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Saisine du 24 septembre 2012. Commentaires Monsanto – Octobre 2012

Monsanto would like to emphazise that the products used in the Seralini et al. study have been the subject of multiple regulatory risk assessments around the world. These assessments have unanimously established the safety of NK603, and glyphosate/Roundup®.The Séralini study (Séralini et al, 2012) has been invalidated by independent experts and does not compromize these conclusions.

Here we provide our views on the Seralini et al. publication and its significance for the safety of NK603 and glyphosate/Roundup.

1. NK603 SAFETY

NK603 maize was developed to improve the effectiveness of in-crop weed control by expression of the CP4 EPSPS protein, which confers tolerance to glyphosate-containing herbicides. The safety of NK603 maize has been assessed and determined according to international (Codex) and EU (EFSA) guidance for the safety assessment of GM plant products and its safety has been confirmed during more than a decade of commercial use globally.

The pre-market food and feed safety assessment of NK603 addressed the following:

- Molecular characterization, including southern blot analyses, PCR and sequence analyses, as well as bioinformatics, inheritance and insert stability analysis to characterize the molecular changes and to verify that the CP4 EPSPS protein is the only new protein produced.
- Compositional analyses of NK603 compared to its conventional counterpart demonstrated that NK603 is compositionally similar to conventional maize.
- The phenotypic and agronomic characteristics of NK603 were typical of conventional maize and did not show any indications of weediness or changes in other characteristics.
- An extensive characterization of the CP4 EPSPS protein expressed in NK603 confirmed that the protein is safe for human and animal consumption. The safety assessment involved the quantification of protein levels in plant tissues, the characterization of the physicochemical and functional properties of the protein, an assessment of the similarity of CP4 EPSPS protein to known allergens, toxins and other biologically-active proteins known to have adverse effects on mammals, the *in vitro* evaluation of the digestibility of CP4 EPSPS protein and the *in vivo* acute oral acute toxicity study with mice.

MONSANTO

- Feeding studies on animals such as broiler chickens, livestock and pigs confirmed the nutritional equivalence of maize NK603 to conventional maize varieties.

- A 90-day sub-chronic toxicity study using rats confirmed that there are no adverse effects associated with the repeated administration of NK603 in the diet at a margin of safety of 84X[1].

The determination of NK603 safety following this comprehensive safety assessment has been confirmed by the history of safe use of NK603 maize over more than a decade. NK603 maize varieties have been grown extensively in the US and Canada since their commercial introduction in 2001 and no unanticipated adverse effects have been reported. Presently, NK603 varieties are being grown in various countries around the world including US, Canada, Argentina, Brazil, Colombia, Honduras, Uruguay, the Philippines and South Africa.

In the EU, NK603 was approved following a comprehensive safety assessment according to Directive 2001/18/EC for import, processing and feed use in July 2004[2]. NK603 maize was further assessed and approved for food use according to Regulation (EC) No 258/97 in 2005[3]. Following an application for approval of the cultivation of NK603 varieties in the EU, as well as for renewal of the approval for food and feed uses mentioned above, EFSA published a further positive opinion on the safety of NK603 [4] in 2009.

In addition to the EU authorizations for the import and food/feed use, NK603 has been assessed for its human safety and has received regulatory approvals for food use by other countries' agencies, including those in Australia/New Zealand (FSANZ), China (Ministry of Agriculture), Colombia (ICA-CTN Pecuario), Indonesia (National Committee for Biotechnology), Japan (MHLW/FSC and MAFF), Korea (KFDA and RDA), Malaysia (Ministry of Natural Resources and Environment), Mexico (Health Ministry), the Philippines (DA-BPI), Singapore (AVA-GMAC), South Africa (Directorate Biosafety of the Agriculture, Forestry and Fishery department), Russia (IACGEA) and Taiwan (DOH).

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[1] Considering: (1) a maize flour consumption for the general central European population (cluster E) of 0.25 grams/kg/day (chronic consumption of 14.7 g/person/day, obtained from GEMS/Food Program at http://www.who.int/foodsafety/chem/en/acute_hazard_db1.pdf, divided by the assumed adult weigh of 60 kg); (2) the highest dietary level/dose in the rat study of 21 grams/kg body weight/day of NK603 grain.

[2] Commission Decision of 19 July 2004 concerning the placing on the market, in accordance with Directive 2001/18/EC of the European Parliament and of the Council, of a maize product (*Zea mays* L. line NK603) genetically modified for glyphosate tolerance (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] Commission Decision of 3 March 2005 authorising the placing on the market of foods and food ingredients derived from genetically modified maize line NK 603 as novel foods or novel food ingredients under Regulation (EC) No 258/97 of the European Parliament and of the Council (2005/448/EC). *OJ* L 158/20, 21.6.2005 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:158:0020:0022:EN:PDF.

[4] Scientific Opinion of the Panel on Genetically Modified Organisms on applications (EFSA-GMO-NL-2005-22 and EFSA-GMO-RX-NK603) for the placing on the market of the genetically modified glyphosate tolerant maize NK603 for cultivation, food and feed uses and import and processing, and for renewal of the authorisation of maize NK603 as existing product (http://www.efsa.europa.eu/en/efsajournal/pub/1137.htm).

MONSANTO

In summary, the human and animal safety of NK603 maize has been well established by comprehensive safety assessments by EU and global regulatory authorities as well as by a history of safe use and consumption over more than a decade.

2. GLYPHOSATE AND ROUNDUP SAFETY

Since glyphosate was first introduced nearly 40 years ago it has been subjected to hundreds of laboratory and field research studies to assess its impact on human health and the environment.

In the EU, glyphosate was last reviewed and approved in 2002 for a period of ten years. The evaluation of safety was based on the results of 130 scientific studies. The overall conclusion from that evaluation was that glyphosate meets all the safety requirements laid down by all relevant EU directives for herbicides and poses no unacceptable risk to human health. This view has been confirmed by safety evaluations conducted by regulatory agencies in the many countries where glyphosate is approved for weed control. Glyphosate is currently undergoing re-evaluation and authorization renewal in the EU.

The safety evaluation of glyphosate was based on the results of acute oral, dermal and inhalation toxicity studies as well as feeding experiments in rats, mice, rabbits and dogs. All these tests confirmed that:

- glyphosate has only very little acute toxicity;
- it does not have mutagenic effects, i.e. it does not alter DNA;
- glyphosate is not detrimental to the reproduction or development of test animals. The numerous studies conducted with rats and rabbits found no indication of any specific hazard posed by glyphosate for reproduction or development of the offspring. Any observed effects seen in these studies were only seen at very high dose levels, which were several thousand times higher than the maximum daily intake for humans;
- glyphosate did not interfere with endocrine (hormone) systems in a wide variety of studies in animals.
- glyphosate is not carcinogenic

Indeed, multiple reviews over the decades have consistently drawn the same conclusion; glyphosate is not carcinogenic. These conclusions include those of the U.S. Environmental Protection Agency in 1993 and 1997 (Category E, evidence of non-carcinogenicity for humans -- based on the lack of convincing evidence of carcinogenicity in adequate studies); the European Commission's Health and Consumer Protection Directorate-General in 2002 (no evidence of carcinogenicity); the U.S. Forest Service (based on standard animal bioassays for carcinogenic activity *in vivo*, there is no basis for asserting that glyphosate is likely to pose a substantial risk); Canadian regulators (no evidence that glyphosate causes cancer); the World Health Organization and Food and Agriculture Organization of the United Nations in 2004 (long-term studies of toxicity and carcinogenicity were conducted in mice

and rats. In the study of carcinogenicity in mice, no toxic effects were observed at up to the highest dose tested (1000 mg/kg bw per day), and there was no evidence of carcinogenicity).

Regarding formulated plant protection products, a full risk assessment (including a wide range of toxicological studies) must be presented to regulatory authorities. While to date, co-formulants in isolation are not subject to specific regulation under the EU plant protection legislation, they require notification and subsequent registration under REACH. In addition questions about the safety of specific co-formulants in plant protection products are addressed on a case-by-case basis; these safety assessments are based on repeat-dose studies with commercial plant protection products. It should be noted that the WeatherMax® formulation employed in the study by Seralini et al. is not registered for use in France.

3. SERALINI ET AL STUDY

Given the established safety of NK603 and glyphosate/Roundup and considering the independent scientific consensus on the shortcomings, flaws and selective reporting in the Séralini, 2012 study, it should be concluded that the Séralini findings do not compromise the established safety of NK603 and glyphosate/Roundup.

Indeed, EFSA[5] noted in its review that the Séralini *et al.* (2012) study has unclear objectives and is inadequately reported in the publication, with many key details of the design, conduct and analysis being omitted. Without such details it is impossible to give weight to the results. Conclusions cannot be drawn on the difference in tumour incidence between the treatment groups on the basis of the design, the analysis and the results as reported in the Séralini *et al.* (2012) publication. In particular, Séralini *et al.* (2012) draw conclusions on the incidence of tumours based on 10 rats per treatment per sex which is an insufficient number of animals to distinguish between specific treatment effects and chance occurrences of tumours in rats. Considering that the study as reported in the Séralini *et al.* (2012) publication is of inadequate design, analysis and reporting, EFSA finds that it is of insufficient scientific quality for safety assessment. Therefore EFSA, concludes that the Séralini *et al.* study as reported in the 2012 publication does not impact the ongoing re-evaluation of glyphosate, and does not see a need to reopen the existing safety evaluation of maize NK603 and its related stacks.

[5] http://www.efsa.europa.eu/en/press/news/121004.htm

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The EFSA review is consistent with reviews of other national authorities. The German Federal Institute for Risk Assessment (BfR) [6] is of the opinion that the experimental data do not support the main statements in the publication. Further, due to shortcomings in the study design as well as in the presentation and interpretation of the data, relevant conclusions drawn by the authors are not comprehensible.

The Dutch NVWA BuRo[7] (Official institute for risk assessment and research, linked the Dutch Ministry of Economic affairs, Agriculture and Innovation) concludes that the study reports treatment related effects that are not scientifically substantiated. The rational for this conclusion is in line with the EFSA and Bfr reviews.

The Australian/New Zealand authority for the safety assessment of GM plants, FSANZ,[8] concluded that the key limitations of the study include the small number of animals in each test group, selective reporting of data and no acknowledgement of the well-known spontaneous occurrence of mammary tumours in this strain of female rats. The claimed toxicity of Roundup is implausible and doesn't align with extensive data from well designed and conducted long-term studies that used the active ingredient of Roundup, glyphosate, in multiple species (i.e. mice, rats, rabbits and dogs) at higher doses where no effects were observed.

In addition to these reviews a wide range of independent experts reacted to the inconsistencies, flaws and conclusions in the Séralini, 2012 study. For example, the DTU National Food Institute in Denmark[9] has reviewed the article thoroughly and found a series of problems with the study which make it impossible to draw conclusions about the effects of either the genetically modified maize or Roundup. Consequently, the data presented in the article provides no basis on which to change previous assessments of either genetically modified maize NK603 or the active substance glyphosate, an ingredient of the Roundup.

All published opinions on the Séralini et al study are provided in Appendix 1

The position of Monsanto is entirely in line with the official- and expert reviews.

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[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 - *Note: this review is in Dutch language. A translation will be available shortly.*

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

[9] http://www.food.dtu.dk/upload/institutter/food/publikationer/2012/vurdering_gmostudieseralini_okt12.pdf - *Note: this review is in Danish language. A translation is available in attachment to this letter (Appendix 1).*

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

Gilles-Eric Séralini, Emilie Clair, Robin Mesnage, Steeve Gress, Nicolas Defarge, Manuela Malatesta,

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.

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[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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