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Reply to letters to the editor

Answers to critics: Why there is a long term toxicity due to a Roundup-tolerant genetically modified maize and to a Roundup herbicide

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ABSTRACT

Our recent work (Séralini et al., 2012) remains to date the most detailed study involving the life-long consumption of an agricultural genetically modified organism (GMO). This is true especially for NK603 maize for which only a 90-day test for commercial release was previously conducted using the same rat strain (Hammond et al., 2004). It is also the first long term detailed research on mammals exposed to a highly diluted pesticide in its total formulation with adjuvants. This may explain why 75% of our first criticisms arising within a week, among publishing authors, come from plant biologists, some developing patents on GMOs, even if it was a toxicological paper on mammals, and from Monsanto Company who owns both the NK603 GM maize and Roundup herbicide (R). Our study has limits like any one, and here we carefully answer to all criticisms from agencies, consultants and scientists, that were sent to the Editor or to ourselves. At this level, a full debate is biased if the toxicity tests on mammals of NK603 and R obtained by Monsanto Company remain confidential and thus unavailable in an electronic format for the whole scientific community to conduct independent scrutiny of the raw data. In our article, the conclusions of long-term NK603 and Roundup toxicities came from the statistically highly discriminant findings at the biochemical level in treated groups in comparison to controls, because these findings do correspond in an blinded analysis to the pathologies observed in organs, that were in turn linked to the deaths by anatomopathologists. GM NK603 and R cannot be regarded as safe to date.

1. Introduction

Our recent publication of research evaluating the long term toxicity of a NK603 Roundup-tolerant genetically modified (GM) maize and of a Roundup (R) herbicide (Séralini et al., 2012) has provoked numerous positive and negative reactions throughout the world. This is the way science moves forward and here we provide a response to this intense debate. Our work is the most detailed study involving the life-long consumption of an agricultural genetically modified organism (GMO), and especially on NK603 for which only a 90-day safety test was previously conducted and using the same rat strain (Hammond et al., 2004). It is also the first long term detailed research on mammals exposed to a highly diluted pesticide in its total formulation with adjuvants. These adjuvants help to stabilize the active principles of pesticides, and promote a better penetration into organisms, and thus more side-effects. R is the most widely used herbicide in the world, which we tested from levels arising in tap water. Indeed in our study, its active principle glyphosate (G) was not studied alone, contrasting with the long term experiments conducted by the manufacturer as part of its application for regulatory approval. As such, the debate in question here is at the cornerstone of science and regulatory issues on this topic. This fact has major economic ramifications for the development of such products, which can explain the severe comments posted within hours of our publication becoming available online. This may explain why 75% of our first criticisms arising within a week, among publishing authors, come from plant biologists, some developing patents on GMOs, even if it was a toxicological paper on mammals, and from Monsanto Company who owns both the NK603 GM maize and R herbicide.

We must firstly focus on science. Our work is a research study; it has not a direct regulatory purpose and should not be considered as a final point in knowing the toxicological effects of NK603 and R. This is a first step in the iterative investigation of the long-term health effects on mammals of these commercial products that should be replicated independently, as well as on developing mammals. It has limits like any study, and here we carefully answer to all criticisms from agencies, consultants and scientists, that

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were sent to the Editor of *Food & Chemical Toxicology* or to ourselves. These challenged our results and the validity of our protocol, some letters even requested the withdrawal of the publication from the journal. All remarks and answers are summarized in Table 1 and with some explanatory details given below.

At this level, a full debate is biased if the toxicity tests on mammals of NK603 and R obtained by Monsanto Company remain confidential and thus unavailable for the scientific community to conduct independent scrutiny of their raw data. This is why, after several exchanges, we requested again from the European Food Safety Agency (EFSA) on September 20th and October 18th 2012 the release on a public website of the raw data on health risks on the basis of which commercialization of these products was granted, in particular results from the longest study of NK603 and Roundup on mammals (Hammond et al., 2004). We ask for a free and transparent exchange of scientific findings, mainly when these are related to public health and environmental risks (Schreider et al., 2010). Examination of industry raw data previously evidenced divergence of regulatory decisions from scientific evidence underestimating toxicological features of G (Antoniou et al., 2012). We recall that the tests on rats are usually considered as a model for mammalian health before clinical trials (for example for pharmaceuticals) or for a direct market release (for novel food and feed, pesticides or chemicals). Moreover, tests on rats are also models for environmental risk assessment, since they are models for other wildlife mammals. The public release of these raw data will reveal if significant differences observed between test and control groups in both studies are coherent and if the statistics are of sufficient power in both cases, thereby allowing the design of appropriate follow-up experiments by others, perhaps through a publically discussed and agreed protocol.

2. Relevance of the scientific context

Some remarks emphasize a lack of context, claiming that the study was performed for non-scientific reasons. The establishment of this protocol was however the consequence of an intense debate about the biological relevance of numerous statistically significant differences compared to controls revealed and admitted to in 90-day feeding studies with agricultural GMOs (Spiroux de Vendomois et al., 2010). This is highly controversial, with companies and regulatory agencies having refuted findings, which were validated by a peer reviewed process in international journals (EFSA, 2007; Séralini et al., 2007). Indeed, regulatory agencies such as EFSA appear to have their own criteria to judge the biological relevance of research findings (Doull et al., 2007), which is markedly at odds with some recent knowledge. This includes cases of sex specific non-linear endocrine disruptions, which were not admitted to as valid at a regulatory level although accepted at a scientific research level (Myers et al., 2009b). In order to overcome the divergence in biological interpretation of early signs of toxicity in blood biochemistry for GMOs, one solution was to prolong 90-day feeding tests to chronic periods. We therefore chose the R tolerant NK603 GM maize because R tolerance is the trait present in approximately 80% of agricultural GMOs (James, 2011) and because statistical differences in the 90-day feeding trial with this maize were admitted to by both the petitioner and regulatory agencies (EFSA, 2009).

3. Originality and limits of the experimental design

Due to the economic and regulatory issues of this topic, it is not surprising that our research study was confounded with pre-commercial regulatory assessments. This is why the most common criticism questions the following of Organization for Economic Co-operation and Development (OECD) guidelines. However, no guidelines exist for GMO toxicity studies in vivo, which are still not mandatory. Published reviews have confirmed that most of the studies conducted to date did not follow specific guidelines or were contradictory (Domingo, 2007; Domingo and Giné Bordonaba, 2011). We compared our design (Table 1 of Séralini et al., 2012) to Hammond et al. (2004) inspired from OECD guideline 408 for chemicals. We have replicated, extended and thus improved the experiments conducted by Hammond and colleagues (Hammond et al., 2004) by measuring outcomes from 3 instead of 2 feed doses and more crucially for a period 8 times longer in duration (90-days vs 2 years), with 11 blood and urine measures of around 50 parameters, 34 organs instead of 17, etc., in order to ascertain if the statistical findings (observed at 90 days; Hammond et al., 2004), were biologically relevant or not in the long term. We thus biochemically measured 10 rats per sex per group as performed by Monsanto. Even for a study of up to two years, we had no reason to monitor biochemical effects on more than 10 animals per sex per group as this is the number recommended in OECD guideline 452 for chronic toxicity testing (OECD 1981 was in application when the study started in 2008), even if 20 animals per group or more are possible.

The purpose of the addition of R treated groups was not to assess R long term carcinogenesis, which needs to follow OECD 453 guideline with at least 50 rats per sex per group (even if 10 rats are then still measured at a biochemical level). The aim of our study was to test R under similar conditions to the GM maize in order to try and understand if residues of R in the feed could explain the possible pathologies that may arise. There were two main potential sources of harm tested in our study: (i) effects from the GM maize itself, treated or not with R, and (ii) herbicide residues alone in drinking water, using 3 doses for each treatment. We recall that the initial investigation published by Hammond and colleagues (Hammond et al., 2004) used 2 doses for each treatment group despite that fact that 3 doses are recommended by OECD guideline 408, which they reported to have followed.

In addition, one of the criteria for biological relevance employed by Monsanto and other critics of our study is the linearity or lack thereof in response to the dose. Such a dose–response relationship cannot be claimed from a trial using only 2 doses of test material as employed in the initial NK603 assessment (Hammond et al., 2004). We therefore find it surprising that the relevance of Monsanto's and the agencies' conclusion of safety was not challenged due to such protocol insufficiencies. A recent review of the literature is often cited as a proof of the safety of GMO consumption on a long-term basis (Snell et al., 2012). However, of the 24 studies they evaluated, only 2 are long-term on rodents, since a 2 year feeding period with pigs or cows do not constitute a life-long experiments. The 2 rodent studies quoted by Snell and colleagues are from Sakamoto et al. (2008) where not all rats fed transgenic soy were analyzed, and Malatesta et al. (2008a) in mice fed again GM soy, which showed at an electronic microscopy level effects of this product on hepatic function. Moreover, of the 24 studies cited, 16 did not mention the use of the closest isogenic non-GM line as a control, many did not describe the methods in detail, and contained additional deficiencies (Snell et al., 2012). However, all these studies were accepted as proof of safety regardless of the inadequacies highlighted here. It would appear that conclusions of safety seem to need fewer requirements than conclusions of toxicity. However, scientifically it is easier to conclude an outcome of toxicity than safety. This was not the first time regulatory agencies used such double standards to minimize independent research findings in regard to industry findings (Hilbeck et al., 2012; Myers et al., 2009a). Our control groups were also questioned and this needs some clarification. Some claimed that controls are lacking for all 4 test groups (GMO+R and GMO alone at 11% and 22%). We compared