OBJECTIONS TO THE APPLICATION MADE BY PIONEER HI-BRED RSA AND DOW AGROSCIENCE SOUTHERN AFRICA FOR COMMODITY CLEARANCE OF GENETICALLY MODIFIED ORGANISMS, SPECIFICALLY 59122 MAIZE TO THE NATIONAL DEPARTMENT OF AGRICULTURE, SOUTH AFRICA

PREPARED BY

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SUMMARY OF LEGAL ISSUES

1. EC TO UPHOLD RIGHT TO SAFE FOOD; REFUSE APPLICATION BASED ON PRECAUTIONARY PRINCIPLE

It is our submission, taking into account our scientific assessment; the Executive Council will flout the constitutionally protected rights of South Africans to safe food if it were to grant a safety approval for Pioneer/Dow's Herculex RW GM maize. Indeed, the Department of Health, who plays an oversight role on the Executive Council in terms of the GMO Act, has on obligation to safeguard the consumer from foodstuffs that are harmful or injurious to human health and ensure a science-based and rigorous review process designed to ensure food safety.

As a Party to the Cartagena Protocol on Biosafety, South Africa is entitled to refuse Pioneer and Dow's application based on the precautionary principle as set out in Article 11(8) of the Protocol.

2. CONTRAVENING INTENTION, SPIRIT AND PROVISIONS OF BIOSAFETY PROTOCOL

The safety approval sought by Pioneer and Dow is in respect of ***non-existent GM maize***, whereas the Biosafety Protocol applies to real situations of cross border trade in GMOs and not to speculative trade in respect of non- existent GMOs.

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 Pioneer'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.

Since no such prior approval exists, 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 Pioneer and Dow. 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.

3. PIONEER, DOW'S APPLICATION WILL WORSEN CRISIS IN GRAIN SECTOR IN SOUTH AFRICA

Since the GMO Act came into effect, the EC has authorised several millions of tons of GM maize to be imported into South Africa from Argentina and the USA by especially the animal feed industry because it is cheaper than if they were to purchase maize produced locally and thereby displacing and placing at risk thousand of jobs in the agricultural sector and related industries.

Already, South African farmers have sounded the alarm bells during January 2005, when GRAIN SA launched a country wide campaign to raise public awareness about the country's agricultural crisis because prices of grains, including maize are being kept low because of the dumping of cheaper subsidised maize from other countries.

Pioneer and Dow's application is intended to enable and expedite the imports of cheap subsidised maize from the USA.

4. LACK OF MONITORING, LABELLING EXACERBATES UNCERTAINTIES

South Africans have been eating GM maize for several years yet, neither the National Department of Health nor any other government agency has conducted any post commercialisation testing and monitoring for the effects of transgenic maize on animal and

human health. This failure only serves to exacerbate on-going scientific uncertainties about the safety of GMOs, and GM maize in particular.

5. SPILLAGE OF GMOS DURING TRANSPORT, STORAGE

We are extremely concerned that if Pioneer and Dow's application should be granted there is a possibility that there may be negative environmental impacts arising form the spillage of whole GM maize grains during transportation and the milling process itself because the transport and storage are not adequately regulated under the GMO Act.

SUMMARY OF SCIENTIFIC ASSESSMENT

An assessment was made of the notifier application especially in terms of the claims by the notifier regarding the lack of allergenicity of the Cry34 protein. Some of the issues raised are:

- Problems associated with testing surrogate proteins extracted from organisms unrelated to the genetically modified plant, especially for the purposes of toxicity testing.

- Contrary to notifier claims, there have been reports of allergic responses to *Bacillus thuringiensis*

- The Cry34 protein is still an unknown quantity as they have not been food constituents. The currently known allergens and their related gene sequences do not therefore represent the full range of possible protein sequences capable of producing an allergic reaction

- Loss of function due to heating is not necessarily an indicator of non-allergenicity, but may reflect conformational changes due to heat application. Loss of function may merely indicate denaturation rather than degradation into short peptides, and could therefore still be allergenic.

- Protein abundance in food is not necessarily an indicator of allergenicity and in the Starlink controversy, levels as low as 20 PPB were considered unacceptable because a lower limit for sensitization could not be determined

- Whilst the gastric assays is widely accepted as a useful test of allergenicity it does not represent the ultimate predictor of an allergic response and much work remains to be done in method development for allergenicity assessments

- The application of the kinetic approach to measure gastric digestion is not widely accepted and is currently the subject of discussion and evaluation by the EPA

LEGAL ISSUES

1. THE RIGHT TO SAFE FOOD

The Constitution of the Republic of South Africa 108 of 1996 is the highest law. The supremacy clause in the Constitution is contained in section 2 which provides:

" This Constitution is the supreme law of the Republic; law or conduct inconsistent with it is invalid; and the duties imposed by it must be performed."

The introduction of the interim Constitution and the final Constitution marked a decisive break with the past. The Constitution is not neutral on fundamental values. The Constitution contains a vision for the transformation of society. The centrality of the Bill of Rights and its foundational values to the newly created democracy is expressed in section 7 of the Constitution, which provides:

"Rights

7 (1) This Bill of Rights is a cornerstone of democracy in South Africa. It enshrines the rights of all people in our country and affirms the democratic values of human dignity, equality and freedom.

(2) The State must respect, protect, promote and fulfil the rights in the Bill of Rights.

(3) ……"

Section 27 of the Constitution forms part of the cluster of socio-economic rights dealing with the right to health care, food, water and social security. These rights, read together with the provisions of section 24 of the Constitution entrenches amongst others, the rights of all South Africans to an environment that is not harmful to health or well-being. It imposes a duty on the state to protect the environment, for the benefit of present and future generations.

The Constitution implicitly obliges the State to ensure that South Africans have the right to safe food-as a critically import socio-economic right. Maize is a critically important agricultural product because it is used as a staple for millions of people not only in South Africa, but also in the Southern African region[2] Section 27 provides that: "(1) Everyone has the right to have access to –(a) …… (b) sufficient food and water; and ….." Implicit in the right to access to food is the right to expect that such food and water is safe for human consumption. Section 27(2) requires the State to take "reasonable legislative and other measures" to achieve such rights. It cannot simply sit back; it must take active measures. The

Constitutional Court has delivered two important decisions on the ambit and justiciability of socio-economic rights:

- Government of the Republic of South Africa and Others v Grootboom and Others 2001 (1) SA 46 (CC)
- Minister of Health and Others v Treatment Action Campaign and Others (No.2) 2002 (5) SA 721 (CC)

It is our submission, taking into account our scientific assessment and the lack of monitoring by the government of the impacts of GM maize on animal and human health, the Executive Council will flout these constitutionally protected rights should it grant the approval sought by Pioneer et al. Indeed, the Department of Health, who plays an oversight role on the Executive Council in terms of the GMO Act, has on obligation to safeguard the consumer from foodstuffs that are harmful or injurious to human health. This general obligation is also created by the Foodstuffs, Cosmetics and Disinfectants Act (No 54 of 1972).

South Africa is a Party to the Biosafety Protocol, it having ratified the Biosafety Protocol on the 14 August 2003. The Biosafety Protocol became binding on South Africa on the 12 November 2003. In terms of Section 231 of the Constitution of the Republic of South Africa, 1996, an international agreement such as the Biosafety Protocol is binding on South Africa.

In terms of the Biosafety Protocol, South Africa as a Party is entitled to take decisions regarding the import of GM maize for food, feed and processing on the basis of the precautionary principle as set out in Article 11(8) of the Protocol, which provides as follows:

"*the lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a LMO on biodiversity, taking into account risks to human health, shall not prevent a Party of import from taking a decision, as appropriate, with regard to the import of the LMO in question.*"

These provisions of the Protocol are seen to represent the most explicit examples of operationalisation of the precautionary principle/approach in any multilateral environmental agreement[3].. As has also been canvassed elsewhere in this submission, it is our submission that, having regard to our objections, South Africa should reject the application by invoking Article 11(8) of the Biosafety Protocol.

2. PIONEER/DOW'S APPLICATION NOT IN COMPLIANCE WITH THE BIOSAFETY PROTOCOL

The safety approval sought by Pioneer and Dow is in respect of ***non-existent GM maize.*** According to Pioneer and Dow, the commodity import of Herculex RW GM maize is only expected to take place during the second half of 2006 at the earliest, subject to cultivation of the said maize in the USA during the 2006-growing season[4]. In any event, as has already been discussed elsewhere, the ACB has established that Pioneer and Dow have not yet been able to secure regulatory approval in the USA or Canada for that matter where field trials are being conducted/were conducted.

The safety approval sought by Pioneer and Dow is in respect of ***non-existent GM maize*** whereas the Biosafety Protocol applies to real situations of cross border trade in GMOs and not to speculative trade in respect of non- existent GMOs. South Africa is a Party to the Biosafety Protocol but it has not yet revised its GMO Act, to give effect to the Biosafety Protocol. South Africa's Constitution does, however, make it clear that the Biosafety Protocol is binding on South Africa.

Article 11 of the Biosafety protocol deals with cross border movement of GMOs for direct use as food, feed or processing. Article 11 is thus the "kick off" point for the regulation of Pioneer and Dow's application.

Article 11 requires that prior to an application being made, certainly prior to the transboundary movement and prior to any approval been given, that authorisation must already have been granted by the Party or country of export for the commercial growing or placing on the market and export of the GMO in question. Indeed, Article 11(1)[5] clearly creates implicit obligations on the Party or country of export to first approve a GMO intended for direct use as food, feed and processing, for:

(a) commercial growing; or
(b) placing on the market; and
(c) export.

before the export can take place and certainly, before the Party of import can and should consider an application for authorisation.

So, in other words, before:

(a) South Africa as a Party to the Biosafety Protocol can even consider Pioneer's application; and
(b) Any decision is made by South Africa in respect to Pioneer and Dow's application

the Party or country of export must first have approved the GMO for either commercial growing or placing on the market. Additionally, an export permit must first be issued before an import permit is granted. These are the necessary pre-requisites in order to comply with the Biosafety Protocol.

It was never within the contemplation of the negotiations of the Biosafety Protocol that authorisation of a GMO in the Party of import would take place prior to the Party or country of export first granting its authorisation (for commercial growing and domestic use).

If the country of export as in the case of the USA, is not yet a Party to the Biosafety Protocol, the provisions of Article 11 apply nonetheless, because Article 24 of the Protocol requires that transboundary movements of GMOs between Parties and non-Parties must be consistent with the objective of the Protocol. The principal objective of the Protocol is to *…contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focussing on transboundary movement."* Implicit in this objective is compliance with the minimum standards of regulation set out for transboundary movement of GMOs in accordance with Article 11 of the Biosafety Protocol.

It must be noted also, that 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.

However, since no such prior approval exists inasmuch as no country in the world has authorised the commercialisation of GM maize in question, it is therefore our

submission that the EC, acting on behalf of the Republic of South Africa as a Party to the Protocol, cannot and should not grant the application sought by Pioneer and Dow. If such application were to be granted, then South Africa may be in violation of the Biosafety Protocol.

3. PIONEER, DOW'S APPLICATION WILL WORSEN CRISIS IN GRAIN SECTOR IN SOUTH AFRICA, EXACERBATE FOOD SECURITY

Since the GMO Act came into effect, the EC has authorised several millions of tons of GM maize to be imported into South Africa from Argentina by especially the animal feed industry in the Western Cape because it is cheaper than if they were to purchase maize produced locally and thereby displacing and placing at risk thousand of jobs in the agricultural sector and related industries. The ACB and other groups in South Africa have consistently raised serious concerns about the detrimental impacts of cheap GM maize imports on the production and sale of maize in South Africa. The ACB is also on record for having called upon the Department of Trade and Industry (DTI and the NDA) to conduct an assessment of the negative socio-economic impacts of such imports, including on the impacts on the production of maize in South Africa; the distortions in the market place caused by the sale of such maize; the long-term food security and food sovereignty impacts for South and Southern Africa; and indeed the predatory pricing policies of these grain exporters and the huge subsidy regimes available to them by their governments that assist in attaining those objectives of market domination and displacement of local producers.

During January 2005, South African farmers under the leadership of GRAIN SA launched a countrywide campaign to raise public awareness about the country's agricultural crisis because prices of grains, including maize are being kept low because of the dumping of cheaper subsidised maize from other countries. Bully Bothma from GRAIN SA is reported to say that South Africa is the dumping ground for the rest of the world and that the benefits of cheaply imported maize do not benefit consumers. Rather, it is the big supermarket buyers that benefit[6].

4. LEGISLATIVE LACUNA: POST COMMERCIALISATION TESTING AND MONITORING FOR THE EFFECTS OF TRANSGENIC FOOD AND FEED

South Africans have been eating GM maize for several years yet, neither the National Department of Health nor any other government agency has conducted any post commercialisation testing and monitoring for the effects of transgenic maize on animal and human health. This failure has arisen because the GMO Act does not address the issue of post commercialisation testing and monitoring adequately or at all.

The GM maize in question, also referred to as 'yellow maize' is used in South Africa as an ingredient in feed rations for diary, beef, poultry and egg production[7]. This maize is also a

raw material for the production of starch used in turn, in the manufacture of sweeteners, syrups, and fermentation products. Maize oil is also extracted from the germ of the kernel. Thus maize products are present in a wide range of processed food products.

The Department of Health nor the Executive Council are in any position to make the assumption that GM maize is safe for human and animal consumption, "because no one has become ill or died as a result of consuming the GM maize" as is so frequently stated. This is particularly pertinent, given that South African legislation does not require the labelling of GM food and feed, and hence authorities in South Africa have no way of monitoring what and how much of GM food and feed has been consumed over any given period of time.

Rationale for Monitoring

The reasons for post commercialisation testing and monitoring include *inter alia,* the following:

(a) To determine if pre-commercialisation testing protocols adequately assess the risks;
(b) Long term monitoring is needed to record trends in predicted effects and to detect effects which were not predicted;
(c) Post-commercialisation testing or validation is part of quality control;
(d) Evidence collected over a period of time can confirm the accuracy of pre-release protocols;
(e) Low probability and low magnitude effects would likely escape detection in test-experiments;
(f) To observe smaller and less frequent health risks, an appropriately long time scale is needed;
(g) Rigorous monitoring reassures the public; and the NDA and DOH cannot continue to ignore public health concerns, to do so is irresponsible;
(h) Pre-commercialisation risk analysis has several weaknesses: small scale experiments are only capable of detecting large effects (order of magnitude differences); and
(i) Different kings of monitoring are required for different needs;

Recommendations

The GMO Act must be urgently amended to include comprehensive provisions dealing with the testing and monitoring of the impacts on the environment, animal and human health of GM food, feed and plants. In regard to the testing and monitoring of GM food and feed, the following preliminary recommendations are made:

Animal Health Monitoring should include inter alia, the following:

- Growth and life span: organ development;
- Disease susceptibility: immune status, pathogenicity, infectiousness; and

- Reproductive function-these should take place over at least 4 generations.
- Short and long term monitoring of animal behaviour: health, physiology and metabolism;

Monitoring of Humans

There is a range of techniques that could be used for this purpose. These include non-invasive techniques such as testing immune responsiveness, consecutive blood sampling, hormone assays, and bacterial status etc.

Invasive techniques could include gastric biopsies, tumour histology, and pathology testing. Testing and monitoring can also take place by using human volunteer studies and in this regard, new microbes (viruses, bacteria) containing GM vector elements should be monitored. Particular attention must be paid to the identification and monitoring and invasion of bacteria with antibiotic resistant genes.

5. DEFICIENCIES IN THE GMO ACT REGARDING SPILLAGE OF GMOS DURING TRANSPORT

We are extremely concerned about the possibility that should Pioneer et al's application be granted, the provisions of section 2(2) of the Regulations to the GMO Act may be invoked and imports of GM maize into South Africa will take place without any biosafety oversight.

This concern is exacerbated by our profound disquiet concerning the negative environmental impacts that may arise from the spillage of whole GM maize grains during transportation and the milling process itself. We note with alarm that the transportation of GMOs as well as storage at silos, and mills to be used in the processing of GMOs are captured by the extraordinarily wide definition of contained use in section 1 the GMO Act. Contained use is defined to mean *"any activity in which organisms are genetically modified or in which such genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which physical barriers or a combination of physical barriers together with chemical or biological barriers or both are used to limit contact thereof, with the environment."*

We strenuously dispute this definition, because the transportation of GMOs and indeed, the storage and milling thereof, constitute releases, requiring appropriate and adequate biosafety measures (which do not in any event exist in terms of the GMO Act) that are designed to prevent ecological harm. This is particularly pertinent given that the GMO Act exercises regulatory functions in respect only of those facilities where actual genetic modifications are conducted. Only academic and research institutions and bodies involved in genetic modifications under contained use, may be required to be registered[8].

Our objections to the deeply flawed and biased provisions of the GMO Act cannot be overemphasised enough. We are aware that the government too, is cognisant of these regulatory deficiencies, and in this regard, Dr Julian Jaftha, the erstwhile registrar of the GMO Act, has recently proposed five measures regarding the importation of genetically modified corn that have only commodity clearance in South Africa. According to the June 2004 issue of the Animal Feed Manufacturers' Association (AFMA) publication, the measures include the following:

- To address spillage or unintentional release during the importation of GM grain with only commodity clearance in South Africa, the transportation of imported whole GM grain is limited. Immediate milling of all consignments imported for use, as commodity in SA is necessary.
- Not all GM corn that have commodity clearance status (food and feed), have general release status as well. Thus, if only one event in the consignment does not have general release status, it means that the whole consignment is subject to immediate milling.
- Milling is to be done as close as possible to the port of entry to minimize the transportation of whole grain. The grain must be transported from the port of entry directly to the miller on a single trip without offloading and reloading until delivered at the miller.
- When applying for clearance, the importer must indicate where the grain is going to be milled and the mode of transport to be used. This information will help the Department of Agriculture to trace any spillage into the environment and to identify the responsible company.
- To prevent the purchase of GM material without informed consent, the seller of GM grains or grain products, e.g. animal feeds must clearly indicate the GM status of the consignment to buyers, as this may influence further trade negotiations and the use of these products.

(Source: Crop biotech update 23 July 2004)

These measures are welcome, but must, however, be given effect to in the Regulations under the GMO Act, for enforcement and compliance purposes. We also point out, that we are not convinced that any or any proper monitoring has or will take place, to ensure that GMOs imported for food and feed does not cause harm to the environment as a result of spillage during import, transport and processing phases. In fact, we are not aware of any measures being taken by either the NDA or the Department of Environmental Affairs and Tourism of such monitoring.

SCIENTIFIC ASSESSMENT

The scientific assessment is based on the information provided as part of the notifier application. The information provided for comment within a period of two weeks is in excess of 1500 pages comprising largely technical scientific data. The information provided is only that deemed unclassified. Notwithstanding this volume of information, there appear to be several omissions. Each section in the notifier application references the associated annexure. No such reference is found in the notifier application for the digestibility assays (page 30 of the notifier application). A great deal of the information relating to the digestion assays was obtained from other researchers who have had sight of this data [29,38].

1. BACKGROUND

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[9]. 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[9].

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)[10], 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[10,11].

The Herculex Maize Varieties

The Herculex Insect Protection Family has been developed by Dow AgroSciences LLC and Pioneer Hi-Bred International, Inc.[12] The insect protection family, containing the original Herculex I, has now been expanded to include Herculex RW and Herculex XTRA[12]. The assessments of the Cry proteins are based on surrogate proteins rather than the transgenic protein produced by the genetically engineered crop. Especially, toxicity assessments, which require larger quantities of the protein for meaningful analyses are conducted using these surrogate proteins. Cry34Ab1 and Cry35Ab1 were produced in P*seudomonas flourescens* for the purposes of the assessment of Herculex RW (page 22 of the notifier application). This practice has come under criticism because of the peculiarities of each transformation event,

which by definition implies a unique gene arrangement[13]. Further, assuming the unlikely chance of precise incorporation into *P. flourescens*, the organism is kingdoms apart from maize with different protein generation and regulatory pathways.

2. HERCULEX™ RW: DESCRIPTION AND CHARACTERISTICS

Gene Modifications

Maize line 59122 otherwise known as Herculex™ RW is a transgenic maize line that has been engineered to produce two insect control proteins Cry34Ab1 and Cry35Ab1 as well as the PAT protein to withstand the use of glufosinate-ammonium herbicides. The Cry proteins Cry34Ab1 and Cry35Ab1 act synergistically to confer resistance against coleopteran insect pests, in particular corn rootworm larvae (*Diabrotica* spp.).

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[9,14]. The pat gene is sourced from the ubiquitous soil fungus *Streptomyces viridochromogenes*[15] The *pat* gene 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[16,17].

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[18]. 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[19], 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[20]. 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[19]. 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[21].

3. THE STARLINK CORN CONTROVERSY

StarLink corn hybrids produced by Aventis Crop contain a plant pesticide protein (Cry9C) derived from *Bacillus thuringiensis* which kills certain destructive pests of corn such as the European corn borer. In 1998 the Environmental Protection Agency (EPA) approved Starlink corn 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[22]. The potential for allergenicity of Starlink corn was not completely ruled out because some tests showed that the Cry9C protein could survive cooking or processing and was hard to digest. The contamination of the human food chain led to a public outcry and massive recall of all products thought to contain the Starlink variety.

4. 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. 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[23]. No test exists that is fully predictive of potential allergenicity[24]. 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[25,24]. 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)[24,26.]

- *Assessment of Allergenicity*

Several elements were considered 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[24]. The gastric stability assay has been widely accepted as an important part of allergenicity assessments of genetically modified and support in the literature continuing through the FAO/WHO consultation in 2001 resulted in acceptance by the Codex Alimentarius[27,28,29.]. 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[24,30]. Typically the test is a measure of comparative resistance to pepsin proteolysis[24]. Variations in human digestive capacity necessitate the application of a standardised protocol for this assessment and Thomas et al (2004)[31] have published one such protocol. In the face of the lack of definitive tests for determining potential allergenicity, it is the most reliable test[29,24, 32].

- *Allergenicity to Bacillus thuringiensis*

Contrary to the statement in the notifier application (Page 28, second paragraph), 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[33]. Aerial spraying of Bt pesticides precipitated increased respiratory health effects in local residents[34].

- *Allergenicity of Novel Proteins*

Cry34 proteins impacts on human exposure are little reported and understood. The value of sequence homology is not immediately apparent as questions regarding homology and allergenicity still have to be answered. Matched sequences in this instance will require more study as the Cry34 protein is still an unknown quantity given that they have not been food constituents, and are not similar to food proteins or known allergens. The currently known allergens and their related gene sequences do not therefore represent the full range of possible protein sequences capable of producing an allergic reaction[29] and negative results in sequence homology searches are not necessarily proof of lack of allergenicity. Allergenic responses to new proteins that have not previously formed part of the food supply cannot therefore be ruled out.

- *Heat Stability and Significance*

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[35,36]. More generally, loss of function may merely indicate denaturation rather than degradation into short peptides, and could therefore still be allergenic.

- *Protein Abundance*

Abundance of a particular protein in food has also been used in predicting the likelihood of allergenicity, since the bulk of known food allergens are typically plentiful proteins[29]. Levels as low as 20 PPB on Starlink were considered unacceptable because a lower limit for sensitization could not be determined[37]. The FAO/WHO assessment was not made by reference to heat stability or protein abundance, but noted that '…allergens can sensitize susceptible individuals at less than milligram levels, possibly at less than microgram levels," and "Thus, level of expression cannot yet be incorporated into the assessment of the allergenicity of genetically modified foods."[28,29].

- *Reliability of Gastric Assays*

It is important to note that whilst gastric assays remain the most reliable form 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[29]. Also the assays may not always be appropriately applied. If, for example, if 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[29]. 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.

- *Proteolysis of Cry34 and Cry35 protein*

Dow submitted two sets of digestion data for the Cry34 proteins. In the first study (MRID 452422-12), Cry34Ab1 was digested within 30 minutes[38]. The Cry34 results prompted Dow to submit a second set of digestion data with the tests carried out under the same conditions with the addition of shaking during incubation[38] (MRID 455845-02). The results that Dow report as being the final results are that the Cry34Ab1 protein was digested under simulated gastric conditions in 6.5 minutes and the Cry35Ab1 protein in under 5 minutes (page 30 – notifier application). Gurian-Sherman (2003)29 in an assessment of the methodology used by Dow to assess allergenicity found that the protocol was flawed. The notifiers in support of their application have developed a kinetic assessment of the degradation of the novel Cry protein Cry34Ab1[38]. Dow measured rate of digestion to determine 90% digestion as opposed to using the longest time-point where SGD test protein can be detected. The kinetic approach to assessing digestion is not widely accepted and the value and significance of this approach is currently the subject of discussion by an open meeting of the FIFRA Scientific Advisory Panel[39].

The regression analysis provided by Dow to determine the 90% digestion time was not accompanied by any statistical analysis of variance, such as a confidence interval. This coupled with apparent variability in the detection gels studied by Gurian-Sherman suggested that the time point 6.2min (DT_{90} – time taken for 90% of the sample to decay) might not be statistically significant. Also, Dow used more than three-fold higher proportion of pepsin-to-test-protein (Cry34Ab1) in its SGD assay which may make Cry34Ab1 appear to be less stable than it would if carried out according to the literature[29].

5. GENE TRANSFER

- *Horizontal Gene Transfer (HGT)*

Horizontal gene transfer (HGT) is the transfer of genetic material between organisms, outside the context of parent to offspring reproduction[40],[41]. It is most commonly recognized as infectious transfer[42]. HGT frequencies are now known to be much higher than originally thought. The evolution of antibiotic resistance, for example, is an indicator of the frequency of gene transfer, given that antibiotics have been used in medicine only for about 50 years[42]. The intentional modification of plants could through horizontal gene transfer result in the unintentional modification of other organisms. What the possible impacts of such gene transfer might be is not known.

- *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[43]. 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[44]. 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[45]. Recombinant DNA fragments and Cry1Ab protein was also found in the gastrointestinal contents of pigs fed genetically modified corn[46].

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[4] Application for commodity clearance of genetically modified organisms submitted jointly by Pioneer Hi-Bred International Inc as represented by Pioneer Hi-Bred RSA (Pty) Ltd and Mycogene Seeds c/o Dow Agrosciences LLC as represented by Dow Agrosciences Southern Africa (Pty) Ltd., January 2005.

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