President of CTNBio

Mr. Flavio Finardi

Ministry of Foreign Relations

Chief of the Division of Agriculture and Primary Products

Mr. Orlando Leite Ribeiro

Brasilia, February 20, 2013

Dear Sir,

In October, 2012, the Presidency of the National Technical Biosafety Commission (CTNBio) sent a document to the Ministry of Foreign Relations that contained a critical analysis of the study by Seralini et. al. (2012), in response to a request from the ministry.

It is our understanding that this document, which was prepared by four scientists, of which two are members of CTNBio, cannot be considered to be the position of the Commission, given that it was not evaluated by a plenary session. Even if it had been, the opinion issued by these doctors does not represent a consensus in this Commission.

On November 12, the journal Food and Chemical Toxicology published on its site an article entitled "Answers to critics: Why there is a long term toxicity due to NK603 Roundup-tolerant genetically modified maize and to a Roundup herbicide," written by Professor Seralini and his staff. It was a response to the numerous criticisms that were quickly triggered by the publication of the first article, which is the focus of this letter. It is worth noting that all of the relevant criticisms sent by the Presidency of CTNBio to the Ministry of Foreign Relations, which by chance reproduce opinions of Monsanto, and others, were properly responded to in that text (Seralini et al., 2012b, in annex). In terms of the other information, which may not have been contemplated in the article by Seralini et al. (2012) - and which are not relevant to its interpretation – the author informs in the text that they involve aspects to be addressed in another article focusing on the toxicity of Roundup, which is in the process of being published in another specialized journal.

As a complement, we will thus take a look at this study, as members and former members of CTNBio who are concerned with Biosecurity and the application of the Precautionary Principle, as called for by current law.

Introduction

In the first place, it is important to clarify that the publication by Seralini et al. (2012) is the only toxicology study that analyzes the effects of the consumption of GM corn tolerant to a herbicide during a period corresponding to the entire life of a model animal (in this case, the rat). The other long term studies referred to by the critics of the study by Seralini et al. (2012) use other model animals (not rats) that have a lifespan that is much more than two years (for ex. pigs and birds). Therefore, they are not comparable to the study by Seralini et al., given that these studies used model animals whose lifespan is superior to two years and in this case this data cannot be considered representative of the whole lifeeffects associated to the material tested. In

other words, the other studies correspond to evaluations of nutrition that do not provide toxicological data based on a biochemical and anatomopathological analysis.

On the other hand, the NK603 corn was approved for commercial use in Brazil in 2008, despite various reports and criticisms from members of CTNBio itself. Most of the critical points raised were related to the absence of scientific proofs sustaining the hypothesis that the product is innocuous to the environment and public health. The content of the dossier presented also does not comply with various items established by current law (RN5). In general, in the dossier presented by the company making the request to CTNBio:

- there was no solid scientific data that proves the equivalence between the protein used in the toxicity/allergenicity tests (produced in *E. colil*) and the protein truly produced by the NK603 corn;

- the proteomic profile of NK603 corn, in addition to the synthesis of the recombinant protein CP4EPSPS, also presented the synthesis of the new protein EPSPS L214P which was not correctly evaluated (from the perspective of biosecurity);

- a good portion of the studies presented in the dossier are based on proteins synthesized in micro-organisms, which do not carry the totality of the information related to the set of interactions associated to the proteins incorporated in the NK603 corn (therefore, they do not allow sustaining the conclusions made by the proponent of the technology, which are related to the proteins synthesized by the corn);

- a substantial equivalence was not scientifically proven.

In addition, in terms of the risks to human and animal health, it is necessary to consider that:

- the allergenic potential in mammals of NK603 (cultivated with the use of the formulated product based on glyphosate in the recommended doses) was not sufficiently qualified or quantified;

- no information in the dossier sent to CTNBio by the proposing company concerning the possible harmful effects of this GMO on animals in gestation phase or pregnant, and or their teratogenic potential (items 4 and 6 of Annex III of the RN5) were simply disconsidered by the majority of the council, which approved the commercial release of NK603 corn, contrary to the rules established by CTNBio itself in this resolution. It can thus be indicated that this authorization did not observe the minimal parameters of the studies required for the commercial release of this GMO;

- the toxicity studies conducted in rats fed with NK603 corn (including Hammond et al., 2006) show statistically significant differences in relation to clinical biochemical parameters of the renal system and also in relation to the weight of the liver.

For these reasons, to which are added other fragilities associated to environmental biosecurity (for example the scarce and near absence of information about the reaction of the different fauna and flora communities to the cultivation of NK603 corn, in the different ecosystems contained in the various national biomes), two reports were issued against the commercial release of NK603 corn. In addition, negative votes were given by representatives of the Ministry of Agrarian Development, the Ministry of Health and from civil society representatives of environmental and health groups.

In this context, given that the NK603 corn also did not undergo food security tests as in-depth as those conducted by the staff of professor Seralini, it can be affirmed that the referred to study offered advances in the scientific knowledge, which are new and important for the biosecurity of GMOs, which should be included in the field of risk evaluation of this and of other events, and it also made methodological contributions that should be employed by proponents of the transgenic plants when complying with biosecurity norms.

About the methodology used by Seralini et al. (2012)

Returning to the discussion about the methodological aspects in the study by Seralini et al. (2012) that were criticized, it is important to highlight the following factors.

1. Choice of the race Sprague-Dawley rats

Apparently the strongest criticism made of the study in the letter sent by CTNBio concerned a supposedly wrong choice of race for the experimental animals. It is obvious that the authors of the study were aware of the characteristics of those animals, which was already indicated in other studies, although the authors had not considered it to be determining factor for the toxicity study that they proposed to conduct.

But, in fact, the use of that race is common in long term studies; as remembered by the European Network of Scientists for Social and Environmental Responsibility, in a letter of support to the study by Seralini et al. (2012) (ENSSER, 2012):

"1. The National Toxicology Program, conducted by the U.S. Department of Health and Human Services commonly uses this race in their two-year studies, and until now without questioning;

2. A preliminary search of the literature published in peer-reviewed journals show that Sprague-Dawley rats were used in studies:

- of 36 months by Voss et al. (2005);

- of 24 months by Hack et al. (1995), Klimisch et al. (1997) , Minardi et al. (2002) , Soffritti et al. (2006) and Gamez et al. (2007);

- of 18 months by Lee et al. (2010) ; and

- of 12 months by Perry et al. (1981) , Conti et al. (1988) , Morcos & Camilo (2001), Flamm et al. (2003) e Gutierrez et al. (2011)."

As emphasized by ENSSER, four of these studies were published in the magazine Food and Chemical Toxicology.

Heinemann (2013) found seven studies from 2004 to 2012, all published in the journal Food and Chemical Toxicology, in which Sprague-Dawley rats were fed with materials of GM plants. According to this author, all of these articles were published by the companies that produced the GM plants used in the study by Seralini et al. (2012). One of the articles was by Monsanto and the others by DuPont/Pioneer. None of the studies extended more than 90 days.

Seralini et al. (2012) also report that similar results had been found previously, which were not questioned at the time.“All treatments in both sexes enhanced large tumor incidence by 2–3-fold in comparison to our controls but also for the number of mammary tumors in comparison to the same Harlan Sprague Dawley strain (Brix et al., 2005), and overall around 3-fold in comparison to the largest study with 1329 Sprague Dawley female rats (Chandra et al., 1992)".

It should be emphasized that the fact that the Sprague Dawley race has a hypersensitivity to the development of tumors makes it a pertinent model for some types of biological studies.

Obviously, greater care must be given to the interpretation of the data obtained after 500 days of life of the animals, a period when unstable or degenerative physiological states may appear, such as menopause or senility. Nevertheless, as highlighted by the authors of the study being evaluated “The first large detectable tumors occurred at 4 and 7 months into the study in males and females respectively”

which does not represent a period propitious to the development of “natural” tumors in this race.

2. Number of animals used

Seralini et al. (2012) used 10 individuals per group and per sex, according to OECD protocol 408 referring to toxicity studies in rats. It should be remembered that this number of animals was accepted by global authorities, although not unanimously among the scientists, for risk evaluation in the study presented by the requesting company referring to the request for commercial release of Mon863 corn (Hammond et al., 2006) for example. It is also the number of animals most used in the toxicological evaluation of GMO consumption in general.

In fact, an experimental protocol designed with this number of animals leads to statistical limitations. This finding is well known by the team of Professor Seralini, which even published a scientific article criticizing the limitations of this sample, given that it practically impedes the identification of statistically significant effects (Spiroux de Vendomois et al., 2009). Nevertheless, it is our understanding that Séralini et al. (2012) expected to obtain better acceptance of the study by conducting it in a manner similar to the previous standard, following a methodology that had already proved to be acceptable by the proponents of the technology and by the agencies that evaluate the risk of GMOs.

On the other hand, it is important to emphasize that the authors compare groups of 10 test rats with groups of 10 control rats, which validates the use of the terms "fold" and "times" in the comparative analysis of the frequency of occurrence of tumors among the groups.

3. Statistical methodology

Professor Seralini and the members of his team did not use conventional statistical methodologies, given that they considered them unsuitable for biological analysis of the risks associated to the consumption of transgenic plants. In fact, they have published various articles in scientific journals warning of the limits – in terms of biological security – of these analyses (Seralini et al., 2009; Spiroux de Vendomois et al., 2010 and Spiroux de Vendomois et al., 2009) without, however, receiving criticisms or questioning by the part of the statistical community.

The statistics used in the other studies underwent anonymous review. Heinemann (2013) also found that, in addition, there is no other peer reviewed evidence that these statistical procedures used in these studies are either the only ones appropriate or valid for use in this type of study. Therefore, the author believes that the statistical analysis used in the study by Seralini et al. is equally valid.

In the case of Mon863, for example, it is perceived that the commercial liberation in Europe and in other locations is supported in 90-day tests for chronic toxicity in rats, also following protocol OCDE 408. In the group of 58 parameters measured by the requesting company (Hammond et al., 2006), all those that presented alterations concern the kidney or liver functioning, the body's two main organs for detoxification. The authors of the study found that the variation of these parameters was not biologically significant given that they present distinct degrees for animals of different sexes.

In fact, the males and females of the test group had different reactions upon eating the ration containing the transgenic corn (in comparison to the control group): the females had an increase in blood triglycerides (of up to 40%), in the size of the liver and of glycemia, unlike the males. Meanwhile, the males had a decrease in kidney size

and of urinary excretions of phosphorus and sodium (of about 30% in some cases), unlike the females.

These results presented only in the form of averages in each group, without distinguishing males from females (as is common in studies presented by the soliciting companies), mask signs of endocrinological disturbances (which by definition would be different between each sex), potentially related to other signs of toxicity. Complementing the statistical analysis of Hammond et al. (2006) with the use of conventional statistical tools (students t test, corrected by Welch or Mann-Whitney test), in addition to sex-dependent metabolic disturbances of the liver and kidney in test animals, Seralini et al. (2007) found statistical differences in animal weight. In fact, there was a weight gain of 3.7% in the females and a weight loss of 3.3 % in the males. This data, of important metabolic significance, was ignored in the statistical analysis by Hammond et al (2006), the only study conducted with Mon863 corn.

It is noteworthy that the commercial release of NK603 corn was based on the article by Hammond et al. (2004), a 13-week toxicity study with rats – in which some 70 significant statistical differences were observed and reported by the soliciting company: 12 related to hematological parameters (hematocrit, platelets, (neutrofils), limphocytes, monocytes, mean (corpuscular) volume and mean corpuscular concentration of hemoglobin), 18 related to the clinical chemical parameters (albumin, blood urea nitrogen, creatinine, phosphorus, sodium, chloride, alkaline phosphatase, calcium, potassium), 9 related to the urinary chemical parameters(creatinine, creatinine clearence, phosphorus, potassium, pH, calcium), 6 related to organ weight (heart, brain, liver), 14 to body weight and change in weight and 8 related to food consumption by the animals.

Surprisingly, the authors concluded that "... rats fed corn grain containing event NK 603 corn responded similarly to rats fed parental and reference control grain" and that "…Roundup Ready NK 603 corn is equivalent to its parent control line and non transgenic commercial corn varieties…".

The study authors, Hammond et al. (2004), made these affirmations based on the fact that the number of statistically significant differences observed is of the same order that could be attributed to chance. On this basis, they concluded statistically significant differences, observed, occurred randomly and therefore, are not relevant and could not be considered as biologically significant. Scientifically this interpretation is not based on solid proof of the absence of biological relations. Consequently, it does not allow disregarding significant differences, particularly considering the biological relevance of these differences for the health of mammals.

In fact, Seralini et al. (2007b) and Spiroux de Vendomois et al. (2009), had previously emphasized weaknesses of the statistical method adopted in the feeding study by Hammond et al. (2004) (use of ANOVA with only one factor instead of ANOVA with two or more factors or even multivaried analysis (example: Analysis of Prinicpal Components – PCA, Data Mining or Manova). They argued, in these two articles, for the need for a distinct biological interpretation for those same statistical results. They therefore indicated the need to use updated scientific knowledge, mainly endocrinological, and requested a revaluation by histopathologists of the statistical differences observed. In parallel, they also recommended reconducting the same studies for a longer period, with use of selected groups, to evaluate the two main risk factors related to the consumption of NK603 corn, which are: the modifications in the plant genome and the accumulation of herbicides based on glyphosate, in the edible portions of the corn.

In this context, it is pertinent to affirm that Seralini et al. (2012) used statistical tools more suitable to the analyses of the biochemical data of the blood and urine obtained in the control groups and tests during the experiment, than the other studies. The method used by Seralini et al., OPLS-DA, is in fact adapted to the treatment of a

large number of variables, as is the case of genome and proteomic studies. These statistics allow determining discriminant variables among each group treated and the control group. It should be emphasized that the use of this statistical methodology is justified when hundreds of variables are used, as in the case of the study by Seralini et al. (2012) (50 parameters measured 11 times in 200 rats).

Thus, it should be clarified that since the main objective of the study by Seralini et al. was not to evaluate carcinogenic properties or those of endocrine disrupters contained in the corn tested, it was not necessary to develop a statistical method for these purposes. However, the observation of a high quantity of tumors in the test groups, with indications of causal relations with the biochemical alterations and physiological failures observed in these animals, cannot be ignored and justifies the inclusion of the mortality rate by tumors in the global interpretation of the study.

Results obtained by Seralini et al. (2012)

The main results of the study, in fact, are the important scientific advances, which concern the finding of sex-dependent metabolic and physiological hormonal disturbances in the test groups. In the males, the processes of necrosis and liver congestion were 2.5 – 5.5 times greater than in the control groups. In the females, the hypophysis was the second organ most affected, after the mammary glands, which developed most of the tumors observed. In addition, the biochemical analyses revealed serious disturbances in renal functions in both sexes, totaling 76% of the parameters altered that were monitored in the study.

As previously mentioned, these sex-dependent disturbances are not unprecedented and had already been reported in articles previously published by the staff of Professor Seralini (Seralini et al., 2007, Seralini et al., 2007b, Spiroux de Vendomois et al., 2009 e 2010). At the time, they were based only on the statistical results obtained in studies of sub-chronic toxicity with rats and that supported decisions favorable to the commercial releases of the GMOs.

In addition, ultrastructural abnormalities of the liver were previously observed in mice fed with RR soybeans (Malatesta et al., 2002). These disturbances were also observed in hepatocytes of rats directly using the herbicide RR (Malatesta et al., 2008) and are, according to the authors, highly comparable to the anomalies observed in Seralini et al. (2012), as confirmed by optical and electronic microscopy.

In fact, Professor Seralini's staff introduced in a pertinent manner the concepts of endocrinological disturbances in the field of evaluation of GMO risk. In the case of intoxication by poisoning, the effects vary linearly with the dose (The dose makes the poison"). However, in the case of endocrinological response, U curves were observed, as well as inverted U, or J profiles.

As reported in the recent publication "Answers to critics: Why there is a long term toxicity due to NK603 Roundup-tolerant genetically modified maize and to a Roundup herbicide", prepared by the team of Professor Seralini (2012b) and published in the same journal of Food and Chemical Toxicology. "The endocrine disturbance is supported by bibliography in human cells (Gasnier et al., 2009) and rat testicular cells, for R residues (Clair et al., 2012), and in this work it is demonstrated by statistical sexual hormonal imbalances and disabled pituitaries. The kidneys and the livers are also sensitive to endocrine disruptors. As the two major detoxifying organs, containing cytochromes P450 or other enzymes involved in xenobiotic or sex steroid metabolism, they often react with sex hormone steroids and related compounds (Pascussi et al., 2008)"

In addition, "Unexpected new active principles for human cell toxicity in G-based herbicides have challenged the relevance of testing G as the active principle in R

(Mesnage et al., 2012). R has been already described as an endocrine disruptor in vivo (Dallegrave et al., 2007; Oliveira et al., 2007; Romano et al., 2012, 2010) with the mechanistic underneath in vitro. Several studies have shown endocrine disrupting effects of R, such as a significant decrease in hCG-progesterone production and decreased levels of Steroidogenic acute regulatory (StAR) mRNA production in MA-10 mouse Leydig cells (Walsh et al., 2000), a significantly decrease in aromatase activity and mRNA levels in JEG3 cells and placental and equine testicular microsomes with R (Richard et al., 2005; Benachour et al., 2007), inhibitions of transcriptional activities of androgen and of both estrogen receptors alpha and beta in cells (Gasnier et al., 2009), and decrease in testosterone production in rat Leydig cells (Clair et al., 2012)". ·

Concerned with the neurological effects of various agrochemicals, including those with a glyphosate base, Colborn (2006), one of the authors of the book “Our Stolen Future,” proposed changes to the norms or principles used for approving agrochemicals in the United States. A new approach to protecting human health is necessary because of the uncertainty that will continue to exist about the security of agrochemicals (COLBORN, 2006). Later, in 2009, the Environmental Protection Agency (EPA) included glyphosate in a revaluation, due to evidence that it causes endocrinological disturbances (Federal Register, Vol. 74, No. 71 I Wednesday, April 15, 2009 I Notice.s).

Thus, the article by Seralini et al. (2012) scientifically proves the involvement of endocrinological disturbances in the toxicological processes responsible for the hepato-renal abnormalities observed in rats fed with NK603 corn, with or without Roundup, which are probably inductors of hormone-dependent cancers in these animals. The absence of a statistical methodology allowing the calculation of statistically significant differences is not a reason to disregard the qualitative results of the study, considering its relevance in the domain of public health. The participation of the herbicide Roundup, in its commercial formulations, in these processes of endocrinological disturbances and of cytotoxicity, are, in addition to being relevant, a scientific advance that should continue to have the attention of scientific and regulatory communities.

Finally, as Heinemann (2013) proposes, from a scientific perspective it is reasonable to admit that no 90-day study of animal feeding can refute the results found in the long term study because the main effects are those that appear only after 90 days of trial.

Evaluation of the documents attached to the CTNBio letter

We believe it is also important to report our evaluation of the materials attached to the letter signed by the President of CTNBio, and other comments that supposedly prove “the defects” of the study by Seralini et al. (2012).

Transgenic plants, patented and dependent on agrochemicals, are increasingly present in our food and environment. Nevertheless, there are still many questions about biosecurity being debated by the scientific community and society in general, notably in relation to the risks of consuming these plants, with or without residues of agrochemicals, in the long term and in their interactions with biodiversity, as well as the socioeconomic impact of the Genetically Modified Plants (GMP) on agrarian and agricultural systems and the rights of consumers and farmers among others (Zanoni & Ferment, 2010). In reality, the publication of studies that point to certain risks or adverse health or environmental impacts from transgenic plants always result in strong campaigns that seek to discredit them (both the authors and the studies). These campaigns basically involve secondary methodological factors and truncated or steered statistical interpretations, indicating factors that were ignored in studies that present opposite conclusions. These reactions against those who present warnings are detailed in the open letter "Seralini and Science" published by the Independent Scientist News in October of this year (http://independentsciencenews.org/health/seralini-

and-sciencenk603-rat-study-roundup/), and signed by some 100 highly qualified doctors and professors from around the world (Annex 2). The pressure and research difficulties suffered by researchers critical of transgenic plants were also reported in two highly regarded scientific journals (Nature and Nature Biotechnologies), by Waltz 2009a and 2009b.

In this case, Seralini et al. (2012b) reported that "75% of our 27 first criticisms within a week, among publishing authors, come from plant biologists, some developing patents on GMOs, and from Monsanto company owning these products." On the other hand, there were few specialists in the fields of toxicology, endocrinology or even statistics who published criticisms of the study mentioned. Faced with the attempts to discredit the author and his qualification in the field of toxicology, it is worth noting that Seralini et al. (2012b) recall having published "more than 26 international scientific peer reviewed papers by the team with the lead author on the topic in the last 5 years, and 11 in toxicological journals on the same period only in PubMed". ·

The document «Avis des Academies nationales d'Agriculture, de Medecine, de Pharmacie, des Sciences, des Technologies, et Veterinaire sur Ia publication recente de G.E. Seralini et al. sur Ia toxicite d'un OGM» [Opinion of the National Academies of Agriculture, Medicine, Pharmaceuticals, Sciences, Technologies and Veterinary related to the recent publication of G.E. Seralini et al. about the toxicity of a GMO] deserves mentioning. As denounced in the petition "Science and Conscience" (Annex 2) signed by 140 French scientists, "The fact that a group of a dozen people who claim to represent six scientific academies have decided to write a common letter without debate, is contrary to the normal functioning of these institutions." It should also be asked, how six academies, which include hundreds of scientists with numerous functions in various scientific institutions, were able to develop a consensual criticism to a study in only one month. Meanwhile, Professor Paul Deheuvels, the only statistician from the French Academy of Sciences, publically declared his support for the statistical methodology used and to the reliability of the results obtained in Seralini et al. (2012) (Attachment 2).

It should also be noted that the study by Seralini et al. (2012) has been supported by more than 160 letters from international scientists (Annex 2).

In addition, the systematic reference to the article by Snell et al. (2012) by the critics of the study by Seralini et al., (2012) as "proof" of the absence of impacts for human and animal health from the consumption of transgenic plants also deserves pertinent analysis. In fact, the article mentions that "Six out of the 24 studies examined here used an appropriate number of experimental animals: three long-term studies (Daleprane et al., 2009a, 2010; Sissener et al., 2009) and three multigenerational studies (Brake et al., 2003; Flachowsky et al., 2007; Haryu et al., 2009)". In relation to these 6 studies, the authors criticize the non-use of an isogenic line as a control in two of them. Two other studies are more similar to nutrition studies and not toxicity studies, because they only consider variables such as weight gain and meat production. In this context, of the 24 studies selected by Snell et al. (2012) in his review of articles that provide information about potential risks of consuming transgenic plants, only two present the set of criteria required by the critics of Seralini et al. Of these two studies, one concerns an experiment that used salmon as an animal model, whose results indicate little about human consumption, and the other concerns Bt corn, a transgenic plant that is not in discussion in this letter, given that the NK603 event is resistant to an herbicide. Therefore, no scientific study published until today can be used as a pertinent reference to demonstrate the absence of risks of consumption of NK603 corn, or other transgenic plants that are tolerant to herbicides with a glyphosate base.

On the other hand, in the group of long term toxicity studies conducted with mammals and available in the scientific literature (12 in total in 2010), half presented significant statistical differences between the control and test groups (the authors of

these studies, although without an evident scientific basis, consider these differences as not biologically significant), 3 present controversial results and 3 point to metabolic and or physiological problems in the test groups (Seralini et al., 2011).

Considering this analysis, accompanying the arguments, facts and clarifications, it is evident that the scientific community truly has a limited quantity of information that can be interpreted and used to develop a position about the long term effects of consumption of transgenic plants. In a recent review of the Brazilian scientific production in the field of public health about the genetically modified organisms, Camara et al. (2009) also indicated the limited number of studies conducted in Brazil, related to possible situations of risk of GMOs to human health.

In fact, it should be recognized that all the studies that are the basis for the commercial release of transgenic plants in Brazil and throughout the world, present scientific deficiencies (notably referring to the duration of the experiment, the representativeness of the material tested, the choice of the hypotheses to be tested, the variables analyzed, the statistical procedures and the statistical power, the consideration of a coefficient of acceptable variation among others) which present alterations in the possibilities for interpretation, considerably limiting their degree of reliability.

By indicating a priori risks discarded by the majority of the world's risk evaluation agencies (some transgenic events were commercially released without any sub-chronic study in vivo), the article by Seralini et al. (2012) keeps the debate open concerning the lack of scientific consensus about food security of transgenic plants, which has gone on for more than two decades. On the other hand, the set of criticisms of the research methodologies used by Seralini et al. emphasize the gaps and scientific weaknesses with which transgenic plants were released in the country, given that none of them underwent experiments as rigorous as those demanded today by these critics, who, for the most part, are part of or were part of CTNBio. In this sense, Heinemann. (2013) suggests that the scientific and regulatory communities be engaged in the validation of the statistical analyses, if there are still contentious issues.

As expressed by the European Network of Scientists for Social and Environmental Responsibility (ENSSER, 2012): "If the Séralini et al. study is found to be insufficient to prove harm due to methodological failings, then all previous studies submitted in support of approvals for food and feed in the EU must be reconsidered regarding their evidence for safety to human and animal health, and must be scrutinized according with the same level of rigour as is applied to such studies showing adverse effects. Likewise, a call for disclosure of all raw data by Séralini et al. must obviously be matched by full disclosure of all the raw data – and crucially also the biological materials at issue - by all applicants. Asymmetrical risk assessments are clearly unacceptable and comply with neither elementary standards of scientific process, nor basic standards of public propriety, nor with the precautionary principle".

Conclusion

The study that is the object of this letter raises pertinent scientific questions about the chronic toxicity of a certain transgenic corn, NK603, which was tested in vivo for two years, either with or without the herbicide to which it is tolerant, Roundup.

In our understanding, the statistical analysis of the biochemical and biological data is sufficient to support the finding of what is called a situation of risk. Moreover, it supports the conclusions and title of the article, corroborating the clinical and anatomopathological observations and those with optical and electronic microscopy.

In addition to the toxicological data provided about the long term consumption of NK603 corn, with or without the associated herbicide, the article by Seralini et al. (2012) supports questionings about the biosecurity and risk evaluation of the transgenic plants, such as:

Different reactions were observed in rats fed with corn with and without the use of herbicide, which shows the need to mandatorily include the use of the herbicide, or other products used in conjunction with the GMO, in the test groups fed with the transgenic plant to be evaluated. It must be remembered that scientific studies demonstrate that the degradation metabolism of herbicides is different in plants tolerant to the herbicide-TH than in conventional plants, thus presenting specific risks. On the other hand, the need to increase the maximum limit of residue for the release of a new event tolerant to the herbicide (there are already cases of RR soybean and RR corn) also represent an argument in favor of including the criteria and additional demands in the RN5, to be attended by the proponents of the technology;

the study in question includes for the first time in risk assessmentfield of transgenics the science of endocrinology, an analysis on the hormonal system, which presents various peculiarities that challenge the conservationist knowledge of science. It should be noted that all the toxicity studies conducted have an approach to risk based on a linear relationship between the dose and toxicity;

the finding that the tumors appear at 4 months in male rats and in 7 in females reinforces the need to apply long term studies, case by case. In this context, the study by Seralini et al. in fact addresses items 4 and 6 of Attachment III of RN5, which were not attended by the proponents of the NK603 technology. In fact, in Brazil, these items were never attended by the proponents of the different technologies, and were not required by the majority of the members of CTNBio, since the publication of the norm, in 2008. In this regard, it is worth remembering that France's National Agency for Sanitary Food Security, the Environment and Labor (ANSES), in a letter of October 19, 2012, referring to the study of Seralini et al, concluded that there is a need to "conduct studies with the objective of describing the potential health effects associated to the long term consumption of GMOs or the exposure to the phytopharmaceutical formulations." It also recommended that "these studies must notably focus on the issues of exposure to GMOs and to the associated phytopharmaceutical formulations" and that "These studies should be conducted in the realm of public financing and be based on detailed experimental protocol that allow responding to the issues raised (effects studied, parameters monitored, methodology of investigation, number and nature of the animals monitored, complexity of the GMO, nature of the exhibitions…)" (Anses, 2012).

Observation of the fact that feeding with the NK603 corn (without Roundup) causes biochemical alterations and physiological failures in test rats demonstrates once again that Substantial Equivalence does not have the scientific basis and robustness capable of sustaining decision making in this field.

The advance in scientific knowledge obtained by the study of Seralini et al. (2012) deserves attention and respect from the scientific and regulatory communities, at the domestic and international level, and in the case of Brazil, the implementation of the principle of precaution, which emerges from the Constitution of 1988 – given that it is incumbent on the government to "control the production, sale and use of techniques, methods and substances that present a risk to life, the quality of life and the environment " (art. 225, § 1°, V) – and which is consecrated as a guideline of the Law

of Biosecurity (art. 1o da Lei 11.105/2005). The relevance of the problems and the denial of the risks involved require, contrary to the position taken, additional systematic and repeated tests of NK603 and of other transgenic plants with similar technology, and it is recommendable that reevaluations be conducted and an accompaniment of the use of these products in food for humans and animals.

On this basis, we hope to have contributed to the clarification and reflection by the staff of the Ministry of Foreign Relations in their work on the international level, as Brazilian negotiators, and on a domestic level, on which they actively participate in decision making and undertake their respective responsibilities in relation to food and environmental security – considering the risks to the Brazilian population and biodiversity – and equally in relation to the development of the country, which can be subject to customs barriers due to these risks and in support of the preservation of the environment and the defense of health in other countries.

Signed by the following CTNBio Members:

Paulo Cezar Mendes Ramos
Antonio Inácio Andrioli
Pedro Ivan Christoffoli
Leonardo Melgarejo
Solange Teles da Silva
Suzi Barletto Cavalli
Daniela Sanches Frozi
Nivaldo Peroni
Marijane Vieira Lisboa
José Maria Gusman Ferraz

And the following former CTNBio members:

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