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Dear Administrator Johnson, Acting Commissioner Crawford, and Secretary Johanns,

On March 22, 2005, the scientific journal *Nature* revealed that the Environmental Protection Agency (EPA), Food and Drug Administration (FDA) and United States Department of Agriculture (USDA) were investigating the distribution by Syngenta Seeds, Inc. of several hundred tons of a variety of genetically engineered corn known as Bt10 from 2001 to 2004.¹ Bt10 contains a Plant Incorporated Protectant (PIP) that has not been registered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), rendering any distribution of or commerce in Bt10 corn illegal. The revelation of this incident only after your agencies had been aware of

¹ Macilwain, C., "U.S. Launches Probe Into Sales of Unapproved Transgenic Corn," *Nature*, March 22, 2005.

Syngenta's wrong-doing for four months is deplorable, and has undermined both consumer and international confidence in U.S. regulatory oversight of agricultural biotechnology products. Unless or until the EPA and FDA subject Bt10 to formal assessments consistent with FIFRA and FFDCA implementing regulations, and make the safety data and detailed agency safety assessments public, the undersigned request that the EPA move to prevent any adverse effects on human health or the environment by taking immediate actions to identify and restrict the use of any and all products containing Bt10 in commerce as allowed under its authority found at 7 U.S.C. §136a and 136k. We also request that FDA take similar recall actions for any food products containing Bt10, as outlined in its regulations found at 21 C.F.R. Part 7, unless or until the Syngenta product has completed the agency's voluntary consultation process. USDA should identify and remove Bt10-contaminated seed lines from the corn seed supply.

A. Inadequate Agency Response

To date, the agencies' public statements that Bt10 poses no human health or environmental threat are unsupportable.^{2,3,4} Neither agency has performed the risk assessments of Syngenta's Bt10 corn consistent with the regulatory procedures previously applied to commercialized genetically engineered crops, nor made public the documentation to substantiate any *ad hoc* assessments cited in press statements. Indeed, current reports do not indicate that EPA or FDA has even requested that Syngenta submit data to complete full assessments. Not only do such agency actions represent arbitrary and capricious regulatory behavior, the negligent *ad hoc* safety pronouncements by the agencies have served to remove the determinations from critical scrutiny. As you know, during EPA PIP registration safety data are typically made public and available for comment, and the FDA at least makes its voluntary consultation reviews public. Without a full and transparent risk assessment, the American public and our trading partners cannot have confidence in the safety of Bt10. Moreover, vague assurances that Bt10 is safe are not sufficient and give the appearance that the agencies are more interested in shielding Syngenta from the ramifications of its negligence than ensuring the safety of our food and feed supply.

More specifically, the safety rationale thus far given by the agencies is insufficient. For example, the purported limited acreage planted to Bt10 is not a reasonable justification for not disclosing in detail the supporting data used by both agencies during its decision processes. Even the EPA's Experimental Use Permits (EUP) for genetically engineered crops have been considered to be of regional or national importance by the agency, and on that basis the data are summarized in the Federal Register and made available for public comment. This is despite the fact that EUPs are typically much smaller than the area purported to be planted to Bt10, and are usually carried out for a shorter duration, often for only one year rather than several years as for Bt10.

² EPA Email communication from Enesta Jones, EPA press office, dated March 21, 2005, "EPA's statement on Bt10"

³ U.S. Environmental Protection Agency's Statement on Bt10, April 27, 2005, http://www.epa.gov/pesticides/biopesticides/pips/bt10_statement.htm

⁴ U.S. Food and Drug Administration's Statement on Bt10, April 27, 2005, <http://www.cfsan.fda.gov/%7Elrd/biobt10.html>

It is also uncertain whether Bt10 has been completely removed from the food supply or the corn seed supply, despite claims to this effect by Syngenta. There has been no public discussion about the details of how the contamination occurred, and whether the seed supply of other varieties, such as Bt11, may have been contaminated by Bt10. Indeed, the fact that Bt10 was mislabeled as Bt11 and sold under the name of this commercialized variety suggests the possibility of widespread contamination. Even after a huge effort in money and other resources to remove StarLink from the food supply, it continued to be reported at least as recently as late 2003 in the US⁵ and this year in corn shipped to Guatemala,⁶ years after contamination was first identified. A recent report by the Union of Concerned Scientists also demonstrates that most supposedly non-genetically engineered varieties of corn, canola, and soybean certified seed stocks are contaminated with GE varieties.⁷ Of particular relevance to the Bt10 situation is the unexpectedly widespread prevalence of Cry9C found in the corn seed supply in 2001. Of 288 seed companies that were never licensed by Aventis to grow StarLink, USDA found that some seed lines of at least 63 of the companies, or nearly one-quarter of the total tested, contained the Cry9C protein.⁸ This at least suggests the possibility that Bt10 and its PIP remain undetected in corn seed being sold to farmers. These events and others demonstrate that contamination occurs readily, and without a thorough assessment that includes extensive testing of other corn varieties, assurances that Bt10 is not still being grown cannot be considered reliable. In the absence of such an ongoing and extensive assessment of other varieties of corn, both conventional and transgenic, it cannot be assumed that public and environmental exposure to Bt10 corn will not continue. Even with extensive testing, exposure to Bt10 may continue, and therefore a thorough human health and environmental risk assessment must be carried out and made public. Seed companies that unwittingly sell Bt10 seed mislabeled as Bt11 or another commercialized variety could be subject to liability for commerce in an unregistered pesticide. Food companies or farmers whose products or produce are contaminated with Bt10 could suffer economic harm from market rejection or lost sales.

B. Unsupported EPA Determination of Safety

To date, public statements indicate that EPA's safety pronouncements concerning Bt10 have been based upon the assumed equivalence of Bt10's Cry1Ab protein to that found in Bt11. The EPA maintains that "the existing food safety clearance for Bt11 applies to Bt10,"⁹ or in other words that Bt10's unregistered PIP falls under the prior tolerance exemptions granted for the registered Cry1Ab genes and proteins found in several commercialized Bt corn varieties (40 CFR 180.1173). Such an interpretation is legally indefensible for several reasons. First, FFDCA tolerances and tolerance exemptions are clearly meant to apply only to FIFRA-registered pesticides. If this were not the case, individuals or companies could completely circumvent FIFRA registration and *legally* introduce an unregistered pesticide into the food supply (subject

⁵ Jacobs, P, "Traces of genetically-modified corn still showing in product supply," December 1, 2003, San Jose Mercury News, CA

⁶ See: http://www.humboldt.org.ni/transgenicos/denuncia_english.htm

⁷ Union of Concerned Scientists, 2004, "Gone to Seed: Transgenic Contaminants in the Traditional Seed Supply," UCS Publications, Cambridge, MA

⁸ "USDA purchases Cry9C affected corn seed from seed companies," USDA press release 0101.01, June 15, 2001.

⁹ EPA's Statement on Bt 10, Enesta Jones, Press Officer, EPA, March 22, 2005

to enforcement action only for *sale* of the pesticide) if that pesticide is claimed to fall under an existing tolerance. Yet it is precisely the characterization and safety assessment mandated for FIFRA registration that are required in order to determine whether a new pesticide such as Bt10's PIP in fact falls under an existing tolerance. EPA's proposed course of action with Bt10's PIP would effectively set an unacceptable precedent whereby *ad hoc* Agency safety assessments (reported via press release) are accepted in lieu of the FIFRA registration process as the basis of tolerance decisions. Secondly, EPA's past practice with PIPs based on the "same" insecticidal protein has been to assess and register each one separately, even when generated in the same plant and grouped under the same tolerance exemption. This is in fact the case with the differing versions of Cry1Ab-based PIPs in Event 176, MON810 and Bt11. Separate product characterization, human health and environmental assessments were collected for each. Each has a distinct EPA registration number and OPP Chemical Code number.¹⁰

The EPA's proposed course of action is also scientifically unsupportable. One cannot assume the identity of the Bt10 version of Cry1Ab and that of the approved Cry1Ab in Bt11 without a thorough characterization of the transgene and protein. Although this characterization should include the full transgene or transgenic protein sequence from Bt10 corn (not just the sequence prior to transformation), EPA and FDA's characterization typically require at least Southern blot data, SDS-PAGE, Western blot or ELISA for immunogenicity, post-translational modification data, bioassays, gastric stability, and often the sequence of the N-terminal portion of the transgenic protein. It is possible that the Bt10 transgene has been altered, truncated and/or fused with corn DNA during transformation, as has been reported for other transgenes, and such changes may have risk implications, such as altering the stability of the protein. For instance, only 70% of the intended full-length Cry1Ab protoxin sequence was incorporated in MON810 due to rupture of the plasmid during transformation, resulting in fusion of the truncated Cry1Ab with corn DNA and generation of a putative 92 kD fusion protein whose properties remain uncharacterized to this day.¹¹ Another example, intentional in this case, is a single amino acid change in StarLink corn's Cry9C, which was reported to be responsible for making it more resistant to degradation by the digestive enzyme trypsin.¹² Digestive stability is widely regarded as a characteristic of food allergens. It is unlikely that a tolerance exemption for Cry1Ab from another Bt corn variety would be adequate to cover the Cry protein in Bt10 if the sequence of the latter had been altered in a manner that affects function in some meaningful way. In sum, without the proper characterization of the transgene and human health assessment of its expression product in Bt10, the safety of the protein and hence its grouping under the existing tolerance exemption for Cry1Ab cannot be assumed. Recent statements by EPA that the sequence of Cry1Ab from Bt10 and Bt11 events are identical need to be followed by making public those sequences and analyses.

Indeed, the basis for the overly broad tolerance exemption for Cry1Ab in 40 C.F.R. §180.1173 apparently being used to make *ad hoc* safety determinations on Bt10's PIP should be

¹⁰ Biopesticides Registration Action Document, Office of Pesticides Programs, US EPA, Oct. 15, 2001.

¹¹ Levine et al, 1995. "Molecular characterization of insect protected corn line MON 810. Unpublished study submitted to the EPA by Monsanto, EPA BRAD No. 436655-01C; Freese, W and Schubert, D, 2004. "Safety testing and regulation of genetically engineered foods," *Biotechnology and Genetic Engineering Reviews*, 21: 299-323.

¹² Lambert B et al, 1996, A *Bacillus thuringiensis* crystal protein with high activity against members of the family noctuidae, *Applied Environ. Microbiol.*, 62(1):80-86

reconsidered as a whole on several counts. First, this single tolerance exemption improperly covers biochemically distinct proteins with distinct properties that, as indicated above, may pose different risks. EPA's separate review and separate FIFRA registration of each Cry1Ab-based PIP in Event 176, MON810 and Bt11 is an implicit admission of this fact. Secondly, as currently written, the tolerance covers Cry1Ab in "all plant raw agricultural commodities," suggesting that *any* version of Cry1Ab in *any* crop transformed to generate it is covered. However, the food matrix may have a substantial influence on the stability of a protein to digestion, and therefore a broad tolerance exemption should not be granted without considering this issue. For example, although purified IGH-1 (insulin-like growth hormone) is rapidly digested, when consumed in milk, it is protected from digestion to a considerable extent by the milk protein casein.¹³ Finally, some of the undersigned have previously submitted comments¹⁴ – as yet with no response from the Agency – disputing the validity of the 2001 re-registration of Cry1Ab-based PIPs for failure to consider, as claimed in the EPA's most recent statement on Bt10,¹⁵ "all of the existing data, public literature and public comments."

C. EPA Environmental Issues

Moreover, the existing tolerance exemption, even if it was shown to apply to Bt10, does not address environmental issues under FIFRA. In particular, expression of the Cry protein in different tissues and under different environmental conditions may not be the same as in other Bt corn varieties containing Cry1Ab genes. The promoter used with Bt10 has not been disclosed, and would be expected to alter expression levels in various corn tissues, at different crop development stages, and under different environmental conditions compared to Bt11's PIP. Position effects that depend on the unique insertion location of each transformation event may also affect expression levels and patterns. Recent comments by EPA that expression of Cry1Ab is less than 1 ng/mg do not specify the tissue in which this measurement was made, or address differences in expression in different tissues or under different environmental conditions.¹⁶

In particular, high levels of expression in pollen may have detrimental environmental effects. Although the levels of expression of Cry1Ab in Bt11 and MON810 in corn pollen were relatively low, and field data suggest that mortality of monarch butterflies is unlikely to be increased by those varieties, the same experiments showed that pollen from Bt event 176 had much higher levels of Cry1Ab, and could cause increased mortality or reduced growth of monarch and swallowtail butterflies, respectively, in some parts of the country (especially the northern plains).^{17 18} On the other hand, low expression levels (as suggested by the 1 ng/mg figure) could mean that Bt10's PIP is not efficacious at killing pests, raising both misbranding

¹³ Kimura T, et al., 1997, Gastrointestinal absorption of recombinant human insulin-like growth factor-1 in rats, *J. Pharmacol Experiment. Therapeut.*, 283(2): 611-618

¹⁴ For instance, see: Freese, B, 2001. "A critique of the EPA's decision reregister *Bt* crops and an examination of the potential allergenicity of *Bt* proteins," Friends of the Earth submission to the EPA, OPP Docket No. OOP-00678B, Dec. 9, 2001. www.foe.org/safefood/comments.pdf.

¹⁵ U.S. Environmental Protection Agency's Statement on Bt10, April 27, 2005, op. cit.

¹⁶ U.S. Environmental Protection Agency's Statement on Bt10, April 27, 2005, op. cit.

¹⁷ Stanley-Horn D et al., 2001, Assessing the impact of cry1Ab-expressing corn pollen on monarch butterfly larvae in field studies, *Proc. Natl. Acad. Sci. USA*, 98(21): 11931-11936

¹⁸ Zangerl AR et al., 2001, Effects of exposure to event 176 *Bacillus thuringiensis* corn pollen on monarch and black swallowtail caterpillars under field conditions, *Proc. Natl. Acad. Sci. USA*, 98(21): 11908-11912

and insect resistance managements issues. This illustrates the importance of performing a thorough environmental assessment of Bt10, rather than an *ad hoc* environmental safety assessment, to justify the continued planting which may be occurring if the corn seed supply has been contaminated.

D. Inadequate Assessment of the Ampicillin Gene

In addition to risks from the Cry1Ab gene and protein, risks from the ampicillin (*amp*) gene need to be thoroughly considered. The primary risk from this gene is transfer directly to disease-causing bacteria, or to resident intestinal bacteria, with subsequent transfer to disease bacteria (which can often occur at relatively high rates). FDA performed a risk assessment for the kanamycin gene in the early 1990s, and EPA considered to risks from horizontal gene transfer during its Bt reassessment in 2000-2001. However, data produced since that time have called into question these earlier safety assessments.

Early published studies concluded that horizontal gene transfer (HGT) rates were undetectably low, while newer data shows that transfer can occur at much higher levels if genetic material from bacteria is present with the resistance gene in the plant.¹⁹ It is common for such genetic material to be present along with the genes of interest in transgenic plants, but this was not adequately considered in previous assessments by the agencies. In addition, a recent paper shows that HGT occurred between transgenic crops and human gut bacteria.²⁰ Furthermore, the EU finds the ampicillin gene to be of concern, and recommends that this gene be restricted to field trial use only.²¹ Use of the *amp* gene is inconsistent with Codex Guidelines on antibiotic markers.²² FDA and EPA need to reconsider the possibility of HGT for the particular DNA in Bt10, and the risks of antibiotic-resistant bacteria if that occurs.

E. Failure to Address Unintended Effects

Finally, the agencies' failure to complete rigorous scientific assessments of Bt10 overlook possible unintended affects associated with the crop. Unintended harmful changes that may occur in genetically engineered plants have been assessed by FDA for previous crops introduced to the food supply. This assessment has been a major component of FDA's safety review of genetically engineered crops and previous assertions of safety. According to FDA staff (personal communication from Dr. Eric Flamm, FDA, to Doug Gurian-Sherman, March 23, 2005), however, a genetically engineered crop consultation was never performed for Bt10. These assessments of unintended effects typically measure a number of crop substances and

¹⁹ Bensasson D et al., 2004, Genes without frontiers? Lawrence Berkeley National laboratory Publication number 53614

²⁰ Netherwood T. et al., 2004, Assessing the survival of transgenic plant DNA in the human gastrointestinal tract, Nature Biotechnology 22(2):204-209

²¹ Opinion of the Scientific Panel on Genetically Modified Organisms on the use of antibiotic resistance genes as marker genes in genetically in genetically modified plants, The EFSA Journal, 2004, 48: 1-18

²² Codex Principles and Guidelines on Foods Derived from Biotechnology, , Section 55, "Alternative transformation technologies that do not result in antibiotic resistance marker genes in foods should be used in the future development of recombinant-DNA plants, where such technologies are available and demonstrated to be safe." <ftp://ftp.fao.org/codex/standard/en/CodexTextsBiotechFoods.pdf>

traits to determine whether they have been significantly altered by genetic engineering. Included in these analyses are nutrients produced by the crop, levels of compounds such as fatty acids and amino acids, and levels of potentially harmful toxicants, anti-nutrients and allergens. Assurances of the safety of Bt10 are incomplete without such assessments. Recently, the National Academy of Sciences reaffirmed that FDA's assessment of unintended effects for genetically engineered crops is important.²³

FDA assertions that unintended effects are unimportant because the amount of Bt10 in the food supply is low needs to be backed by a formal, careful, and public analysis of exposure to those amounts, including exposure from possible continuing contamination, and an analysis of possible unintended changes in Bt10 corn. Such a course of action is consistent with the FDA's latest and best thinking on this subject. The agency's proposed rule on Premarket Notice Concerning Bioengineered Foods explicitly acknowledges the need for event-specific analysis for unintended effects even when a crop engineered with the same gene has previously been found to be unobjectionable, and makes special reference to the need for event-specific analysis of crops engineered to generate pesticidal proteins.²⁴ Thus, the agency's *ad hoc* dismissal of Bt10-associated food safety concerns based on the unsubstantiated assumption that Bt10 "makes up a small part of the total food or feed supply"²⁵ is unacceptable.

Conclusions

Whether or not exposure to Bt10 is safe for human health and the environment can only be determined by a thorough risk assessment. Until such assessments are complete and made public, the Federal government should not stand idly by and allow continuing contamination of the food and feed supply by unapproved genetically engineered crop varieties.

In addition to the immediate safety concerns associated with Bt10, perhaps a bigger issue is the integrity of the U.S. regulatory process. Transparency at EPA has been generally commendable, with data and reasoning behind regulatory decisions made public. Although FDA has regrettably not been as transparent concerning safety data, at least its voluntary consultations on genetically engineered crops have been made public. Neither has occurred with Bt10. Transparency for a controversial technology is essential for public confidence, especially when a clear error in the regulatory system has occurred, as with Bt10. Especially in such situations, transparency and scientific rigor, and proper procedures are needed to reassure the public. Unless FDA and EPA come into the light of the public square promptly with a full disclosure of

²³ National Research Council, 2004, "Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects," The National Academies Press, Washington, DC

²⁴ "Because some rDNA-induced unintended changes are specific to a transformational event (e.g., those resulting from insertional mutagenesis), FDA believes that it needs to be provided with information about foods from all separate transformational events, even when the agency has been provided with information about foods from rDNA-modified plants with the same intended new trait and has had no questions about such foods. ***Similarly, the agency believes that it needs to be provided with information about foods from rDNA-modified plants whose intended change is the introduction of a pesticidal protein subject to oversight by the Environmental Protection Agency (EPA) rather than by FDA, because the transformational event that is used to introduce the pesticidal trait may also cause unintended changes to the food that would raise adulteration or misbranding questions subject to FDA jurisdiction***" (emphasis added), *Federal Register*, Vol 66, No. 12, January 18, 2001.

²⁵ U.S. Food and Drug Administration's Statement on Bt10, April 27, 2005, <http://www.cfsan.fda.gov/%7Elrd/biobt10.html>

safety data and analysis for Bt10, require additional data to conform to usual safety assessments for genetically engineered crops, and thoroughly assess the extent of contamination for harvested corn and the seed supply, further erosion of public confidence in genetically engineered crops, both in the U.S. and abroad, will be the likely result.

Accordingly, we request that the agencies immediately take the following steps:

- 1) Disclose all available information relating to where and how much Bt10 is known to have been planted and distributed, both domestically and overseas;
- 2) Implement a testing program to test for the presence of Bt10 in grain, food products and seed stocks (particularly Bt11 seed stocks) to establish its prevalence in the food chain;
- 3) Unless or until Bt10's PIP successfully completes a formal FIFRA registration process, remove any goods contaminated with Bt10 from the food chain; and
- 4) Make publicly available any scientific documentation on Bt10 and its PIP, including product characterization data and any formal or informal U.S. government safety assessments of the same;

We also recommend the following general improvements to U.S. regulation of genetically engineered foods to better protect public health, the environment and the economic interests of farmers and food companies:

- 5) Establish mandatory and scientifically-based pre-market safety testing of genetically engineered foods;
- 6) Institute traceability regulations and mandatory labeling of foods specifying ingredients derived from genetically engineered crops in order to permit consumer choice and allow any human health or environmental impacts caused by such crops or foods to be traced back to their source; and
- 7) Establish clear rules assigning liability to developers of genetically engineered crops for any harms (whether human health, environmental or economic) caused by those crops.

We would be happy to discuss any of these concerns or recommendations with you at your convenience.

Sincerely,

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