

EXECUTIVE DIRECTOR

02 MAR. 2012

Parma,  
Ref. CGL/PB/EW/NP/shv (2012) **6277344**Ms Paola Testori Coggi  
Director-General  
Health and Consumers  
Directorate-General  
European Commission  
B-1049 Brussels**Subject: EFSA – Request of support related to the parliamentary question E-11817/11**

Dear Ms Testori Coggi,

*Dear Paola,*

In response to your letter (Ref. SANCO/E1/TB/mm ARES (2011) 1502908) requesting EFSA to review the findings of the study of Zhang et al. 2012 in Cell Research and to consider the significance of their findings for the safety assessment of GM food and feed, EFSA informed the GMO Panel and requested its molecular characterisation working group to carefully analyse the article.

Please find enclosed the analysis performed by the molecular characterisation working group of the EFSA GMO Panel which concluded that this is a first study of its kind and, whilst interesting, needs to be confirmed before its implications can be further evaluated. This issue of miRNAs might be of general importance for food/feed impact on health. In addition, the working group acknowledges that, GM plants in which changes in gene expression are targeted using miRNA will need to be risk assessed taking into account further developments in this area. It should be noted that no such applications have been received by EFSA.

Furthermore, given the novelty of the topic and the potential impact of these findings on other domains within the remit of EFSA, EFSA will bring the publication to the attention of its Scientific Committee and might identify the need to address this issue on a broader level.

Yours sincerely,



Catherine Geslain-Lanéelle

Cc: Ms André, Mr Miko, Mr Poudelet, Mr Vanhoorde, Mr Walsh, Ms Pelsser – DG SANCO  
Mr Detken, Mr Wolff, Mr Liem, Ms Schoonjans, Ms Waigmann, Mr Bergman, Ms Podevin –  
EFSA

**Annex: Analysis of the molecular characterisation working group of the EFSA GMO Panel**

**Annex: Review of Zhang et al. 2012 (Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Research, 12, 107-126) by the molecular characterisation working group of the EFSA GMO Panel during its 16 February meeting**

The paper of Zhang et al. (2012) reported that 5% of the microRNAs (miRNAs) in tested human and calf sera are of plant origin and in this particular study are probably derived from rice and green rich fodder which were major components of the diet. Plant miRNAs were detected in serum, plasma and in various tissues, including liver, small intestine and lung. Compared to endogenous mammalian miRNAs known to be stably present in animal serum, these plant miRNAs were relatively low in concentration. The paper analysed in detail one miRNA (miR168a), which was one of the two most abundant plant miRNAs in the sera of Chinese test persons. The miRNA168 is well studied in plants and regulates *AGO1* mRNA levels. This miRNA168a has sequence complementarity with the mammalian *LDLRAP1* (low Density Lipoprotein Receptor Adaptor Protein 1) mRNA. Zhang et al. (2012) reported that the level of LDLRAP1 protein decreased in mice fed rice compared to those fed chow. Similar effects were observed with animal miRNA supplied in the mouse diet indicating that this effect is not specific to plant miRNAs. Zhang and co-authors (2012) concluded that a plant and animal miRNA acquired through food intake can influence gene expression in mammals. This paper does not specifically address the issue of impact on human and animal health.

This is a first study of its kind and, whilst interesting, needs to be confirmed before its implications can be further evaluated. Furthermore, the data provided in the corrigendum indicate that care should be taken in the interpretation of the data on the levels of LDLRAP1 protein in conjunction with the plant miRNA.

These results raise the question whether food-derived miRNAs could play an active role in human/animal health and this question is valid for both plant and animal miRNAs. It is likely that these findings will result in further investigations in order to determine the precise impact of miRNAs in food on human and animal health. The question remains how many plant miRNAs have sufficient complementarity to mammal mRNAs and can be present in high enough levels in mammals to impact on mammalian gene expression. Consideration may also need to be given by the scientific community to other small non-coding RNAs, their uptake by humans and animals and potential impact on gene expression.

The molecular characterisation working group of the EFSA GMO Panel concludes that this item could be of general importance for food/feed impact on health and acknowledges that GM plants in which changes in gene expression are targeted using miRNA will need to be risk assessed taking into account further developments in this area.