Commentaires dans le cadre de la saisine du 24 septembre 2012 relative à l'étude Séralini et al. (2012).

En réponse à votre lettre en date du 5 Octobre 2012, Monsanto entend souligner que les produits visés par l'étude en référence ci-dessus ont fait l'objet de multiples évaluations réglementaires dans le monde entier. Ces évaluations ont toutes unanimement confirmé la sécurité du maïs NK603, ainsi que la sécurité du glyphosate et du Roundup ®. La récente étude Séralini et al. (2012), invalidée par des experts indépendants, ne remet pas en cause les conclusions des évaluations réglementaires.

1. Sécurité du maïs NK603 :

Le maïs NK603 a été développé pour améliorer l'efficacité du désherbage dans les cultures grâce à l'expression de la protéine CP4 EPSPS, qui confère une tolérance aux herbicides à base de glyphosate.
La sécurité du maïs NK603 a été évaluée et déterminée conformément aux lignes directrices internationales (Codex) et Européennes (EFSA) d'évaluation du risque applicables aux plantes génétiquement modifiées. Son innocuité a été confirmée par plus d'une décennie d'utilisation au niveau mondial.

L'évaluation avant mise sur le marché de risques de NK603 dans l'alimentation humaine et animale a porté sur les points suivants :

• Caractérisation moléculaire, incluant des analyses « Southern blot », des analyses PCR, des analyses de séquences de bases, des analyses bio-informatiques, des analyses de la stabilité et de l'héritabilité des inserts pour caractériser les changements moléculaires et vérification que la protéine CP4 EPSPS est la seule protéine nouvelle.
• Analyses de la composition de NK603 comparées à son homologue conventionnel qui ont démontré que le maïs NK603 est de composition similaire au maïs conventionnel.
• Analyses des caractéristiques phénotypiques et agronomiques du maïs NK603, aux résultats similaires à ceux du maïs conventionnel, et qui ne montrent ni comportement de type mauvaise herbe ni autres caractéristiques particulières.
• Caractérisation approfondie de la protéine CP4 EPSPS exprimée dans le maïsNK603 qui confirme qu'elle est sûre pour la consommation humaine et animale. L'évaluation du risque a pris en compte la quantification du niveau de protéine dans les tissus végétaux, la caractérisation des propriétés physico-chimiques et fonctionnelles de la protéine, une évaluation de la similitude de la protéine CP4 EPSPS avec des allergènes connus, des toxines et d'autres protéines biologiquement actives connues pour avoir des effets indésirables sur des mammifères, l'évaluation in vitro de la digestibilité de la protéine CP4 EPSPS et l'étude de toxicité aiguë par voie orale aiguë in vivo sur des souris.
• Etudes alimentaires sur divers animaux comme la volaille, les bovins et les porcins ont confirmé l'équivalence nutritionnelle du maïs NK603 avec les variétés de maïs conventionnelles.

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• Etude de 90 jours de toxicité sub-chronique qui a confirmé l'absence d'effets indésirables suite à l'administration répétée de NK603 dans la ration alimentaire de rats, et montré une marge de sécurité de 84x[1]

La sécurité du maïs NK603 déterminée à la suite de cette évaluation approfondie a été confirmée par plus d'une décennie d'utilisation du maïs NK603. Les variétés de maïs NK603 ont été largement cultivées aux États-Unis et au Canada depuis leur introduction sur le marché en 2001 et aucun effet indésirable non anticipé n'a été rapporté.

Les variétés de maïs NK603 sont aujourd'hui cultivées dans divers pays à travers le monde, y compris les États-Unis, le Canada, l'Argentine, le Brésil, la Colombie, le Honduras, l'Uruguay, les Philippines et l'Afrique du Sud.

Dans l'Union Européenne, NK603 a été approuvé pour l'importation, la transformation et l'alimentation animale en juillet 2004, suite à une évaluation du risque complète conformément à la Directive 2001/18/CE[2]. Le maïs NK603 a en outre été évalué et approuvé pour usage alimentaire en 2005, conformément au Règlement (CE) n° 258/97[3]. Suite à une demande d'autorisation pour la culture de variétés de maïs NK603 dans l'UE, ainsi que pour le renouvellement de l'autorisation d'utilisation en alimentation humaine et animale déjà mentionnée ci-dessus, l'EFSA a publié un nouvel avis positif sur la sécurité de NK603 en 2009.[4]

En plus des autorisations de l'UE pour l'importation et l'utilisation en alimentation humaine et animale, la sécurité de NK603 vis-à-vis de l'homme a été évalué et ce maïs a reçu les autorisations réglementaires pour l'utilisation pour l'alimentation humaine des agences d'évaluation d'autres pays, comme celles d'Australie / Nouvelle-Zélande (FSANZ), de Chine (Ministère de l'Agriculture), de Colombie (ICA-RCT Pecuario), d'Indonésie (Comité national pour la biotechnologie), du Japon (MHLW / FSC et MAFF), de Corée (KFDA et RDA), de Malaisie (Ministère des Ressources naturelles et de l'Environnement), du Mexique (Ministère de la santé),

[1] Considérant (1) une consommation de farine de maïs pour la population générale de l'Europe centrale (le groupe E) de 0.25 grammes/kg/jours (consommation chronique de 14.7 g/personne/jour, obtenus du GEMS/Food Program at http: // www.who.int/foodsafety/chem/en/acute_ha zard_db1.pdf, divisé par le poids présumé d'un adulte de 60 kg);
(2) le plus haut niveau/dose dans l'étude chez le rat de poids corporel de 21 grammes/kg / jour de NK603

2 Décision de Commission du 19 juillet 2004 concernant la mise sur le marché, conformément à la Directive 2001/18/EC du Parlement européen et du Conseil, d'un produit de maïs (Zea mays L. ligne NK603) génétiquement modifié pour une tolérance au glyphosate (2004/643/EC). OJ L 295/35, 18.9.2004 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:295:0035:0037:EN:PDF

[3] Décision de Commission du 3 mars 2005 autorisant la mise sur le marché de produits alimentaires et ingrédients alimentaires tirés de ligne de maïs génétiquement modifiée NK 603 comme nouveaux produits alimentaires ou nouveaux ingrédients alimentaires conformément à Règlement (CE) Non. 258/97 du Parlement européen et du Conseil (2005/448/EC). OJ L 158/20, 21.6.2005 (http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:158:0020:0022:EN:PDF.

[4] Avis du groupe scientifique sur les organismes génétiquement modifiés de l'Autorité européenne de sécurité des aliments (EFSA) sur deux demandes (références EFSA-GMO-NL-2005-22 et EFSA-GMO-RX-NK603) concernant la mise sur le marché du maïs génétiquement modifié tolérant au glyphosate NK603 en vue de sa culture, de son utilisation dans l'alimentation humaine et animale, de son importation et de sa transformation industrielle, ainsi que le renouvellement de l'autorisation de produits existants obtenus à partir du maïs génétiquement modifié NK603 (http://www.efsa.europa.eu/en/efsajournal/pub/1137.htm).

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des Philippines (DA-BPI), de Singapour (AVA-GMAC), d'Afrique du Sud (Direction de la prévention des risques biotechnologiques Agriculture, des Forêts et de la Pêche département), de Russie (IACGEA) et de Taiwan (DOH).

En conclusion, la sécurité humaine et animale du maïs NK603 a été bien confirmée par des évaluations approfondies du risque, menées par de nombreuses autorités réglementaires dans l'UE et au niveau mondial, ainsi que par un historique d'utilisation dans l'alimentation humaine et animale depuis plus d'une décennie.

2. GLYPHOSATE ET SÉCURITÉ ROUNDUP

Depuis que le glyphosate a été découvert, il ya près de 40 ans, il a été soumis à des centaines d'études en laboratoire et sur le terrain afin d'évaluer son impact sur la santé humaine et l'environnement.
Dans l'Union Européenne, le glyphosate a été examiné et autorisé en 2002 pour une période de dix ans. L'évaluation de sa sécurité s'est appuyée sur les résultats de 130 études scientifiques. La conclusion générale de cette évaluation est que le glyphosate répond à toutes les exigences de sécurité fixées par toutes les Directives de l'UE applicables pour les herbicides et ne pose aucun risque inacceptable pour la santé humaine.

Cette conclusion a été confirmée par les évaluations de sécurité menées par les Autorités Réglementaires dans les nombreux pays où le glyphosate est homologué pour le contrôle des mauvaises herbes. Le glyphosate est actuellement en cours de réévaluation et de renouvellement d'autorisation dans l'UE.

L'évaluation de l'innocuité du glyphosate a été basée sur les résultats d'études de toxicité aiguë par voie orale, cutanée et par inhalation ainsi par des études d'alimentation menées sur rat, souris, lapin et chien. Tous ces tests ont confirmé que:

• le glyphosate a une très faible toxicité aiguë;
• Le glyphosate n'a pas d'effets mutagènes, c'est à dire qu'il ne modifie pas l'ADN;
• Le glyphosate n'est pas préjudiciable à la reproduction ou au développement des animaux testés. Les nombreuses études menées sur des rats et des lapins n'ont mis en avant aucun indice d'un danger spécifique du glyphosate pour la reproduction ou le développement de la descendance. Les seuls effets dans ces études n'ont été observés qu'à des doses très élevées, qui étaient plusieurs milliers de fois supérieures à la dose journalière maximale pour les humains;
• Le glyphosate n'interfère pas avec le système endocrinien (hormonal) sur la base d'une grande variété d'études animales,
• Le glyphosate n'est pas cancérigène.

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En effet, de nombreuses études menées au fil des décennies ont toujours débouché sur la même conclusion : le glyphosate n'est pas cancérigène.
Ces conclusions sont celles de :

- l'Agence américaine de protection de l'environnement (US EPA) en 1993 et 1997 (catégorie E, preuve de non-cancérogénicité pour l'homme - fondée sur l'absence de preuves convaincantes de cancérogénicité dans les études adéquates);
- la Commission européenne - Direction générale de la protection de la santé et du consommateur - en 2002 (aucune évidence de cancérogénicité),
- le US Forest Service (Selon les essais biologiques standards, sur animaux, pour l'activité cancérogène in vivo, il n'existe aucune base pour affirmer que le glyphosate est susceptible de poser un risque significatif),
- les Organismes réglementaires canadiens (aucune preuve que le glyphosate provoque le cancer),
- l'Organisation mondiale de la santé et Organisation pour l'alimentation et l'agriculture des Nations Unies en 2004 (les études à long terme de toxicité et de cancérogénicité ont été menées chez la souris et le rat Dans l'étude de cancérogénicité chez la souris, aucun effet toxique n'a été observé jusqu'à la plus forte dose testée (1000 mg / kg pc par jour), et il n'y avait aucun signe de cancérogénicité).

En ce qui concerne les produits phytopharmaceutiques formulés, une évaluation complète des risques (incluant un large éventail d'études toxicologiques) doit être présentée aux autorités réglementaires avant toute homologation.

Alors que jusqu'à présent les coformulants en tant que tel n'étaient pas soumis à une réglementation spécifique dans le cadre de la législation européenne sur la protection des plantes, ils font désormais l'objet d'une notification puis d'une homologation au titre de REACH. De plus, des questions relatives à la sécurité des co-formulants utilisés dans les produits de protection des plante ont été traitées au cas par cas ;

Les évaluations sur leur sécurité étaient basées sur des études de doses effectuées avec les formulations commerciales. Il est à noter que la formulation WeatherMax n'est pas homologuée pour une utilisation en France.

3. Séralini et al. (2012)

Compte tenu des évaluations de sécurité existantes sur le maïs NK603 et le glyphosate /Roundup, et étant donné le consensus de la communauté scientifique concernant les lacunes, les défauts et l'orientation des conclusions de l'étude Séralini et al., 2012, il convient de conclure que les résultats de cette dernière ne remettent pas en cause l'évaluation de la sécurité établie sur le NK603, le glyphosate et le Roundup.

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En effet, l'EFSA[5] a noté dans son avis que l'étude Séralini et al. (2012) a des objectifs flous et mal retranscrits dans la publication, avec de nombreux détails clés concernant la conception, la conduite et l'analyse qui ont été omis. Sans ces détails, il est impossible de donner du poids aux résultats. Aucune conclusion ne peut être tirée concernant la différence sur l'incidence des tumeurs entre les groupes traités sur la base de la conception, de l'analyse et des résultats présentés dans l'étude de Séralini et al. (2012).
En particulier, Séralini et al. (2012) tire des conclusions sur l'incidence des tumeurs basées sur 10 rats par traitement et par sexe, ce qui est un nombre insuffisant d'animaux pour distinguer les effets spécifiques du traitement des cas fortuits de tumeurs chez les rats.

Considérant que l'étude Séralini et al. (2012) telle que rapportée dans la publication 2012), est insuffisante en termes de protocole, d'analyse et de présentation des résultats, l'EFSA conclut qu'elle est d'une qualité scientifique insuffisante pour l'évaluation de la sécurité. Par conséquent l'EFSA conclut que l'étude Séralini et al., telle que rapportée dans la publication 2012, n'a pas d'impact sur la réévaluation en cours du glyphosate, et ne voit pas la nécessité de ré-ouvrir les actuelles évaluations du maïs NK603, seul ou avec des gènes empilés.

L'évaluation de l' EFSA est conforme aux avis d'autres autorités nationales. Ainsi, l'Institut fédéral allemand d'évaluation des risques (BfR)[6] considère que les données expérimentales ne soutiennent pas les principales déclarations contenues dans cette publication. En outre, en raison de lacunes dans le protocole d'étude, ainsi que dans la présentation et l'interprétation des données, les conclusions tirées par les auteurs ne sont pas compréhensibles.

En Hollande, l'Institut pour l'évaluation des risques et la recherche, lié au ministère des affaires économique et l'agriculture (NVWA Buro)[7], a conclu que l'étude signale des effets liés au traitement qui ne sont pas scientifiquement fondés. Le rationnel de cette conclusion est en accord avec les avis de l'EFSA et de BfR.

En Australie et Nouvelle Zélande, le FSANZ[8] (Agence d'évaluation des risques pour les plantes génétiquement modifiées) a conclu que les principales limites de l'étude sont le petit nombre d'animaux dans chaque groupe d'essai, la communication sélective des données et l'absence de prise en compte de la présence bien connue de tumeurs mammaires spontanées chez cette souche de rats femelles.
La toxicité revendiquée du Roundup est invraisemblable et ne correspond pas à l'ensemble des nombreux résultats obtenus avec des études à long terme bien menées et bien conçues qui ont utilisé la matière active du Roundup, le glyphosate, sur de multiples espèces (c'est-à dire souris, rat, lapin et chien) à des doses plus élevées, auxquelles aucun effet n'a été observé.

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[5] http://www.efsa.europa.eu/en/press/news/121004.htm
[6] http://www.bfr.bund.de/en/press_information/2012/29/a_study_of_the_university_of_caen_neither_constitutes_a_reason_for_a_re_evaluation_of_genetically_modified_nk603_maize_nor_does_it_affect_the_renewal_of_the_glyphosate_approval-131739.html
[7] http://www.rijksoverheid.nl/onderwerpen/biotechnologie/documenten-en-publicaties/notas/2012/10/03/advies-vwa-bij-onderzoek-naar-gezondheidsgevolgen-ggo-mais-en-roundup.html -

[8] http://www.foodstandards.gov.au/consumerinformation/gmfoods/gmfactsheets/responsetosralinipap5676.cfm

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En plus des avis de ces différentes autorités, un large éventail d'experts indépendants a réagi aux incohérences, aux lacunes et aux conclusions de l'étude Séralini, 2012. La DTU National Food au Danemark[9] a par exemple lu l'article de manière détaillée et a trouvé un certain nombre de problèmes qui ne permettent pas de tirer des conclusions sur les effets ni du maïs génétiquement modifié, ni du Roundup.
Par conséquent, les données présentées dans l'article ne fournissent aucune base lui permettant de remettre en cause ses évaluations antérieures du maïs génétiquement modifié NK603 et du glyphosate, matière active du Roundup.

Tous les commentaires détaillés, y compris les revues officielles sont ajoutés à l'annexe 1.

La position de Monsanto est tout à fait en ligne avec les évaluations officielles et celles des experts.

[9] http://www.food.dtu.dk/upload/institutter/food/publikationer/2012/vurdering_gmostudieseralini_okt12.pdf -

Monsanto Detailed Technical Comments on the Long term toxicity of a Roundup[1] herbicide and a Roundup-tolerant genetically modified maize.

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Didier Hennequin, Joël Spiroux de Vendômois

Food and Chemical Toxicology (electronic ahead of press)

http://www.sciencedirect.com/science/article/pii/S0278691512005637

Experimental design

The authors of this study assert that it was conducted in a GLP environment and according to OECD guidelines. They did not follow OECD GLP guidelines nor OECD testing guideline (TG) 453 for conduct of a combined chronic toxicity/carcinogenicity study. OECD GLP's require "Detailed information on the experimental design, including a description of the chronological procedure [e.g. start date, end date] of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any)" and… "The study should be conducted in accordance with the study plan". Apparently, the authors' original intent was not to conduct a carcinogenicity study "…we had no reason to settle at first for a carcinogenicity protocol using 50 rats per group." (Seralini et al., 2012), but at some point during the in-life phase, they changed the purpose of the study by extending it for 2 years to assess potential carcinogenicity. Assuming they had a protocol at the start of the study, they did not follow it as they substantially altered the purpose and the design of the study while it was in progress. This should be considered a violation of GLP guidelines as the study was not conducted in accordance with the original study plan. If they wanted to carry out a carcinogenicity study, they should have terminated the existing study, and prepared a new study plan adapted from OECD TG 453.

[1] 1 Roundup agricultural herbicides are registered trademarks of Monsanto Technology, LLC.

They did recognize, as stated above, that they needed a larger number of animals (a minimum of 50 rats/sex/group) for a carcinogenicity study, instead of the 10 rats/sex/group that they had in their existing study. For reasons which will be discussed later, their study did not have enough animals to draw any meaningful conclusions.

Rodent carcinogenicity studies must be sufficiently powered not only to detect an increased incidence of rare tumor types, but also to discriminate treatment-related effects from spontaneous, or background, incidence of common tumor types. For this reason, US (US EPA 1998; FDA, 2006) and OECD (1995a) regulatory guidelines for the conduct of carcinogenicity studies in rodents specify the use of at least 50 animals per sex per treatment group. In addition, OECD states that "it is unlikely that a regulatory authority would find a study using a lower core number of animals per sex and per group acceptable for regulatory purposes, since a sufficient number of animals should be used so that a thorough biological and statistical evaluation can be carried out" (OECD, 1995b). OECD further states that "for strains with poor survival such as SD rats, higher numbers of animals per group may be needed in order to maximize the duration of treatment (typically at least 65/sex/group)."(OECD, 1995b). For this reason, the US EPA specifies that survival in any group should not fall below 50% at 18 months or below 25% at 24 months (US EPA, 1998), while the US FDA specifies survival of a minimum of 25 rats per sex per group at study termination (FDA, 2006). The SD rat has been widely used in toxicology research, including numerous chronic studies, but these studies employ many more animals than used by the authors in consideration of their lower survival rate and high background tumor rates, especially mammary tumors in females.

Statistical analysis and presentation of data

The authors have a history of inappropriate application of statistical methods to analyze toxicology data (Séralini et al., 2007; Spiroux de Vendômois et al., 2009) which has been criticized by regulatory agencies and other experts (EFSA 2007, EFSA 2010 ; FSANZ 2009; HCB 2009; Doull et al., 2007). There are numerous problems in the way the data were statistically analyzed in this study.

For example, in Table 3, mean values are not presented for each group and sex to allow comparison of measured parameters. Control data are not presented. Instead, the authors used a statistical method that is not traditionally used to present toxicology data, a multivariate technique called Partial Least Squares Discriminant Analysis (PLS-DA). Mean differences (%) of variables (discriminant at 99% confidence intervals) were presented to investigate the relationship among 48 blood and urine measurements relative to the different treatment groups. PLS-DA can be used to identify patterns in the data and to develop a function which can be used to discriminate between the groups. However, any differences between groups must be further evaluated for toxicological relevance. Presentation of the data in this manner does not lend itself to straightforward interpretation of the study findings.

In Figure 5, the same PLS-DA procedures were followed with jack-knifed confidence intervals at 99% confidence level. This procedure may be familiar to statisticians, but it is not commonly used to present toxicology data and is difficult to interpret, particularly when the data used to construct these graphs are not presented. Examination of Figure

5a would suggest that the majority of measured parameters fall within 99% confidence intervals with the exception of serum and urine electrolytes. Unfortunately, no data were provided from other intervals when these data were collected to determine if the same patterns were evident. No lab historical data were provided to put these data in perspective. As stated earlier, just because one can discriminate between the groups, it does not make the result toxicologically relevant. There was no presentation of actual statistical analysis to compare the means for each measured parameter.

To determine if there are patterns of differences in toxicologically related findings, the toxicologist expects to see the actual mean data for each parameter/group and the standard deviation and the control data should also be provided for comparison. The test and control values for measured parameters should also be compared to the historical control data from the testing laboratory and/or the literature to determine if differences were within or outside of the normal range. As presented, the reader has no way of determining whether the conclusions drawn by the authors are supported by the actual data, or are merely statistical anomalies resulting from non traditional analysis. The manuscript contained figures with graphs that were difficult to read because lines overlapped, and percent variations were presented rather than the mean test and control data which is the more standard practice in presenting toxicology data. For instance, incidences of 1 vs. 2 or 5 vs. 10 both represent a change of 100%, however, these absolute values would likely result in different conclusions.

The same criticism can be made for Figure 2 and Table 2 where the data are not broken out in the tables so the reader can actually see what changes were observed for each group. The incomplete presentation of study data, which was acknowledged by the authors - “all data cannot be shown in one report, and the most relevant are described here -” precludes meaningful review and evaluation of study results (Seralini et al., 2012). For example, histopathology incidence/severity data are not presented (e.g. Table 2); nor is any laboratory historical control data provided to help interpret the biological relevance of clinical pathology and histopathology findings. Did the testing laboratory have historical pathology data for chronic studies? The generalized statements of increased liver disorders cannot be verified without presenting the actual data in a table to review.

Misinterpretation of study findings

Mortality data

The authors stated that male and female rats in all treatment groups had more and earlier deaths than the controls. However, they acknowledge that mortality was not dose related. For example, according to Figure 1, low dose males fed NK603 grain (unsprayed with Roundup) had more early deaths and overall mortality (5/10), while the mid and high dose group mortality near the end of the study was similar to controls (3/10). In the male group fed NK603 (sprayed with Roundup), the mid dose males had more early deaths (4/10), followed by the low dose, and the high dose had the lowest mortality of the NK603 fed groups. For rats administered Roundup in drinking water, high dose males had the lowest mortality compared to the other Roundup treated groups. Similar examples of lack of dose relationships in mortality were observed in the treated female groups. In consideration of the fact that there were 9 treatment groups

compared to one control group, some variability in mortality between groups would be expected by chance and could well have explained the distribution of mortality in the study. Given the small group size of 10 rats/sex/group, differences in mortality between groups generally involved only a few animals, and it would be difficult to interpret the biological relevance of such small differences. If dose is not important in this design, it is a 90% probability that one of the test groups would numerically have the highest incidence of mortality.

The authors should have used the adjusted analysis of survival to determine if there were more dead animals in the treated groups compared to the control group, and if there were earlier deaths in the treated groups than in the control group. The most useful statistical approach used to compare survival between groups (not followed by the authors) is the following procedure: Adjusted survival rates are estimated using Kaplan Meier estimation procedures (Kaplan E.L. and Meier, P., 1958). Kaplan Meier estimates are calculated separately for each sex and treatment group. Mortalities which are the result of animals dying following accidents (accidental trauma, died during anesthesia, killed at study director request) or at scheduled sacrifice have to be considered as censored observations. In a second step, statistical significance of differences in survival rates between treated and control groups and dose related trend in survival could be assessed using Cox's and Tarone's tests on life table data.

The authors did not indicate whether the tumor classification was done according to the PETO codes (incidental, fatal, observed in life). At least a PETO analysis or a mortality-adjusted analysis for tumor incidences should have been performed.

The authors reported higher survival than is typically reported for female Harlan SD rats in 2-year studies. According to Figure 1, only 2 of 10 animals died before the end of the study resulting in survival rate of 80%. The SD rat is known to exhibit low and variable survival after 18 months of age (Nohynek et al., 1993; Keenan, 1996). Therefore, as discussed earlier, many more animals than 10/sex/group would be needed to ensure that there would be a sufficient number surviving to the end of the study. This would be needed to conduct a meaningful statistical analysis and to draw solid conclusions regarding biological significance. Average survival in 7 NTP 2-year studies with female Harlan SD rats was reported to be 41.5% (Brix et al, 2005). In a later published review, a survival rate of 42.5% was reported for 2-year studies conducted by the NTP with female Harlan SD rats (Dinise et al., 2010). Charles River SD female rats were reported to have a 2-year survival ranging for 20 to 60% with an average of 37% (Giknis and Clifford, 2004). Given the high survival rate of female rats in this study, it would be very interesting to learn what the historical 2-year survival rate was for female Harlan SD rats in the testing facility that performed the authors' study. No historical control data from the testing laboratory were provided for any of the parameters measured.

Tumor findings

The manuscript misleads readers by attributing the tumors observed in the study to treatment with NK603 grain administered in the diet or Roundup via drinking water. For example, the authors failed to acknowledge that mammary and pituitary tumors observed in this study are very common in untreated female SD rats fed *ad libitum* for 2 years. They included color pictures of treated rats bearing large mammary tumors, but

did not did not include photos of control rats or acknowledge that similar tumors were also observed in controls. Mammary gland tumors are observed not only in older control female SD rats, but can also appear early in a chronic study (Durbin et al., 1966). Older control female Harlan SD rats have a high background tumor incidence, eg. for the mammary gland, adenoma 3%; adenocarcinoma 11%; fibroadenoma 71%; adenomas of the pituitary gland are reported at an incidence of approximately 41% (Brix et al., 2005). Pituitary adenomas (prolactinomas) contribute to the development of mammary tumors in SD rats. These historical observations can account for the finding of one mid dose female in the mid dose NK603 group (unsprayed) exhibiting a mammary tumor earlier in the study, and the other mammary and pituitary tumors observed in both control and treated female groups later in the study. In Table 2, the authors report that treated females had more mammary tumors/rat than controls. However, they do not follow the standard convention of listing the tumor types confirmed pathologically for each group and incidence of animals in each group bearing those tumors. The authors have instead combined all of the tumors together/animals in a group so the reviewer cannot compare the actual tumor data by type between groups. The absence of a dose relationship in some of tumor findings was evidenced by the high dose Roundup group females having lower incidence of total tumors than the low dose group. The authors also noted that the size and number of tumors were not proportional to the treatment dose. Since the low dose of Roundup administered in drinking water was orders of magnitude lower than the high dose, yet the lowest dose had a higher tumor incidence, the data are clearly not dose related and most likely reflect normal variability in the incidence of common tumors that have a high background rate.

Other pathologic findings

Other pathological changes reported by the authors as treatment- related are similarly prevalent in the aged SD rat, including multiple diet-related disorders, degenerative renal and endocrine diseases, etc. (Keenan, 1996).

The authors reported treatment-related liver and kidney pathologies in males. As evidence of kidney effects, they refer to Table 2 where the incidence of chronic progressive nephropathy (CPN) was 3/10 control animals compared to 7/10 animals in the high dose NK603 group (non-sprayed). However, they neglect to mention that the incidence of CPN in the NK603 sprayed groups and the Roundup groups are similar and that the high dose groups had the lowest incidence. They did not report the severity grades of CPN to learn whether it was increased in a dose related manner. A similar pattern was observed for liver findings, although Table 2 does not state what the liver pathologies were. This is an unacceptable way to present pathology data. As the study progressed, there were insufficient numbers of male animals left to make meaningful comparisons for liver and kidney pathology changes. The authors reported that only 3/10 control male animals were found to have CPN. This pathologic change has been reported to occur commonly in male rats (Hard and Khan, 2004) and in one chronic rat study with Harlan SD male rats , the incidence was 100% in control male rats (Petersen et al., 1996). One might have expected a higher incidence of CPN in control males. In Petersen et al. (1996), CPN accounted for 48% of the early deaths in control males. Given the very high background incidence of this disease, and the fact that 9 treatment groups are being compared to one control, some variation in the number of CPN

afflicted animals would be expected between groups. Unfortunately, no historical control lab data for pathologic lesions were made available for comparisons. The author's misquoted the aforementioned Hard and Khan (2004) publication stating that only elderly rats are sensitive to CPN whereas the publication states "Although usually regarded as a disease of the aging rat, incipient lesions of CPN are detectable in hematoxylin and eosin (H&E)-stained sections of male rat kidney at least as early as 2 months of age."

The authors have asserted in previous publications (Séralini et al., 2007; Spiroux de Vendômois et al., 2009) that GM crops cause liver and kidney pathologies based on their statistical re-analysis of published 90 day feeding studies mentioned earlier. However regulatory agency scientists and other experts have not supported these claims and find no evidence of treatment related liver or kidney pathology changes in any of these studies (EFSA, 2007; EFSA, 2010; FSANZ, 2009 a,b; HCB, 2009; Doull et al., 2007).

The authors also presented clinical pathology data in Figure 5 and Table 3 which they interpreted to show changes in serum and urine electrolytes supporting their hypothesis of kidney damage. However, as stated earlier, the presentation of the data does not permit comparison of the actual measured values to controls since control data were not presented. No actual mean data for the urine and serum electrolytes were provided to provide comparisons between test and control groups as well as historical control ranges for these parameters from the testing laboratory.

Glyphosate safety

Since a number of the changes observed in this study were not dose related, the authors conjectured that these findings were hormone and sex dependent, and exhibited a threshold response at a single dose, which happened to be the lowest dose tested. They state categorically that Roundup is a "sex endocrine disruptor" that contributed to the tumors and other pathologies observed in their study, with no scientific basis for this statement.

To respond to these allegations, it is necessary to review what is known about the potential toxicology of Roundup and its active ingredient, glyphosate. WEATHER MAX ® herbicide is a typical commercial Roundup formulation that is essentially the potassium salt of glyphosate with 10% surfactant in water. The category of surfactant in this Roundup™ formulation was evaluated by the US EPA in 2009 and was considered acceptable for this use in pesticide products based on the results of multiple repeat dose studies, including reproductive and developmental toxicology (US EPA, Federal Register, 2009a). It should further be noted that consumers have regular exposure to surfactant materials in the form of shampoos, soaps, and cleaning products. These are similarly not believed to present reproductive/endocrine risks, but in any event, exposure to surfactant residues as a result of pesticide exposure represents a very small portion of human surfactant exposure. There is no evidence that the surfactant categories used in Roundup are endocrine disruptors (Williams et al., 2012).

Glyphosate is a structural analogue of the amino acid glycine, it has a methylphosphonate group at the amino terminus instead of a carboxyl group. Amino acids are not endocrine disruptors. Extensive in-vitro (test-tube) and animal data

indicate glyphosate is not an endocrine disrupter. Although glyphosate was included in the EPA's initial substances for the endocrine disrupter screening program, EPA has stated "This list should not be construed as a list of known or likely endocrine disruptors. Nothing in the approach for generating the initial list provides a basis to infer that by simply being on this list these chemicals are suspected to interfere with the endocrine systems of humans or other species, and it would be inappropriate to do so." (US EPA, Federal Register, 2009b). Furthermore, the EPA specifically rejected the assertions presented in Richard et al. (2005) that glyphosate was an endocrine disruptor based on (i) exceedingly high doses, over 40 times the maximum acceptable concentration for this study type, (ii) failure to actually meet the criteria for a positive result in this assay, despite the high dosing, and (iii) lack of demonstrated study proficiency including no concurrent positive controls to demonstrate assay validity (US EPA 2011).

The cited *in vitro* studies conducted by the Seralini laboratory have repeatedly been reviewed and considered irrelevant to *in vivo* exposures by numerous authoritative bodies. *In vitro* test systems are not appropriate for evaluating surfactants due to their physico-chemical properties impairing cell membrane integrity, including mitochondrial membranes. The selective use of literature, without consideration of research (Levine et al., 2007) demonstrating that the effect is the result of surfactant impacts on mitochondrial membranes and occurs with a range of surfactants, including those with much greater consumer exposure, demonstrates consistent and undeterred bias in the authors' publication record. Numerous authoritative body reviews have discounted the relevance of the Seralini team's research to human health risk assessment; such as, French Ministry of Agriculture and Fish, Committee for Study of Toxicity (2005), French Agency for Food Safety, AFSSA (2009), and BfR (2009).

The safety of glyphosate has been assessed in numerous chronic/carcinogenicity studies conducted by various registrants over the years, as glyphosate has gone off-patent, and none of these studies have found any evidence that glyphosate causes mammary cancer or any other kind of cancer. The WHO/FAO Joint meeting on Pesticide Residues reviewed several glyphosate toxicology data sets including five chronic rat and two chronic mouse studies in 2004, concluding no evidence of carcinogenicity (WHO/FAO 2004a, WHO/FAO 2004b). The US EPA's classification as "Group E carcinogen (signifies evidence of non-carcinogenicity in humans)" is based on review of two chronic rat and one chronic mouse study (US EPA, 1993) and the EU Commission conclusion of "no evidence of carcinogenicity" is based on review of four chronic rat and four chronic mouse studies (EC 2002). The dosages used covered a broad range of exposures, and the highest dosages used were much greater than those tested by the authors and many, many times higher than human potential exposures since glyphosate can be dosed at high levels in animals as it is not very toxic. Thus, the overwhelming weight of evidence indicates glyphosate is not an animal carcinogen.

In the authors' chronic study, there were 20 control and 180 test rats (sexes combined) divided into 9 different groups. In contrast, the FAO/WHO (2004b) review of glyphosate referenced above included a total of 2330 rats in 5 chronic rat studies. Included in this number were 540 control rats. In the recent EU Annex 1 Renewal dossier submitted in Europe for glyphosate, there were 9 chronic rat studies with a total of 3938 rats (additional studies from new manufacturers of glyphosate) of which 942 were control rats. The new chronic studies also reported no evidence of carcinogenicity. The authors

failed to mention the many toxicology studies carried out on glyphosate that confirm it does not cause cancer or liver and kidney pathologies as reported by the authors.

The authors did not acknowledge that there was another chronic rat study carried out with glyphosate tolerant soybeans where the investigators reported no evidence of treatment-related adverse effects including cancer. This was a more robust study as it contained 50 rats/sex/group (Sakamoto, Y. et al., 2008.).

The authors also reported blood hormonal analyses (estradiol, testosterone), although no specified times during the day were given for blood sampling. Hormonal parameters exhibit significant diurnal variations. For this reason, proper analysis must include the historical variation observed in the performing laboratory, but no information was provided in this study – a very significant omission. Secondly, the results of hormone analysis on just one day are not representative of what is going on throughout the study, especially for hormones characterized by episodic secretion. No dose-response relationship in hormone levels was observed. It is not possible to correlate the hormone levels observed at one time point in this study with the development of mammary tumors as proposed by the authors. Further, in rats, the main mode of action for development of mammary tumors is an increase of prolactin level and then an increase of pituitary tumors. Thus, we question the increase of tumor incidence with concomitant decrease of estradiol and increase of testosterone. It is not logical.

The authors also propose another hypothesis to explain their data, that the introduction of the CP4 EPSPS enzyme that imparts tolerance to topically applied glyphosate caused metabolic disturbances in secondary metabolites. In particular, they report a statistically significant reduction in the levels of secondary metabolites caffeic and ferulic acid in the NK603 diets. The levels of ferulic acid in the NK603 diet (exact diets not specified) were reported to be from 735 to 889 ppm compared to 1057 ppm in the control. Since they report differences in the diets, it is unclear whether other ingredients in the diet could have contributed to these differences. No details were provided on the dietary components in the formulated diets except the level of NK603 and control grain that were added.

In a published study summarizing compositional analysis of NK603 grain, Ridley et al. (2002) reported no differences in ferulic acid levels between NK603 and its control comparator. The range of grain ferulic acid was 1500 to 2500 ppm (mean 2000 ppm) for glyphosate sprayed NK603 maize. Control maize levels ranged from 1700 to 2300 ppm (mean 2000 ppm). Ferulic acid levels can vary considerably in non GM maize ranging from 174 to 3540 ppm (fw) with a mean of 1950 ppm (ILSI Crop Composition Data Base, v4.2).

Questions on EM methods

The authors reported finding glycogen dispersion or appearance of lakes, etc. following electron microscopic (EM) examination of livers from animals fed NK603 (sprayed) or animals administered Roundup in drinking water. Manuela Malatesta, who performed the EM work described in this publication, has been previously criticized for technical deficiencies regarding EM work carried out in mice fed presumably glyphosate tolerant soybeans (Williams and DeSesso, 2010).

The authors do not describe the fed/fast state of the animals at the time of terminal killing. The liver is a dynamic organ that stores and releases glycogen quickly. Different feeding states of animals in the same treatment/control group could give samples that look like all three micrographs in Figure 4.

The authors' statements regarding the quality of the methods used are not backed up by the description in the publication. The electron microscopy is based on an unknown number of samples from one control, one low dose and one mid dose animal. These animals were reported to exhibit the greatest degree of liver pathology yet the authors report no procedures to ensure a balanced investigation of treated versus control samples. The micrograph of the control portion of a hepatocyte shows tissue from an area 13 µ X 13 µ. The total area is of the picture is the area is about the size of 3 red blood cells. This is a very small amount of tissue on which to draw a conclusion.

The most significant issues with the limited amount of selective microscopy used to support the authors' contentions relate to the anatomy of the liver. The liver is a large organ (the largest internal organ in the body) that has great diversity in its anatomy. If a sample were taken from the edge of the liver and were compared to a sample from the middle of the same liver near the entry of the portal vein, the cells would look different. The fact that the tissue was diced and not put in fixative precludes knowing whether the samples were taken from the same section of organ across all treatment groups.

Not only is the liver diverse across the organ, but also within its internal structure. One of the ways histologists describe the organization of the liver is by speaking about the liver lobule. For the purpose of this discussion, the method that describes a liver lobule as liver cells surrounding the central vein of the lobule will be used. In that description, the lobule is conceptualized as consisting of three concentric layers of cells that surround the central vein in a hexagonal shape. (There are thousands of these lobules in a lobe of the liver.) The arterial supply to the liver lobules is derived from arteries at the angles of the hexagon. In the fed state, glucose arrives via the arteries and is processed into glycogen by the hepatocytes. The outer layer takes up glycogen first; later the middle layer will take up glycogen; and finally, if sufficient glucose is left, glycogen will be found in the inner layer. Glycogen stores are depleted in reverse order. Consequently, the innermost layer tends to look glycogen-depleted most of the time; under fed conditions the outer layer has many glycogen granules; and the middle layer is intermediate in appearance. One could find all three of the conditions illustrated in Figure 4 by looking within a single (or several) lobules from the same tissue sample. Mitochondria also have various appearances depending on their proximity to the oxygen rich arteries or oxygen depleted central vein.

In the absence of rigorous morphometric analysis that also accounts for the anatomy of liver lobules, the photographs in Figure 4 have neither context nor toxicological meaning,

In Figure 3, necrotic foci are considered to be either clear focus or basophilic focus: which is scientifically wrong as these foci are pre-neoplastic entities. Moreover basophilic focus with atypia is not part of the international microscopic nomenclature. Furthermore, microscopic pictures cannot be interpreted properly (bad quality and low magnification). Macroscopic pale spots cannot be correlated to a necrotic focus.

Questions regarding materials and methods, missing data

No information was provided regarding the identification of the near isoline to confirm that it had similar genetic background. The location, growing conditions, watering and agrochemical treatments of crops were not detailed. This could have had an impact on the composition of crops and then on the outcome of the study.

No information was provided on the potential mycotoxins that might be found in the control and NK603 treated crops and might have impacted the study. Was the grain stored adequately during the 2 years of the study to minimize mold growth and mycotoxin contamination? How often were batches made, were they checked periodically by PCR methods to confirm that the control diets contained only control and not test maize and visa versa. How were the diets stored?

No information was provided regarding (a) detailed diet formulation and manufacturing processes as well as nutrient composition of the diets (b) drinking water contaminant analysis methods or results (c) homogeneity, stability or concentration of ROUNDUP in drinking water formulations. How often were drinking water solutions produced?

The control group was reported to contain 33% non-GM maize in the diet. Low and mid dose NK603 groups (sprayed, unsprayed) reportedly contained 11% and 22% NK603 maize grain. Results from the low and mid dose groups cannot be compared to the control group if they had lower levels of corn grain added to the diets.

There was no drinking water control group for comparison to the treatment groups fed different concentrations of Roundup in drinking water.

Missing data

In Table 1, the study design represents that behavioral studies were conducted twice. There is no mention of behavioral studies in methods and no results were presented.

Ophthalmology was reported to be conducted twice. There is no mention of ophthalmology evaluations in the methods and no results were presented.

Microbiology was to be conducted in feces and urine. There is no mention of microbiology evaluations in the methods and no results were presented.

Evaluation of glyphosate residues in tissues was reported to be performed, but no information on methods or data generated was provided. Tissue residues are usually evaluated after administration of radiolabelled test materials under toxicokinetic testing guidelines such as OECD 417 (OECD, 2010). For glyphosate, the results of such studies have been evaluated by the WHO/FAO Joint Meeting on Pesticide Residues (2004 a,b) and other regulatory agencies around the world.

Evaluation of the transgene in tissues was reported. There was no mention of transgene analysis in methods or results sections, with the exception of confirmation NK603 in maize grain and formulated diets by qPCR.

Food, water consumption and body weights were reported to be measured in the study, but the data were not presented in the manuscript. This is basic information that should be provided for a chronic feeding study to assess potential adverse effects.

Clinical pathology data was reported to be measured at eleven different intervals during the study but only data from month 15 was summarized, and not in a manner it could be easily reviewed. Further, data from the two sexes was presented differently. No historical control information from the testing laboratory for measured parameters was presented.

Conclusion

As a result of methodological failures, incomplete data presentation, and lack of proper statistical analysis, Seralini et al.'s conclusions regarding NK603 and/or Roundup cannot be supported by the presented data. Indeed, the fundamental flaw in regards to the number of animals employed makes it highly unlikely that any of the purported findings can be statistically supported using standard approaches to analysis even if more data were to be provided by the authors.

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