Technical Opinion no. 1597/2008

Proceedings: 01200.00.000062/2006-21
Applicant: Syngenta Seeds Ltda.
CNPJ: 49.156.326/0001-00
Address: Avenida Nações Unidas, 1801, 4º Andar, 04795-900 São Paulo, SP.
Matter: Commercial release of Genetically Modified Corn.
Previous extract: 421/2006, Published on 02.21.2006.
Meeting: 116th CTNBio Regular Meeting, held on September 18, 2008.
Decision: GRANTED.

CTNBio, following approval of an application for Technical Opinion related to commercial release of genetically modified glyphosate tolerant corn (GA21 Corn, Event GA21), as well as all progenies originated from the GA21 transformation event and its derivatives of crossing of non transgenic corn lineages and populations with lineages carrying event GA21, was favorable to the GRANTING under the terms of this technical opinion.
Syngenta Seeds Ltda. requested a CTNBio Technical Opinion for the free registration, use, essays, tests, sowing, transportation, storage, marketing, consumption, import, release and discarding of glyphosate tolerant corn (Zea mays, L.). Event GA21 was produced through microprojectile bombarding with a suspension of culture cells, using plasmid pDPG434, derived from vector pSK, which is commonly used in molecular biology and is in turn derived from pUC19. Elements for insertion in the gene are contained within NotI restriction fragment, containing the expression cassette used to generate event GA21. GA21 corn contains the rice actin 1 gene that acts as promoter; mepsps gene (modified corn epsps gene) that codifies the mEPSPS protein and grants tolerance to glyphosate herbicide; nos gene, responsible for transcription termination; and OTP sequences, responsible for digesting the mEPSPS protein to chloroplast. The genic construct used to insert the mepsps gene in corn resulted from stable insertion of a functional copy of such gene, which granted plants tolerance to the glyphosate herbicide. The mEPSPS enzyme amino acid sequence expressed in GA21 corn is 99.3% identical to the conventional corn endogenous enzyme sequence , which is expressed in a concentration significantly lower than mEPSPS protein of GA21 event. Quantifiable concentration of mEPSPS protein has been detected in most part of tissues of plants derived from GA21. No sequence introduced in event GA21 or of its donors is known to be pathogenic to humans or animals. EPSPS proteins are ubiquitous in nature and are naturally present in food derived from plant and microbial sources, included in the everyday diet of humans and animals. Bromatology tests and procedures for quantification of corn kernel different nutritional components have been conducted. The analyses suggest that the level of measured components have not changed beyond corn natural variation. No consistent pattern emerged suggesting that biologically significant changes in composition or nutritive value of the kernel or forage took place following the transformation or expression of the mepsps transgene. Analysis of amino acids inserted in mEPSPS enzyme reveals no homology with toxic proteins for mammals and toxic potential for humans is not expected. Absence of toxicity was also verified in studies with animals using high doses of purified protein. The mEPSPS enzyme expressed in corn with the GA21 event has no typical characteristics of known allergens. There is no homology regions when the

introduced sequence is compared with sequences of known allergens. The data submitted indicate an extremely low likelihood that the intact protein may be absorbed through the intestine mucosa during consumption and establish immunochemical affinity to antibodies, including IgE antibodies, primarily responsible for allergic reactions. In addition, mEPSPS enzyme is promptly degraded by acid and enzymatic hydrolysis when exposed to fluids similar to gastric and intestinal fluids. According to data on nutritional and compositional equivalence of GA21 corn with its conventional isogenic version, no GA21 corn metabolite has potential to concentrate in the food chain, in addition to what may be expected from the widely cultivated conventional corn. In Brazil, there are no kindred species of corn distributed in nature. However, genic flow for local open pollination varieties is possible, however this flow is as risky as the one caused by commercial genotypes available in the market. Coexistence of cultivars is possible between conventional corn (improved or local varieties) and transgenic from the agronomic viewpoint. The likelihood of a transgenic plant changing into a weed, as well as of originating a weed by crossing GA21 corn with other corn plants is negligible, due to the biologic characteristics of the species and the fact that corn does not survive well without human intervention. Therefore, it is expected that GA21 corn has an environmental behavior similar to that of common corn. The likelihood that a mepsps gene of a transgenic plant migrates to other organisms is practically inexistent. The epsps gene is common to plants, fungi and microorganisms, is abundant in nature, and is not a significant risk for soil microbiota. Besides, there is evidence that plant genes have sometimes been transferred to bacteria in natural conditions. Glyphosate is registered with the Ministry of Agriculture and Supply – MAPA, Ministry of Environment – MMA and a monograph on glyphosate is approved by the National Sanitary Surveillance Agency – ANVISA. The use of the glyphosate herbicide in GA21 crops shall comply with applicable rules, such as Law no. 7,802, of July 11, 1989 (Agricultural Defensives Act). CTNBio reached a conclusion that cultivation and consumption of GA21 corn are not potential causes of significant degradation to the environment and do not risk human and animal health. For these reasons, there are not restrictions to the use of this corn and derivatives, except in locations mentioned by Law no. 11,460, of March 21, 2007. Coexistence between cultivars of conventional corn (improved or local varieties) and transgenic corn is possible from the agronomic viewpoint and shall comply with the provisions of CTNBio Ruling Resolution no. 4. The applicant shall conduct a post-commercial release monitoring plan under CTNBio Ruling Resolution no. 3 and shall have a term of thirty (30) days from the date of publication of this Technical Opinion to adequate its proposed post-commercial release monitoring plan, according to Annex 1 of CTNBio Ruling Resolution no. 5, of March 12, 2008. Under Article 14 of Law no. 11,105/2005, CTNBio holds that the request complies with applicable rules and legislation aimed at securing the biosafety of the environment, agriculture and human and animal health.

CTNBio TECHNICAL OPINION

I. GMO Identification

GMO name: GA21 corn, Event GA21.

Applicant: Syngenta Seeds Ltda.

Species: Zea mays – Corn

Inserted characteristics: Tolerance to glyphosate herbicide

Method of insertion: Particle bombarding (biobalistics)

Prospective use: Production of fodder and kernels for human and animal consumption of the GMO and its derivatives.

II. General Information

Zea mays L., corn, is a species of the Maydae tribe, included in subfamily Panicoidae, family Graminea (Poacea). Genera belonging to the Maydae tribe include Zea and Tripsacum in the Western Hemisphere. Corn is a separate species within the Zea subgenus, with a chromosome number 2n = 20,21,22,24(16).

Corn is a cereal essentially of American origin, the continent where its closest wild relatives, teosinte and Tripsacum(31), may be found. One assumes that the specific region of corn birth is Mexico and that it originates from teosinte, Z. mays Mexicana (Schrader) Itis, over eight thousand years ago. Teosinte may be found in Mexico and some locations of Central America, where it may cross with cultivated corn in production fields. Cultivated corn may also cross with a most distant genus, the Tripsacum. This crossing seldom happens and results in a male-sterile progeny.

Maize is an annual plant, high and robust. It is one of the most efficient plants in converting solar energy into food and is the raw-material of several products, being one of the most important food sources in the world. Over the past eight hundred years, cultivated corn gained several valuable agronomic characteristics, at the cost of losing the ability to survive in nature.

Out of all cultivated plants, corn is probably the one possessing the largest genetic variability. Today, about three hundred races of corn are identified and, within each such race, there are thousands of cultivars. Corn is currently the cultivated species that reached the highest degree of domestication and it may only survive in nature when raised by man(6). Normally, the maintenance of this genetic variability has been achieved through individualized storage, in germplasm banks, under controlled humidity and temperature. There are several germplasm banks, in Brazil and all over the world. Embrapa, the Brazilian Agricultural Research Agency, has two germplasm banks, one at Embrapa Recursos Genéticos e Biotecnologia, Embrapa Genetic Resources and Biotechnology, in Brasília, Federal District, Brazil, and another at Embrapa Milho e Sorgo, Embrapa Maize and Sorghum, in Sete Lagoas, Brazil. Corn is farmed in over 100 countries, with a total estimated production of 705 million tons per year.

Brazil is the world third largest corn producer, with an output of about 35 million tons in 2005, behind the United States of America (282 million tons) and China (139 million tons)(18). In Brazil, corn is planted basically in two different crops (summer and safrinha, or small crop) and cultivated in practically all the domestic territory, with 92% concentrated in the Southern Region (47% of production), Southeastern Region (21% of production) and Center Western Region (24% of production)(9).

Corn is one of the most efficient plants in converting solar energy in food and is used as raw material for several products. The increase in corn consumption exceeded 100 million tons between 1993 and 2001, representing an average yearly increase of 11.1 million tons per year. A large part of this increased production was due to genetic improvement, leading to ears containing about 1,000 seed-corns. Increased corn production and consumption all over the world is associated to its multiple uses, population growth, changes in feeding habits, and growth in the number of farmed swine and poultry.

Weeds are among the main corn culture problems in Brazil. There are some alternatives for controlling weed and treatment with herbicides is the most used method. Brazil is the world's third largest consumer of pesticides. The country has currently over 140 pesticides registered for corn and the use of agricultural defensives is one of the important factors affecting farmers' health in Brazil, where it is responsible for intoxication of one million individuals each year(2). In this environment, the use of corn cultivars containing event GA21 would be one extra alternative to turn.

Development of GA21 represents one option to control weeds that compete negatively with corn production. GA21 was obtained by transforming a culture of corn lineage through microprojetile bombardment (biobalistics) and expressed as a corn 5-Enolpiruvylshikimate-3-Phosphate double mutated synthase protein (mEPSPS), which grants tolerance to glyphosate herbicide. GA21 corn is already commercial released for cultivation in Argentina (1998), Canada (1998), Japan (1998) and USA (1997). It is used in human and animal food in Australia (2000), Canada (1998), European Union (2005), Japan (1999), Korea (since 2002), China (2004), Argentine (2005), Mexico (2002), Philippines (2003), South Africa (2002), Taiwan (2003) and USA (1996) (1).

III. Description of the GMO and Proteins Expressed

Corn plants of event GA21 express the mutated double corn 5-Enolpyryvilshikimate-3-phosphate synthase protein (mEPSPS). The enzyme belongs to the shikimic acid metabolic pathway, involved in the biosynthesis of aromatic amino acids (phenylanine, tryptophan and tyrosine), present in plants, fungi and bacteria, yet absent in animals (Figure 1).

Figure 1 – Shikimic acid pathway

Event GA21 was produced through microprojectile bombardment of a suspension of culture cells(23), using plasmid pDPG434, derived from vector pSK, which is commonly used in molecular biology and is derived from pUC19. Elements for the insertion of the gene of interest are within the restriction fragment NotI, containing the expression cassette used for generating event GA21:

(a) Actin 1: Region 5' of rice (Oryza sativa) actin 1 gene containing the promoter, the first exon and intron(27);

(b) OTP: N-terminal sequences of chloroplast transit peptide (CTP) based on CTP sequences of sunflower Helianthus annus) and corn (Z. mays), present to drive the mEPSPS protein to the chloroplast(24);

(c) mepsps: sequence coding the corn (Z. mays) mEPSPS modified protein, granting tolerance to glyphosate(25);

(d) nos: region 3' not translated of T-DNA Agrobacterium tumefaciens nopaline synthase gene, which terminates transcription and guides mRNA polyadenylation(10).

The epsps genes are ubiquitous in nature. Mutant gene epsps (mepsps) results from two changes in corn epsps gene and were introduced to alter two specific amino acids of the wild epsps protein. The mutations are in the location of the 102 (from threonine to isoleucine) and 106 (from proline to serine) amino acids. Transformed corn plants with gene mepsps synthesize the mEPSPS protein that grants tolerance to herbicide products containing glyphosate.

The result of the Chi-Square Test ($X^2>3.84$ for all generations) accepts the hypothesis that the glyphosate tolerance characteristics behaves in a Mendelian way and segregates at rate of 1:1. The number of transgenic loci in the insertion of event GA21 was examined by Southern blot, using digestion with EcoRV and hybridization with two probes generated by PCR that represent the functional elements contained in the NotI transformation segment of pDPG434. The analysis showed that the whole of the GA21 insertion is in one single locus and is contained in a hybridization band of 20.5 kb. Southern blot hybridization analysis data on three generations of event GA21 showed that the insertion of the event is inherited in a stable way in all generations of plants derived from the event.

The amino acid sequence of mEPSPS enzyme expressed in GA21 Corn is 99.3% identical to the sequence of the conventional corn endogenous enzyme. The EPSPS endogenous protein is expressed in a significantly lower concentration than the GA21

mEPSPS protein. Quantifiable concentrations of the mEPSPS protein were found in most tissues of plants derived from event GA21. In all growth phases of event GA21 hybrids, average concentrations of mEPSPS measured in leaves ranged from about 0.2 *f*Ýg/g of fresh weight to 15 *f*Ýg/g of fresh weight (<0.3 to 7.0 *f*Ýg/g of dry weight); in roots, average concentrations ranged from about 2 *f*Ýg/g to 15 *f*Ýg/g of fresh weight (<14 to 44 *f*Ýg/g of dry weight); and in the whole plant, ranged from about 3 *f*Ýg/g to 15 *f*Ýg/g of fresh weight (8 to 68 *f*Ýg/g of dry weight). Average concentrations measured in kernels in seed maturity and senescence ranged from about 4 to 7 *f*Ýg/g of fresh weight (5 to 10 *f*Ýg/g of dry weight). Concentration of the mEPSPS protein overnight in the air exhibited an average of about 16 *f*Ýg/g of fresh weight on the two GA21 event hybrids. mEPSPS concentrations in corn chips and corn oil samples were below detection limits.

IV. Aspects Related to Human and Animal Health

The arrangement proposed to estimate risk in whole food, either conventional or genetically modified, is different from the one classically conducted for well chemically characterized products, with a defined purity, with no relevant nutritional value and to which humans are exposed in low doses, as food additives, drugs, cosmetics and chemical substances of industrial use. Whole foods, however, are complex chemical mixtures, each of them subject to changes along time in its composition and nutritional value, which limits their use in toxicological essays with experimentation animals, as they are validated. The difficulty in performing traditional toxicological tests with whole foods, including GMO, led to an alternative proposal for assessing its food safety based on comparative analysis between a certain product and its similar, with an acceptable record of safe consumption. The idea behind this approach coincides with the concept of substantial equivalence, considered the most practical way of treating safety in foods and food components produced by biotechnology. This approach, formulated by FAO/WHO during the 1990s, was used by reference institutions, such as OECD(30), Codex Alimentarius(17), the North-American FDA(43), the European Food Safety Agency(12), and the American Society of Toxicology(33).

In the substantial equivalence approach, an GMO is compared to its closest natural similar to identify intentional and non-intentional differences, taking into consideration: identity, source, transformation process, composition, effects of processing, characteristics of recombinant DNA (stability of insert; potential genic transfer); toxic, allergenic and other potential effects of the protein expressed by the transfene; and possible side effects of the new gene expression (interruption of metabolic pathways, interference with macro- and micronutrients). Validation of substantial equivalence is an important phase, yet it shall not be misinterpreted as assessment of food risk itself. In case there are any likelihood or risk, be it toxic or nutritional, the assessment shall proceed to attempt and establish its nature and severity, including the possible conduction of in vivo toxicological tests. The requirement of such tests for assessing the safety of the GMO or its derivatives shall be decided on a case-by-case basis. Especially in the case of new proteins, tests shall be performed when:

(1) there is no detailed record of previous safe consumption of the GMO and its products, by humans or by animals raised for food;

(2) available information on its safety is perceived as insufficient;

(3) its biochemical and functional characterization was deemed insufficient: molecular weight, amino acid sequence, homology with proteins that cause adverse effects, subsidiary enzymes, stability during processing and storage, resistance to digestion, products from breaking, among others;

(4) there is a possible interference of the new protein with metabolic and functional pathways or relevant structures;
(5) there is the possibility that the transgenicity may trigger unexpected genetic changes in the transgenic plant (silencing or overexpression of endogenous genes);
(6) the substantial equivalence analysis indicates dissimilarity with the original product with which the GMO was compared.
Naturally, toxicity essays of the GMO with experimentation animals (repeated exposure, 28 or 90 days), implies appropriate strategies to harmonize the offer of test-materials to animals (form of presentation, dose levels, etc.). When the transgenic product is a modified protein, it may be isolated from the GMO itself or synthesized by microorganisms and offered to test-animals in this isolated form. In this latter case, the isolated protein shall keep biochemical and functional correspondence with the protein of the transgenic product. In very special situations, the test may be conducted with the whole food that, in this case shall be supplied in the same form and at least in the amount consumed by humans.
Safety assessment of foods derived from genetically modified raw materials is based on risk analysis, a scientific methodology comprising the phases of assessment, risk management and risk communication. In the risk assessment phase, a quantitative and qualitative characterization is pursued of potential adverse effects, guided by the substantial equivalence standard, in order to identify any differences between the new food and its corresponding conventional food.
In order to assess safety of a genetically modified alimentary raw material or its equivalence to the conventional food, it is recommended that four mail elements are analyzed in some depth:
(1) parental variety, that is to say, the plant that originated the new genetically modified raw material;
(2) transformation process, including full description of the construct used and resulting event;
(3) product of the inserted gene and potential toxicity and allergenicity; and
(4) composition of the new variety resulting from genetic transformation.
The set of data of such analyses shall enable an identification and description of potential adverse effects associated to consumption of the new raw material, to be used as basis for the phases of risk management and communication.
Z. mays is a well characterized species, with a solid record of safety for human consumption. In the proceedings, information comprising origin, domestication, taxonomy, reproduction and changes in its composition are mentioned(45), reflecting the high degree of knowledge about this species. Corn is used basically as a component of food by peoples through the whole world, and is one of the most important grains used in the production of animal food for being one of the most concentrated forms of energy, containing more energy able to be metabolized – or digestive nutrients – than any other grain. Corn plants and kernels are not considered toxic for humans, domestic animals or wild species. The cereal is at the base of nutrition for large groups of people in Latin America, Asia and Africa. In the United States and Japan, corn is generally used as food for animals. Corn is palatable, readily digested by humans and monogastric and ruminant animals and has a safe record of use as a human and animal food.
GA21 corn was obtained by bombarding the plant material with particles covered with the genetic material of interest. Since this is a physical process of transference of DNA molecules, without intermediation of any biological agent and is performed in aseptic conditions, the likelihood that DNA

molecules that are not in the genic construct present in the particles are transferred to the plant cells is practically negligible. No sequence induced in GA21 event or its donors are known as pathogenic for humans. EPSPS proteins are ubiquitous in nature and are naturally present in food derived from plant and microbial sources present in the normal diet of humans and animals(5, 13, 20).

Chemical composition analysis of the variety obtained by genetic modification, mainly at the levels of its nutrients and any toxic components that may be present, aims at securing that this new variety is as safe and nutritive as its conventional equivalent. Therefore, the analysis verifies that the intentional effects of the modification did not affect negatively its security nor resulted in unintended effects. Presence and levels of natural constituents in human animal food were analyzed and compared with genetically unchanged contour lines and data from the literature(22). Bromatologic analyses and quantification of different nutritional components of corn kernels, such as carbohydrates, proteins, humidity, fat, ashes, starch, fibers, minerals, vitamins, amino acids, fatty acids, secondary metabolites and anti-nutrients(35). The analyses suggested that the measured levels of components have not changed more than the natural variation found in corn. No consistent pattern emerged that suggested significant biological changes in composition or nutritional value of the kernel or forage took place as a result of the transformation or expression of the mepsps transgene. The data corroborate the studies of Grant and his collaborators(19) who concluded that the use of corn for silage or kernel does not change the nutritional value of the food. Erickson et al.(14) verified the lack of change in nutritional value in cattle feeding. Similarly, studies carried out with birds in specific GMO diets did not reveal changes(42).

As mentioned above, the mEPSPS enzyme amino acid sequence expressed in GA21 corn is identical to the conventional corn endogenous sequence. Analysis of amino acids inserted in mEPSPS enzyme fails to display homology with proteins toxic for mammas and it is not deemed to have any potential toxic for humans. Absence of toxicity was also verified in studies with animals using high doses of purified protein. Studies lasting 90 days in rodents did not indicate any change in the animals with doses up to 400mg/kg of CP4 EPSPS derived from Eschericha Coli. The protein is degraded in less than 15 seconds in the presence of pepsin and in 10 minutes in the presence of trypsin. Susceptibility of the mEPSPS protein to proteolytic degradation was assessed in simulated mammal gastric fluid containing pepsin. Protein mEPSPS obtained from E. coli and corn was rapidly degraded, and was not detected intact in a sample of reaction mixture in the first sampling interval (one minute). No immune-reactive fragment of mEPSPS could be detected after incubation for five minutes in mammal simulated gastric fluid(37). These data corroborate the EFSA(11) understanding, maintaining that there are no toxicity or allergenicity changes foreseeable by bioinformatics in studies of in vitro digestibility and in in vivo experimental studies.

Toxicity of mEPSPS protein (83%p.p. pure) was assessed by forced oral intake in a single dose of 2,000mg/kg of body weight to CD-1 mice of both sexes. The dose was selected for it represents the borderline dose for this type of study. After fifteen days, the animals were sacrificed and submitted to full necropsy. There was no evidence of effects on food ingestion, body weight and weight gain, hematologic profile and histology of all organs that might be associated to exposure to GA21 corn. Some alterations recorded in serum biochemical tests were deemed inconsistent and not associated to exposure to transgenic corn(39).

In another study, ALpk:APf SD male and female rats received GA21 corn in

concentrations of 10% or 45% in their food. Selection of corn offer levels was made assuming that the lowest concentration (10%) represents a level "at least equivalent to the human chronic dietary intake of corn (3mg/kg/day". The highest level (41.5%) was selected as "the highest attainable level without causing nutritional imbalance to animals."(40). The control used was a corn negative for event GA21, supplied in the same concentrations. Experimental food was offered for ninety days, and at the end the animals were sacrificed and submitted to full necropsy. There was no evidence of effects in weight and body gain, food consumption, clinical condition and functional performance during the study, hematologic profile, organ weight and histology, as well as no records of changes to ophthalmoscopy and serum biochemistry of animals exposed to GA21 corn(40). In this context of GA21 toxic effect absence in both studies, it is important to emphasize that there was no record of homology in the amino acid sequence of corn 5-Enolpiruvylshikimate-3-Phosphate double mutated synthase protein (mEPSPS) with any other proteins already identified as toxic(36). The result corroborates the European Food Safety Authority (EFSA) conclusions(13) that the results of the studies fail to indicate occurrence of adverse effects in GA21 corn consumption.

The mEPSPS enzyme expressed in event GA21 corn does not have the typical features of known allergenic substances, since the behavior of allergenic proteins in the digestive tract is well described(4, 7, 21). There are no homology regions when the introduced sequence is compared with sequences of known allergens. Besides, many food allergens are known for being stable when submitted to heat. Data collected evidenced that incubation for thirty days at 65ºC or 95ºC deactivated the mEPSPS specific enzymatic activity(38), indicating a extremely low likelihood that the whole protein might be absorbed through the bowel mucosa during consumption and establish immunochemical affinity for antibodies, including IgE antibodies, primarily responsible for allergic reactions(34). In addition, available data in the literature(44) indicate normal digestibility for transgenic corn varieties released for human consumption. Indeed, the mEPSPS enzyme is rapidly degraded by acid and enzymatic hydrolysis when exposed to fluids that are similar to gastric or intestinal fluids.

For the foregoing, the likelihood of mEPSPS protein to interfere in metabolic or functional pathways or in relevant structures is negligible, in view of the plant morphology, its agronomic performance, biochemical composition, nutritive content and digestibility. Therefore, it is not foreseen that transgenic modification could cause unexpected genetic changes in the plant (silencing or overexpression of endogenous genes) and, in case such changes do occur, they will not imply adverse effects.

According to data on GA21 corn nutritional and compositional equivalence as regards its isogenic conventional, no GA21 corn metabolite has potential to concentrate in the food chain, in addition of that already expected for the widely cultivated conventional corn. Studies on acute oral toxicity in mice conducted with mEPSPS protein indicated that the mEPSPS protein failed to have any acute toxic effect on the animals at the highest tested dose. No mortality associated to the test substance took place during the study and no clinic signal attributable to the test substance was observed(39).

Besides, GA21 corn was already released for human and animal consumption in the United States, Japan, Canada, Argentina, Mexico, South Africa, Australia, New Zealand, Philippines, Thailand and China, and in some of these countries for over ten years, displaying a safe history of consumption without adverse effects scientifically proven(1).

For the foregoing, one reaches a conclusion that there are not indications that consumption of GA21 corn or products derived from this event pose any risk to life and

health of animals or humans, being as safe as the conventional corns commercialized in Brazil, and that the likelihood that it may harm human and animal health is negligible.

V. Environmental aspects

Corn is a monoic plant: a single individual contains male and female flowers located separately. Corn plants are crossed fecundation plants and largely pollinated with the help of wind, insects, gravity and others. The introduction of genic elements described above failed to change the reproductive characteristics of the plant. Therefore, the same likelihood of crossed fecundation existing between hybrids and lineages of conventional corn – non-genetically modified – will occur between event GA21 and other corn plants.

Genic flow of corn may occur through transfer of pollen and dispersion of seeds. Dispersion of seeds is easily controlled, since domestication of corn eliminated the ancestor mechanisms of seed dispersion and pollen movement is the only effective means for genes escaping from corn plants. Corn is an annual and allogamous plant, predominantly pollinated by wind, and distances covered by pollen depend on the wind pattern, humidity and temperature. Corn pollen disperses freely near the area cultivated with this grass, and may reach the stigmas of the same or different genotypes and, under adequate conditions, starts its germination, originating the pollen tube that promotes fecundation of the ovule within an average period of 24 hours. Studies on corn pollen dispersion have been conducted, and some of them show that corn pollen may travel long distances. However, most of the pollen released is deposited near the culture, with a very low translocation rate to outside the source culture: over 95% of the pollen reaches distances within 60m from its source(32). The predominant pollinating agent in corn is the wind, and the distance that viable pollen may cover depends on wind patterns, humidity and temperature. Luna et. al.(26) assessed the isolation distance and control of pollen, and showed that crossed pollination took place within a maximum distance of 200 m and that no crossed pollination occurred in distances exceeding 300 m from the pollen sources, in conditions of absence of detasseling. The results indicate that pollen viability is maintained for two hours and that crossed pollination was not observed in distances exceeding 300m from the pollen source.

Comparing concentrations at 1 m from the source culture with winds ranging from low to moderate, one estimates that about 2% of pollen are recorded at 60m, 1.1% at 200m and 0.75-0.5% at 500m from the source. Ten meters away from a field, the average number of pollen grains by unit of area is ten times less that the figure recorded at 1m from the border. Therefore, if the established distances of separation developed for corn seed production are observed, one expects that the transfer of pollen to adjacent varieties is minimized, being unlikely the presence of glyphosate tolerant genetic material.

In Brazil there are not kindred corn species in natural distribution. However, the genic flow to local varieties of open pollination is possible, but poses the same risk as commercial genotypes available in the market. In the specific case of crossing between GA21 corn and local (creole) varieties there is no expected selective pressure from management by small farmers: the transgene shall not be incorporated to the genome of creole varieties because, in practice, the small farmer does not use herbicides. From the agronomic viewpoint, coexistence between conventional (improved or creole) corn and transgenic(8,28) cultivars is possible. Old communities and modern farmers have been able to easily live together with different corn cultivars, while keeping their genetic identities across time.

The likelihood of a transgenic plant to change into a weed species, as well as the

likelihood of a GA21 corn crossing with other corn plants and originate a weed is negligible, in view of the biologic characteristics of the species and the fact that corn does not survive well without human intervention, a result of a selection made along the plant evolution. Corn is the species reaching the highest degree of domestication among cultivated plants and lost its natural surviving characteristics as, for instance, the elimination of shucking. Therefore, corn is a plant unable to survive in natural conditions, without technical assistance. In this context, one expects the GA21 corn to display an environmental behavior similar to ordinary corn being therefore negligible the likelihood of changing into an invading plant or weed.
The likelihood of the transgenic plant mepsps gene to pass to other organisms as, for instance, soil microorganisms is practically null(29,41). The epsps gene is common to plants, fungi and microorganisms, its occurrence is abundant in nature, and does not result in significant risk to the soil microbiota. In addition, there are is no evidence that plant genes have ever been transferred to bacteria under natural conditions.
Glyphosate is an organic compound that does not affect the nervous system and is highly efficient in eliminating weeds, besides being held as little toxic (toxicological class IV). It is a large spectrum, non selective, herbicide that kills plants by inhibiting the 5-Enol-pyruvylshikimate-3-phosphate (EPSPS) synthase enzyme, important in the biosynthesis of aromatic amino acids. Glyphosate is registered with the Brazilian Ministry of Agriculture and Supply (MAPA), Ministry of the Environment (MMA) and has a monograph approved by the National Sanitary Surveillance Agency (ANVISA)(3). Use of the glyphosate herbicide in crops of GA21 corn shall observe the applicable rules as, for instance, Law no. 7,802, of July 11, 1989 (Pesticide Act).
VI. Restrictions on the use of the GMO and its derivatives
As established by Article 11 of Law no. 11,460, of March 21, 2007 “research and cultivation of genetically modified organisms may not be conducted in indigenous lands and areas of conservation units.”
Studies submitted by applicant demonstrated that there is no significant difference between hybrids of corn derived from unmodified lineages and GA21 corn regarding agronomic characteristics, reproduction methods, dissemination and ability to survive. All evidence submitted in the proceedings and bibliographic references confirm the transgenic variety level of risk as equivalent to non transgenic ones regarding soil microflora, as well as other plants and human and animal health. Therefore, cultivation and consumption of GA21 corn are not potentially a source of significant degradation to the environment or of risks to human and animal health. For the above reasons, there is no restrictions to the use of such corn or its derivatives, except in places as mentioned by Law no. 11,460, of March 21, 2007.
Vertical genic flow for local varieties (the so called creole corn) of open pollination is possible and poses the same risk caused by commercial genotypes available in the market (80% of conventional corn cultivated in Brazil comes from commercial seeds that have been genetically improved). Coexistence of conventional corn cultivars (either improved or creole) and transgenic corn cultivars is possible from the agronomic viewpoint(8,28) and shall comply with the provisions of CTNBio Regulating Resolution no. 4.
After ten years of use in different countries, no problem has been detected for human or animal health or the environment that may be attributable to transgenic corns. It shall be emphasized that the lack of negative effects in cultivating transgenic corn plants is not a guaranty that such effects cannot occur. Zero risk and absolute safety do not exist in the biology world and, although there is a host of trustworthy scientific information

and a safe history of use of ten years that enable us to affirm that GA21 corn is as safe as the conventional versions. Therefore, applicant shall conduct post-commercial release monitoring according to CTNBio Regulating Resolution no. 3.

VII. Consideration on the particulars of different regions of the Country (Information to supervisory agencies)

In Brazil, there are no kindred species of corn in natural distribution.

VIII. Conclusion

Considering that the corn (Zea mays) GA21 belongs to a well characterized species with a solid background of safety for human consumption and that the mepsps gene introduced in this variety codifies a protein that is ubiquitous in nature, present in plants, fungi and microorganisms participating in the alimentary diet of humans and animals.

Considering that the genic construct used to insert the gene in corn resulted from the stable insertion of a functional copy of mepsps, which granted tolerance to the glyphosate herbicide.

Considering that centesimal composition data failed to identify significant differences between the genetically modified and conventional varieties, suggesting nutritional equivalence between them.

Considering, in addition, that:

1. Corn is the species that reached the highest domestication level among cultivated plants, and is unable to survive in nature with no human intervention.

2. In Brazil, there are no wild species with which corn may intercross, since the closest wild corn species is teosinte, found only in Mexico and in some Central America locations, where it may cross with corn cultivated in production fields.

3. The mEPSPS protein was detected in low levels in tissues analyzed and displayed great susceptibility to digestion in simulated gastric fluids, lacking acute toxicity in mammals and similarity with known allergens.

4. The genetic modification introduced in GA21 event did not result in important differences of chemical composition regarding nutrients, which are within the normal variation range found between conventional varieties.

5 The DNA molecule is a natural food component and there is no evidence that this molecule may have adverse effect to humans when ingested in food in acceptable amounts (no direct toxic effect).

6. There is no evidence that intact plant genes may be transferred and functionally integrated to the genome of human or other mammals exposed to this DNA or to food produced with such elements(15).

7. The applicant answered all questions stipulated by CTNBio Regulatory Instruction no. 20 and that no topic indicated that this corn may have adverse effect in human and animal food.

8. The likelihood of a transgenic plant to change into a weed species, as well as the crossing of GA21 corn with other corn plants originating a pest is negligible.

9. The mEPSPS protein is common to plants, fungi and microorganisms and the exposure of living organisms and the environment to this protein is an event that occurs abundantly in nature without resulting significant risk to soil microbiota.

10. The coexistence between cultivars of conventional corn (either cultivated or creole) and transgenic corn cultivars is possible from the agronomic viewpoint, under the provisions of CTNBio Regulatory Resolution no. 4.

11. Annex III of the Cartagena Protocol on Biosafety (Decree no. 5,705, of February 16, 2006) provides that risks associated to modified living organisms or to products derived therefrom, to wit, improved materials originated from a modified

living organism containing new detectable combinations of replicable genetic material obtained by modern biotechnology shall be considered in the context of the risks posed by the unmodified receptors in kindred organisms in the probable receiving environment.
12. The worldwide use history of this transgenic variety points out to a host of trustworthy scientific information indicating that the variety is as safe to the environment and human and animal heath as the hybrid corn varieties that have been used.
13. After ten years of use in different countries, no problem was detected to human and animal health or the environment that may be attributable to transgenic corns.
For the foregoing and considering the internationally accepted criteria in the process of analyzing the risk of genetically modified raw materials, one may reach a conclusion that GA21 corn is as safe as its conventional equivalent.
CTNBio considers that the activity is not potentially a cause of significant degradation to the environment or aggravation to human and animal health. Use restrictions of the relevant GMO and its derivatives are determined by the provisions of Law no. 11,460, of March 21, 2007, CTNBio Regulating Resolution no. 03 and CTNBio Regulating Resolution no. 04.
CTNBio analysis took into consideration opinions issued by the Commission members; ad hoc consultants; documents forwarded by applicant to the CTNBio Executive Secretariat; results of planned releases to the environment; lectures, texts and discussions of the public hearing held on 03.23.2007. Third party independent scientific studies and publications submitted by applicant were also taken into consideration and consulted.
Under Annex I of Regulating Resolution no. 05, of March 12, 2008, applicant shall have a term of thirty (30) days from publication of this Technical Opinion to adapt its proposed post commercial release monitoring plan.
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Walter Colli
President of CTNBio

Dissenting Votes:
The following CTNBio members, Doctors Graziela Almeida Silva (Permanent Sector Subcommission for Human Health), Kenny Bonfim (Permanent Sector Subcommission for Human Health), José Maria Gusman Ferraz (Permanent Sector Subcommission for the Environment) and Leonardo Melgarejo (Permanent Sector Subcommission for the Environment) voted against the commercial release of GA21 corn.
Doctor Paulo Yoshio Kageyama (Permanent Sector Subcommission for the Environment), author of the technical opinion, issued an opinion against the product

based on:
1. The genetic and molecular characterization of GA21 was either insufficient or inadequate: new tests and data would be necessary.
2. Allergenicity tests, as well as the nutritional analysis of GA21 corn, were insufficient.
3. Comparison studies of GA21 with isogenic maize are necessary to assess aspects of plant survival, flowering, pollen grain morphology, genetic compatibility and pollinating rate.
4. Studies of horizontal transfer of gene mepsps gene are necessary for adventitious plants and rhizosphere bacteria.
5. Studies shall be conducted on the impacts of GA21-herbicide corn technology on non-target organisms.
6. Studies on environmental impact are necessary including data on reaction of fauna communities to GA21 corn culture on different Brazilian ecosystems and with the use of glyphosate-based herbicides.
7. Studies are necessary to identify the succession effects of glyphosate-resistant corn-soybeans in the same area of studies and on the possibility of developing plants that are resistant to glyphosate-based herbicide.
8. Applicant shall submit more scientifically reliable results in what regards the 24 experiments enclosed, with a discussion on the uncertainties identified.
Doctor Leonardo Melgarejo (Permanent Sector Subcommission for the Environment), author of the technical opinion, issued an opinion against the product based on:
1. There are important risks associated to evidences of likely genome disorders associated to lack of precision in the biobalistic method and sustained by international scientific literature.
2. The genetic stability of the transgene through several generations is not sufficiently demonstrated.
3. Absence of harmful effects for health derived from GA21 corn is not sufficiently demonstrated.
4. No satisfactory answers to issues 1, 3, 6 and 7 of Annex II of CTNBio Regulating Resolution no. 5 were made available.
5. The maintenance of nutritional and biologic features of corn after insertion of the transgene is not consistently demonstrated, and the possible interactive effects between Brazilian environment – plant metabolism were discarded.
6. Studies related to agronomic efficacy were contradictory and equivocated, aggravated by lack of data obtained during planned releases authorized by CTNBio.
7. There is large risk potential to which family farmers are submitted given the unavoidable contamination of their crops by a transgene whose stability and innocuousness are not yet established.
8. There is a large and growing potential for an expansion of tolerant and resistant plants, with impacts on the increasing use of the chemical product harmful to the environment.
9. Environmental impacts were not correctly assessed and make room for concerns related to corn culture sustainability, mainly in the part under the control of family farmers.
10. Environmental impacts were assessed without regard to direct and indirect impacts of the new technology on its whole over the non-target fauna and flora, water and soil, as well as on the systems therein established.
11. Environmental impacts were superficially assessed, with no scientific basis and lacking adequate answers to issues 3, 4, 7, 8, 10 and 12 of Annex IV of CTNBio

Regulating Resolution no. 05.

12. Brazil has already expressed its decision to abide to the Precaution Principle, sanctioned by the Cartagena Protocol, effective as of January 22, 2004, as well as the Article 1 of Law no. 11,105/2005.