Bioveiligheidsraad
Conseil de Biosécurité

19-10-2012

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2012_0898

Title: Advice of the Belgian Biosafety Advisory Council on the article by Séralini *et al.*, 2012 on toxicity of GM maize NK603

Issue

On 19 September 2012, the Journal Food and Chemical Toxicology published online a research paper, written by G-E. Séralini *et al.*, entitled: "Long term toxicity of a Roundup herbicide and Roundup-tolerant genetically modified maize"[1].
The authors presented this study as the first detailed documentation of long-term adverse effects arising from the consumption by rodents of a genetically modified (GM) glyphosate-tolerant maize and of the Roundup herbicide, a commercial glyphosate-containing formula. The paper states that *the study clearly demonstrates that low levels of complete agricultural glyphosate herbicide formulations induce severe hormone-dependent mammary, hepatic and kidney disturbances*. Further, it is stated that *disruption of biosynthetic pathways that may result from overexpression of the epsps transgene in the GM maize NK603 can give rise to comparable pathologies that may be linked to abnormal or unbalanced phenolic acids metabolites, or related compounds, without excluding other mutagenic and metabolic effects of the edible GMO*.

Mandate

As a result of the publication of the abovementioned research paper, the Federal Minister of Public Health asked the Biosafety Advisory Council (BAC) on 21 September 2012 to evaluate the paper. The BAC was asked to inform the Minister whether this paper (i) contains new scientific information with regard to risks for human health of GM maize NK603 and (ii) whether this information triggers a revision of the current authorisation for commercialisation for food and feed use of this GM maize in the European Union (EU).

Procedure

Within the framework of this mandate, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted scientists with expertise in statistics, toxicology, oncology, haematology, anatomopathology and clinical biology to review the research paper. They were invited to consider in particular the robustness of the conducted research, the applied methods and the interpretation of the results. To avoid any conflicting interest, experts of the common list drawn up by the BAC and the Biosafety and

[1] Séralini GE., Clair E., Mesnage R., Gress S., Defarge N., Malatesta M., Hennequin D., de Vendômois JS. 2012. Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food Chem. Toxicol. doi: 10.1016/j.fct.2012.08.005

Biotechnology Unit (SBB) who were involved in previous safety assessment of GM plants were explicitly not invited to participate in this consultation.
The following experts answered positively to this request and provided their feedback:
Prof. Adelin Albert (Université de Liège), Prof. Dominique Cassart (Université de Liège), Prof. Corinne Charlier (Université de Liège), Prof. Dr. Dirk De Bacquer (Universiteit Gent), Dr. Bart De Ketelaere (Katholieke Universiteit Leuven), Prof. Joris Delanghe (Universiteit Gent), Prof. Philippe Delvenne (Université de Liège), Prof. Frédéric Farnir (Université de Liège), Prof. Pascal Gustin (Université de Liège), Dr. Dominique Lison (Université catholique de Louvain), Dr. Ir. Viviane Planchon (Centre wallon de Recherches agronomiques, Gembloux).

This document provides a summary of the main elements and conclusions addressed by the experts in their analysis reports as well as the conclusions drawn by the BAC on this basis.

Background information

The GM maize NK603 (Unique Identifier MON-ØØ6Ø3-6) has been developed for tolerance to glyphosate by the introduction, via particle gun acceleration, of a gene coding for 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) from *Agrobacterium sp.* strain CP4 (CP4 EPSPS).
This GM maize is currently authorised for commercialisation in the EU for food and feed use (for further details, see the EU Register of authorised GMOs at http://ec.europa.eu/food/dyna/gm_register/index_en.cfm).

In October 2005, Monsanto has submitted to EFSA under Regulation (EC) No 1829/2003 an application (Reference EFSA-GMO-NL-2005-22) for authorisation of NK603 for cultivation, food and feed uses and import and processing, as well as an application for renewal of the authorisation of existing feed materials and food and feed additives produced from maize NK603 (Reference EFSA/GMO/RX/NK603).

In the frame of the evaluation of these two applications, the BAC has issued a comprehensive advice on 2 October 2009 (Reference WIV-ISP/BAC/2009_01367). In this advice, the BAC concludes that it agrees with the GMO Panel of EFSA that no major risks for human and animal health associated with the use of GM maize NK603 in food and feed were identified.
When drafting this advice, the BAC took into consideration all relevant available information, including a 90-day study in rats fed GM maize NK603 either as 11% or 33% of the total diet, or a control diet containing 11% or 33% non-GM maize having a comparable genetic background to GM maize NK603 (data published in Hammond et al., 2004)[2].

General information about the design of the Séralini'study and toxicity/carcinogenicity studies

The paper of Séralini et al. presents a long-term (2 years) experiment on feeding trials using 200 Virgin albino Sprague-Dawley rats (100 males and 100 females). The 100 animals of each sex have been randomised into 10 distinct groups of 10 rats each. For each sex, one control group had access to plain water and standard diet containing 33% of the closest isogenic non-GM maize control; six groups were fed with diet containing 11, 22 and 33% of GM NK603 maize either treated or not with RoundUp. The final three groups were fed with the control diet and had access to water supplemented with three different concentrations of Roundup.

[2] Hammond B., Dudek R., Lemen J., Nemeth M. 2004. Results of a 13 week safety assurance study with rats fed grain from glyphosate tolerant corn. Food Chem. Toxicol. 42, 1003–1014.

The aim of the study, as far as can be judged from the publication, was to carry out a prolonged oral chronic toxicity study in rodents to investigate the effects of GM maize NK603 (treated or not treated with Roundup) consumed over the long term. The starting point to design the study was the usual parameters for a 90-day toxicity study (OECD Guideline No 408[3]) to which the authors added some additional parameters and prolonged biochemical and haematological measurements or disease status as recommended for combined chronic toxicity/carcinogenicity studies (they refer to OECD Guideline No 453[4]).

The OECD Guideline No 453 recommends that each dose group and concurrent control group intended for the chronic toxicity phase of a study should contain at least 10 animals of each sex, while for the carcinogenicity phase of a study each group should contain at least 50 animals of each sex. The recommended period of dosing and duration of the study is 12 months for the chronic phase, and 24 months for the carcinogenicity phase (representing the majority of the normal life span of the animals to be used). The Guideline also states that "*interpretation of the data from the reduced number of animals per group in the chronic toxicity phase of a combined study will however be supported by the data from the larger number of animals in the carcinogenicity phase of the study.*"

Information for the design of long-term chronic toxicity studies is also available in the OECD Guideline No 452[5]. For rodents, it is recommended that at least 20 animals per sex per group should be used at each dose level so that at the end of the study enough animals in every group are available for thorough biological and statistical evaluation. The Guideline is designed as a 12 month chronic toxicity study, although longer or shorter durations may also be chosen depending on specific requirements.

Analysis of the research paper published by Séralini et al. (2012)
Summary of the main elements addressed by the experts in their analysis reports

Design of the study

- Three experts were of the opinion that the long duration of this study is a positive aspect since most of the toxicity studies on GMOs are performed on shorter periods.

- Seven experts considered the number of animals used by Séralini et al. (10 rats/sex/group) as being too low and not fully complying with the recommended standards for a long-term toxicity study and/or for a carcinogenic study (see general information above).
However, one expert referred to biocides toxicological evaluation in the frame of REACH where sub-chronic or long-term studies are performed on 10 or 15 animals, which is quite the same as in the Séralini paper. Although the OECD recommends the use of at least 20 animals, 10 animals in each group is better than what is made in many other studies.

- The study was performed using Sprague-Dawley (SD) rats. While this strain is commonly used in studies for drug discovery and in short-term toxicity studies, its relevancy in a two-year study was questioned by five experts in particular in the context of the analysis of tumour incidence. There are indeed numerous references in the scientific literature showing that SD rats have a high background incidence for certain types of tumours, especially mammary and pituitary tumours, with probabilities that rapidly increase during the last quarter of their life, and suggesting a clear effect of feeding strategy. These studies also show that there is a non-

[3] OECD (1998). Test No. 408: *Repeated Dose 90-Day Oral Toxicity Study in Rodents*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing.
[4] OECD (2009). Test No. 453: *Combined Chronic Toxicity/Carcinogenicity Studies*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing.
[5] OECD (2009). Test No. 452: *Chronic Toxicity Studies*, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing.

negligible variability in this probability, probably related to specific "settings" of the studies (feed type and amount, …).
In such a situation confidence intervals for small sample sizes (such as n = 10) are broad. Moreover, this can create a problem of interpretation of the lesions with a possible confusion between lesions possibly related to age and lesions caused by the products tested.

- Three experts noted that it is somewhat unusual that only 10 control animals per sex were used for a total of 90 animals per sex in the experimental groups. The interpretation of the reported results will depend largely on the expected survival rate / tumour incidence rate of control animals. Therefore, in order to determine a control group probability of developing pathologies, a substantial amount of control animals is compulsory, 10 being considered too low. Through this power imbalance in favour of the exposure groups, the importance of the observations in the control group as reference is not sufficiently emphasized. To partly accommodate this, thorough balanced statistical analysis would therefore be necessary, but is made difficult in this case due to the low number of animals per group.

- One expert indicated that the number of animals per cage was unclear. Section 2.3 refers to "two animals of the same sex per cage" while Table 1 refers to "one or two animals of the same sex by cage". Although this might be seen as a detail, it should be noted that rats are rather gregarious and isolation could generate endocrine deregulation potentially leading to the apparition of tumours (reference to a scientific paper was cited).

- One expert indicated that the experimental design was not “complete”, in the sense that not all possibilities generated by diet and water were utilised. Actually, the experimental design consists of two distinct “dose-response” studies using the same control group, respectively (control + 3 groups fed with 11, 22 and 33% of GM NK603 maize either treated or not with RoundUp) and (control + three groups fed with the control diet and water supplemented with three different concentrations of Roundup). Interestingly, the authors do not explicitly look at the groups as originating from dose-response experiments. The 10 groups are viewed as qualitatively distinct, i.e. without any ordering (see the OPLS analysis on biochemical parameters). Indeed, nowhere in the paper have the groups been considered or treated as “ordered”.

Endpoints

According to one expert, the endpoints of this study have not been clearly defined. What is the primary endpoint, what are the secondary endpoints? Several possible endpoints (or outcome measures) can be identified:

- Survival or death over the study period (binary variable)
- Time to death (time-to-event variable with censoring)
- Tumour development (binary variable Yes/No)
- Time to tumour development (time-to-event variable with censoring)
- Number of tumours developed (count variable: 0, 1, 2 …)
- Number of pathological findings (count variable: 0, 1, 2 …)
- Biochemical tests (quantitative continuous variables repeated over time)

These endpoints can be binary, time-to-event or lifetimes, counts or quantitative variables. Appropriate statistical methods should be used to analyse the corresponding data. This has not been done.

Anatomopathological observations

- Three experts commented this part of the study. Their general feeling was that the paper does not clearly specify the type of tumours that have been observed. Table 2 is unclear and mixes different categories of tumours. The legend of Figure 3 refers to adenocarcinomas and fibroadenomas. These should be clearly distinguished as they correspond respectively to

benign and malignant tumours. Galactoceles and hyperplasias are also mentioned in Figure 3 although it is unusual to consider them as tumours.

- One expert noted that while, from the data presented, the diagnosis of fibroadenomas can be considered likely, histological analysis does not allow to formally conclude the presence of adenocarcinomas. Research of myoepithelial cells by immunohistochemistry may be useful to confirm the histological diagnosis (adenocarcinoma *vs* fibroadenoma). Accordingly, it is surprising, given the size of tumours, that only two animals had developed metastases (a characteristic of malignant tumours - results not shown). Another expert concluded that it was impossible to know, from the data available, whether the reported lesions were regressive, inflammatory or neoplastic (i.e. with the potential to evolve in cancer).
It should also be noted that in human pathology, fibroadenoma (a dual - epithelial (glandular) and fibre - component tumour) is not considered the precursor of the classical mammary adenocarcinoma. Indeed, its degeneration into cancer is considered exceptional.

- One expert noted that, even though the authors state several times in the paper that tumours were studied by electron microscopy, the results are not reported nor discussed.

Biochemical analyses

- One expert noted that the results were presented in a way that makes their interpretation very difficult. Table 3 reports only about the percentages of variation of tested parameters. The main limitation in this approach is that biochemical parameters often reveal large variations between animals, so presenting percentages of variation is not sufficient. Crude data should be provided as well as other information such as description of the analytical methods used for all determination (section 2.4 only states that parameters were assessed "according to standard methods"), total error or standard deviation of the methods...

- One expert was of the view that the authors' opinion that biochemical parameters indicate kidney and liver failures is questionable. In particular he noted that:
- The hepatic biochemical parameters (ALT, total protein, cholesterol synthesis, coagulation) are very similar between control and treated groups and do not indicate serious liver disease.
- The biochemical parameters for kidneys are also satisfactory. The reported reduced levels of creatinine in urine for all treatment groups in comparison to female controls (Table 3) should be interpreted very carefully, in particular given the absence of any information about the methodology used. Creatinine levels in rats are much more lower than in humans, which makes their measurement very unreliable (see new standard SRM 967 for use in establishing calibrations for routine creatinine measurement procedures in human serum). Moreover the reported nephropathies in the treated groups seem unlikely due to the very limited changes in urea and creatinine levels.
- The significance of the observed changes in Na and Cl excretion is very unclear. Contrary to what should be expected, no hyponatraemia is observed. In case of salt-losing nephritis an "Urémie par manque de sel" should normally be detected. The study of the possible renal tubular damage (typically associated with kidney injury) is very superficial in the paper.

Statistical analyses

- Four experts noted that the differences in the incidence of the primary health effects that were observed, namely mortality and tumour development (Figures 1 and 2), were not subjected to statistical testing.

- One expert suggested that the following statistical design should have been performed: Proportions (e.g. death rates) in the various groups should be compared by a chi-square test

or by Fisher exact test. To account for the ordering of the groups (dose effect), it would even be better to apply a logistic regression analysis. To compare counts, a Poisson regression model should be used, to compare lifetimes in different groups or according to dose, a Cox PH regression model would be required. For continuous variables, the classical multiple regression analysis should be used.

- One expert noted that the SEM (standard error of mean) used by the authors in Figure 1 and 2 is known to reduce standard deviation.

- Under the heading "Mortality" of the results section, the authors state that "*30% control males (three in total) and 20% females (only two) died spontaneously, while up to 50% males and 70% females died in some groups on diets containing the GM maize*". Some experts indicated that such a statement needs to be considered with great caution. By applying other hypothesis tests to this scenario (e.g. Fisher's exact test), it appears that for both male and female animals, these differences in mortality are all but statistically significant. In other terms, results could have well been observed by chance alone. Therefore, there is no sufficient statistical evidence to demonstrate differences between the groups.

- One expert noted that the fact that the experiment includes a large number of experimental groups necessitates a multiple comparison correction to control the number of false positive discoveries. However, this important aspect was ignored by the authors. It could simply be done e.g. by a Bonferroni adjustment of the significance level.
Comment: This expert provided a detailed and extensive statistical simulation study showing that the (interpretation of the) results depend(s) heavily on the control probability for developing pathologies, a quantity that is not estimable with high precision based on only 10 control animals for each sex.

- Given the limited sample size of animals per exposure group, one expert wonders whether a statistical analysis is even feasible. In consequence it is unclear to what extent the observed differences can be explained as being coincidence or not.

- To illustrate this, one expert noted that due to the small samples size, it would be critical to have larger differences between the control and treated groups (for example, the maximum difference of tumours incidence between control groups (30%) and “worst” treated groups (80%) is only significant with $p = 0.03$).
However, one expert was of the opinion that even if the control animals developed some tumours, the frequency in tested rats was significantly higher than in the control group.

- A statistical analysis was performed for the biochemical parameters, based on the OPLS-DA (Orthogonal Partial Least Squares Discriminant Analysis) regression technique. Although there are some arguments for the choice of this technique[6] it is important to note that it seemingly aims to find differences than rather testing whether there can be differences demonstrated in the measured biochemical parameters between tested and control groups. A discriminant analysis starts therefore from *a priory* belief that two groups are different.

- One expert was of the view that biochemical parameters should be analysed by the more advanced “General Linear Mixed Model (GLMM)” which accounts for repeated measurements of the laboratory tests in the comparison of the groups.

- One expert was of the opinion that the discriminant analysis performed in this case on the biochemical data seems to present some shortcomings because of (i) the small sample size for each analysis made, and (ii) the validation strategy chosen, excluding a testing phase on an independent test set.

[6] OPLS-DA is often used in cases where the number of variables is large when compared to the number of samples taken, and where a large correlation amongst the variables is present.

- One expert noted that given the multitude of comparisons that are made (because of the many biochemical data as well as the number of groups being compared), a correction of the significance threshold is required to reduce the risk of "false-positive" findings ("multiple testing"). This was not considered in the paper. Here again, the statistical analysis provided in the paper should be interpreted with great caution and does not support the conclusion of any treatment-related toxicity or carcinogenicity.

- One expert was of the view that more detail would be needed in order to better understand some seemingly paradoxical results: although most (76%) discriminant variables are kidney related, kidney related pathologies do not seem significantly more frequent in diets than in controls. Probably, this only indicates disturbances in the kidney parameters, but with no clear marked effect on the occurrence of a disease.

- Some experts noted that OPLS-DA for biochemical data (Figure 5) are only presented for one group (females that had received feed with 33% NK603 maize compared to the control group), and in a way that does not provide a clear basis to perform a statistical evaluation with sufficient accuracy. Moreover data were only analysed at 15 months ignoring time evolution and group ordering.

Other issues

Some experts noted that the paper lacks information on some aspects and basic parameters that are important for a proper assessment of the reported effects and should be reported for this type of study. Although the authors state (page 4) that "*All data cannot be shown in one report, and the most relevant are described here*", it is unclear on which basis specific pieces of data were included or not into the paper. If only those data "showing the largest differences" were selected, the authors introduced a selection bias into their results. Complementary data should have been provided in an appendix or online supplement, as it is usual for peer-reviewed articles. Missing information mentioned by the experts includes:

- Details on diet composition. The authors state that "*All feed formulations consisted in balanced diets, chemically measured as substantially equivalent except for the transgene, with no contaminating pesticides over standard limits*". However, detailed and clear information on rodents diet is important since differences observed amongst animals may be due to dietary compositional differences. For instance, no information is available regarding the levels of herbicide residues in treated corn, the presence of plant metabolites, or the potential presence of confounders such as mycotoxins.

- Figures for feed and water consumption. The amount of feed and water animals consumed can also have an important influence on many aspects of animal responses, including tumour development and kidney function. In particular in SD rats, it has been reported in the literature that diet restriction increases 2-year survival when compared to *ad libitum* feeding. Although the feeding regime is not described in full detail in the paper, it can be assumed that rats were fed *ad libitum* (in section 2.3 it is stated that animals had "free access to feed and water").

- Information about whether or not the study was blinded. In such studies where anatomopathological data (tumour size measurements, etc.) are used, the investigator should not know the exposure group from which a tested animal is coming from. This is crucial to minimise the risk of biased interpretation of the observations.

Interpretation of results

- One expert noted that Figure 1 shows that the various diets have similar mortality rates in males, although few individuals seem to be dying earlier in the GMO+Roundup diet. The

situation in females seems more in favour of an hypothesis of increased morbidity for the GMO and Roundup diets, with higher mortality and higher euthanasia rates.

- On page 8 the authors state that "*Our data show that, as is often the case for hormonal diseases, most observed effects in this study were not proportional to the dose of the treatment, non-monotonic and with a threshold effect*".
Three experts were of the opinion that the apparent absence of dose-response relationship rather argues against a genuine treatment-related effect. The hypothesis offered by Séralini et al. to explain the absence of dose-response relationship (non-monotonic responses) is not supported by the data of the study or by the general toxicological literature. At least, this indicates that the findings of this study should be interpreted with great caution.

- Another expert commented on the variability within the groups: assuming, as the study suggests and as the authors discuss, that potential deleterious effects of the GMM and/or Roundup are threshold dependent, various doses somehow correspond to replicates of similar situations. Using that argument, it can be observed from the results (for example, from Table 2), that the variation across samples is quite high (for example, for pathologies of the pituitary gland, some diets show less problems than the controls, while for others, the incidence is doubled with respect to controls). This observation again underlines the need for larger samples sizes.

- On page 9, the authors suggest that adverse effects associated with consumption of GM maize NK603 could be explained by reduced levels of caffeic and ferulic acids (secondary metabolites of the plant shikimate pathway) in the GM diets. The authors add that such reduced levels may result from overexpression of the *epsps* transgene in maize NK603. According to the authors, "*this may lower their protective effects against carcinogenesis and even mammalian tumors. Moreover, these phenolic acids and in particular ferulic acid may modulate estrogen receptors or the estrogenic pathway in mammalian cells.*"
One expert was of the opinion that the hypothesis of possible protective effects of caffeic and ferulic acids on tumour development is a matter of discussion and can not be fully substantiated by relevant scientific information. He provided references to scientific papers where adverse effects associated with these components are reported.

Conclusions of the experts

- The experimental design used in this study allows estimation of the effect of water contamination and of the effect of GMO diet, but not the cumulative effect of both combined, in male and female rats. The endpoints are not clearly defined and so are the statistical methods used to test the null hypotheses at hand. The study lacks expert data modelling which would lead to scientifically sound conclusions.

- The study provides some indications that GMO and Roundup based diets potentially might have deleterious effects on health, at least in rats. A major result of the paper is that the (potential) occurrence of problems takes time well above the usual duration used for this type of experiences, which strongly indicates that future experimentations should consider longer terms effects than what is usually done.
No definitive conclusion can be drawn before the experience is repeated with a similar design but with larger cohorts, and maybe with other rat lines. The dose-effect relationship would deserve more attention. And, assuming a threshold effects as done by the authors, a better characterisation of the allowable threshold should be made in order to eventually come with recommendations.

- The results of the study have to be considered with many caution, and of course further experimentations are needed to confirm or not the present findings.

- One can say that the way the study was designed, the data were analysed and the results selectively proposed, is not sufficiently convincing to reach the conclusions mentioned in the paper. Despite the many methodological shortcomings, it can nevertheless be stated that the results of Séralini et al could give rise to further, larger and independent research on the health long term effects of genetically modified food.

- It seems reasonable to assume that the publication of Prof. Séralini, without providing definitive conclusion as to carcinogenicity in rats and even less about the underlying mechanisms, provides a reasonable and sufficient doubt to promote research on the impact of GMOs and pesticides associated with this type of culture, on the fauna and flora as well as mammals exposed. Rather than rejecting these results, should we not, according to the scientific approach, encourage new experiments to verify the reproducibility of the results by correcting any shortcomings of the current publication. All this calls for extreme caution and to discuss these issues with great care.

- Results of the Séralini study can not be regarded as results to take decisions. They must be accompanied by other studies that confirm (or not) the results of this exploratory study.

- This study is not really convincing and a lot of question marks remain.

- The results are rather suggestive than scientifically well-backed and additional/new experiments are needed in order to invalidate former tests performed on GMO and that did not reveal an increased toxicity / risk.

- Challenging existing knowledge and paradigms is of course the basis of scientific progress, and revisiting those current views could be appropriate and welcome. It would need, however, to apply solid scientific standards; the paper by Séralini et al. fails largely in this respect. The work is scientifically very weak, with flaws in the experimental design, in the interpretation of the results as well as their (over)interpretation and reporting. It should never have been accepted for publication in a scientific journal. The process of peer review which is usual before acceptance for publication in scientific journals has clearly failed here.

Conclusions of the Biosafety Advisory Council

1. Given the shortcomings identified by the experts regarding the experimental design, the statistical analysis, the interpretation of the results, the redaction of the article and the presentation of the results, the Biosafety Advisory Council concludes that this study does not contain new scientifically relevant elements that may lead to reconsider immediately the current authorisation for food and feed use of GM maize NK603.

2. Considering the issues raised by the study (i.e. long term assessment), the Biosafety Advisory Council proposes EFSA urgently to study in depth the relevance of the actual guidelines and procedures. It can find inspiration in the GRACE project to find useful information and new concerted ideas.

p.o. Dl. Ph. Herman
Prof. D. Reheul
President of the Belgian Biosafety Advisory Council

Annex I: Minority opinion

Annex 1: Minority opinion

"Considering the uncertainties on long term effects of GM maize NK603 on health, we ask for a reassesment of the advice of the BAC on the initial dossiers of the maize NK603, regarding effects on human and animal health, using the same critical analysis that was applied by the BAC's experts to the Seralini *et al.* study."

Jean-Claude Grégoire, Damien Winandy, Lucette Flandroy and Philippe Baret