply to non-food proteins, would apply to Ventria's transgenic rice proteins. We will assume that is does, and illustrate the potential for persistence or amplification of "low-level" presence of regulated GE proteins through examining cultivation of Ventria's pharmaceutical rice in two situations: in California from 1997 to present; and the company's plan to grow this rice in southeastern Missouri starting in 2005.

i) **Sexually compatible cultivars/weeds in vicinity:**

Ventria or its predecessor, Applied Phytologics, has grown its pharmaceutical rice mainly in California's northern Central Valley. This is the heart of California rice country, so there is ample cultivated rice to which Ventria's pharmaceutical transgenes could wander. Wild rice (*Oryza rufipogon*) is a federally listed noxious weed that has been introduced into California, and gene flow between cultivated rice (*Oryza sativa*) and wild rice is well known.[11] Annual red rice (also *O. sativa*) was recently identified in the northern Central Valley's Glenn County, by some accounts in certified rice seed, and is considered a "serious risk to the California rice industry."[12]

Ventria has applied to USDA for permits to grow pharmaceutical rice in 2005 in three Missouri counties (Cape Girardeau, Scott, Mississippi) on the northern edge of one of the heaviest rice-growing regions in the country (northeast Arkansas/southeastern MO).[13] As in California, there is ample cultivated rice in the vicinity that could easily become contaminated. But while weedy red rice is

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[9] For a fuller treatment of Ventria's pharmaceutical rice, including potential human health impacts not addressed here, see Freese et al (2004). "Pharmaceutical Rice in California," by Friends of the Earth, The Center for Food Safety, Consumers Union and Environment California, 2004, at http://www.foe.org/biopharm/.

[10] Freese et al (2004). "Pharmaceutical Rice in California," Friends of the Earth, The Center for Food Safety, Consumers Union, Environment California, 2004. Available at www.foe.org

[11] Chen L.J. et al. (2004) Gene flow from cultivated rice (*Oryza sativa*) to its weedy and wild relatives. *Ann. Bot.* (*Lond.*) 93(1):67-73; Song Z.P. et al. (2004) Fitness estimation through performance comparison of F1 hybrids with their parental species *Oryza rufipogon* and *O. sativa*. *Ann. Bot.* (*Lond.*) 93(3):311-316.

[12] "What is Red Rice," from: California Rice Commission newsletter, Vol. 6, No. 2, Nov/Dec 2003. http://www.calrice.org/industry/2003_11/page5.html.

[13] "Plant-Made Pharmaceutical Company Developing Health Solutions for the Global Community," Ventria Bioscience press release, 12-22-04.

less prevalent in California, it is one of the biggest concerns of rice growers in Missouri and rice-growing states to the south.[14]

ii) **Recurrent field trials in same area:**

Ventria or Applied Phytologics has been growing pharm rice in California since 1997, with the possible exceptions of 1999 and 2002. All of these trials have reportedly taken place "in the northern Central Valley, the heart of California rice country."[15] The precise location of these trials is kept secret, though we do know that one trial was conducted in Butte County (1997)[16] and one in neighboring Sutter County (2001).[17]

Assuming Ventria obtains the required permits, 2005 would be the first year for pharm rice cultivation in MO.

iii) **Scale of planting:**

The permitted acreage for CA trials in 1997 and 1998 is not reported. The reported acreage grows from 6 acres in 1999 (though this trial might have involved something other than pharmaceutical proteins) to 7 acres in 2000, 100 acres in 2001 and perhaps 2002, to 93 acres in 2003.[18] An application for a field trial of 120 acres in 2004 was rejected by USDA and the California Dept. of Food and Agriculture. In 2004-2005, Ventria has a permit for cultivation of just a single acre of pharmaceutical rice.

Ventria's proposed field trials in MO would cover 200 acres,[19] making them the largest field trials for pharmaceutical crops that have yet been conducted in the United States, and a substantial source of transgene outflow.

iv) **Gene confinement and regulation:**

Ventria's draft protocol for its proposed 2004 field trial in CA was reported to be "light on some details, including how Ventria will prevent birds from spreading its rice; what constitutes 'proper' disposal of rice plants; and whether the company will notify nearby growers."[20] Jose Carrancho, 40-year rice grower and past president of the Rice Producers of California, said of Ventria's protocol: "This is probably the most stringent protocol I've ever seen. And it's not

[14] "Red Rice," fact sheet by TAES, Beaumont, Texas, available at http://beaumont.tamu.edu/RiceContestStudyGuide/2004/Red%20Rice.pdf.
[15] Lee, M. and Lau, E. (2004). "Biotech company cultivates new field," Sacramento Bee, January 25, 2004.
[16] "Environmental Assessment and Finding of No Significant Impact" for USDA Permit No. 96-355-01, op. cit.
[17] "Amberwaves Calls for a Moratorium on Genetically Engineered (GE) Pharmaceutical Rice in California," Amberwaves Press Release, Sept. 7, 2001.
[18] Information gleaned from USDA's website of experimental GE crop field trials: www.nbiap.vt.edu/cfdocs/fieldtests1.cfm. Under "Institution" category, search on "Applied Phytologics" and "Ventria Bioscience."
[19] Lauck, S. "Biofarming faces few Missouri rules," St. Joseph News-Press, Jan. 23, 2005.
[20] Lee & Lau (2004), op. cit.

enough."[21] In its review of Ventria's draft protocol, the California Rice Commission was concerned that pollination by bees and other insects could spread Ventria's pharm traits. The CRC also persuaded Ventria to supply an ELISA test for its recombinant proteins to a third party for contamination testing purposes,[22] which is more than the USDA requires of GE field trial applicants. While these observations refer to a draft protocol for a proposed 2004 field trial, prior field trials by Ventria/Applied Phytologics are unlikely to have been any more stringent with respect to gene containment, and were probably ***less stringent*** because they did not require CRC approval. In fact, one press account of a letter from USDA to Ventria suggests that Ventria may have already committed a permit violation by planting its rice "within 100 feet of rice intended for human and animal food."[23]

If Ventria's MO field trials proceed, it is unclear how effective gene containment practices would be. Ventria proposes not to plant its pharm rice within 5 miles of food-grade rice.[24] This would mitigate one risk – that of cross-pollination between pharm and food-grade rice. Yet two other factors make some level of contamination a virtual certainty: animal, especially bird, dispersal of transgenic seed; and the prevalence of cross-compatible weedy red rice in the area. Both Ventria and the USDA have discounted the contamination potential of animal dispersal, yet birds in particular are voracious rice eaters, and even if only a tiny percentage of ingested (transgenic) rice grains are passed in viable form in feces (a phenomenon documented with other seeds and other birds),[25] birds could represent a significant vector for transgene flow. A USDA study identified red-winged blackbirds as the most prevalent avian rice pest in southeast MO. A population of over 3 million red-winged blackbirds was found to be roosting in rice fields near Sikeston, MO, the area where Ventria plans to plant its pharm rice.[26] Clearly, blackbirds and other birds could consume pharm rice and defecate viable grains miles from the pharm rice sites, including in fields of food grade rice. Volunteer rice sprouting from these bird-transported transgenic seeds (perhaps after lying dormant for an indeterminate period) could cross-pollinate with food-grade rice, directly transferring the pharmaceutical genes to food, or with weedy red rice. Weedy red rice is prevalent in Missouri.

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[21] As quoted in: Garofoli, J. (2004). "State's rice farmers fear biotech incursion," *San Francisco Chronicle*, April 8, 2004.

[22] California Rice Commission's comments on Ventria's draft protocol (3/24/04) for cultivation of its pharmaceutical-producing rice varieties.

[23] Silber, J. (2004). "Permit for biotech rice is denied," Contra Costa Times, April 9, 2004.

[24] Ventria press release, 12-22-04, op. cit.

[25] For a valuable discussion of animal (especially bird) dispersal of viable seed through ingestion and defecation, see: Kinney, W. (2004). "Briefing on the Proposed Protocol for Pharmaceutical Rice," Attachment 2, submitted to the AB2622 Advisory Board of the California Rice Commission, March 5, 2004, by Californians for GE Free Agriculture.

[26] See www.aphis.usda.gov/ws/nwrc/research/rice/project.html

If the pharmaceutical traits enter weedy red rice, as seems inevitable, it could act as a "genetic reservoir" for the pharmaceutical genes, which could be passed back to food-grade rice in subsequent years. This risk is aggravated by the long dormancy of red rice, which may lay dormant for years before sprouting. The twin factors of ubiquitous weedy red rice growing in close association with cultivated rice and huge rice-eating bird populations virtually ensures that Ventria's pharmaceutical traits will contaminate the food supply if it is permitted to be grown in southeastern MO.

v) **Beneficial traits:**

Three pharmaceutical traits expressed in Ventria's rice – lysozyme, lactoferrin and alpha-1-antitrypsin – have antimicrobial, antifungal and/or insecticidal properties. Recombinant human lysozyme expressed in transgenic tobacco[27] has been shown to confer enhanced resistance to the fungus *Erysiphe cichoracearum* and the phytopathogenic bacterium *Pseudomonas syringae pv. tabaci.* Carrots transformed to express recombinant human lysozyme exhibit enhanced resistance to the carrot pathogens *Erysiphe heraclei*, a fungus causing powdery mildew, and *Alternaria dauci,* a pathogen of leaf blight.[28] Alpha-1-antitrypsin is a serine protease inhibitor, a class of compounds being tested in many plants as potential plant pesticides.[29] It is likely that these same proteins will lend rice resistance to similar rice pathogens. If these traits are transferred to red rice or wild rice, they would likely confer a fitness boost to these weedy species, enhancing their survival and making these already noxious weeds still more difficult to control. Crossing with cultivated rice would likely create volunteers with enhanced survival. As noted above (see table), even single gene flow events can increase to fixation if the trait confers a survival advantage. Enhanced weeds could then serve as a genetic bridge or reservoir to transfer the traits back to cultivated rice.

Sheath blight, caused by the fungus *Rhizoctonia solani*, and blast, caused by the fungus *Pyricularia oryzae*, are two of the greatest disease threats to MO rice.[30] If Ventria's pharmaceutical traits were to lend weedy red rice resistance to either of these common diseases, it could make this already noxious weed still worse.

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[27] Nakajima, H. et al (1997). "Fungal and bacterial disease resistance in transgenic plants expressing human lysozyme," *Plant Cell Reports* 16: pp. 674-79;

[28] Takaichi, M. & Oeda, K. (2000). "Transgenic carrots with enhanced resistance against two major pathogens, *Erysiphe heraclei* and *Alternaria dauci*," *Plant Science* 153(2), pp. 135-144.

[29] "Mammalian Toxicity Assessment Guidelines for Protein Plant Pesticides," FIFRA Scientific Advisory Panel to the EPA, SAP Report No. 2000-03B, September 28, 2000.

[30] See http://agebb.missouri.edu/rice/ricehist.htm.

This case study suggests that even an initially intermittent and low-level "adventitious presence" of regulated traits in related weeds or cultivars could persist or amplify to create significant agronomic problems.[31] [footnote: for potential human health concerns from exposure to these recombinant proteins, see Freese et al (2004)].

Since pharm and "value-added protein" crops are subject to more stringent isolation measures than "notification" field trials, and the latter are generally much larger, there are many other examples of GE crop field trials that pose still greater risks of spreading their traits more widely than assumed in this adventitious presence proposal.

4) Special concerns relating to "adventitious presence" of transgenic traits in seed

Rubber-stamping (i.e. sending letters indicating "no further questions" to companies that participate in the "early food safety assessment") the "adventitious presence" of experimental GE traits in conventional or organic *seed stocks* would raise concerns above and beyond those associated with contamination of commercial crops, food or feed. First, it would represent a grave breach of trust and a violation of the principle of informed consent vis-à-vis farmers. While farmers who wish to remain GE-free can at least take some measures (e.g. temporal isolation) to protect their crops against field contamination (assuming they have knowledge of field trials in their vicinity, which is by no means certain), there is nothing they can do to guard against contamination of the seed they buy, short of extensive PCR testing that is prohibitively expensive (and in any case virtually impossible with undisclosed experimental traits). Second, because "approval" of "adventitious presence" means that farmers would ***unwittingly*** buy contaminated seeds, they would not have the knowledge base to employ the agronomic practices that are needed to prevent further spread of the experimental trait(s) to their own or other farmers' crops. This risk of persistence and amplification is especially pronounced with the two transgenic traits most common in both commercial and experimental plantings – herbicide and insect resistance – because each confers a selective advantage in the agricultural setting. In the case of canola, for instance, the undisclosed presence of HR traits in seed stock (see below) has almost certainly contributed to the growing problem of herbicide-resistant volunteer plants in Canada.

There are next to no data on the frequency or level of ***experimental*** transgenic trait contamination of conventional/organic seed stocks. This is due to the confidential nature of most such traits and the consequent lack of test reagents (e.g. PCR primers), the secrecy surrounding the location of test sites, and the failure of the USDA to

[31] For human health concerns associated with Ventria's pharmaceutical proteins, see Freese et al (2004), op. cit.

conduct monitoring for such contamination. Yet there are at least a few reports that give an idea of the scope of the problem with respect to ***commercial*** GE traits.

5) An overview of seed stock contamination with commercial GE traits:

The issue first came to light during the StarLink corn debacle. Besides the well-publicized contamination of over 300 corn products and up to 22% of the corn supply,[32] StarLink's cry9c gene turned up in some seed lines of 63 to 71 of 288 corn seed companies *that never grew StarLink*. This is the result of a USDA-sponsored testing program; USDA spent some $13 to $18 million to purchase these contaminated seeds from the companies upon condition that they be destroyed.[33] Two Canadian studies demonstrate that one factor in the spread of herbicide resistance traits in Canadian canola is seed stock contamination. In a 2002 study of 70 certified canola seed lots, 59% were found to have detectable herbicide resistance, with 25% above the maximum acceptable standard for certified seeds (0.25%). A second study in 2003 involving 27 certified seed lots found 95% contaminated with an HR trait, and 52% exceeding the 0.25% purity standard for certified seeds.[34] ***According to Walter Fehr, director of the Office of Biotechnology at Iowa State University, Ames, contamination of breeder seed stocks of corn and soybeans in the U.S. with transgenic traits "happens routinely.***"[35] This startling revelation is corroborated by a recent study by the Union of Concerned Scientists (UCS).[36] UCS commissioned testing of 6 batches of certified seed of each of three crops – soy, corn and canola – by two labs. One of the labs found that 5 of 6 batches of each crop were contaminated with transgenic DNA. The testing commissioned by UCS was by necessity limited to commercial GE traits for the reasons described above.

6) Lessons from seed stock contamination

The frequency with which commercial GE traits are showing up in conventional certified seed stocks has troubling implications. This is because seed crops, unlike

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[32] For an overview, see: Freese, B. (2001). "The StarLink Affair," report submitted to the EPA's Scientific Advisory Panel on behalf of Friends of the Earth, July 2001. See www.foe.org/safefood/starlink.pdf.
[33] "USDA purchases Cry9C affected corn seed from seed companies," USDA News Release (6/15/01). See ww.usda.gov/news/releases/2001/06/0101.htm.
[34] Downey, R.K. & Beckie, H. (2002). "Isolation Effectiveness in Canola Pedigree Seed Production," Internal Research Report, Agriculture and Agri-Food Canada, Saskatoon Research Centre, Saskatoon, Saskatchewan, Canada, 2002, 14 pages; Friesen et al (2003). "Evidence of contamination of pedigreed canola (*Brassica napus*) seedlots in western Canada with genetically engineered herbicide resistance traits," *Agronomy J.* 2003, Vol. 95. It should be noted that the 0.25% maximum contaminant (tolerance) standard was established for contamination by other conventional varieties, not transgenes. Canada does not have standards for transgenic contamination of certified canola cultivars.
[35] Charman, K. (2002). "Seeds of Domination," *In These Times*, 2/10/02.
[36] Mellon, M. & Rissler, J. (2004). "Gone to Seed: Transgenic Contaminants in the Traditional Seed Supply," Union of Concerned Scientists 2004. See: www.ucsusa.org.

commodity crops, are grown according to strict isolation protocols designed to mitigate gene flow so as to maintain the purity of the variety. If seed crops are nonetheless being contaminated with GE traits, by some accounts "routinely," this clearly implies that these isolation protocols are ineffective, or at least much less effective than thought. And since the USDA has based its isolation standards for the vast majority of GE crop field trials (i.e. those falling under the "notification" system) on these very same protocols employed by the seed industry, it strongly suggests that experimental transgenic traits are not being properly contained, which in turn casts great doubt on the assumption that the "adventitious presence" of such traits in commercial crops, food, feed and seed is "intermittent" and at "low levels" (however that is defined).

The aggregate acreage of current experimental GE crop plantings is impossible to ascertain, though they represent a sizeable source of contamination. A rough idea is provided by the USDA's GE crop field trial database (run by Virginia Tech).[37] It shows that as of September 14, 2004, there were 1,017 permits in effect covering at least 56,000 acres. These totals exclude 63 permits for which no acreage is cited. Seven permits authorized plantings over 1,000 acres, 12 permits were for 500-1,000 acres, and 26 permits were 250-500 acres in size. Clearly, these larger trials in particular will give rise to substantial transgene flow that in at least some cases will result in contamination of commodity and seed crops beyond the "intermittent" and "low-level" presence presumed in OSTP's proposal.

7) Timing of "early food safety assessment" left up to petitioner rather than before the first field trial

Because contamination can and probably will occur at some level beginning with the very first outdoor field trial, that is when the FDA should encourage applicants to submit their food safety assessments. Instead, the FDA inexplicably pretends that there is some specific point in the field testing process when the contamination risk arises (from thin air, so to speak), and that applicants are competent to judge when this magical point might be. In the FDA's words, the food safety evaluation should be submitted "prior to the time you have concerns that the new protein could enter the food supply, for example via pollen flow or commingling as you increase the size or extent of field testing."

That this assessment process is driven by applicant "concerns" rather than objective criteria (which would demand serious testing before any field trial took place) is one of many signs that this guidance is unscientific and has little or nothing to do with food

[37] See www.nbiap.vt.edu/cfdocs/fieldtests1.cfm.

safety. We will address the applicant "concerns" being addressed by this guidance in section IV.

8) Guidance will result in increased contamination due to reduced incentive to stop spread of novel transgenic crop material

To understand this, we must first note that there is a *de facto* "zero tolerance" standard for material from experimental, genetically engineered (GE) crops in the commercial food and feed supply based on the status of such crops as regulated articles under the jurisdiction of the U.S. Dept. of Agriculture (USDA). Experimental GE crops producing pesticidal proteins are under the joint jurisdiction of USDA and the U.S. Environmental Protection Agency (EPA) when grown in field trials of 10 acres or more. Unless or until such crops are granted "non-regulated" status by USDA or, in the case of GE pesticidal crops, the transgenic pesticidal protein(s) generated therein are registered by the EPA, these crops are not allowed for commercial sale as food or feed. What holds true for the regulated GE crop also applies to constituents of the crop present in commercial grain, feed or seed as "adventitious presence."

The FDA proposes to send applicants a letter regarding its evaluation of the company's food safety evaluation (addressed in II and III below). One of four options is a letter stating that FDA has "no questions at this time regarding your view that the new proteins raises no food safety concerns…"

As discussed more fully in IV., companies that receive this letter will regard it as a tool to defuse concern over, and evade liability for, contamination incidents involving their novel crops. In other words, the letter will likely be used to sidestep the current "zero tolerance" standard for experimental GE traits in food-grade crops. If successful, this will reduce the threat of liability for such contamination, and thereby decrease the incentive of companies conducting field trials to comply with gene containment protocols. The inevitable result will be more, not less, contamination.

II. The "Early Food Safety Evaluation" Will Not Ensure Safe Food

The FDA anticipates increased contamination from the rising number and acreage of experimental GE crop field trials. That is the stated reason for this guidance. Yet due to the factors discussed in Section I – the FDA's failure to quantify or in any way delimit what it means by "intermittent" and "low-level" contamination, the potential for transgenes to persist and amplify in the environment for future transfer to food crops,

the likely increase in contamination levels resulting from this guidance, etc. – we must proceed on the assumption that contamination is in principle unlimited. In other words, the food safety evaluation must be based on the worst-case scenario of "100% contamination," or exposure to 100% unmixed experimental GE crop. This is not only the only logical course, it is also consistent with the precedent established in the StarLink case, where Aventis CropScience and the EPA based their estimates of exposure to StarLink's Cry9C insecticidal protein on a variety of corn products made from 100% StarLink corn. If it was proper to follow this course in the case of StarLink, where intensive assessment had already established the magnitude of contamination and the corresponding levels of exposure for various subgroups, then it is still more appropriate in the case of this guidance, which purports to cover ***all manner*** of transgenic GE crop proteins as contaminants in food ***for the indefinite future*** with ***no attempt*** to estimate the extent of contamination in any particular case or in the aggregate.

The StarLink case also demonstrates the potential for low-level presence of a transgenic protein to pose a health risk. According to the EPA's Scientific Advisory Panel on StarLink, which included leading U.S. allergists:

> *"... the Panel concluded that based on reasonable scientific certainty, there is no identifiable maximum level of Cry9C protein that can be suggested that would not provoke an allergic response and thus would not be harmful to the public."*[38] *(p. 35)*

1) Unintended effects of genetic engineering excluded from evaluation

The most serious defect of the "early food safety evaluation" is that it proposes to examine only the potential risks from the contaminating transgenic protein, while completely ignoring the unintended and potentially harmful effects of genetic engineering on the contaminating transgenic crop material and the commercial grain, feed or seed it contaminates. Unintended effects are implicitly ignored in two additional contexts: 1) The FDA's decision not to provide for evaluation of experimental GE crops involving metabolic alterations or compositional changes rather than novel proteins; and 2) The FDA's decision to not evaluate transformation events expressing similar proteins based on the "same" transgene once the transgenic protein from a single such event has been evaluated. This latter exclusion makes it extremely clear that the FDA neglects the potential for harmful unintended effects.

Yet the plant transformation and tissue culture techniques used in plant genetic engineering generate an extremely high rate of unintended effects relative to traditional

[38] "Assessment of Additional Scientific Information Concerning StarLink Corn," EPA's Scientific Advisory Panel, SAP Report No. 2001-09, p. 35. http://www.epa.gov/oscpmont/sap/2001/july/julyfinal.pdf.

selection-based breeding methods for the following reasons: imprecision of techniques, frequent mutagenesis and interspecific incompatibilities.

Imprecision: FDA officers[39] and others speak of rDNA techniques as "precise," yet all of the rDNA techniques applied to plants (i.e. chiefly, *Agrobacterium*-mediated gene transfer and particle bombardment via "gene gun") are in fact crude and haphazard. None of these techniques permit control over the genomic site of insertion or the number of transgene copies inserted. All allow for fragmentation of the genetic construct, resulting in incorporation of gene fragments and hence possible generation of fusion proteins. Unbeknownst to the FDA, whose consultation documents are sadly in error on these and other points, Monsanto's Bt corn event MON810 contains an unintentionally fragmented cry1Ab gene, and may well generate an odd-length fusion protein.[40]

Mutagenesis: The mechanisms by which plant genomes integrate transgenic DNA in Agrobacterium-mediated transformation and particle bombardment are poorly understood, but are thought to involve a wound response that triggers DNA repair and degradation enzymes.[41] As recently documented in great detail, these techniques and tissue culture invariably cause deletions of plant genomic DNA, random mutations and chromosomal rearrangements.[42] Examples include translocations of up to 40 Kbp,[43] scrambling of transgene and genomic DNA,[44] large scale deletions of over a dozen genes,[45] and frequent random insertions of plasmid DNA.[46] Genome-wide mutations are also common. Several studies suggest that 35-58% of Agrobacterium-mediated transgene insertion events disrupt functional plant DNA (Ibid), with a corresponding potential for alterations in native toxins and regulatory proteins, and associated disruptions in cellular metabolism.

Interspecific incompatibilities: The components of cells from a particular species/tissue have evolved to work together seamlessly, and cannot be introduced into

[39] Kessler et al (1992). "The safety of foods developed by biotechnology," *Science*, 1747-1832.
[40] Freese, W. & Schubert, D. (2004). "Safety Testing and Regulation of Genetically Engineered Foods," *Biotechnology and Genetic Engineering Reviews*," Vol. 21, Nov. 2004, see pp. 308-313.
[41] Kohli, A et al (1998). "Transgene organization in rice engineered through direct DNA transfer supports a two-phase integration mechanism mediated by the establishment of integration hot spots," Proc Natl Acad Sci USA 95: 7203-7208.
[42] Wilson, A. et al (2004). "Genome Scrambling – Myth or Reality? Transformation-Induced Mutations in Transgenic Crop Plants," EcoNexus, Technical Report, Oct. 2004, www.econexus.info.
[43] Tax & Vernon (2001). "T-DNA-associated duplication/translocations in *Arabidopsis*: Implications for mutant analysis and functional genomics," Plant Physiol 126: 1527-1538.
[44] Makarevitch et al (2003). "Complete sequence analysis of transgene loci from plants transformed via microprojectile bombardment," Plant Mol Biol 52: 421-432.
[45] Kaya, H et al (2000). "*hosoba toge toge*, a syndrome caused by a large scale chromosomal deletion associated with a T-DNA insertion in *Arabidopsis*," Plant Cell Physiol 41(9): 1055-1066.
[46] See Wilson et al (2004), op. cit., section 1.1.2, p. 9 for references.

a foreign genomic context without unpredictable consequences. For instance, DNA polymerases exhibit much elevated error rates when replicating transgenes from other species,[47] while host organisms often do not express unmodified transgenes at appreciable levels. Genetic engineers have learned various tricks to overcome these incompatibilities, such as the use of powerful viral promoters, bacterial enhancers and codon optimization of the transgene to match the host A-T:G-C ratio, but little is known of the mechanisms underlying either the interspecific incompatibility of cellular components or the *ad hoc* fixes.

The factors presented above must be viewed in the context of what little we know of plant functional genomics. Estimates of the number of chemical compounds in the combined plant kingdoms range from 90,000 to 200,000 different molecules, with a single species such as *Arabadopsis* containing roughly 5,000.[48] The production of these compounds at appropriate levels is controlled by exceedingly complex and interactive cellular processes of which we are largely ignorant. Functional genomics studies are only beginning to parse out this complexity. One technique used in such studies is genetic modification. For instance, in a study of just 88 metabolites in potatoes, Roessner et al (see previous reference) found that ***the majority*** exhibited significantly altered levels in one or more of 4 lines transformed for altered sucrose metabolism relative to conventional potatoes. In addition, nine ***novel*** metabolites undetected in conventional potatoes were also found in one or more of the transgenic lines. These effects of genetic modification – significant alterations in the levels of over half the metabolites measured, plus generation of nine novel metabolites – clearly give rise to concern. If we assume for the moment that this example is typical, and scale up from 88 metabolites to a theoretical 5,000 constituents for the typical plant, genetic engineering can be expected to significantly alter the levels of literally thousands of native plant constituents and generate dozens or perhaps hundreds more novel compounds. And while the vast majority of such alterations and novel compounds will likely be unobjectionable, the much larger-than-expected pool of putative changes raises the likelihood that undesirable or harmful alterations will be found among them.

Compositional changes are common in transgenic food crops. Haslberger and Kuiper et al give a sampling of unintended effects in transgenic plants that have been detected.[49] They include increased or reduced glycoalkaloid content, impaired

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[47] Kunkel, T. (1985). "The mutational specificity of DNA polymerases α and γ during *in vitro* DNA synthesis," Journal of Biol Chem 260(23): 12866-12874.

[48] ROESSNER, U., LUEDEMANN, A., BRUST, D., FIEHN, O., LINKE, T., WILLMITZER, L. AND FERNIE, A.R. (2001). Metabolic profiling allows comprehensive phenotyping of genetically or environmentally modified plant systems. *The Plant Cell* **13**, 11-29.

[49] HASLBERGER, A.G. (2003). Codex guidelines for GM foods include the analysis of unintended effects. *Nature Biotechnology* **21**(7) , 739-741; KUIPER, H.A.., KLETER, G.A., NOTEBORN, H..P,J.M., KOK, E.J. (2001). Assessment of the food safety issues related to genetically modified foods. *The Plant Journal* **27**(6), 503-528.

carbohydrate transport and adverse tuber tissue perturbations in transgenic potatoes; necrotic lesions in GE wheat; and formation of unexpected carotenoid derivatives in rice engineered to express provitamin A. Yeast engineered with multiple copies of a native gene expressed 3-fold higher levels of phosphofructokinase, resulting in an unexpected 40- to 200-fold increase (depending on the transformation event) in methyglyoxal, a toxin and mutagen.[50] Such unintended effects have also been detected in GE plants after their commercialization (see section III).

Given the data presented above, the FDA's arbitrary exclusion of unintended effects from its "early food safety evaluation" is scientifically indefensible, as is its extremely inadequate evaluation of compositional changes during the premarket voluntary consultation process. Currently, testing for unintended compositional changes in GE crops is mostly limited to measurement of overall lipid, carbohydrate and protein levels, together with targeted measurement of amino acids and a few arbitrarily selected nutrients, anti-nutrients and allergens. Obviously, large numbers of potentially harmful alterations, including novel metabolites, will go undetected. As noted by Kuiper et al (2001), with such limited targeted analysis "unexpected changes are merely identified by chance." Since such changes cannot be predicted to be neutral, beneficial or harmful, rigorous testing is required to identify those that have the potential to cause harm. The urgent need for such testing is highlighted by the dozens of deaths and over 1,000 crippling disabilities in people who contracted eosinophilia myalgia syndrome from consuming a tryptophan food supplement produced in genetically modified bacteria.[51] While other mutagenic plant breeding techniques (e.g. irradiation and chemical mutagenesis) are little used today, their products should also be subjected to increased scrutiny.

2) Hazards related to the novel transgenic protein not properly evaluated

a) <u>Only two endpoints considered, many others ignored:</u>

The FDA considers only the potential of the novel transgenic protein to be toxic or allergenic. Yet proteins can have numerous other effects that require analysis.[52] For instance, proteins can be antinutrients, like avidin, which binds biotin and thus

[50] Inose, T & Murata, K (1995). "Enhanced accumulation of toxic compound in yeast cells having high glycolytic activity: a case study on the safety of genetically engineered yeast," *International Journal of Food Science and Technology* 30: 141-146.

[51] Though never established beyond doubt due to the manufacturer's destruction of the culpable strains, the increased concentration of tryptophan in the GE bacteria (versus the unmodified strains previously used without incident) is thought to have fostered generation of toxic byproduct. For an excellent weighing of the available evidence, see Fagan, J. "Tryptophan Summary," Nov. 1997, http://www.psrast.org/jftrypt.htm.

[52] For a general discussion, see "Mammalian Toxicity Assessment Guidelines for Protein Plant Pesticides," FIFRA Scientific Advisory Panel to the EPA, SAP Report No. 2000-03B, September 28, 2000.

causes vitamin B deficiency. Proteins like lactoferrin have immunomodulatory activity. Proteins like lysozyme and lactoferrin have bactericidal properties in some situations, while lactoferrin actually promotes the growth of certain pathogenic bacteria by supplying them with needed iron in others.[53] Improperly folded proteins are implicated in brain-wasting prion diseases, and are even thought to be the actual infectious agent. Transgenic proteins that differ in subtle respects from the "same" protein in its native version can elicit destructive immune system responses, as is thought to be the case with recombinant human erythropoietin generated in certain E. coli systems, which is implicated in over 100 cases of red blood cell aplasia.[54] Small peptide breakdown products of proteins have been shown to have teratogenic and other effects, as have unusual amino acid analogs. Clearly, the FDA needs to broaden its range of endpoints beyond toxicity and allergenicity[55].

b) Recommended tests inadequate to address the two endpoints considered:
The tests recommended by the FDA in the guidance are ridiculously inadequate even to judge the two endpoints it does consider – allergenicity and toxicity. Proper evaluation of the toxicity and allergenicity of novel transgenic proteins demands much more than a simple *in vitro* digestibility test and a database search for amino acid homology to known allergens and toxins. Toxicity testing requires animal feeding trials, preferably at least a subchronic 90-day feeding trial in a rodent model, with careful examination for gastrointestinal tract damage as well as the typical signs of toxicity. Such transgenic-protein-specific trials should be supplemented with multigenerational trials of rodents fed the whole GE food to test for harmful unintended compositional alterations. Allergenicity testing should include animal studies to determine whether ingested proteins reaches the bloodstream and otherwise follow the decision-tree protocol specified in FAO-WHO 2001.[56]

III. The "early food safety assessment" is unscientific and fosters "regulatory junk science"

[53] Freese et al (2004), op. cit.; Weinberg, E.D. (2001). "Human lactoferrin: a novel therapeutic with broad spectrum potential," *J. Pharmacy & Pharmacology* 53(10), pp. 1303-10. http://munstermom.tripod.com/HumanLactoferrin2001.htm.
[54] Freese, B (2003). "Comments on draft guidance for industry: Drugs, biologics and medical devices derived from bioengineered plants for use in humans and animals," Friends of the Earth, Jan. 2003, pp. 23-25. http://www.foe.org/biopharm/commentsguidance.pdf
[55] See Freese & Schubert (2004), op. cit. and Wilson et al (2004), op. cit. for recommendations.
[56] FAO-WHO (2001). Evaluation of Allergenicity of Genetically Modified Foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, Jan. 22-25, 2001. http://www.fao.org/es/ESN/food/pdf/allergygm.pdf

Section II addressed the inadequacies in the FDA's "early food safety assessment" scheme and the sorts of testing needed in order to detect potentially harmful effects of transgenic proteins or compositional changes in novel genetically engineered foods. In this section, we will address the need to critically evaluate whatever studies are conducted and ensure that they meet accepted standards of scientific practice and integrity. The need for such critical evaluation should be obvious, given the fact that companies with a financial interest in the success of their products normally also conduct the tests to evaluate their safety. If this conflict of interest situation was not clearly perceived before, the recent antidepressant and Vioxx scandals should bring it into sharp focus. As Don Kennedy outlined in a recent *Science* editorial, some of the major shortfalls in the FDA's drug review process are the dependence upon manufacturers to voluntarily submit information, their disregard of advice from expert FDA scientists and outside advisory committees, and the lack of a robust reporting system once a product is released.[57]

These inadequacies in the FDA's drug review process are also present in its handling of GE foods. Only the situation is worse. Here, the chief difficulties are: 1) The GE food review process is voluntary rather than mandatory; 2) The FDA does not have an adequate evidentiary basis to conduct a critical evaluation; 3) As discussed in Section II, premarket testing is woefully inadequate; and 4) There is absolutely no post-marketing surveillance system to catch potential health impacts after release of the crop.

Several specific instances of the weakness of this system are:

1) In several instances, biotech companies have refused to respond to FDA requests for additional information beyond that which they initially submitted. Since their participation in a consultation with the FDA was voluntary, they were under no obligation to do so.[58] In at least one instance, a company seems to have submitted false information regarding the molecular characterization of its transgenic crop, or FDA badly misinterpreted whatever summary data were submitted.[59]

2) Companies have neglected to test for levels of toxins and antinutrients in their GE food crops, or at least to submit such data to regulators:
   a) Examples include the failure of companies to submit data on levels of the antinutrient phytate in GE corn and on several toxicant alkaloids in GE tomatoes.[60]

[57] "Clinical trials and public trust," Science 306: 1649.
[58] Gurian-Sherman, D. (2003). "Holes in the Biotech Safety Net: FDA policy does not assure the safety of genetically engineered foods," Center for Science in the Public Interest, Washington, DC.
[59] Freese & Schubert (2004), op. cit., see section with case study on Bt corn.
[60] Gurian-Sherman, D. (2003), op. cit.

b) Company fails to test for the presence of the pollen-sterilizing toxin barnase in the kernels of GE male-sterile corn.[61]

3) Potentially harmful unintended effects have been completely missed in the consultation process:
   a) Tomatoes genetically engineered with 1-aminocyclopropane-1-carboxylic acid deaminase (ACCase) for delayed ripening were discovered to accumulate higher levels of dangerous heavy metals (e.g. in one event, 5 times more cadmium) than conventional tomato plants; though these particular ACCase tomatoes never underwent FDA's consultation process, very similar ACCase tomatoes passed safety review at the FDA in 1994 without even testing for a similar effect 6 years before academic researchers made this finding;[62]
   b) Corn hybrids derived from 2 transformation events involving the Bt protein Cry1Ab (MON810 and Bt11) exhibited 33-97% higher lignin levels in stem tissue.[63] Lignin is non-digestible, presenting potential animal feed and biodegradation issues, and it is also a product of the shikimic acid pathway in plants, which generates aromatic biomolecules that are constituents of up to 35% of the dry mass of plants, including plant toxins such as rotenone, which has been implicated as a possible cause of Parkinson's disease. This finding was published by academic scientists six years after these two varieties of Bt corn went on the market in 1996 after passing through FDA's voluntary consultation process without detection of this major disruption to normal plant metabolism or any possible related, yet undetected, effects.

4) Potential allergenicity of Bt corn goes undetected by regulators

We will deal in more detail with this example because it involves regulatory breakdown in the very area of allergenicity assessment addressed by this guidance. The Cry1Ab protein present in both MON810 and Bt11 exhibits substantial digestive stability as well as amino acid homology to a known allergen (vitellogenin), both considered suggestive evidence of allergenicity. Yet neither FDA nor EPA acted on these findings.

EPA relied on a Monsanto *in vitro* digestive stability study on Cry1Ab that seemed to demonstrate rapid degradation. Yet EPA ignored other studies in its files that demonstrated Cry1Ab had substantial digestive stability. Comparison of these studies reveals that Monsanto's experiment was conducted under aberrant conditions – an

[61] Freese, B. (2003). "Genetically Engineered Crop Health Impacts Evaluation – GAPS Analysis," Friends of the Earth, Washington, DC. http://www.foe.org/safefood/gapseval.pdf

[62] Gurian-Sherman, D. (2004). "A Look at the Unintended Effects of Genetically Engineering Food Plants Re: the National Academy of Sciences Report on Unintended Effects," The Center for Food Safety, Washington, DC.

[63] SAXENA, D. AND STOTZKY, G. (2001). *Bt* Corn Has a Higher Lignin Content than Non-*Bt* Corn. *American Journal of Botany* **88**(9), 1704-1706.

extremely low pH (1.0) not representative of gut conditions and a huge excess of digestive enzyme (pepsin) relative to Cry1Ab. One or both of these factors likely explain the rapid digestion Monsanto observed, for other tests conducted by academic scientists at pH 2.0 and a smaller excess of pepsin to Cry1Ab revealed up to 60-fold greater digestive stability. Since the latter conditions are closer to (though still harsher than) digestive stability test conditions recommended by international experts (FAO-WHO 2001), the tests by academic scientists indicating digestive stability should have carried more weight than the faulty study conducted by the financially-interested GE crop developer.

FDA research scientist Steven Gendel discovered amino acid sequence homology between Cry1Ab and vitellogenin, an egg-white allergen. EPA ignored this finding in its re-registration of Cry1Ab-generating Bt corn in 2001 even though it had no or very little data on file from either Monsanto or Syngenta. Instead, EPA requested that Monsanto submit its own amino acid homology study, largely without specification of search parameters.

By failing to specify test conditions for corporate testing, or at least subjecting corporate tests to critical scrutiny, the EPA missed two pieces of suggestive evidence indicating Cry1Ab could cause allergies. FDA needs to learn from this experience. The guidance does not specify conditions to be followed for digestive stability or amino acid homology tests, but rather only cites possible guidelines. This gives corporate GE crop developers ample leeway to manipulate test conditions to obtain "desired" results, as Monsanto clearly did in the digestive stability study cited above. Since FDA does not demand methodological information on either test, it will not be able to critically evaluate the results and decide whether they are valid or not.

Thus, the FDA's claim to provide "a scientific framework in which to evaluate the safety of new proteins" is simply not true. Instead, the "early food safety assessment" must be labeled an open invitation to "regulatory junk science." Regulatory junk science is a form of pseudoscience in which an assay or other scientific procedure conducted for regulatory purposes is deliberately designed to achieve a preconceived, "desired" result that assures regulatory approval or non-action concerning an identified or potential hazard. It sometimes involves many iterations of the "same" test with arbitrary manipulation of test conditions each time until the "desired" result is achieved. Such junk science is insidious because it fosters a false sense of confidence concerning the safety of a product, in this case a novel transgenic protein.

IV. The True Purpose and Likely Impacts of this Guidance

Clearly, FDA's guidance has nothing to do with enhancing food safety. In a recent speech,[64] Lester Crawford, acting Commissioner of the FDA, didn't even mention safety as a reason for the guidance, but rather mentioned other, quite different purposes:

> *"The development of this guidance is a high priority for the Administration and the industry, to* ***enhance public confidence, avoid product recalls, and provide an international model*** *to address the presence of low levels of bioengineered plant material in non-bioengineered crop fields." (emphasis added)*

A joint press release[65] from the Biotechnology Industry Organization (BIO) and various grain trade groups explicates Crawford's comments further:

> *"The NGFA, NAEGA, BIO and other groups noted that trace amounts of biotech-enhanced events in commodity crops that have not completed the regulatory review process can result from a plant's natural physiology (pollen flow) or inadvertent mixing during harvest and transportation. But they noted that the U.S. regulatory system imposes a zero tolerance on the presence of such unapproved biotech-enhanced events in food and feed, regardless of the risk level.*
>
> *"This 'zero-tolerance' policy exposes grain handlers, food processors and feed manufacturers to the risk that any presence in general commodity crops of biotech-enhanced events that have not been approved for food and feed under the U.S. regulatory process could render such crops adulterated and subject to seizure under federal law," the groups said. Such risks are even more complex for agricultural exporters, which confront a lag time in biotech approvals by foreign governments, they said. Further, the groups subsequently noted that this policy is inconsistent with other food regulations that have established thresholds for trace amounts of unexpected materials."*

In other words, the risk being addressed by this guidance is not risk to human health, but that of liability to biotech and grain-trading companies for their failure to keep transgenic traits from contaminating conventional or organic crops.

At first glance, providing legal cover to agribusinesses to help them avoid liability for failure to keep their transgenes to themselves may seem like a godsend to farmers, grain handlers and the food industry. It is true that this measure might have the short-term

[64] Lester M. Crawford, Acting Commissioner of the FDA. Speech before The U.S. Vatican Mission's Conference "Feeding A Hungry World: The Moral Imperative Of Biotechnology," September 2004 www.agbioworld.org

[65] "US Grain Industry, BIO Urge US Government to Expedite 'Trace-Amounts' Policy for Biotech Products," press release, Biotechnology Industry Organization & National Grain & Feed Association, and other trade groups, April 7, 2004, www.bio.org/newsroom/newsitem.asp?id=2004_0407_01.

effect of freeing food chain players from certain liabilities they now face with a de facto zero tolerance standard for experimental GE traits. However, in the longer term this measure would increase contamination, harm organic farmers and the organic food sector as a whole, replace strict legal liability with still greater market-based liability, trigger large food & grain export losses, exacerbate already strained agricultural trade relationships with importing countries, and ultimately undermine confidence in the safety and wholesomeness of the American food supply both domestically and internationally.

The most immediate effect of legalizing contamination will be to substantially decrease the incentive of biotech companies and their contract farmers to adhere to gene containment protocols, which in some cases are even now viewed as cumbersome and unnecessary "red tape." In 2001, former ProdiGene-Stauffer CEO Anthony Laos, speaking of the then-prevailing isolation distances for corn engineered to produce enzymes and pharmaceuticals "of 660' for industrial enzymes and 1320' for pharmaceutical products," told farmers: "We will be dealing with these distances until we can gain regulatory approval to lessen or abandon these requirements altogether."[66] Scott Deeter of Ventria Bioscience has already spoken of reducing the fallow period following cultivation of its pharmaceutical rice from two years to one year, presumably to reduce costs,[67] even though this increases the likelihood of volunteer pharm rice contaminating conventional cultivars. By easing the liability enforced by the zero tolerance standard for experimental traits, FDA will encourage Mr. Deeter and others in his position to cut corners still further, which will likely result in an increase in "adventitious presence" well beyond present levels and frequencies.

Organic farmers and the organic farming sector as a whole will likely be damaged by legalizing contamination. Heirloom seed corn grower Laura Krouse has already lost 50-75% of her business selling seeds to organic farmers thanks to Bt trait contamination, despite efforts to temporally isolate her crop.[68] As a result of contamination by herbicide resistance traits, the Canadian organic canola industry has been basically destroyed, eliminating the opportunity for Canadian growers to capture the 100% price premium offered for organic canola.[69] Canadian organic farmers have filed a class action lawsuit against the purveyors of herbicide-resistant canola, Monsanto and Bayer, to recoup $14 million in organic premiums already lost due to near universal

[66] Stauffer Letter (2001). Letter from Anthony Laos to Customers, Summer 2001, formerly available at www.staufferseeds.com.
[67] See transcript of Scott Deeter's presentation at the 6/17/03 meeting of the USDA AC21 [an ag biotech advisory committee], www.usda.gov/agencies/biotech/ac21/meetings/mtg_june03/jun17ac21v1.txt.
[68] Lucas, M. (2001). "Seed producer fears biotech corn may contaminate genes," *Cedar Rapids Gazette*, 1/29/01; personal communication.
[69] Smyth et al (2002). "Liabilities and economics of transgenic crops," Nature Biotechnology, Vol. 20, June 2002, p. 539.

contamination of Canadian canola with HR traits.[70] The increased contamination entailed by abandonment of the zero-tolerance standard for experimental traits will further damage the interests of organic farmers. Food companies looking to capitalize on the booming market in organic food products would find it increasingly difficult to find domestic sources of corn, wheat, soybeans, rice and other major food crops that are free of both commercial and experimental GE traits. This may force them to find supplies overseas at increased cost.

Conventional farmers could also suffer severe economic harm. For example, food companies that specifically contract for GE-free supplies may sue for breach of contract if the supplies prove to have experimental GE content, whether or not that content is officially judged to be "adventitious," and whether or not the FDA has issued a letter indicating "no questions" about the safety of the transgenic protein in an experimental GE crop.

Export markets that already reject many GE crops that are deregulated in the U.S. will take a still dimmer view of shipments contaminated with experimental traits – again, irrespective of the label the USDA chooses for this "legalized contamination." The result is likely to be still greater agricultural export losses. European and Japanese regulatory authorities will almost certainly reject anything less than a zero-tolerance standard for these GE traits. Most importantly, **the complete lack of a science-based justification for this "adventitious presence" policy (as detailed above) ensures that the U.S. government will not succeed in having this policy accepted by international standard-setting agencies such as *Codex Alimentarius.***

The perception that the U.S. government is doing the bidding of the Biotechnology Industry Organization (BIO) and associated groups will not help its cause:

> *The NGFA, NAEGA, BIO and other organizations said that once such a policy is established,* ***the U.S. government "must vigorously promote global adoption" of compatible regulatory systems*** *that meet the same standards for being science-based and transparent. "A U.S. policy on adventitious presence is a key element in a much-needed comprehensive and harmonized global approval system for regulation of agricultural products of modern biotechnology," the groups said* (emphasis added).[71]

[70] Lyons, M. (2002). "Organic farmers seeking class action," The Leader-Post (Regina), 12/21/02.
[71] "U.S. Grain Industry, BIO Urge U.S. Government to Expedite 'Trace-Amounts' Policy for Biotech Products," Biotechnology Industry Organization (BIO) press release, April 7, 2004. http://www.bio.org/newsroom/newsitem.asp?id=2004_0407_01

Beyond export losses, there is little doubt that attempts to foist this unscientific policy on European countries and other nations would further damage already strained agricultural trade relationships. Particularly puzzling is the failure of the U.S. government to understand how legalizing contamination of grain, food, feed and seed with experimental GE traits will harm its prospects in the current WTO case against Europe on traceability and labeling standards.

Finally, and most importantly, U.S. food companies, millers, grain traders and other food chain players should clearly understand that this policy carries the grave risk of undermining, perhaps irreparably, confidence in the safety and wholesomeness of the American food supply. It is difficult to place a dollar figure on such confidence – perhaps because it is priceless.

APPENDIX 1

TRANSGENIC CONTAMINATION EPISODES[72]

The following are just a few of the dozens of incidents in which contamination from GM crops caused seed or product recalls, and/or other problems for farmers and consumers.

May 1997 — Monsanto is forced to recall 60,000 bags of canola seed when it discovers the seed contains unapproved gene-altered DNA, due to contamination from a planting error by a seed producer.

December 1997 — Unapproved GMO sugar beet from a Monsanto test field is sent to a sugar refiner, where it contaminates natural sugar sold for animal feed.

September 2000 — Over 300 food products were recalled due to contamination by a GMO corn (StarLink, produced by Aventis CropScience), not approved for human food. Experts estimated that half of the state's corn – about 1 billion bushels – could be contaminated. Exports of corn to Japan decreased by 44% in one year. StarLink contamination is still being discovered in US corn shipments three years later.

May 2000 — Nearly 15,000 acres of farmland in five European countries are contaminated with unapproved GMO canola when pollen from the unapproved variety blows into a non-GMO seed producers' field. In addition, French authorities reveal that unapproved GMO seeds have contaminated nearly 10,000 acres of corn planted there.

April 2001 — Just months after the StarLink fiasco, Monsanto is forced to recall thousands of bags of canola seed contaminated with a GMO variety not approved for sale to Canada's major export markets. Incineration is planned for over 10,000 acres of fields already planted with the unapproved crop.

July 2001 – Austrian authorities order thousands of acres of corn destroyed when tests show contamination of non-GMO seed by two unapproved GMO corn varieties.

Sept 2001 – Scientists were surprised to discover GM crop material in wild maize in Oaxaca, Mexico despite the country's moratorium on GM crop cultivation, in effect since 1998. It is thought that GM maize seed in food aid shipments from the US was saved and planted.

April 2002 — Corn grown in Argentina and sold as corn flour in Europe is discovered contaminated with a GMO variety that is not approved for planting in Argentina or for human consumption in Europe.

September 2002 — A pharmaceutical corn, produced by ProdiGene, contaminates corn and soybean fields in Iowa and Nebraska. 155 acres of corn is destroyed and $3 million worth of soybeans are quarantined at the elevator and destroyed.

April 2002 — Corn grown in Argentina and sold as corn flour in Europe is discovered contaminated with a GE variety that is not approved for planting in Argentina or for human consumption in Europe.

[72] Based on: BRIEFING ON THE PROPOSED PROTOCOL FOR PHARMACEUTICAL RICE, Attachment 2, Submitted to the AB2622 Advisory Board of the California Rice Commission, March 5, 2004, Prepared by Californians for GE-Free Agriculture

May 2003 — Tests show that biotech crops have contaminated wheat grown in the US, even though GMO wheat is not approved for marketing. Grain industry experts warn that approving GMO wheat could mean the end of US exports to Europe and Asia.

July 2003 — Over 100 farmers in Italy discover that the non-GMO corn seed they planted was contaminated with an unapproved GMO variety.

December 2003 — UC Davis researchers discover that, for seven years, they had been mistakenly distributing for research purposes GMO tomato seed in place of a conventional variety.