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The Registrar: Genetically Modified Organisms
National Department of Agriculture

The Chairperson: Executive Council
Genetically Modified Organisms Act

Per Email

27 May 2005

The African Centre for Biosafety (hereinafter referred to as "the Centre") is a non-profit organisation, working on biosafety issues, in the public interest. The Centre hereby submits its objections to the application made by Syngenta ("the Applicant") to the National Department of Agriculture ("NDA"), the Registrar: Genetically Modified Organisms Act No. 15 of 1997 ("GMO Act") and the Executive Council ("EC") established in terms of section 3 of the GMO Act for authorisation for commodity clearance of event MIR604.

We have a reasonable expectation that in considering our objections to the Applicant's application, the EC will act in accordance with the principle of procedural and substantive fairness as enshrined in section 33 of the Constitution and the Promotion of Administrative Justice Act 3 of 2000.

Yours truly,

Mariam Mayet

OBJECTION TO THE APPLICATION BY SYNGENTA FOR COMMODITY CLEARANCE OF SYNGENTA MIR604 MAIZE TO THE NATIONAL DEPARTMENT OF AGRICULTURE, SOUTH AFRICA

PREPARED BY

AFRICAN CENTRE FOR BIOSAFETY

27 MAY 2005

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SUMMARY OF ISSUES RAISED IN OBJECTION

The discussion below details our concerns against the possible granting of a permit to Syngenta for the commodity clearance of MIR604 maize against the background of both scientific and historical evidence that points to the need for more rigorous testing of the event in question.

In summary our concerns are:

- The safety approval sought by Syngenta in respect of genetically modified (GM) maize MIR 604, still subject to field tests in the US, appears to be in conflict with the principles and provisions of the Cartagena Protocol on Biosafety to which South Africa is a Party, because the Protocol applies to real situations of cross border trade in genetically modified organisms (GMOs) and not to speculative trade in respect of non- existent GMOs.

- The currently applied techniques for the genetic modification of higher plants is imprecise and exposes consumers to powerful promoters usually of non-food origin to which they might not ordinarily be exposed. The impact of such exposure is not sufficiently well understood.

- The event MIR604 is still in experimental stage in the United States and the application for clearance of MIR604 is still pending in the United Kingdom. South Africa should be as or more rigorous in its assessment of applications for GE foods.

- Several mainstream American food companies such as McDonalds and Kraft which have international footprints are not sourcing even approved GM foods because of negative consumer responses to their use. Further these companies are requiring more stringent testing than that applied by the US authorities.

- The US Environmental Protection agency (EPA) has granted a temporary exemption of a requirement from tolerance to the modified cry3A protein found in event MIR604. The EPA has for several similar applications by developers of GE foods not applied its own minimum assessment criteria and there is an apparent bias towards GE foods in the US. The South African Authorities should not take its cue from the US EPA.

- The methods applied by the US EPA for allergenicity testing is not in compliance with the widely adopted 2001 FAO-WHO standard, a standard required by Kraft foods.

- The digestive stability test accepted by the US EPA in the assessment of MIR604 does not meet the standard and is not in accordance with the protocol of the FAO-WHO and is in fact applied by the developer of MIR604 at pH 1.2, a pH more likely to show digestive stability than the widely accepted pH 2.0.

- Cry3A, of which the modified form mCry3A is found in MIR604, has been found to have sequences homologous to a known allergen which raises the possibility that mCry3A is a potential allergen.

CONTRAVENING THE INTENTION, SPIRIT AND PROVISIONS OF BIOSAFETY PROTOCOL

The safety approval sought by Syngenta is in respect of ***non-existent GM maize*** , that is maize that is still in the experimental stage in the United States. Article 11 of the Biosafety Protocol deals with cross border movement of GMOs for direct use as food, feed or processing and is thus the "kick off" point for the regulation of Syngenta's application. It is implicit in Article 11 of the Protocol, that prior approval for commercial growing and domestic consumption by the Party of Country of export is required before the transboundary movement can commence alternatively, before the Party of import grants any approval.

It was never within the contemplation of those negotiating the Biosafety Protocol that a Party of import would be required to grant a food safety approval of a GMO, in the absence of such approval by the Party or country of export. In fact, Article 11(1) of the Protocol goes further than requiring mere authorisation. It requires that a Party of export inform other Parties to the Protocol of its decision (approval) through the Biosafety Clearing House by way of furnishing to the Biosafety Clearing House, at a minimum, the information specified in Annex II of the Protocol titled "Information Required Concerning Living Modified Organisms Intended for Direct Use as Food or Feed, or For Processing." These requirements put the other Parties to the Protocol "on notice" that the GMO in question may be exported for food, feed and processing use; and to provide relevant information on that GMO in order for such other Parties to use in making a decision whether or not to allow the import of that GMO for food, feed or for processing.[1]

This form of indirect notification serves as a trigger for the provisions of Article 11 to kick in. It stands to reason therefore, that prior approval in the Party/country of export is the first step in the chain of regulatory events that pertain to the transboundary movement of GMO. The second event is the notification by the Party/country of export via the Biosafety Clearing House. The third significant event in this chain is then consideration of the application and decision-making based on the precautionary principle. Mir604 is still in the experimental stage in the US and it is our respectful submission that the EC, acting on behalf of the Republic of South Africa as a Party to the Biosafety Protocol, cannot and should not grant the application sought by Syngenta. If such an application were to be granted, then South Africa could well be in violation of the principles, objectives and provisions of the Biosafety Protocol.

BACKGROUND

The Application

Syngenta have submitted an application for commodity clearance in respect of genetically modified maize MIR604.

Maize

Maize or corn (Zea mays L.) is grown commercially in over 100 countries primarily for the kernel, which is processed into a wide range of food and industrial goods.[2] The greater proportion of maize produced is used for animal feed with under 10% of the maize used as human food products. Starch produced from maize is converted into sweeteners, syrups and fermentation products.[2]

Bacillus thuringiensis: Mode of Insecticidal Action

Bacillus thuringiensis (Bt), a common soil bacterium produces insecticidal proteins during sporulation. Each of the several thousand strains of Bt that exist produces its own unique insecticidal crystal protein (delta endotoxin),[3] each of which displays differing insecticidal activity, but with a similar mode of action. Typically, ingested delta endotoxins are dissolved in the insect midgut liberating the protoxins of which they are comprised. These undergo proteolysis and one of the fragments binds to the cells of the insect midgut epithelium, disrupting the osmotic balance and forming pores in the cell membrane causing cell lysis, gut paralysis and death within a few hours of ingestion.[3,4]

SYNGENTA MIR604 MAIZE: GENETIC MODIFICATIONS TO PRODUCE EVENT MIR604

Description and Characteristics

The information detailed below regarding the description and characteristics of event MIR604 is derived largely from information provided by Syngenta Seeds S.A.S. to the European Food Safety Authority (EFSA) in its application submitted in February 2005 for use as food and feed, which is still awaiting a decision by the EFSA.[5]

Maize line MIR604, designated SYN-IR604-5, is a transgenic maize line that has been engineered to express a modified *cyr3A* (*mcry3A*) gene encoding mCry3A protein. MIR604 confers field protection against the Western Corn rootworm (WCRW) (*Diabrotica virgifera virgifera*), the Northern Corn rootworm (NCRW) (*D. longicornis barberi*) and other related coleopteran species. The gene is under the control of a promoter derived from the maize metallothione in-like (MTL) gene providing root preferential expression and the termination sequence of the nopaline synthase (NOS) gene isolated from *Agrobacterium tumefaciens*.[5]

The *pmi* (*manA*) gene from *Escherichia coli* is also expressed, producing a marker protein, PMI, that allows the plants to utilise mannose as a carbon source, and acts as a selectable marker.[5] The *pmi* gene is under the control of the ZmUbiIntron promoter derived from a maize ubiquitin gene together with the 1st intron of the gene and the termination sequence of the nopaline synthase (NOS) gene, isolated from *Agrobacterium tumefaciens.*[5]

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 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.[6] 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.[6]

Uncertainty is a key element of the Biosafety Protocol (Cartagena Protocol on Biosafety to the Convention on Biological Diversity.[7] 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 "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation".

ALLERGENICITY

Background

Food allergies are adverse reactions to what might otherwise be considered to be harmless food or food components. Almost all known food allergens are protein in nature and the body of knowledge relating to the range of known food allergens still has large gaps.[8] The responses arising out of food allergies range from mild to life-threatening responses. Allergies to food are potentially life threatening for an estimated 2% of adults and 8% of children.

Conventional plant breeding has increased the range of food proteins introduced into human diet, with little or no adverse impact. Changes in food production can by contrast have severe implications for the development of food allergies. The nature of genetic modification of higher plants results in the production of novel proteins which might cause allergic reactions. Starlink corn, a case in point, produced by Aventis to express Cry9C which kills the European corn borer was approved by the Environmental Protection Agency (EPA) in 1998 for use only as animal feed and set a zero-tolerance level for its use in human food based on the fact that this particular Bt protein does not break down easily in the human digestive system, is heat resistant, and could prove allergenic. In 2002 however, StarLink corn was detected in taco shells.[9] The contamination of the human food chain led to a public outcry and massive recall of all products thought to contain the Starlink variety.

Assessment of Allergenicity

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.[10,28] 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 (ILSI), the International Food Biotechnology Council (IFBC), the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).[28,11.]

In 1996 the IFBC and the ILSI suggested a decision-tree approach.[8] A joint FAO/WHO[8] consultation in 2000/1 addressed the overall safety of GE foods revised

and refined this approach and it is widely accepted that the three main elements for assessing allergenicity are sequence homology to known allergens, digestive behaviour and heat stability. Additionally, 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 were suggested as additional criteria for consideration of allergenicity.

Sequence Homology to Known Allergens and Toxins

The rationale behind studying sequence homology is that there is a greater likelihood of an engineered protein being allergenic if it displays sequence homology to a known allergen or allergens. The 1996 ILSI/IFBC approach recommends at a minimum the detection of a sequence of eight contiguous amino acids homologous to a known allergen. There have been several refinements suggested to this procedure amongst others, the identification of four and six amino acids. Steve Gendel, a scientist with the Food and Drug Administration (FDA) in the United States who has done great deal of work in this area found sequence homology between Cry3A and _-lactoglobulin consisting of 7-10 amino acids in length.[12,29] Cry3A is the endotoxin found in Monsanto's New Leaf potato of which the mCry3A in MIR604 is a modified form. Public disquiet about the use of New Leaf potatoes in the United States led to both Burger King and McDonald's refusing to accept this line from their potato suppliers. The impact on planting was massive with total acreage dropping from 50000 acres in 1988-89 to 5000 acres in 2000 (0.4% of the total US potato acreage).[13] The Cry3A similarity to a known food allergen found in cow's milk, _-lactoglobulin, suggests a very strong possibility that mCry3A in MIR604 is a potential allergen.

Digestive Behaviour/Stability Testing

The gastric stability assay is widely used as an important part of allergenicity assessments of genetically modified plants. 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.[28,14] Typically the test is a measure of comparative resistance to pepsin proteolysis.[28] Variations in human digestive capacity necessitate the application of a standardised protocol for this assessment. Both *in vivo* and *in vitro* tests have been proposed as part of a decision-tree approach for assessing protein stability.[15] A paper by Helm (2001) served as a starting point for discussion of the Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology. This working paper recommends several pepsin tests at pH values of "1.0, 1.5, 2.0, 4.0 and 6.0 due to the pH variation in the stomach following a meal."[16]. The final FAO-WHO expert consultation recommended a slightly modified version and recommends testing only at pH 2.0 though with far more specific details about what the protocol should contain.[17]

The EPA assessment of MIR604 however is based only on the result of simple *in vitro* pepsin tests. The pH at which the test was carried out, 1.2, is not truly representative of human gastric conditions and does not for example take account of the antacid effect of food. Human gastric pH varies widely between individuals and over time in the same individual. Typical values however are 1-2 under fasting conditions, rising

to a value of over 5 during a meal.[18] The test carried out by Syngenta as reported to the EPA[19] at pH 1.2 is more characteristic of fasting pH. The use of such acidic conditions for digestive stability testing of novel proteins has been criticized by a leading expert on Bt proteins and GM crop safety testing, Dr. Hubert Noteborn: "The continual setting of the pH value of 1.2 does not mimic accurately the kinetics of the physiological events in the human stomach."[20,18]

Heat Stability

According to the EPA, mCry3A "is inactivated when heated to 95ºC for 30 minutes,".[19] Loss of function from heating is not necessarily an indicator of non-allergenicity. Some milk allergens for example, can have either conformational or linear epitopes, where the latter may reflect sensitization to the denatured form of the protein.[21,22] More generally, loss of function may merely indicate denaturation rather than degradation into short peptides, and could therefore still be allergenic.

Resistance of DNA to Digestion

There are several reported cases in the literature of both the persistence and transfer of gene sequences after ingestion of GM products. Polymerase chain reaction (PCR) has been used to demonstrate the presence of large fragments of M13 phage DNA, which had been fed to mice, in the faeces and bloodstream and in white blood cells.[23] Research published by the UK government in 2002 has shown that bacteria in human intestines had in fact taken up a novel gene from processed food containing GM Soya.[24] It has been reported that people with ileostomies (i.e. who make use of a colostomy bag) are capable of acquiring and harbouring DNA sequences from GM plants in the small intestine.[25] Recombinant DNA fragments and Cry1Ab protein was also found in the gastrointestinal contents of pigs fed genetically modified corn.[26]

OTHER TESTING CONCERNS

Scientific Bias

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[27]. No test exists that is fully predictive of potential allergenicity.[28] Sound scientific method necessitates independent verification of developer results and research resources need to be allocated to such independent study.

Limitations of Allergenicity Assessments

Allergenicity assessments are limited by the fact that amino acid sequences of most allergens remain unknown. Further, several allergens remain undetected and the state of current knowledge on allergens is that there are full length sequences for just 198 major allergens of which 30 are food allergens. Therefore, whilst matches to known allergens are of concern, failure to make a match does not rule out possibility of novel protein being allergenic.[29]

The EU Scientific Steering Committee notes that 'no absolute correlation exists" between pepsin degradation and allergenicity.[30] It is important to note that whilst gastric assays remain a useful part of currently used allergenicity tests, there have

been several instances where food allergens have been found to be unstable in the gastric assay, as well as some instances where supposed non-allergenic proteins have been stable. This makes interpretation more difficult, but does not invalidate the assay.[31] Also the assays may not always be appropriately applied. If, for example, stability is correlated with allergenicity because the protein must reach immune tissue in the intestines for sensitization to occur, then oral allergy syndrome allergens may not fit the model because sensitization may occur through the respiratory homologue of the food allergen.[31] Similarly, assays of the uncooked form of the protein may not be relevant if the food is always eaten in a cooked form, which degrades the GE protein or makes it more susceptible to digestion. The application of the gastric digestion should therefore be correctly applied and interpreted.

Appeals to Safety of Bt

Bt in its native form has been widely used by organic farmers as a means of pest control. According to the EPA, Syngenta claims that the modified protein " came from Bacillus thuringiensis which is not a known allergenic source".[19] Contrary to this statement there have been reports of allergenicity to B. thuringiensis. In instances where there has been exposure, e.g. on farms where farm workers were exposed to conventional Bt sprays, 2 out of 123 workers exhibited sensitivity to Bt formulations.[32] Aerial spraying of Bt pesticides precipitated increased respiratory health effects in local residents.[33]

Genetic Modification versus Conventional Plant Breeding

Syngenta claim that "Event MIR604 maize and products derived from it are not different from those of its conventional counterpart."[5] This is not to be taken as an apparent truth. The ability of ecosystems to develop gradually, the ability to anticipate environmental health effects and very importantly, the establishment of regulatory mechanisms that can effectively, efficiently and credibly manage risks associated with the use of GMOs has not kept apace with the rapid introduction of GMOs. Traditional breeding practices have an established history of safe use dating back several years as opposed to the application of recombinant DNA technology for human use, which is as young as 22 years when genetically modified bacteria-produced insulin was first introduced and even younger for genetically modified plants at ten years.6

STATUS OF APPLICATION IN THE UNITED STATES AND UNITED KINGDOM

The application for commodity import into the United Kingdom is still pending[5] and filed trials are still being conducted in the United States. The product has not reached a point of commercial release.[19]

RECEPTIVITY TO THE MODIFIED FOOD PRODUCT

The American food industry, led by McDonald's and Burger-King, has rejected GM potatoes containing Cry3A protein, of which the mCry3A protein produced in MIR604, is a modified form. There is a growing backlash over crop biotechnology in the United States and McDonald corporation have told their French-fry suppliers to

stop growing NewLeaf potatoes containing Cry3A.[13] There appears to be a retreat by American farmers from using GM seed.[13]

Kraft foods have also come out in support of consumer concerns and state clearly on their website that "Because all new food crops, including those developed through biotechnology, have the potential to include new or unintended proteins that could produce allergic reactions in sensitive individuals, these foods need to be thoroughly assessed for potential allergenicity. If the food contains an allergen that consumers would not expect to be present based on the name of the food, that allergen should be disclosed on the label." Further, Kraft categorically states their support for the "decision-tree approach to determine allergenicity of foods derived from biotechnology" and "encourage national governments to use it when evaluating foods and ingredients".[34]

South African regulatory authorities should exercise greater caution in granting permits and not set a pattern of granting clearance to GM crops that are still in the experimental stage or awaiting clearance in the US and Europe.

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