Notification for placing on the market according to Article 13 of Directive 2001/18/EC: Glufosinate-tolerant rice transformation event LLRICE62 from Bayer CropScience Ltd (C/GB/03/M5/3)

Comments from GeneWatch UK
February 2004

GeneWatch UK is writing to object to the application for a part C (marketing) approval under the GMOs Deliberate Release Directive 2001/18 for Bayer's glufosinate tolerant genetically modified rice LLRICE62.

As pointed out by the applicant, rice "is the staple food for more than one-half of the world's population" and many EU citizens consume rice as a staple food. The Cartagena Protocol On Biosafety to the Convention On Biological Diversity notes that there are "*limited capabilities of many countries, particularly developing countries, to cope with the nature and scale of known and potential risks associated with living modified organisms*". The decisions by the European Union with respect to this GM rice will, therefore, be extremely influential in countries with limited resources to undertake their own regulatory review: Africa is one of the largest importers of rice, particularly sub Saharan African countries[1]. This means that the EU has a moral obligation to undertake the most thorough and exhaustive analysis of the safety of this new GM crop, in order to be sure that it is safe for consumption and the environment where it is grown.

GeneWatch UK does not consider that a sufficiently rigorous assessment has been undertaken. In particular:

- the molecular characterisation indicates that an endogenous gene has been disrupted and no data are provided about the consequence of this, so the possible alteration of the plant's metabolism cannot be ruled out;
- no examination of the GM organism has been taken to rule out the possibility of unanticipated changes to its metabolism or the production of novel compounds;
- changes have been observed in known compositional constituents, including an increase in the composition of native anti-nutritional factors and allergens which demand further investigation;
- one poultry feeding study was judged to be of "limited capacity" to identify adverse effects. In the other pig feeding study, a different response (increased weight gain) was observed for consumption of the GM rice compared to non-GM rice.

Furthermore, the environmental risk assessment and monitoring plan do not give sufficient consideration to the possibility of the escape of this GM organism through accidental spillage of grains in southern Europe, where rice could grow and contaminate non-GM crops or weedy red rice.

1. Integration of inserted gene sequence into a coding sequence of a 'novel gene'

Bayer's notification details how the inserted gene sequence is integrated into '*a coding region of a novel gene*' (Annex 5, p25). Bayer detect 18 similar gene sequences to the one disrupted elsewhere in the rice genome and on several different chromosomes. Despite having no knowledge of the function of the novel

[1] USDA trade figures for rice show that while the EU imported 0.9 million tonnes in 2002/3, countries in sub-Saharan Africa imported 6.2 million tonnes

gene and no data to support their claim, they conclude ‘*’These data allow to assume that disruption of the gene that occurred in Oryza sativa elite event LLRICE62 most likely does not influence the activity of the genome’*. Loss of expression of one copy of a gene may affect the overall plant metabolism and function which may not have been detected in the kinds of gross measures of agronomic performance, reproductive and vegetative fitness undertaken by Bayer. Further study is required.

2. Lack of consideration of unanticipated changes

A key concern relating to GM foods is whether the genetic modification has led to unanticipated changes to the genetic functioning of the organism, its metabolism and hence its safety. Bayer consider the composition of the LLRICE62 by measuring levels of the basic known constituents of rice – certain amino acids, proteins, and micro-nutrient levels etc. However, nowhere in the dossier is there any evaluation of whether there have been any unexpected changes leading to entirely new compounds being produced as a result of the genetic modification process. This lack is of particular concern given the evidence presented of gene disruption through integration of the transgenes.

Codex agreed its guidelines on ‘the conduct of food safety assessment of foods derived from recombinant-DNA plants’ in July 2003, and these should now be followed internationally[2]. The guidelines recognise the necessity for risk assessment of foods produced using genetic modification and require a *“pre-market safety assessment of...both intended and unintended effects, identifying new or altered hazards and identifying changes relevant to human health"*. This is because, according to a WHO expert, *“for plants generated by recombinant technology, unanticipated effects may additionally arise from the process of introducing foreign genes or as a result of the effects of environmental factors/genetic background”* [3].

The lack of any data, such as mRNA analysis, looking for unanticipated changes is a serious shortcoming in the application.

Furthermore, guidance by the former Scientific Committees on the safety assessment of GM foods notes that it should “*not only include studies on newly expressed proteins but also the consequences of any genetic modification (e.g. gene silencing or over-expression of an endogenous gene)*.”[4]

It goes on to state that “*the safety assessment must consider the presence of proteins expressed as result of the genetic modification, the potential presence of other novel constituents and/or possible changes in the level of natural constituents beyond normal variation*.”

For LLRICE62, compositional differences between the GM rice and a non GM counterpart were found for a number of factors measured. The UK authority’s assessment report notes that: “*For a number of nutrients (including some fatty acids, iron, vitamin B1 and Vitamin E) compositional analysis was not achieved at all sites and all comparisons*”.

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[2] Guideline for the conduct of food safety assessment of foods derived from recombinant-DNA plants. CAC/GL 45-2003.

[3] Haslberger, A. (2003) Codex guidelines for GM foods include the analysis of unintended effects. *Nature Biotechnology* 21: 739-741.

[4] Guidance Document For The Risk Assessment Of Genetically Modified Plants And Derived Food And Feed 6-7 March 2003 Prepared for the Scientific Steering Committee by *The Joint Working Group on Novel Foods and GMOs* Composed of members of the Scientific Committees on Plants, Food and Animal Nutrition. Paragraph 4.4

"*Fat, protein, ADF [acid detergent fibre], NDF [neutral detergent fibre], and ash were markedly lower in transgenic rice bran than non-transgenic rice bran, while total carbohydrates were higher. For fat and NDF, these exceeded the 20% bio equivalence range*".

These differences were not investigated further, but were dismissed because "*consistent trends*" were not identified. This is a judgement which appears to have been made in the applicant's interest, not the interest of the public.

There are also some questions raised in relation to the limited animal feeding studies. A poultry feeding study showed no differences between GM and non-GM fed birds, but the UK authorities noted this was of "*limited capacity*" to identify adverse effects. It is unclear whether glufosinate treated rice was used to feed the birds. This is essential because in glufosinate tolerant crops using the *pat* or *bar* gene, a glufosinate metabolite is produced in the plant if it is sprayed with glufosinate[5], and this could affect the nutritional value of the feed.

A second feeding study, over 100 days and using pigs, found that the animals fed the GM rice treated with the herbicide glufosinate gained weight more than animals fed untreated GM rice or non-GM rice. This effect does not appear to have been investigated further.

3. Inadequate examination of existing allergic potential.
Rice is known to cause allergic reactions and has also been found to cause protein induced enterocolitis syndrome in infants[6], an uncommon but severe form of food hypersensitivity. Even the applicant notes that "Recent studies showed, that the rice protein fraction contains proteins with an allergenic potential"

The guidance by the former EU Scientific Committees on the safety assessment of GM foods states that:
"*If the host of the introduced gene is known to be allergenic, any potential change in the allergenicity of the whole GM food/feed should be tested by comparison of the allergen repertoire with that of the conventional non-GM variety*.**"**

The allergenic proteins found in rice have been identified and characterised and are in the class of trypsin inhibitor proteins. According to Bayer's Nutritional Impact Assessment report, increases in these proteins were observed for LLrice62.

> Trypsin inhibitors in the GM rice were substantially higher in the bran of the GM rice (2.27 (TIU/mg protein) than in the conventional rice (1.36 (TIU/mg protein)[7].

Although reactions to rice are rare, they can be extremely serious, particularly for affected infants, and so considering the wide influence of the EU's opinion and the fact that rice can form the major part of the diets of the less affluent, serious consideration must be given to this before approval is granted.

The antinutritional compound phytic acid is also found in rice bran, preventing absorption of minerals. Rice bran is the main by product of rice processing used in animal feeds and, according to Bayer's Nutritional Impact Assessment report, phytic

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[5] OECD (2002) Series on harmonization of regulatory oversight in biotechnology, No 25. Module II: Phosphinothricin. ENV/JM/MONO(2002)14
[6] Nowak-Wegrzyn A (2003) Food protein-induced enterocolitis syndrome caused by solid food proteins *Pediatrics* 111(4) 829-835
[7] Bayer. Report No NI 01 EUR 01 C011512 *Nutritional Impact Assessment Report on Glufosinate Tolerant Rice Transformant LLRICE62* Table 4.18.1

acid content was also higher in the GM rice bran (5.14) than the non GM rice bran (4.49), although it is unclear what from the document what units these figures express.

So the levels of potentially allergenic and anti-nutritional compounds are increased in the GM rice in comparison to its non-GM counterpart. These findings were dismissed because the differences are not statistically significant, but considering the difficulties in sampling and resulting small sample sizes, which means that only extremely large differences would be statistically significant, as well as the fact that this is a staple food for many consumers both in and outside the EU, further investigation of these observed differences must be undertaken. At the very minimum the statistical power of the experiments needs to be determined to know what changes would be considered significant.

4. Shortcomings in the assessment of the potential for adverse impacts on the environment

The application concerns the importation of GM glufosinate tolerant rice (*Oryza sativa)* for use in food and feed and does not include cultivation. Rice is grown in 5 southern EU member states – Italy, Spain, Greece, Portugal and France. Although gene flow to crop rice or weedy red rice is possible in such areas[8,9,10], Bayer consider this risk to be '*theoretical'*, because LLRICE62 is not intended to be grown in Europe (Page 43 of notification). However, nowhere in the notification does Bayer provide data on:

- where in Europe imports of rice take place (to determine where geographical overlap may arise);
- the proportion of imported product that may contain viable rice and whether or where spillages of imported rice have occurred in the past.

If there was an accidental spillage of the GM rice in southern Europe, it may germinate and cross pollinate farmed rice or wild red rice. The introduction of herbicide tolerance genes into weedy rice could pose considerable problems for farmers in southern Europe. If non-GM rice were to be contaminated, farmers could suffer economic losses. About 0.89mt of rice are imported into Europe annually, and on such a scale the potential for rare events to occur must be given some consideration.

GeneWatch UK considers that for the above reasons, LLRICE62 should not be granted approval for import and marketing in the EU, because there is insufficient evidence that it will not cause adverse effects to human health and the environment.

[8] OECD (1999) Series on Harmonization of Regulatory Oversight in Biotechnology No.14. Consensus document on the biology of *Oryza sativa* (rice). ENV/JM/MONO(99)26

[9] Messegeur, J. *et al* (2001) Field assessments of gene flow from transgenic to cultivated rice (*Oryza sativa L.*) using a herbicide resistance gene as tracer marker. *Theoretical and Applied Genetics* 103: 1151-1159.

[10] Zhang, N., Linscombe, S. & Oard, J. (2003) Out-crossing frequency and genetic analysis of hybrids between transgenic glufosinate herbicide-resistant rice and the weed, red rice. *Euphytica* 130: 35-45.