OBJECTIONS TO THE APPLICATION MADE BY BAYER CROPSCIENCE GmbH

IN RESPECT OF A COMMODITY CLEARANCE APPLICATION FOR EVENT LLRICE62

TO THE NATIONAL DEPARTMENT OF AGRICULTURE, SOUTH AFRICA

PREPARED BY
AFRICAN CENTRE FOR BIOSAFETY
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SCIENTIFIC ASSESSMENT

Bayer CropScience (formerly Aventis) have submitted an application to the National Department of Agriculture of South Africa for commodity clearance of glufosinate ammonium-tolerant rice LLRICE62. A 229-page dossier containing information deemed unclassified has been made available for public comment. On the basis of this limited and selective information an attempt is made here to assess the merits of the particular event.

1. BACKGROUND

Rice

Rice is the staple food of half the world's population[i,ii] and provides more calories than any other single food, about 90% from carbohydrates and 10% from protein.[iii] The mapping of the rice genome has increased focus and interest on the genetic modification of rice. Sub-Saharan Africa is projected to import 6.7 million tonnes of rice in 2006 with South Africa accounting for 11% of this figure, mainly parboiled rice from Thailand and India.[iv] The United States was once a major importer of rice to South Africa, a position it no longer holds.[iv] There are two cultivated species of rice, viz., *Oryza Sativa* (widely known as Asian cultivated rice including two ecospecies *indica* and *japonica)* and O. *glaberrima* (called the African cultivated rice). The African cultivated rice appears to have originated in West Africa from the wild species O. *barthii*. The African cultivate rice is grown widely in West Africa, where a high degree of genetic diversity exists, developed and conserved by farming families over the past ten millennia or even more.[v]

The African Centre for Biosafety has received from the South African Revenue Service (SARS), on the 8th and 9th May 2006, information pertaining to the import into and export out of, South Africa, of rice for the periods 2003, 2004 and 2005. An analysis of this information reveals that South Africa is a net importer of several different varieties of rice, from a number of countries including, Australia, China, Indonesia, India, Pakistan, Suriname, Thailand, Taiwan, the US, Uruguay, and Vietnam.

Although South Africa is a net importer of rice, rice is exported from South Africa to a wide variety of countries in Africa, including, Angola, Benin, Cameroon, Ethiopia, Democratic Republic of Congo, Ghana, Mali, Malawi, Mozambique, Tanzania, Togo, Rwanda, Cote D' Ivoire, Togo, Senegal, Kenya, Uganda, Congo (Brazzaville), Zambia and Zimbabwe.

This Application

This application is for commodity clearance for the import of rice grain for food and feed use with parboiled milled rice being the main rice commodity being imported.[vi] The *Oryza sativa* rice variety that is tolerant to the herbicide glufosinate (trade name Liberty), commercially registered as LibertyLink rice is the organism under consideration. This event, designated LLRICE62, was produced by biolistic (particle acceleration) transformation of a US rice variety (cv. Bengal)[vi] with a 1.5kb *Hin*dIII/*Pvu*I fragment of

plasmid pB5/35S*bar* which includes a copy of the *bar* gene engineered to be under the control of the cauliflower mosaic virus 35S promoter and terminator sequences.[viii] Expression of the bar gene encodes the PAT protein which confers tolerance to glufosinate ammonium herbicides.

The following discussion details the main features of LLRICE62 and those features or aspects of the application that are cause for concern.

2. LLRICE62: DESCRIPTION AND CHARACTERISTICS

Glufosinate Ammonium and the *bar* Gene

Glufosinate-ammonium salt (or phosphinothricin), often referred to as just glufosinate, is a broad-spectrum contact herbicide that behaves sufficiently like the amino acid glutamate to enable it to disrupt the conversion of glutamate to glutamine. It disrupts the enzyme mediated reaction by inhibiting glutamine synthetase activity in susceptible plants, resulting in reduced glutamine production. Glutamine synthetase also regulates ammonia levels by detoxification and disruption of the enzyme activity results in elevated ammonia levels.[vii] The *bar* gene, derived from the soil actinomycete *Streptomyces hygroscopicus,*[viii] codes for phosphinothricin-N-acetyltransferase, an enzyme which catalyses phosphinothricin acetylation effectively rendering it inactive and thereby enabling transformed plants to withstand phosphinothricin based herbicide applications.

CaMV Promoter

The cauliflower mosaic virus (CaMV) is a DNA-containing para-retrovirus replicating by means of reverse transcription. It contains within its genome a viral promoter called 35S, a general strong plant promoter which has been used to secure expression of transgenes in a large proportion of commercialised GMOs. There are several studies indicating the potential for transcriptional activation of the 35S CaMV promoter in mammalian systems.[ix,x]

The CaMV 35S promoter has been found to have a recombination hotspot where it tends to fragment and join with other double stranded DNA in a very non-specific manner.[xi] These hotspots are flanked by multiple motifs involved in recombination and functions efficiently in all plants, green algae, yeast and *Escherichia coli*. The potential exists for the viral genes to recombine with other viruses to generate new infectious viruses,[xii] carcinogens and mutagens as well as to reactivate dormant viruses.

Detractors claim that virus infected cabbages and cauliflowers have been consumed for years with no ill effects and that similar pararetroviral sequences occur widely in plants, causing no apparent harm.[xiii] That the intact virus causes no obvious harm in the natural host is related to the fact that its integrity is maintained and that it is adaptive to the host biology. This is unlike the fragments of naked DNA as in the transformed plant where the natural regulatory mechanisms are not present.[xii] A call has been made that the use of

the CaMV promoter in transgenic plants be phased out due to the structural instability arising out of its use.[xiv]

3. MOLECULAR CHARACTERISATION

Position of the Genetic Construct

An Aventis internal report by Berghmann,[xv] indicates that genetic modifications to produce LLRICE62 may have resulted in the interruption of a coding region of an endogenous rice gene.[xvi] The paper in question is not included in the application to the South African Authorities but forms part of the dossier in applications to the EU. Interruption of a genetic sequence may have unpredictable and unintended effects. Despite this, it is simply assumed that there are negligible effects on the whole genome functioning. Any adverse effects may not be immediately obvious, but may become apparent under conditions of stress, e.g. drought.xvi The resultant open reading frame is reported not to be transcribed.[xvi] This claim needs to be subjected to greater scrutiny and more investigation. Extra gene fragments in Monsanto's Roundup Ready Soya were also claimed to be non-functional and not-transcribed[xvii], but were later found to be transcribed to produce RNA[xviii,xix]. The lack of sophisticated methods for targeted insertion, especially in higher organisms necessitates more rigorous research into possible position effects prior to the granting of any release of transgenic organisms into the environment.

Genetic Modification: Degree of Certainty

In general, genetic modification by the application of recombinant DNA technology is characterised by scientific uncertainty. This stems from several factors including the inherent imprecision of currently employed recombinant DNA techniques, the use of powerful, often viral, promoter sequences in genetic constructs and the generation, as a result of genetic modification, of novel proteins to which humans and animals have never previously been exposed[xx]. Additionally, the gaps in the knowledge regarding composition and functioning of the genomes that are often subjected to genetic manipulation and ill-designed experiments compound such scientific uncertainty.[xx]

Uncertainty is a key element of the Biosafety Protocol (Cartagena Protocol on Biosaftey to the Convention on Biological Diversity).[xxi] The lack of sufficient relevant scientific information and knowledge regarding the extent of potential adverse effects allows the Precautionary Principle referenced in the Biosafety Protocol to be triggered. The precautionary principle states that "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be use as a reason for postponing cost-effective measures to prevent environmental degradation". The discussions above have identified potentially dangerous effects from LLRICE62. Further the available scientific information, as provided by Bayer, does not allow for a full evaluation or determination of the associated risks of the use of the said transgenic line.

4. OUTCROSSING AND GENE TRANSFER

Rice Spillage: Potential for Gene Transfer

At several places in the Summary Notification Information Format (SNIF)[xxii] to the United Kingdom the possibility of outcrossing is conceded. It is stated that "Gene flow can occur into an adjacent rice crop and into weed red rice, however, the rate is likely to be very low" and that "Gene flow to red rice or other crop rice is possible in rice producing areas of Europe".xxii The SNIF further states that "Milled rice grain is not viable seed. The qualities of the grain are the same as other rice in commerce and do not constitute an environmental hazard. In the case of accidental spillage of LLRICE62 in transit or at the processing facility, the area will be monitored for one season for the germination and plant establishment of the spilled rice grain."xxii The suggestion is clear that the milled rice contains some viable seed.

However, the assertion by Bayer in the risk assessment to the South African Authorities does not allow for any of this uncertainty and states "there is no LMO for which detection in the environment might be necessary" (25: Page 13 of 21)vi and that there are no actions to address uncertainty regarding the level of risk because "there is no uncertainty regarding the risk level" (30: Page 13 of 21).vi Experience of similar imports of maize for food and feed without cultivation in Mexico contradicts this claim. Local maize landraces were found to be contaminated with GMO constructs[xxiii,xxiv]. This was thought to be as a result of the inadvertent planting of GM maize grains that had been sold for food and feed. There is no assurance that this will not happen in South Africa and a monitoring plan is therefore essential to ensure that any GM rice sold for food and feed is restricted to this purpose. Whilst rice is not grown commercially in South Africa, there is small-scale rice farming in the Makhatini Flats and there is always the possibility of some of the rice grain making its way into cultivated areas.

As already discussed above, South Africa exports rice to several African countries, including several countries in West Africa where traditional varieties of rice are grown. Currently, Bayer has already been granted permission to cultivate its LLRice62, although farmers in the US have not planted the GM rice commercially. However, if the South African authorities were to grant Bayer's application for approval, it will encourage rice farmers in the US, to convert from GM-free rice farming, to GM farming. Imports of GM rice into South Africa may be co-mingled during the transportation, storage, processing and re-export to other African countries, taking into account that South Africa does not have any mandatory segregation and traceability systems for GMOs. Contaminated rice exported from South Africa into the rest of Africa, may be planted out in those countries. If this happens in West Africa, the GM rice will outcross with wild and native varieties, and lead to the extinction of traditional varieties. The importance of protecting centres of diversity and treating such centres as precious world resources cannot be overstated enough.

5. NUTRITIONAL INFORMATION

In Annex 1 of the Bayer application dealing with Food and Feed Safety Data (page 14 of 21) it is stated that "Rice grain of LLRICE62 has the same nutritional quality and identical allergen profile as rice in commerce" and that "nutritional compositions for whole grain and processed products of rice grain were not different from the standards of rice in commerce".[vi] The paper cited in support of this claim is Oberdoefer et al. (included in the dossier) which states in the abstract that "most results for nutritional components fall within the range of values reported for rice commodities in commerce."[xxv] Equivalence was demonstrated for "most minerals", [xxv] not all. The WHO/FAO Codex guidelines consider determination of substantial equivalence to be an entry point rather than an end point and any differences necessitate much more vigorous further investigation.

Use of Surrogate Proteins

It is common for developers of GM plants to carry out supporting studies using the naturally occurring or surrogate proteins, rather than the GM plant-produced product. This is usually because it is time consuming and expensive to isolate adequate quantities of transgenic proteins from transgenic crop lines. According to Bayer, the "DNA sequence of the gene in *E. coli* used to produce the PAT/*bar* protein is **nearly identical** to the DNA sequence of the gene introduced in rice, event LLRICE62"[xxvi], differing by a serine amino acid in rice rather than an aspartic acid in *E coli*. Toxicology and allergenicity studies of LLRICE62 have been conducted by Bayer using this surrogate protein.[xxvi] The practice of using surrogate proteins has been widely criticised in particular by expert committees of the National Academy of Sciences[xxvii] and the Environmental Protection Agency.[xxviii,xx]

6. ALLERGENICITY

The nature of genetic modification of higher plants results in the production of novel proteins which might cause allergic reactions. Allergies to food are potentially life threatening for an estimated 2% of adults and 8% of children. Rice is known to cause a relatively rare but uncommon protein induced allergic reaction in infants called enterocolitis syndrome in infants, which is a severe form of food hypersensitivity.[xxix] One reason for the failure of identification of GM crops as allergenic is related to the fact that the testing and assessment thereof is left up to the developer of the transgenic organism and that no standardised agreed-upon protocols exist for such testing.[xxx] No test exists that is fully predictive of potential allergenicity.[xxxi]

The need for the assessment of allergenicity was first recognised when Pioneer transferred Brazil nut genes for a high methionine 2S albumin into soybeans and detected its allergenic potential and voluntarily stopped development of the product.[xxxii,xxxi] This highlighted the need for a sound assessment strategy for allergenicity and over the past ten years, several bodies have applied themselves to this including the International Life

Sciences Institute, the International Food Biotechnology Council, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).xxxi[xxxiii] A Bayer report [xxxiv] found that trypsin inhibitors were substantially higher in the bran of the LLRICE62 rice (2.27 (TIU/mg protein) than in the conventional rice (1.36 (TIU/mg protein). Despite the rarity of the reactions to rice, their severity necessitates a rigorous investigation into their allergenic potential especially for any nutrients elevated in GM varieties relative to conventional rice and especially given that rice often forms the major part of the diet of less affluent communities.

Assessment of Allergenicity

Regulatory authorities considered several elements for testing including the source of the gene, sequence homology to known allergens, specific serum screening, comparative resistance to pepsin, target serum screening (the immunoreactivity of the novel protein with serum IgE from individuals with known allergies to species that are broadly related to the source of the transferred DNA) and the use of animal models. The latter two methods were not considered sufficiently well understood or developed methodologies for regulatory purposes and to date, the allergenicity assessment of genetically modified food crops relies on the four former-mentioned methods[xxxi].

The gastric stability assay has been widely accepted as an important part of allergenicity assessments of genetically modified products and support in the literature continuing through the FAO/WHO consultation in 2001 resulted in acceptance by the Codex Alimentarius[xxxv,xxxvi,xxxvii.]. This experiment is based on the hypothesis that food allergens must exhibit sufficient gastric stability to have a chance of reaching the intestinal mucosa where absorption and sensitising will occur[xxxi,xxxviii]. Typically the test is a measure of comparative resistance to pepsin proteolysis[xxxi]. In the face of the lack of definitive tests for determining potential allergenicity, it is the most reliable test[xxxvii,xxxi,xxxix]. Only Appendix 6 of an Analytical report on Rice Allergenic Protein[vi] has been supplied as part of the dossier and not the protocol deviations which were reviewed by the Aventis Study Director and filed, making a true assessment of the allergenicity testing very difficult if not impossible.[vi]

7. CONCLUSIONS

The main conclusions that can be drawn from the information provided in the dossier to the South African Authorities are:

- the genetic modification has resulted in the likely interruption of an endogenous gene by the genetic construct
- the potential for spillage and outcrossing cannot be ruled out
- the nutritional information in different submissions by Bayer for the same event and in Bayer's own studies suggest that the nutritional content of the GM rice is

not exactly the same as in the conventional rice and this requires further investigation

- the potential for allergenic reactions requires much more rigorous investigation

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