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ACB's objection to Monsanto and Mycogen Seeds c/o Dow AgroScience's application for commodity clearance of a multi stack event MON89034 x TC1507 x MON88017 x DAS-59122 (Smartstax)

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Introduction

The African Centre for Biosafety (ACB) is a non-profit organisation, working on biosafety issues, in the public interest. The ACB hereby places on record its objections to the application made by Monsanto Company and Mycogen Seeds c/o Dow AgroSciences to the Department of Agriculture Forestry and Fisheries (DAFF) for commodity clearance of a multi stack event. The event in question is MON89034 x TC1507 x MON88017 x DAS-59122 (the event).

The application received by the ACB is marked "CBI Deleted" and the excluded information extends to references used in support of the claims made by the applicant making a full assessment of the claims impossible. Regardless, on the basis of the documents received, our comments on the event are outlined below.

The event is an eight trait maize that incorporates previously approved GE traits of herbicide tolerance (Roundup/Glyphosate and glufosinate herbicides) and insect resistance into one seed variety for the first time providing comprehensive insect and weed control, according to a Monsanto press release.[1] Two herbicide tolerance and six insect resistance traits are effectively combined in the event.

The respective resistances are conferred to the event by contributions of 4 recombinant maize lines as follows:

1. MON89034: Maize resistant to Lepidoptera (cry1A.105, modified cry2Ab2)
2. TC1507: Maize tolerant to glufosinate herbicide and resistant to Lepidoptera (cry1F, *pat*)
3. MON 88017: Maize tolerant to glyphosate herbicide and resistant to Coleoptera (cry3Bb1, *cp4 epsps*,)
4. DAS-59122: Maize tolerant to glufosinate herbicide and resistant to Coleoptera (cry34, cry35, *pat*)

The eight insect resistance (cry) proteins and herbicide tolerance traits are:

- *Pat:* phosphinothricin N-acetyltransferase (from *S.viridochromogenes*) for glufosinate herbicide two copies of the pat gene and its promoter and terminator are present, one in each of the events DAS-59122 and TC1507.
- *CP4 epsps:* (event MON 88017), 5-enolpyruvylshikimate-3-phosphate synthase (*Agrobacterium tumefaciens* CP4) for glyphosate herbicide tolerance. The genome has one copy of the MON88017 event.
- *cry1A.105:* (event MON 89034), a chimeric Cry1 delta endotoxin (*Bacillus thuringiensis*) for insect (Lepidopteron, moth) resistance. The genome has one copy of the event MON89034.

- *cry2Ab:* (event MON 89034), Cry2Ab delta endotoxin (*Bacillus thuringiensis*) for Lepidopteron (moth) resistance. The genome has one copy of event MON89034
- *cry3Bb1:* (event MON 88017), Cry3Bb1 delta endotoxin (*Bacillus thuringiensis* subsp.kumamotoensis strain EG4691) for Coleopteran (corn rootworm) resistance. There is one copy of the event MON88017
- *cry1Fa2:* (event TC1507), Cry1F delta endotoxin (*Bacillus thuringiensis* var.aizawai) for Lepidopteron (moth) resistance. There is one functional copy of the event
- *cry35Ab1:* (event DAS-59122-7), Cry35Ab1 delta endotoxin (*Bacillus thuringiensis* strain PS149B1) Insect Coleopteran (corn rootworm) Resistance. There is one copy of the *cry35Ab1* transgene in the genome.
- *cry34Ab1*(event DAS-59122), Cry34Ab1 delta endotoxin (*Bacillus thuringiensis* strain PS149B1) for Coleopteran (corn rootworm) resistance, here is one copy of *cry34Ab1* transgene in the genome (note *cry34Ab1* and cry 35Ab1 are combined in a single event DAS-59122).

On July 15, 2009 Monsanto and Dow AgroSciences announced that approval has been received to introduce the event into Canada and the US.[2] The approvals were not accompanied by any environmental risk assessment. Further, the EPA has concluded that "a lower corn rootworm (CRW) refuge of 5% is scientifically justified".[3] The Canadian Biotechnology Action Network (CBAN) has questioned the approval procedure on the basis that Health Canada did not conduct a health assessment and viewed this to be in contravention of the Codex Alimentarius Food safety Guidelines which require stacked events to undergo a full assessment as a new event due to the possibility of unintended effects arising from synergistic effects of the crossed transgenic events.

The Austrian Federal Department for Health have come out very strongly against such untested approvals of stacked events on the basis of previous approvals of the individual events stating that "a stacked organism has to be regarded as a new event, even if no new modifications have been introduced. The gene-cassette combination is new and only minor conclusions could be drawn from the assessment of the parental lines, since unexpected effects (e.g. synergistic effects of the newly introduced proteins) cannot automatically be excluded. Furthermore, it should not be neglected that two of the parental lines, GM maize MON89034 and GM maize MON88017, have not yet gained authorisation within the European Union."[4]

GENE FLOW IN MAIZE

Gene flow is a natural process by which genes move from one location to another, either from one genome to another, or by the movement of pollen from plants into a new environment.[5] Transgenes from GM crops may flow to GM plants or to wild relatives or into

new environments. 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.[6] Dispersal of transgenes into maize landraces was first reported in 2001 in the Mexican state of Oaxaca.[7]

The import for commodity and the possibility of accidental spillage is not unlikely. In South Africa, maize has undergone hybridisation with other maize varieties or landraces. Maize has undergone many generations of breeding and natural selection to create numerous locally prized varieties suited to South Africa (adapted for increased resistance to amongst others soils, drought and pests). This forms part of the indigenous knowledge systems and unique seed banks of maize varieties and landraces. Many small-scale farmers will plant improved varieties adjacent to local varieties in an attempt to promote hybridisation between the varieties. Given the subsistence nature of a lot of these farming practices and the small acreage of small-scale farms, neighbouring farms are very close and often maize plants are within out-crossing distance of their neighbours. Traditional small-scale African farmers also practice livestock farming almost always under free-range conditions. Often, the animals are grazed communally under an open access or common property tenure system which is accompanied by widespread manure dispersal.[8]

Since GMO maize will freely cross-pollinate with non-GMO maize, there are risks of contamination of South Africa's landraces and loss of South Africa's unique maize seed diversity. A lack of co-existence of GMO with non-GMO maize can result in rejection of maize from importing countries that have not approved this transgenic as well as the spread of herbicide resistance, and non-target effects on other plants animals[9] and soil microorganisms[10,11,46] After almost three decades of world-wide use, confirmed resistance to glyphosate exists in *Lolium rigidum* (annual ryegrass) in Australia, South Africa, and California; *Lolium multiflorum* (Italian ryegrass) in Chile, *Eleusine ind*ica (goosegrass) in Malaysia; and *Conyza Canadensis* (marestail) in certain states of North America.[12]

In the event that unintentional field release does occur, the farmer may still incur financial liability since the event is patented. Farmers are potentially susceptible to prosecution for violation of this patent especially in the event of crop flow or seed sharing and exchange with other farmers using conventional seeds. Monsanto has prosecuted farmers whom it considers guilty of infringing its intellectual property and patents. Canadian Percy Schmeiser, whose field was contaminated by Monsanto-developed oilseed rape (Canola) pollen from a neighbouring farm growing the variety, was found guilty under Canadian patent law of patent infringement even though there was no way that he could have prevented the contamination. The Center for Food Safety in their 2005 report "Monsanto vs. US Farmers" revealed that Monsanto had filed 90 lawsuits against U.S. farmers in 25 states that involved 147 farmers and 39 small businesses for patent infringement.[13]

Dr Lukeshni Chetty is the Deputy Director of the GMO Monitoring Research Unit at the South African National Biodiversity Institute (SANBI).[14] SANBI is tasked with conducting research into the environmental impacts of genetically modified organisms (GMOs) in South Africa including research on non-target organisms, target organisms, gene flow and ecological impacts. SANBI has the very clear mandate to "monitor and report regularly to the Minister on the environmental impacts of all categories of genetically modified organisms, post commercial release, based on research that identifies and evaluates risk".[14]

To date, not much research has been carried out into gene flow in South Africa.

Dr Chetty is a co-author with Chris Viljoen on a paper recently presented at the International conference on "Implications of GM crop cultivation at large spatial scales" held in Bremen in March 2010. The title of the talk was" An African perspective of GM maize gene flow ".[15] Whilst the conference papers are yet to be published on the conference website,[16] a summary of the proceedings has been published:[17]

"In their talks, Chris Viljoen from South Africa and Denis Aheto from Ghana gave an impression of the conditions of agriculture in Africa. Not only because of the climatic conditions but also because the high importance of subsistence agriculture and partly very small fields the conditions for regulation differ considerably from the situation in Europe and other countries on the Northern hemisphere. In South Africa, several genetically modified varieties are commercially used; however, no regulations on segregation distances or identity preservation systems or labelling regulations are in place. Also data on actually existing geneflow between GM and conventional crops are widely lacking. This could impact on the development perspectives of conventional as well as organic agriculture."

To make assumptions about no negative possible impacts on the environment due to claims in the application that no cultivation will take place, is to ignore the local conditions and cultural values and habits of much of the small-scale maize growing community, who rely most on these varieties for their subsistence.

GLUFOSINATE AND GLYPHOSATE

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.[18,19]

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.[20] 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.[21] The mechanism for this effect is still to be determined.[22] Glyphosate use, an integral part of planting Roundup Ready crops, has indicated several unwanted effects on aquatic systems,[23] terrestrial organisms[24] and ecosystems.[25] Negative impacts on human,[26,27] rodent[28] and fish[29] health have also been observed. There is a paucity of experimental studies devoted to health or environmental effects of glyphosate-tolerant GMOs or glyphosate itself.

EXPOSURE TO AND CONTAMINATION BY GLUFOSINATE AND GLYPHOSATE

The Ministry of Agriculture, Fisheries and Food (MAFF)[1] reported glufosinate residue levels in commodities for animal feeds were high at 50 mg/kg in barley straw and pea stalks and 20 mg/kg in wheat straw and field bean stalks. When cereal crops were processed, 10-100% of the residue remained.[30] Herbicide residues left on food crops are of concern especially on processed maize, or peas and in liver and kidney from animals fed on contaminated cereal straw.[31] FAO and WHO recommendations set the acceptable daily intake (ADI) for glufosinate at 0.02 mg/kg.

ALLERGENICITY

An increasing area of concern related to GM plants, is the health concerns of the transgenic plant itself e.g. the chemical reactions that occur during the cooking of novel foods, may result in exposure to allergenic compounds.

Dealing with food allergies i.e. adverse reactions to what might otherwise be considered harmless food or food components is hampered by gaps in the body of knowledge relating to the range of known food allergens.[32] The responses arising out of food allergies range from mild to life-threatening responses and are potentially life threatening for an estimated 2% of adults and 8% of children. Whereas conventional plant breeding has increased the range of food proteins introduced into human diet, with little or no adverse impact, genetic modification of higher plants yields novel proteins which might cause allergic reactions.

An example is Starlink corn, produced by Aventis to express Cry9C which kills the European corn borer. Starlink was approved by the EPA in 1998 for use only as animal feed with a zero-tolerance level for its use in human food based on the fact that this particular Bt

[1] Ministry of Agriculture, Fisheries and Food, a former department of UK government, replaced in 2001

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.[33] The contamination of the human food chain led to a public outcry and massive recall of all products thought to contain the Starlink variety.

The need for assessing 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.[34] 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).'[35.]

In 1996 the IFBC and the ILSI suggested a decision-tree approach. A joint FAO/WHO 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.[32] 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 β-lactoglobulin consisting of 7-10 amino acids in length.[36,]

HEAT STABILITY

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.[37,38] 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.[39] 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.[40] 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.[41] Recombinant DNA fragments and Cry1Ab protein was also found in the gastrointestinal contents of pigs fed genetically modified corn.[42]

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.[43]

EXPOSURE TO CRY PROTEINS

According to the Codex Alimentarius Guidelines:

"Information about the known patterns of use and consumption of a food, and its derivatives should be used to estimate the likely intake of the food derived from the recombinant-DNA plant. The expected intake of the food should be used to assess the nutritional implications of the altered nutrient profile both at customary and maximal levels of consumption. Basing the estimate on the highest likely consumption provides assurance that the potential for any undesirable nutritional effects will be detected. Attention should be paid to the particular physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems"[44]

The commodity import of maize may include maize kernels (seed), flour and oil to be used in animal feed and human food. In a South Africa where maize is a staple for the majority of the population, exposure analysis should be carried out. The modifications in this event result in novel proteins that impact on risk assessments carried out simply by virtue of the fact of differing consumption patterns i.e. Africans consume larger quantities of maize per capita than do Americans, therefore exposure and possible adverse impacts to novel proteins for Africans is higher than for Americans (Table 1).[48,45]

CONSUMER	ANNUAL/CAPITA (KG)	PROPORTION DAILY CALORIES/CAPITA	PROPORTION DAILY PROTEINS/CAPITA	PROPORTION DAILY FAT/CAPITA
AFRICA (DEVELOPING COUNTRIES)	38	0.1	0.2	0.06
MEXICO	126	0.3	0.3	0.1
NEW ZEALAND	3	0.007	0.005	0.008
USA	13	0.03	0.02	0.002

A protein or amino based food hazard is a quantitatively different risk for Mexicans and Africans than it is for Americans and New Zealanders because of different exposures. That is why international food safety guidelines allow consumption patterns to be taken into account.[48,44] Furthermore, maize (kernels, cobs, leaves, stalks) are a popular animal feed in South African husbandry and the increased exposure raises increased risks of possible toxic or allergenic effects to animals used in agriculture (predominantly chickens and cattle).[46]

TOXICITY OF CRY PROTEINS IN Bt-TRANSGENIC PLANTS

It is very clear that the Bt-toxins expressed in transgenic plants have never been intensively analysed, but what is clear is that they are vastly different from the bacterial *Bacillus thuringiensis* protoxins, used in organic and traditional farming and forestry for decennia. Already, at the gene level, the coding is for active Bt toxins which might have a number of potentially unwanted biological characteristics, ranging from solubilization of the protein under natural conditions and effects on insect and mammalian cells, to persistence and non-target effects in the environment.[47] Further, there may be post-translational modifications that may influence conformations, cellular targets and biological effects of GM plant-expressed Cry toxins. What these post-translational modifications might be has not been the subject of intensive study.[48]

Some initial observations of possible health risk are starting to emerge in the body of scientific literature:

- Human and monkey cells exposed to Cry toxins from the extra- or intra-cellular environment are killed or functionally disabled[49,50]
- Influenza A infections in mice were changed from silent to lethal encounters by co-exposing the animals to Cry toxin[51]
- Farm workers exposed to Bt spores developed IgG and IgE antibodies to Cry toxin (Cry1Ab)[52,53,54]
- Cattle fed the Bt176 maize variety demonstrated undegraded Cry1Ab through the whole alimentary tract, and the intact toxin was shed in faeces[55]

Occupational exposure to novel proteins, and potential allergic sensitization, has had little study, but could be of public health significance. An amazing number of foods have been proven to evoke allergic reactions by inhalation[56] Inhalant exposure to Cry toxin containing GM crop materials may take place through pollen in rural settlements and also through dust in workplaces where foods are handled or processed.

CONCLUSIONS

The ACB strongly urge DAFF not to approve the application for the event because:

- The ACB is concerned that a full and truly participatory public process is not possible due to the lack of completeness of information of the version of the application made available for public assessment
- This stacked event must be treated as a new event and not be rubberstamped on the basis of the claim that the individual events have been previously approved. To do so would be to ignore any possible synergistic or antagonistic effects that might arise from crossing to produce the stacked event
- Exposure issues to both the herbicide and insecticidal proteins have not been adequately assessed
- Patterns of consumption of maize have to be considered and associated risks arising from these need to be assessed
- The commodity import of the maize event carries unacceptable risks of gene escape since maize bought for feed is saved for seed by farmers and planted. Furthermore, evidence from other countries shows that these seeds will be spilled along transportation routes or on farms (where the seed has been purchased for seed) and feral plants may be established. This will impact food security and sovereignty of South Africa's landraces and may jeopardize maize exports (that are contaminated with the event
- In order to comply with local and international legislation, a monitoring system with a detection system specific for the event must be put in place so that impacts on biodiversity, gene escape and transboundary movements can be detected.

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