OBJECTIONS TO SYNGENTA'S APPLICATION FOR GENERAL RELEASE OF GM MAIZE EVENT Bt11 X GA21

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1 INTRODUCTION

An application has been submitted by Syngenta Seed Company to the Department of Agriculture, Forestry and Fisheries for the general release of a stacked event, Bt11 X GA21 maize in South Africa. A copy of the application submitted by Syngenta, excluding Confidential Business Information (CBI), has been furnished to the African Centre for Biosafety (ACB).

This application includes:

- a brief description of the genetically modified plant, conditions for general release, description of a any plant-derived product, a brief summary of field trials undertaken and responses to specific questions as defined in DAFFs application regarding: gene flow, the gene products, resistance, human and animal health, environmental impacts and protection, socio-economic impacts, monitoring and accidents and pathogenic and ecological impacts, approaches to waste disposal and risk management and a monitoring and post market monitoring plan.
- The Risk Assessment Form;
- Affidavit
- A List of the References (excluding the references themselves);
- A List of Appendices (excluding the Appendices except Appendix 6)

Crucially, this version of the application excludes the appendices which detail: Weed and efficacy monitoring of GA21 and Bt11X GA21 maize under South African growing conditions, the evaluation of Bt11 and Bt11X GA21 for control of the African Stem Borer under South African conditions, the Southerns of the individual events and stacked event, comparison of the transgenic protein expression in the individual and stacked events and the evaluation and quantification of the stacked event when fed to broiler chickens.

Event Bt11 codes for a Cry1Ab protein that confers resistance to certain lepidopteran pests and for a phosphinothricin acetyl transferase protein that confers tolerance to herbicides containing glufosinate.

Event GA21 was developed by subjecting maize plants to biolistic transformation to yield a glyphosate-tolerant (Roundup Ready) maize line.

2 BT11 AND GA21

In both GA21 and Bt11 events, there appears to be uncertainties in respect of the nature and integrity of the transgenic cassettes.

2.1 BT11

Bt11 expresses a synthetic truncated *crylAb* transgene from the soil bacterium *Bacillus thuringiensis kurstaki* that is effective against many Lepidopteran insects and a synthetic *pat* transgene from *Streptomyces viridochromogenes* for resistance to glufosinate herbicides. Each of these is driven by the 35S-CaMV promoter and terminated with the 3' untranslated region of the nopaline synthase (*nos*) sequence-

There are therefore in fact, two transgenic cassettes each driven by 35SCaMV promoter. The company's dossier claimed a single copy insert with the structure:*35S-CaMV-Int II-pat-tnos-35S-CaMV Int VI-crylAb-tnos.* However*,* analyses by the Belgian Council for Biosafety revealed "primary insert with rearrangements, truncations and unexpected insertions", and "it is not certain if only one copy of the insert is present". Furthermore, 1.1kbp of the plasmid sequence was present at the 5' end of the insert, followed by plant DNA with homology to a 180bp knob specific repeat sequence.

The presence of plasmid sequence is of particular concern since this may contain genetic origins of replication (Col1E1) and the marker gene *pat* that confers resistance to the antibiotic from *Streptomyces viridochromogenes* (phosphinothricin is an antibiotic naturally produced by *Streptomyces viridochromogenes).*The use of the viral CamV 35S promoter also increases biosafety risks.

There are risks in the use of 35S-CaMV due to increased rearrangements/deletions affecting genome integrity and stability and evidence from the laboratory[1,2] and field studies[3,4] that the 35S-CaMV is a recombination hotspot. The increased recombination with other viral elements and may result in the creation of new risk such as the creation of new viruses.[5,6,7]

2.2 GA21

The transgenic cassette GA21 maize is comprised of gene duplications and deletions. There are six contiguous regions derived from the 3.49 kb NotI restriction fragment from pDPG434 employed in the generation of GA21 maize (copies 1-6). Copy 1 contains the rice actin promoter that has a 5' deletion of 696 bp, the actin first exon and intron, the optimized transit peptide, the mepsps gene and the NOS terminator. Copies 2, 3 and 4 are intact versions of the 3.49 kb NotI restriction fragment from pDPG434. Copy 5 contains a complete rice actin promoter, the actin first exon and intron, the optimized transit peptide and the first 288 bp of the mepsps gene which ends in a stop codon and does not contain the 3' end of the mepsps gene nor the NOS terminator. Copy 6 contains the rice actin promoter and a truncated actin first exon only and contains no other elements from pDPG434.

What is of concern here is the possible production of novel proteins from the transcription of these unintended GA21 fragments. According to Monsanto, these are not transcribed[8] and hence do not produce protein.

The European Commission Scientific Committee on Food[9] has stated that the lack of transcription or translation signals from Northern and Western blots, does not 'preclude absolutely the possibility that the truncated gene is expressed but the possibility that this is the case will be extremely remote'.[9] Inserted gene sequences may interrupt native gene sequences and/or their promoters and additional code fragments are not necessarily non-functional and may be transcribed. Extra gene fragments in Monsanto's Roundup Ready Soya for example, were also claimed to be non-functional and not-transcribed,[10] but were later found by Monsanto to be transcribed to produce RNA.[11,12]

The complete biosafety risks of these unintended genetic changes are unknown and uncertain, but may include the production of novel allergenic or toxic proteins, changes in cellular gene expression and metabolism as well as increased recombination and horizontal gene transfer (HGT). There is therefore an urgent need to present a full molecular characterisation of the cassette of BT11xGA21 and to assess the stability and integrity of this transgenic maize in the field.

3 GENE FLOW

If transgenes behave just like naturally occurring genes, then they have the potential to be inherited in the same way and persist indefinitely in cultivated or free-living populations. Any mixing of native and transgenic plants whether by dispersal, improper handling etc., can result in the spread of transgenes. The consequences, both ecological and evolutionary of crop-to-crop gene flow are only now beginning to be investigated in any meaningful way and the possible exposure of non-target organisms, including humans to novel proteins cannot be discounted.[13]

The Syngenta application acknowledges the inevitability of some seed dispersal (Page 16) and the possible germination and establishment of volunteers. But states that it is "highly unlikely" that the glyphosate tolerance trait is transferred to other plants since there are no wild relatives. Maize is a staple crop in South Africa and is widely grown, commercially, by small-scale farmers and in home gardens. Small scale South African farmers have over time nurtured and developed their own locally prized varieties of maize which are potentially under threat from the effects of gene flow.

Whilst it is true that the maize pollen grains are round and heavy with a high water content, which limits their dispersal range, small amounts of pollen can travel 400m or more and remain viable.[14] We know that transgenes flow - transgene fragments have been detected in mammals.[15] There is still much work that needs to be done to determine behaviour of these fragments. The original field trials were not designed to monitor low probability risks, such as gene transfer and no assessment was made of the impacts on non-target organisms despite the various papers that have been published on the subject.

In a letter penned by the Vice-president of the Health Council of the Netherlands to the Dutch Minister of Health, Welfare and Sport in 1999, regarding the assessment of safety of

GA21 for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients, it was clearly stated that "The applicant *(Monsanto)*[1] says horizontal transfer is so unlikely that this facet is considered irrelevant in the risk assessment. The Committee does not concur with this. Humans have large daily intakes of plant and animal DNA. It is conceivable that parts of this DNA, in the form of intact gene fragments, could enter the small intestine where they could be transferred to the resident microflora."

4 HERBICIDE TOLERANCE AND USE

4.1 MECHANISM OF GLYPHOSATE TOLERANCE

EPSPS plays a role in chloroplast amino acids synthesis, particularly tyrosine, phenylalanine and tryptophan and the naturally occurring plant form is inhibited by glyphosate. The modified plant EPSPS enzyme as found in GA21 has reduced affinity to glyphosate and hence confers tolerance[16] by allowing the plant to function normally in the presence of the herbicide.

4.2 GLUFOSINATE

Glufosinate ammonium herbicide formulations are not currently approved for use on the South African market and Syngenta therefore will not market Bt11 X GA21 locally for this trait.

4.3 HERBICIDE TOLERANCE AND EFFECTS ON NON-TARGET SPECIES

The main environmental concern related to introducing herbicide resistance into transgenic plants is the development of weed populations that are resistant to particular herbicides, the so-called superweeds.[17.] These weeds may then be able to successfully outcompete other non-herbicide–resistant weeds.[18] This may result in increased use of herbicides in greater volumes and varieties with possible negative impacts on soil and groundwater.[19] Increased herbicide use may also result from less restrained herbicide application arising from producer confidence that the desirable plant will be unaffected.

4.4 HERBICIDE USE AND GM CROPS

One of the draw cards, as claimed by seed companies for the use of GM seed is the benefit of reduced herbicide use. Research in support of this claim is by and large carried out by the developers of GM seeds in field scale evaluations.

Trends in the degree and extent of herbicide applications with the advent of GM crops are only now emerging. In the USA, planting of GM crops has led to a substantially greater use of herbicides than non-GM crops with significant year on year increases particularly for GM soya and maize. Between 2001 and 2003, the planting of GM crops resulted in 73 million pounds more agrochemicals being applied in the USA.[20]

[1] ACB Addition, for point of clarification

Benbrook examined agrochemical use on GM crops[20], including most recent impacts (since 2002). His data is in agreement with USDA estimates for earlier years. He observed that 'proponents of biotechnology claim that GE varieties substantially reduce pesticide use. While true in the first few years of widespread planting it is clearly not the case now'. Further he found that there is now 'clear evidence that the average pounds of herbicides applied per acre planted to herbicide tolerant (HT) varieties have increased compared to the first few years of adoption.

From a previous Syngenta application for a field trial of GA21 in South Africa, a concern was raised by the ACB that the length of field trials was too short for an adequate assessment of the impacts of herbicide use. The practice of examining herbicide use for a single season, as typically occurs with most field trials, and as was proposed for the field trial is not sound. Examination of agrochemical usage for GM crops suggest that for a full assessment of the extent of herbicide use, changes in herbicide use need to be monitored over full crop rotation cycles, not just a single harvest as is typical of a number of field scale evaluations.[21]

4.5 INCREASED GLYPHOSATE USE IMPACTS ON OTHER PLANT SPECIES

The dramatic increase in the use of glyphosate over the past decade has resulted in weedy morning glories in the South-eastern United States developing tolerance to glyphosate. The repeated use of herbicides exerting strong selection pressure on crop weeds has led to more than 250 documented cases of herbicide resistance, a process that is 'likely to accelerate with increased reliance on herbicides'.[22] A strong positive directional selection in the presence of glyphosate and strong negative directional selection in its absence was observed.[23]

Common ragweed found in a 22 acre patch of north-central Arkansas dryland has survived heavy, and repeated, shots of Roundup.[24] Laboratory studies are still in progress, but preliminary indications are that resistance to glyphosate (Roundup) has developed in these plants. The presence of resistant ragweed is unlikely to cause major waves amongst agriculturalists as ragweed is not a threat to any major crop and there are herbicides besides Roundup to control the weed. The larger issue is the potential for agriculturally important weeds such as pigweed, tall waterhemp or lambsquarter to develop resistance. Monsanto is well aware of the problem ragweed and is evaluating sample plants in St. Louis.[25] Developing weed resistance is a growing concern amongst farmers and Syngenta have acknowledged that 'many of these concerns with resistant weeds are realistic'.[25]

4.5.1 HEALTH AND ENVIRONMENTAL EFFECTS OF GLYPHOSATE AND GLYPHOSATE-TOLERANT GMOS

There is a paucity of experimental studies devoted to health or environmental effects of glyphosate-tolerant GMOs or glyphosate itself. Glyphosate is a broad spectrum herbicide and its usage may result in harmless plant species being destroyed. The large scale cultivation of glyphosate resistant crops will result in an increase in the use of glyphosate with concomitant negative environmental impacts. The full impact of glyphosate on groundwater can only really be determined by long-term monitoring programmes. In terms

of impacts on human health, glyphosate is acutely toxic to humans and in California has been reported to be the third most commonly reported pesticide related illness amongst agricultural workers.[26] A study on mice fed GM soybean suggested that *epsps*-transgenic soybean intake was impacting on the morphology, particularly the nuclear features of liver cells, in both adult and young mice.[27] The mechanism for this effect is still to be determined.[28] Glyphosate use, an integral part of planting Roundup Ready crops, has indicated several unwanted effects on aquatic systems,[29] terrestrial organisms[30] and ecosystems.[31] Negative impacts on human,[32,33] rodent[34] and fish[35] health have also been observed.

Research carried out on the nature and extent of herbicide applications with Roundup Ready soya in the USA found that 2 to 5 times more herbicide needed to be applied compared to other popular weed management systems.[37]

4.5.2 ROUNDUP READY CROPS: THE ARGENTINEAN EXPERIENCE

Argentina was one of the first countries to authorise GM crops with the cultivation of Monsanto's Roundup Ready soya in 1997.[39,36] Large areas of Argentina's most fertile farming region in the Pampas had been suffering from serious soil erosion. Farmers experimenting with a no-tilling approach to alleviate the problem saw the introduction of a herbicide tolerant crop as a heaven-sent solution.[36] Impoverished smallholders, largely peasant farmers, leased their land out to soya farmers and by 2002 almost half of Argentina's arable land -11.6 million hectares was planted with soya, almost all of it GM, compared with just 37,700 hectares of soya in 1971.[36,37]

The demand for arable land for planting soya saw cultivation extending into more environmentally fragile areas; Argentina has lost three-quarters of its native forest to farming over the past century.[38] In 2001, Benbrook reported that Argentinean Roundup Ready soya growers were using more than twice as much herbicide as conventional soya farmers, largely because of unexpected problems with tolerant weeds.[36,37] His warning of shifts in the composition of weed species, the emergence of resistant superweeds, and changes in soil microbiology under the existing herbicide application regime went unheeded. The outcome is the emergence of several previously uncommon species of glyphosate tolerant weed, a decline in soil bacteria, changes in soil structure and fitness with soil becoming inert thereby inhibiting the usual process of decomposition.[36] On top of all of this is a proliferation of volunteer soya. Rivals to Monsanto in the agrochemical industry began promoting their products to eradicate these volunteers with Syngenta itself, prior to obtaining GA21, advocating the use of Paraquat and atrazine[36,39] and Dow AgroSciences recommending a mixture of glyphosate with metsulfuron and clopyralid.[36,39]

Spraying of RR soya crops has resulted in devastating impacts on the health of local populations and on their environment, livestock and food crops. Studies carried out by the University of Formosa Province reported serious health problems in peasant communities arising from such fumigation on RR soya fields.[39,36] The Argentinean experience also raises

issues of food security. Argentina has gone from being known as one of the world's best beef producers and the breadbasket of the world to an economy dependent on near monoculture.[37] The proliferation of soya has provoked an exodus of people from the rural areas to the cities and into extreme poverty since they cannot produce their own food.[36,37] RR soya has also won out against traditionally grown crops such as sweet potatoes, sweet maize, lentils (a staple), peas and cotton. Argentina used to produce food sufficient to feed eight times its population, now it imports milk. 'Now, in beef country, the poor are being fed with crops used for animal feed in the first world'.[37]

4.6 EFSA AND DEFRA

In the midst of a crucial debate last year in the EU on the reform of the EU authorization system for genetically modified organisms (GMOs), the European Food Safety Authority (EFSA) went ahead and issued positive opinions on a Syngenta pesticide-producing maize (Bt11) and a Pioneer-Dow pesticide-producing and herbicide-tolerant maize (1507).[40] The European Commission health and environment director-generals recently wrote to EFSA's executive director urging the authority to assess health and environmental impacts related to the increased use of herbicides because of GM crops. In April 2008, the EFSA GMO Panel agreed to undertake a two year process to improve its capacity to assess the long-term and indirect impacts of GMOs.[40]

The UK Department for Environment Food and Rural Affaires (Defra) carried out an assessment of an application from Syngenta for authorisation for the cultivation of GA21 maize in the EU, and provided an opinion on environmental risks of this application to EFSA. The Advisory Committee on Releases to the Environment (ACRE) carried out the assessment for DEFRA and found that there were potential impacts on biodiversity associated with cultivation, management and harvesting techniques of this GM maize. Although the ACRE assessment was for EFSA and pertains to the EU there is no reason why the same findings cannot be applied to South Africa. These findings refer specifically to information about herbicide regimes and the fact that herbicides regimes are evolving and cannot be strictly applied across different regions.

5 PERSISTENCE OF BT TOXIN IN THE ENVIRONMENT AND EFFECTS ON NON-TARGET ORGANISMS

All living organisms that interact with the transgenic plant (bacteria-birds and human beings) are exposed to high levels of the expressed transgene which is new to their physiology so adverse immunological or allergic responses are possible. For example, non-target organisms may be harmed either directly or indirectly from feeding of insects pests that have consumed the Bt maize plant. Earthworms have been shown to be affected[41] and significant reductions in populations of the beneficial parasites *Microplitis sp*. (88.9% reduction) and *Campoletis chloridae* (79.2% reduction) in *Bt* GMO plants fields have also been recorded.

Since the Bt toxins are expressed continuously at high levels throughout the growing season in the GM maize plant, the levels of Bt toxin can accumulate. It is of concern that Bt can persist in certain soil types for up to 234 days.[42] There is no evidence to address the degradation of Bt toxins from these events in the environment (soil degradation data from trial field study) nor are these plans included in post-release monitoring. Recent evidence indicate that toxins in transgenic crop by-products affect headwater stream ecosystems by causing mortality on non-target stream insects.[43]

This contravenes South Africa's obligations under the Biosafety Protocol on Biosafety, National Environmental Management Act (NEMA, 1998) and the and Biosafety Bill (#1576) in failing to monitor changes in biodiversity as well as monitor GMO transboundary movements. A specific and sensitive method is required so that Bt11xGA21 can be distinguished from the single events Bt11 and GA21. PCR with primers flanking or over-lapping the insertion site would easily enable the events to be distinguished, but this has not been carried out. There is also no proposed method for the specific and sensitive detection of Bt11xGA21 so that transboundary movements as well as contamination or comingling with other maize in the field as well as the food and feed chain can be monitored.

6 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.[44] Additionally, the gaps in the knowledge regarding composition and functioning of the genomes that are often subjected to genetic manipulation compound such scientific uncertainty.44

Syngenta makes the claim that the genetic modification does not introduce any new category of risk as compared to risks from conventional breeding. 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.44

Uncertainty is a key element of the Biosafety Protocol (Cartagena Protocol on Biosafety to the Convention on Biological Diversity).[45] 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”. The discussions above have identified potentially dangerous effects from the use of GA21. Further the available scientific information, as provided by Syngenta, does not allow for a full evaluation or determination of the associated risks of the use of the said transgenic line.

7 CONCLUSIONS

In terms of the molecular characterisation of the event:

- It indicates several irregularities including open reading frames and a truncated constructs which could give rise to unintended gene effects
- The transfer of the herbicide-tolerant trait to weeds could result in increased herbicide application. The potential for economically important weeds developing herbicide tolerance is a cause for concern
- Glyphosate use has resulted in several unwanted effects on aquatic systems and terrestrial organisms and ecosystems
- The US experience of Roundup Ready field trials has shown a marked increase in herbicide usage, particularly glyphosate
- In the Argentinean experience, the large scale uptake of Roundup Ready Soya has had devastating impacts on food security and the environment
- The proposed field trials are to assess agronomic performance and do not address risks to biodiversity and are not accompanied by an adequate monitoring program in order to detect transgene escape. This is required under local (NEMA) and international (Biosafety Protocol) legislation.

It is our contention that the Syngenta application cannot be adequately assessed. The information provided is sketchy at best, key information required for a full and thorough assessment of the event in question is designated confidential business information and therefore not made available to the very public who are expected to consume the product and the time allocated to review of the information is unrealistically short. In respect of the event in question, claims are made regarding gene stability and behaviour by reference to information provided by the developer of the GMO and not to any independent objective source. The basis of these claims is therefore in question. The impression gained from the Syngenta application is that any possible impacts of the release of the transgene are negligible and that the transgenic line is equivalent to the conventional type – this is a view not supported by the published literature. At a minimum, the literature indicates that a great deal more investigation has to be carried out on the impacts of transgenes before their release into the environment. The longer review process of similar applications by the EU, which are themselves often not considered rigorous enough, bear out these concerns.

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