



United States
Department of
Agriculture

Animal and
Plant Health
Inspection
Service

Biotechnology
Regulatory
Services

4700 River Road
Riverdale, MD
20737

March 08, 2012

Gary W. Rudgers, Ph.D.
Global Regulatory Leader - New Ventures
Dow AgroScience LLC
9330 Zionsville Road
Indianapolis, IN 46268

Re: APHIS review as to whether plant varieties created using zinc-finger nucleases techniques for targeted gene deletion are regulated by APHIS.

Dear Dr. Rudgers:

This is a follow-up letter to our previous letter of May 26, 2010. In that letter, APHIS confirmed that, as described by Dow during a March 18, 2010 presentation and an article by Shukla et al. (2009), Dow's ZFN-12 maize plants, which contain deletions at the IPK1 gene due to the use of zinc-finger nuclease technology, were not considered regulated articles. Since the time of the May 2010 letter, APHIS has received and answered other inquiries about the regulatory status of plant varieties created using targeted gene deletion nuclease technologies. Therefore, here, we provide you with our assessment of the regulatory status of plants containing targeted deletions made using zinc-finger nuclease technology.

APHIS regulations for genetically engineered organisms are codified at 7 CFR part 340, "Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason To Believe Are Plant Pests." Under the provisions of these regulations at §340.1, a genetically engineered (GE) organism is deemed a regulated article if it has been genetically engineered from a donor organism, recipient organism, or vector or vector agent listed in §340.2, and the listed organism meets the definition of "plant pest" or is an unclassified organism and/or an organism whose classification is unknown, or if the Administrator determines that the GE organism is a plant pest or has reason to believe it is a plant pest.

GE plants containing targeted deletions, caused by naturally-occurring DNA repair after the targeted break is made by zinc-finger nucleases, and in which no genetic material is inserted into the plant genome, are not regulated articles under CFR part 340. The nucleases used are not from a plant pest and no plant pest sequences are inserted into the plant genome using this technology. There is also no reason for the Agency to believe that changes to the plant genome generated by the deletion process would generate a plant pest, as long as no DNA is inserted into the plant genome during the deletion process. However, if the engineered plant is already a plant pest (i.e., parasitic plant), or if the given nuclease is delivered into the plant using a plant pest, the engineered plant would be regulated under 7 CFR 340.



Safeguarding American Agriculture
APHIS is an agency of USDA's Marketing and Regulatory Programs

An Equal Opportunity Provider and Employer

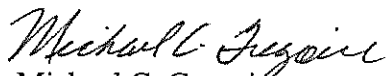
Gary W. Rudgers, Ph.D.

Page 2

Zinc-finger nuclease techniques may also be used to create base-pair substitutions or insertion of genetic material into a plant genome. The Agency will consider case-by-case inquiries regarding the regulatory status of plants produced by these zinc-finger nuclease methods. Please be advised that the accidental release of a regulated article may be a violation of our regulations.

Further, please be advised that genetically engineered plants using zinc-finger nuclease techniques may still be subject to other applicable regulatory authorities such as EPA and FDA.

Sincerely,



Michael C. Gregoire
Deputy Administrator
Biotechnology Regulatory Services

References

Shukla, V.K., Y. Doyon, J. C. Miller, R. C. DeKolver, E. A. Moehle, S. E. Worden, J. C. Mitchell, N. L. Arnold, S. Gopalan, X. Meng, V. M. Choi, J. M. Rock, Y.-Y. Wu, G. E. Katibah, G. Zhifang, D. McCaskill, M. A. Simpson, B. Blakeslee, S. A. Greenwalt, H. J. Butler, S. J. Hinkley, L. Zhang, E. J. Rebar, P. D. Gregory & F. D. Urnov. 2009. Precise genome modification in the crop species *Zea mays* using zinc-finger nucleases. *Nature* 459, 437-441 (21 May 2009). doi:10.1038/nature07992