Monsanto Commentary

Seralini et al, Food and Chemical Toxicology, 2012

Monsanto Scientific Affairs

Contact: daniel.a.goldstein[redacted]

Links- Paper and associated Media

Long term toxicity of a Roundup 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, 50(11):,4221–4231, Nov. 2012

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

Associated website and videos:

http://www.ogm-alerte-mondiale.net/?lang=en

http://www.youtube.com/channel/UCktZ44yjV7cq0yFhQlrpyOg?feature=guide

http://www.dailymotion.com/Lieurac_Productions

Monsanto.com Response to Seralini et al 2012

(with link to more detailed responses)

http://www.monsanto.com/newsviews/Pages/monsanto-responds-to-french-rat-study.aspx

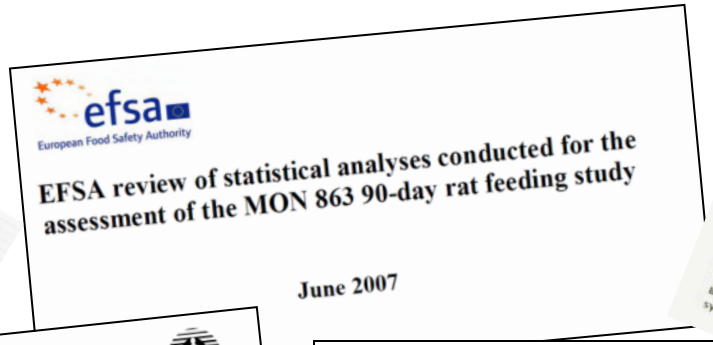
GILES-ERIC SERALINI

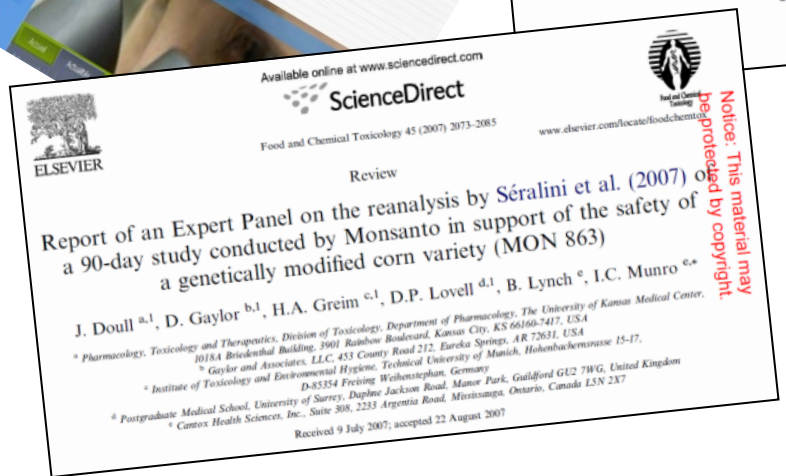
- A long-term anti-biotech activist / "scientist"
  - Holds PhD in molecular biology.
- University of Caen / CRIIGEN*
  - *Committee for Research and Independent Information on Genetic Engineering*
- Long history of anti-GM/anti-glyphosate activity:
  - Publications
  - "Re-analysis" of Monsanto product data
  - Press/media events, Videos
  - Political activity / "Tours"
  - Litigation (Libel suits against opponents)
  - Multiple colleagues at CRIIGEN and elsewhere.
  - Affiliated / funded- Greenpeace, Sustainable Food Trust, etc.
  - Evidence French Supermarket chains financed current study (*L'Express*)

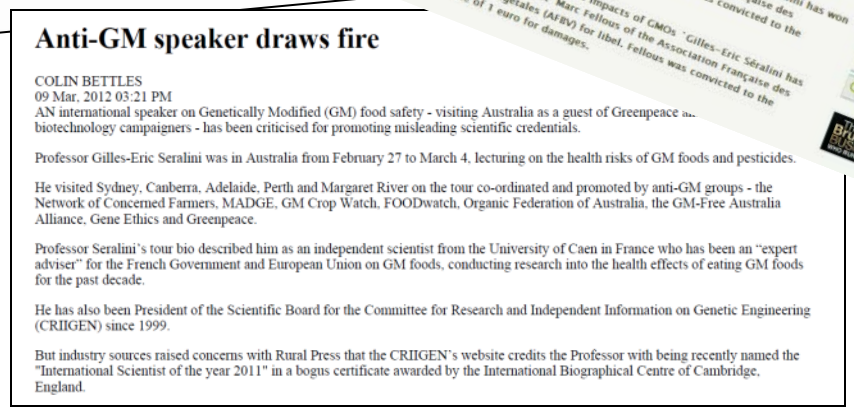
* CRIIGEN- Committee for Research and Independent Information on Genetic Engineering

Seralini- Lack of Credibility

- Scientific publications widely criticized by regulatory agencies (EFSA/FSANZ) and scientific community.
- Recent Australia/New-Zealand tour cut short with little impact / local criticism.
- Recent use of purchased credentials for self promotion ("International Scientist of the Year").

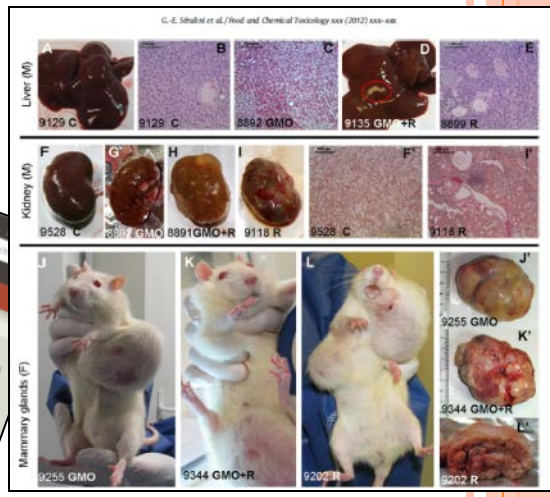






SERALINI ET AL 2012…

- In Press - Journal of Food and Chemical Toxicology
  - Respected journal with papers from academic, government and industry scientists.
  - Publishes many key papers on GM safety assessment
  - Has published critiques of Seralini in the past
- Early press embargo with selected media, restrictions on obtaining scientific review.
- Accompanied by press releases, videos in 3 languages, and a book.
- All co-authors with long history of anti-GM activity.
- Triggered inquiry from Regulatory Agencies around the globe.
- Extensive secondary media coverage.



Summary - Seralini et al., (2012)

Diets/treatment:

- **33% conventional corn**
- **11% NK603 corn +/- Roundup treatment**
- **22% NK603 corn +/- Roundup treatment**
- **33% NK603 corn +/- Roundup treatment**
- **Control diet + water with $1.1x10^{-8}$% of Roundup**
- **Control diet + water with 0.09% of Roundup**
- **Control diet + water with 0.5% of Roundup**

Animals:

Sprague-Dawley rats at 5 weeks of age
10 rats/treatment/sex

Summary - Seralini et al., (2012)

- **Observations**: **Observation and palpation of animals**
  Recording of clinical signs
  Measurement of tumors
  Food and water consumption
  Individual body weights.

- **Biochemical analyses: Before treatment and after 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months. 47 parameters were measured in blood and urine**

- **Anatomic pathology: 36 tissues were collected, although Table 1 indicates histopathology on 34 tissues.**

- **Statistical analysis: Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) of selected biochemical data.**

Primary Study Claims by A

VERSION WITHOUT COMMENTS

- Greater / earlier mortality in treated vs control groups.
- More / earlier tumors in treated vs control groups.
- Results are “hormone and sex dependant.”
- Elevated rates of liver and kidney pathology.
- Biochemical abnormalities of kidney and liver function.
- Significant “chronic kidney deficiencies”
- Endocrine disruption.

Primary Claims by Authors with Brief

VERSION WITH COMMENTS

- Greater / earlier mortality in treated vs control groups.
  - No dose response, no statistical analysis.
- More / earlier tumors in treated vs control groups.
  - No dose response, no statistical analysis
- Results are "hormone and sex dependant."
  - No supporting data, simply based on variation between sexes.
- Elevated rates of liver and kidney pathology.
  - No data.
- Biochemical abnormalities of kidney and liver function.
  - No consistent data presentation*, missing data, no control data.
- Significant "chronic kidney deficiencies"
  - No data*. Common in SD rat.
- Endocrine disruption.
  - No data*.

* "Data" presented as % variation without mean or control data is un-interpretable.

Primary Defects

SINGLE SLIDE VERSION

- Research protocol does not meet OECD sta
- Source and quality of corn used is unclear.
- Critical details on diet preparation and dietary intake absent.
- Complete lack of data pertaining to microscopic changes in liver or kidney tissues or laboratory testing of blood and urine.
- Lack of statistical analysis for mortality or tumor incidence.
  - Monsanto analysis of deaths based on visual approximation of graphical data indicates lack of statistical significance even at $p < 0.10$).
- Mortality rates and overall tumor incidence in all groups within historical norms for this strain of laboratory rat.
- Data presented are highly selective (ex- different methods for male and female), and not sufficient to support conclusions.
- Complete lack of dose-response relationship throughout the study.
- No plausible mechanism for the results reported with genetically modified maize.
- Glyphosate results inconsistent with extensive experience and scientific study.
  - Nine chronic rat studies (8 2-yr),1000's of animals (over 500 controls), no evidence of cancer.
- Extensive animal and *in-vitro* data demonstrates glyphosate does not cause cancer or tumors, and is not an endocrine disrupter.

Primary Defects

TWO- SLIDE VERSION
1 of 2

- Research protocol does not meet OECD standards (451 or 453).
- Source and quality of corn used is unclear.
- Critical details on diet preparation and dietary intake absent.
- Complete lack of data pertaining to microscopic changes in liver or kidney tissues or laboratory testing of blood and urine.
- Lack of statistical analysis for mortality or tumor incidence.
  - Monsanto analysis of deaths based on visual approximation of graphical data indicates lack of statistical significance even at $p < 0.10$).
- Mortality rates and overall tumor incidence in all groups within historical norms for this strain of laboratory rat.

Primary Defects

TWO SLIDE VERSION
2 of 2

- Data presented are highly selective (e.g. different methods for male and female), and not sufficient to support conclusions.
- Complete lack of dose-response relationship throughout the study.
- No plausible mechanism for the results reported with genetically modified maize.
- Glyphosate results inconsistent with extensive experience and scientific study.
  - Nine chronic rat studies (8 2-yr),1000's of animals (over 500 controls), no evidence of cancer.
- Extensive animal and *in-vitro* data demonstrates glyphosate does not cause cancer or tumors, and is not an endocrine disrupter.

SD or not SD…. That is the question..

- Some sources criticize the choice of Sprague-Dawley (SD) rats in this study do to high frequency of tumors and poor survival of this strain.
  - Mammary tumors may occur in over 70% of animals in lifetime studies.
- SD rats ARE used routinely for long term / cancer studies.
  - This includes many Monsanto studies of GM (up to 90 days) or chemical products.
- HOWEVER- the use of this strain requires adequate numbers of animals per test/control group and adequate historical data to support statistical analysis. (See OECD 451 or 453)
- Monsanto concludes that SD rat is an appropriate model strain for this type if study- but the study must be conducted properly, including the use of 50 or more animals per sex per test group.

Creating the illusion of Illness and Death

While it is proper to use equal numbers of animals in control and test groups:

- Statistical analysis must be used to determine whether differences in tumors or mortality rates are likely to represent random variation.
- Seralini et al used 9 test groups (3 doses GM, 3 doses Roundup, and 3 doses of GM + Roundup) vs a single control group.
- Given that time of death or tumor occurrence is randomly distributed, a few will occur early in life.
- **The observation that early occurrence of deaths or tumors in some test groups is to be expected-** There are 9-times more animals in these groups than in controls.

Regulatory Responses

- German Federal institute for Risk Assessment (BfR) – link
- *"the authors' main statements are not sufficiently corroborated by experimental evidence, due to deficiencies in the study design and in the presentation and interpretation of the study results."*
- Initial Review: European Food Safety Authority (EFSA) – link
- *"insufficient scientific quality to be considered valid for risk assessment."*
- *"design, reporting and analysis of the study, as outlined in the paper, are inadequate."*
- Australian New Zealand Food Standards (FSANZ) – link
- *"Key limitations 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"*
- *"FSANZ will publish a detailed response shortly, however, there is insufficient data in this published paper to enable a complete analysis."*

EFSA Final Review

- EFSA published a detailed analysis on November 28,2012, including an Annex with detailed statistical analysis and a compilation of regulatory opinions.
  - Statement: EFSA Journal 2012;10(11):2986 link
  - Annex: link
- **Abstract:**
- …As requested by the European Commission, EFSA reviewed [Seralini et al 2012] taking into consideration assessments conducted by Member States and any clarification given by the authors. **The assessments of Member States and EFSA revealed an overall agreement**. **The study as reported by Séralini et al. was found to be inadequately designed, analysed and reported.** The authors of Séralini et al. provided a limited amount of relevant additional information in their answer to critics published in the journal Food and Chemical Toxicology. Taking into consideration Member States' assessments and the authors' answer to critics, EFSA reaches similar conclusions as in its first Statement (EFSA 2012). **The study as described by Séralini et al. does not allow giving weight to their results and conclusions as published. Conclusions cannot be drawn on the difference in tumour incidence between treatment groups on the basis of the design, the analysis and the results as reported.** Taking into consideration Member States' assessments and the authors' answer to critics, EFSA finds that the study as reported by **Séralini et al. is of insufficient scientific quality for safety assessments. EFSA concludes that the currently available evidence does not impact on the ongoing re-evaluation of glyphosate and does not call for the reopening of the safety evaluations of maize NK603 and its related stacks.** EFSA's evaluation of the Séralini et al. article is in keeping with its role to review relevant scientific literature for risk assessment on an ongoing basis to ensure that the advice it provides is up-to-date.

MORTALITY DATA

- Statistical analysis by French HCB as provided in EFSA Final Opinion Annex-1, page 128.

Here, the data provided by the Harlan Company indicates a 2-year survival rate of 32% for males and 48% for females. For each sex, the number of rats alive after 2 years is a binomial random variable for which we can calculate 90% and 95% prediction intervals[22].

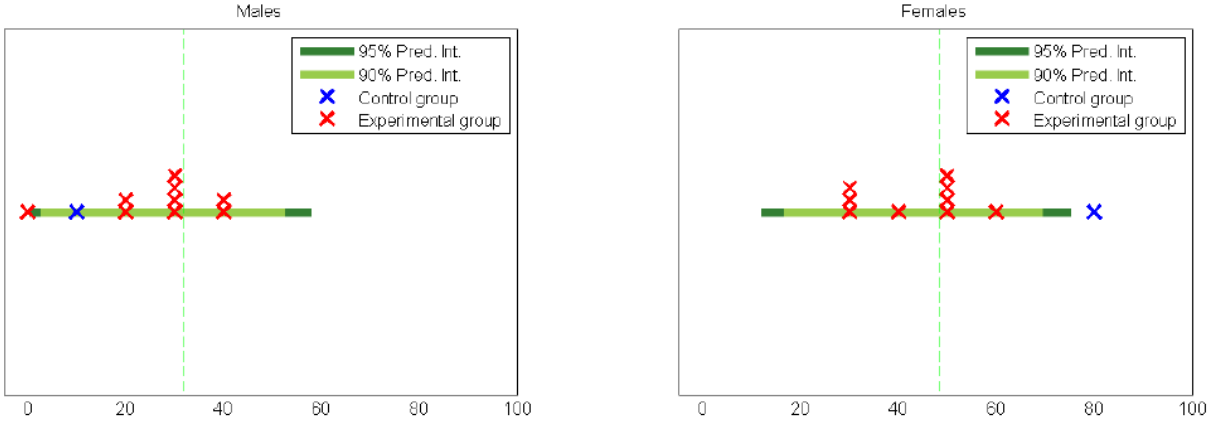


Fig. 3. 90% and 95% prediction intervals for 2-year survival rate obtained from data from the Harlan Company, and the survival rate observed in the experimental and control groups.

The experimental groups are for the most part distributed within these prediction intervals. With 18 groups, it is entirely normal that one observation be found on the edge of the 95% prediction interval. The 2-year survival rates are entirely in agreement with the reference data provided by the company when the rats are raised in normal conditions.

The use of reference data provided by the Harlan Company confirms that we cannot explain the differences observed in the survival curves of different experimental and control groups by invoking the effect of diet.

SURVIVAL DATA

- Statistical analysis by French HCB as provided in EFSA Final Opinion Annex-1, page 129-130.

The following figure presents for each sex the survival curves of the 9 experimental groups and the 90% and 95% prediction intervals.

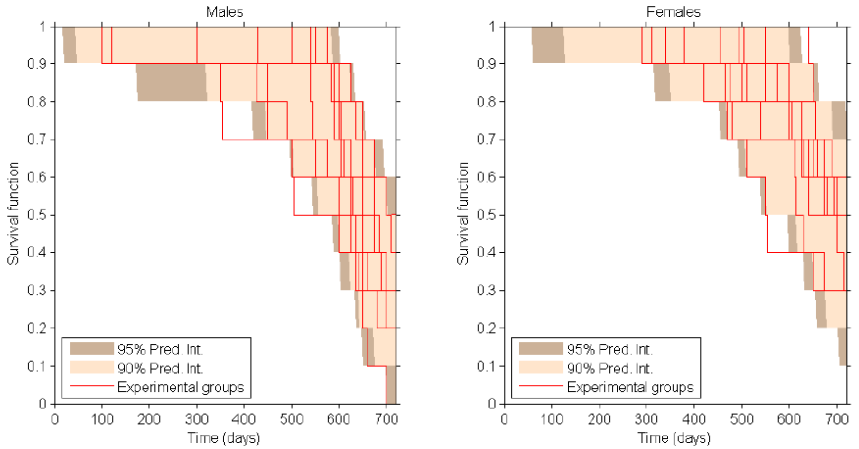


Fig. 5. 90% and 95% prediction intervals for the survival of the combined experimental groups, and the survival curves of the 9 experimental groups seen individually.

The next figure shows for each sex the same prediction intervals, but now with the survival curve of the control groups:

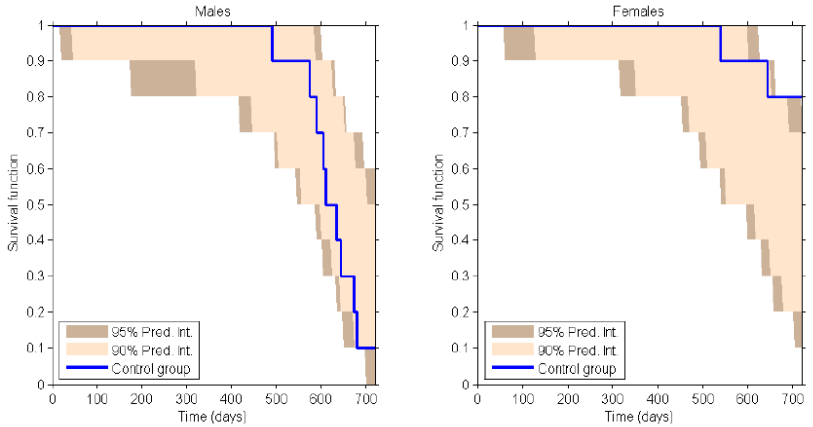


Fig. 6. 90% and 95% prediction intervals for the survival of the combined experimental groups, and the observed survival curves of the control groups.

The survival curves of the control groups are essentially inside the prediction bounds:

We cannot conclude that there is a statistically significant difference between the survival of the control and experimental rats.

TUMOR DATA

- Statistical analysis by French HCB as provided in EFSA Final Opinion Annex-1, page 133.

The following figure shows for each sex, the number of tumors of the 9 experimental groups and the 90% and 95% prediction intervals:

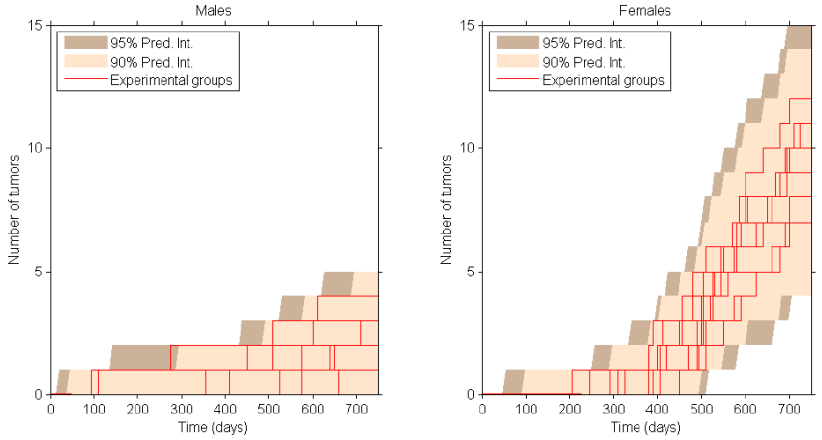


Fig. 12. Intervalles de prévision de niveau 90 % et 95 % des nombres de tumeurs du groupe expérimental et nombres de tumeurs observées des groupes expérimentaux.

The following figure then shows for each sex the same prediction intervals, this time along with the evolution of the number of tumors in the respective control group:

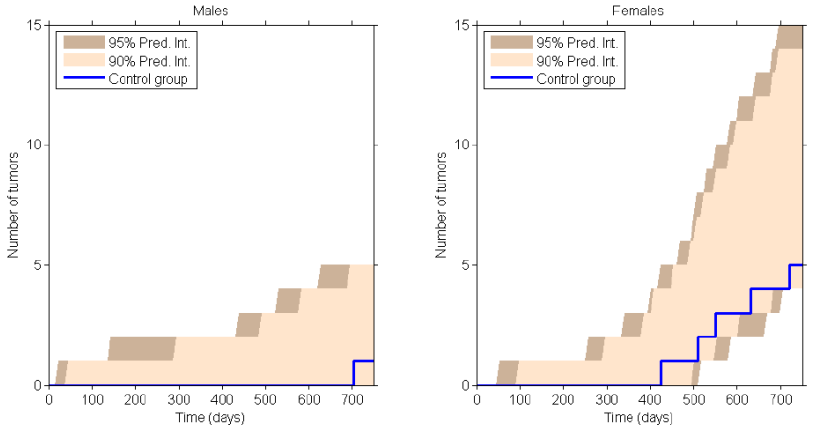


Fig. 13. 90% and 95% prediction intervals for the number of tumors in the experimental groups, and the evolution of the number of observed tumors in the control groups.

The curves for the number of tumors in the control groups are inside both prediction intervals:

We cannot conclude that there is a statistically significant effect of diet on the number of tumors.

Further Details- German BfR (1)

- The published study was not conducted in accordance with internationally accepted standards.
- Sprague Dawley strain provided by the breeder Harlan, is known to develop spontaneous tumours, particularly mammary and pituitary tumours,
- A number of 10 animals per sex and group is too low to confirm a trend or an effect.
- No statements on statistically significant dose-response-relationships can be made..
- The publication does not inform whether the diets of all groups contained a total of 33 per cent maize.
- Data on feed and water consumption as well as body weight development are missing.
- There are also no further details on the identity of the control maize line.
- Maize varieties used in the study were not analysed for the presence of mycotoxins.

Further Details- German BfR (2)

- Mortality, tumour incidences and other pathological changes were presented without statistical analyses.
- The incomplete and undifferentiated presentation of the data makes evaluation very difficult.
- A statistical analysis was performed with a special kind of principal component analysis (OPLS-DA = Orthogonal Partial Least Squares Discriminant Analysis).
- The authors stated the adverse effect would be due to the adverse effect on the endocrine system. The authors refer to a recent review published by Vandenberg et al. (2012). However, a detailed look into this paper reveals that its content is not correctly reflected by Séralini et al.. Vandenberg et al. explicitly question the existence of a threshold for adverse effects induced by endocrine disruptors. Thus the cited literature is not suitable to support the authors' claims.

ANSES The French agency for Food, Environmental and Occupational Health Safety

Excerpts From Press Release: (Link to report)

- ***ANSES was requested by the French Government to examine the paper by Séralini et al. published on 19 September 2012. The collective expert assessment carried out by the Agency concluded that the results of this research do not cast doubt on previous regulatory assessments of NK603 maize and Roundup. However, ANSES emphasizes the small number of published studies dealing with the potential long-term effects of the consumption of GMOs in association with pesticides and recommends undertaking research into these issues. In addition, the Agency calls for national or European funding to enable large-scale studies and research for consolidating our knowledge of insufficiently documented health risks.***

  After the publication on 19 September of a study by Séralini et al. on the long-term toxicity of the plant protection product Roundup and the genetically-modified, "glyphosate-ready" NK603 maize, ANSES received requests from the Ministers for Health, Ecology, Agriculture and Consumer Affairs to examine the article.

  The expert assessment carried out by the Agency concludes that the results of this research do not cast doubt on the previous assessments of genetically-modified NK603 maize and Roundup.

- **Monsanto Response to ANCES Report:**
  - An extensive body of scientific evidence, reviewed by regulatory agencies around the globe, supports the safety of plant biotechnology in general as well as the specific safety of NK603 maize and Roundup herbicide.
  - We believe the HCB and ANSES should help society understand this evidence rather than call for new long term tests for which there is no scientific need. Methodology for assessing the safety of biotech crops is well established in the EU and globally and approved products have a long history of safe use.

The French agency for Food, Environmental and Occupational Health Safety is a public administrative institution reporting to the Ministers for Health, Agriculture, the Environment, Labour and Consumer Affairs. http://www.anses.fr/galaxieEN.html

HCB HIGH COUNSEL FOR BIOTECHNOLOGY / HAUT CONSEIL DES BIOTECHNOLOGIES

- **Press Release- French- link Press Release- English- link**
- **Scientific Committee Report- French- link**
- **Scientific Committee Executive Summary- English- link**
- **Economic, Ethical & Social Committee-French- link**
- **Excerpt- Press Release:**

  In its opinion delivered on 19 October 2012 following a multidisciplinary expert assessment, the HCB Scientific Committee (SC) notes that the experimental design, the statistical tools used by the study's authors, and their interpretation of the results suffer from missing data and information and unacceptable methodological flaws that offer no support for the proposed findings. The SC concludes that the study provides no substantiated scientific information on possible health risks linked to consumption of maize NK603, whether or not treated with Roundup.

  For its part, the HCB Economic, Ethical and Social Committee (EESC) observes that the article is not conclusive. Nevertheless, to answer the questions raised by society, the EESC recommends that an independent and transparent long-term replication study be undertaken under the aegis of the public authorities regarding the safety of maize NK603.

- **Monsanto Response to HCB Reports:**
  - An extensive body of scientific evidence, reviewed by regulatory agencies around the globe, supports the safety of plant biotechnology in general as well as the specific safety of NK603 maize and Roundup herbicide.
  - We believe the HCB and ANSES should help society understand this evidence rather than call for new long term tests for which there is no scientific need. Methodology for assessing the safety of biotech crops is well established in the EU and globally and approved products have a long history of safe use.

About HCB: http://www.hautconseildesbiotechnologies.fr/spip.php?rubrique5

Response from global Regulators- Russia

"Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" where the results of the studies on the adverse health effects in rats of genetically modified maize NK603, Rospotrebnadzor *started investigation of this data obtained by the authors of the said article.

A respective request to examine the correctness of the conclusions of the European scientists has been directed to the Institute of Nutrition. In addition, an official letter of request to comment on the situation and to provide the position of the European Union on this matter was sent to the Director General of the Directorate General for Health and Consumer Protection of the European Commission.

Temporarily, until the complete information on the subject is obtained, the import of genetically modified maize NK603 into Russia and its sales in Russia is suspended. ”

* Federal Service for Supervision of Consumer Rights Protection and Human Welfare

Regulatory Responses

- Denmark- DTU National Food Institute - link
- *"…finds that the new study has not been designed correctly, that the correct statistics have not been used, and finally, that the authors do not discuss their data as scientific practice prescribes within the field of toxicology. The DTU National Food Institute concludes that the article is of poor academic quality and that it should not have been published in a peer-reviewed periodical."* (Professional translation, available on request)

- Netherlands- Bureau for Risk Assessment (BuRo)- link
- *"Following the scientific risk assessment study of Séralini and coauthors (2012) NVWA*-BuRo concludes that French researchers make connections between treatment and effects that are not scientifically substantiated."* (from "Conclusions")

- Romania ANSVSA (in Romanian)- link

*NVWA : De Nederlandse Voedsel- en Warenautoriteit (Netherlands Food and Consumer Product Safety Authority). The NVMA is part of the Ministry of Economic Affairs, Agriculture and Innovation.

Detailed Response from VIB (1)

(Flemish Institute of Biotechnology)

Conclusion (emphasis added)

The two-year long rat study conducted by Séralini and his colleagues displays, from a scientific point of view, considerable shortcomings. The most serious of these can be found in the fact that the study used far too few rats per treated group and that there were too few control groups. In one fell swoop this entirely removes the basis for the conclusions that Séralini et al. draw. In addition to this, for every conclusion that they draw there is sufficient evidence in their own text to undermine them completely. There are also other shortcomings and numerous other questions that remain unanswered. One thing is clear: **Séralini et al. have not been able to substantiate in any way whether genetically modified NK603 maize or Roundup is harmful or not**. The only thing that the study confirms is that Sprague-Dawley rats, like many other laboratory rats, develop relatively speaking many pathologies and that, as a consequence of this, many of the animals do not reach two years of age. But we have known this since the 1960s.

Detailed Response from VIB (2)
(Flemish Institute of Biotechnology)

Detailed response

- The experiment does not meet the OECD guidelines for carcinogenicity tests in rats.
- There is no data about the quality of the maize that was used.
- There is no mention of how the nutritional balance was kept in the various diets.
- There is no data about the body weights of the animals.
- The type of statistics that was used is never used in the interpretation of tumor data.
- It is not clear whether the NK603 maize that was sprayed with Roundup was also treated with other herbicides and, if so, which.
- This study does not contain any appropriate statistical analysis of mortality, tumor incidence and general pathological findings.

GERMAN BVL* (FEDERAL OFFICE OF CONSUMER PROTECTION AND FOOD SAFETY)

- German BVL agrees with German BfR that conclusions by Seralini et al are not supported by the data

- **EXCERPTS (emphases added)** Full text (German) available here.

- *In its initial, preliminary evaluation…the German Federal Office of Consumer Protection and Food Safety agrees with the German Federal Institute for Risk Assessment and **has concluded that the authors' findings are not justified**. The reasons for this are the flaws in the design of the study and the method of data analysis and data presentation.*
- *[BVL]therefore used the mortality rates for the test animals presented in Figure 1 of the publication for performance of an appropriate statistical analysis. [BVL] performed a Kaplan-Meier analysis to estimate the survival function and, on the basis of this analysis, **arrived at the conclusion that the group sizes and the differences observed in the survival function for the separate groups are too small to allow statistical extrapolation of possible treatment impact on survival duration**.*
- *On the basis of this preliminary analysis, the German Federal Office of Consumer Protection and Food Safety is of the opinion that the statement that rats administered with NK603 maize in feed and/or Roundup in drinking water tend to die earlier is not substantiated by the results published by Seralini et al. in 2012. **The inadequate presentation of the results renders statistical evaluation of other data impossible, e.g. the tumour incidence.***

- *Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Brazil- CTNBio Response

- CTNBio link (Portuguese)
  - Portuguese: http://www.ctnbio.gov.br/index.php/content/view/17599.html
  - English: http://www.ctnbio.gov.br/upd_blob/0001/1725.pdf
- Excerpts (English language translation by CTNBio)
  - *The President of the Brazilian National Technical Commission on Biosafety - CTNBio, in response to the demand of the Ministry of Foreign Affairs, appointed a committee comprised of four distinguished researchers who evaluated the work of Séralini and his collaborators in prior publication on the journal Food and Chemical Toxicology… The result of this evaluation is below.*

  - *In an overall assessment, this study represents a strong commitment to assess the consequences of a diet with genetically modified (GM) plants, exposed or not to the herbicide to which they are resistant, as well as with the herbicide itself, to rats after a long-term treatment.* ***Results generated could potentially bring valuable information about the issue raised by the authors, however, the study completely fails to reach such purposes…***

  - *Basic statistics on mortality data (ANOVA) is not presented, figures that do not contribute towards the elucidation of the facts are exploited as if they were new scientific results and the analysis of the changes in the biochemical profiles is questionable, since it advocates the thesis that these are caused by tumors, which in turn are inherent to the growth of the Sprague-Dawley strain.*

  - Reviewers: Prof. Dr. José Fernando Garcia – School of Veterinary Medicine, São Paulo State University Júlio de Mesquita Filho, Araçatuba, São Paulo; Prof. Dr. Fernando Salvador Moreno – School of Pharmaceutical Sciences, Department of Food and Experimental Nutrition, University of São Paulo, São Paulo, SP; Professor. Dr. Nance Beyer Nardi - Stem Cell and Tissue Engineering Laboratory, Lutheran University of Brazil, Canoas, RS

Health Canada

- Health Canada has issued an opinion in both English and French.
- Excerpt:
  - *Based on Health Canada and CFIA's review of this information, the authors' conclusions concerning the long term safety of NK603 corn and glyphosate are not supported. As a result, Health Canada and CFIA scientists have concluded that no change to the existing authorization of Roundup Ready Maize NK603 or the herbicide glyphosate would be recommended at this time. To permit further comprehensive analysis, Health Canada and the CFIA have requested the complete set of raw data from the study authors.*

  - *Selon l'examen de ces renseignements par Santé Canada et l'ACIA, les conclusions auxquelles sont parvenus les auteurs au sujet de l'innocuité à long terme du maïs NK603 et du glyphosate ne sont pas étayées. Par conséquent, les scientifiques de Santé Canada et de l'ACIA ont déterminé qu'actuellement, aucun changement n'est recommandé aux autorisations existantes dont font l'objet le maïs NK603 Roundup Ready et l'herbicide glyphosate. Dans le but de permettre l'approfondissement de leur analyse, Santé Canada et l'ACIA ont demandé aux auteurs de l'étude l'ensemble complet des données brutes issues de leurs travaux.*

Belgium Biotechnology Advisory Council (BAC)
http://www.bio-council.be/docs/BAC_2012_0898_CONSOLIDE.pdf

- The BAC issued an opinion on 19-10-2012 concluding that the Seralini study "does not contain new scientific elements that may lead to reconsider immediately the food and feed authorization [of NK603]"

- The BAC also requested that EFSA urgently undertake a re-assessment of the current evaluation process

Scientific Organizations and Media Responses

- Council for Biotechnology Information
- ABNE (African Biosafety Network of Expertise)
- ACB (African Centre for Biosafety)
- Science Media Centre – Comments-various scientists
- Science Media Center- Oct. 9 Editorial
- VIB – a life sciences research institute, Belgium
- New Scientist
- Nature editorial and Nature News
- Letter signed by scientists (original in French)
- Science 2.0
- Food Navigator

- Others listed in Monsanto response

Letters to the editor- Responses

- The links below are to draft versions of letters to the editor of FCT posted November 7, 2013. (Note- original Monsanto conflict-of-interest statement stated no conflict and is incorrectly recorded. Corrections sent to FCT)

Berry	link
Cockburn	link
deSouza	link
Dung	link
Grunewald	link
Hammond, Goldstein, and Saltmiras (Monsanto)	link
Heinemann	link
Langridge	link
Olivier	link
Panchin	link
Pilu	link
Schorsch	link
Tester	link
Trewavas	link
Tribe	link
Wager	link
Williams	link

- Seralini et al Response to Letters to the Editor: link

Six French Science Academies…

- Académies nationales d'Agriculture, de Médecine, de Pharmacie, des Sciences, des Technologies, et Vétérinaire Full text (French) available here.

Press release (available here):

- Les Académies nationales d'Agriculture, de Médecine, de Pharmacie, des Sciences, des Technologies, et Vétérinaire ont pris connaissance, en même temps que le grand public, de l'article récemment publié par l'équipe de Gilles-Eric Séralini dans la revue Food and Chemical Toxicology selon lequel un effet tumorigène et toxique important résulterait, chez le Rat, de la consommation du maïs génétiquement modifié NK 603 ou de l'exposition à de faibles doses du désherbant Roundup auquel il est résistant. Les six Académies estiment qu'en raison de nombreuses insuffisances de méthodologie et d'interprétation, les données présentées dans cet article ne peuvent remettre en cause les études ayant précédemment conclu à l'innocuité sanitaire du maïs NK603 et d'une manière plus générale à celle des plantes génétiquement modifiées dont la consommation par les animaux ou les humains a été autorisée.

- The National Academies of Agriculture, Medicine, Pharmacy, Science, Technology, and Veterinary Medicine became aware, at the same time as the general public, of the article recently published by the team of Gilles-Eric Seralini in the journal *Food and Chemical Toxicology* reporting a significant toxic and tumorigenic effect in rats following consumption of GM maize NK 603 or exposure to low doses of Roundup herbicide to which it is resistant. **The six academies believe that due to many deficiencies in methodology and interpretation, the data presented in this article do not cast doubt on the studies which have previously concluded the health safety of NK603 and more generally that of genetically modified plants whose consumption by animals or humans has been authorized.**

  (official translation pending)

Reviews and Opinions- GM Safety

- **American Medical Association (2012):** Link

  "AMA recognizes the continuing validity of the three major conclusions contained in the 1987 National Academy of Sciences white paper…:

  (a)There is no evidence that unique hazards exist either in the use of rDNA techniques or in the movement of genes between unrelated organisms;

  (b) The risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods;

  (c) Assessment of the risk of introducing rDNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.)"

  "Our AMA believes that as of June 2012, there is no scientific justification for special labeling of bioengineered foods, as a class, and that voluntary labeling is without value unless it is accompanied by focused consumer education."

- **Argentine Society of Nutrition (2012):** Link

  "It is our SAN position that, based on the compiled evidence to date, Foods derived from transgenic crops have showed to be safe to human and animal health"

Over 700 Scientists Demand Seralini Release Data

Petition at: http://www.ipetitions.com/petition/dr-seralini-please-release-data/

- **The Petition**

To: Dr. Giles Éric Séralini

From: The undersigned members of the scientific community
Re: Your paper in Food and Chemical Toxicology, 2012

Your recent paper in Food and Chemical Toxicology has elicited unprecedented levels of interest around the world. Yet, invoking lack of space, much of the data were not published.

Accordingly, we the undersigned members of the scientific community, invoke the following clause from Elsevier (http://www.elsevier.com/wps/find/authorsview.authors/rights):

Data access and retention
Authors may be asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data (consistent with the ALPSP-STM Statement on Data and Databases), if practicable, and should in any event be prepared to retain such data for a reasonable time after publication.

and urge you to make every effort to release all the data. Given the attention and implications of your work, we appeal that you make every effort to make such a release practicable as soon as possible. Only a full disclosure of the data can quell any uncertainties over the results you published.

Signatures (link)

Media Coverage (link to: Food Navigator)

European Toxicological Pathologists also weigh in….

- French Society (SFPT)
- *…SFPT feels compelled to point out weaknesses in the paper by Séralini et al (2012), the number and importance of which make the study reported very difficult to interpret scientifically.*
- *In our opinion, the study as reported demonstrate a critical failure in the ethical supervision.*

- European Society (ESTP)
- *"The ESTP comes to the conclusion that the pathology data presented in this paper are questionable and not correctly interpreted and displayed…. The pathology description and conclusion of this study are unprofessional."*
- *"As most members of the ESTP are veterinarians, we were shocked by the whole body photographs of animals bearing very large tumors…. We believe those animals should have been euthanized earlier as imposed by European legislation on laboratory animal protection."*

European Federation for Biotechnology

Excerpts from Opinion:

The European Food Safety Authority has just released a review of the paper by Seralini et al. published by Food and Chemical Toxicology....

The European Federation of Biotechnology would like to stress two additional aspects of this event.

The first one is the peculiar way the authors handled the communication about the study and its dissemination: a very unusual strategy for researchers, more focused to its impact on the media than to the science behind their findings. It is reported by several journalists that early access to the paper before publication was only allowed upon signature of a very peculiar non disclosure agreement: such an agreement would have prevented the journalists from approaching third-party researchers for comment. Additionally, a dedicated website opened at the same time of the release of the paper, with dedicated dissemination material, and ready-to-use messages. The paper also anticipates the release of a book, mostly based on those findings.

The second aspect is the peer-review process this paper was subject to. The Federation cannot explain how the reviewers chosen by the Journal did not address the same major observations highlighted by the EFSA and the scientific community at large. Nor our community can explain how Food and Chemical Toxicology allows the publication of images and graphics with emotional rather than scientific relevance. This paper represents a dangerous case of failure of the peer-review system, which threatens the credibility not just of the Journal but of the Scientific method overall.

About EFB: Established by European scientists in 1978, the European Federation of Biotechnology (EFB) is Europe's non-profit federation of National Biotechnology Associations, Learned Societies, Universities, Scientific Institutes, Biotech Companies and individual biotechnologists working to promote biotechnology throughout Europe and beyond. Additional information here.

Animal Rights Organizations Criticize Ethical Basis of Study

- BUAV link and ECEAE link (jointly issued)
  - *"A broad range of scientists have strongly criticised the research on statistical grounds and because the strain of rats used are prone to develop cancer as they age anyway. The BUAV believes the experiment should also be strongly criticised on animal welfare grounds."*

  - *Photographs of rats with shockingly large tumours were seen in the paper published in the journal Food and Chemical Toxicology. According to the UK Co-ordinating Committee on Cancer Research (UKCCCR) the "tumour burden should not usually exceed 5% of the host animal's normal body weight in the case of animals being used for routine tumour passage, or 10% in animals involved in therapeutic experiments. (This latter size, i.e. 10%, would typically represent a mean subcutaneous flank tumour diameter of 17mm in a 25g mouse or 35mm in a 250g rat)." The US Institutional Animal Care and Use Committee (IACUC) also states that "tumour size should not exceed 4.0cm in adult rats." The tumours shown in this experiment reached at least 7.0cm in length and in one photo two of these appallingly large tumours can be seen on either side of one rat's body.*

AFBV (French association for Biotechnology Vegetables)

COMMUNIQUE DE PRESSE DE L'AFBV

- Paris le 22 Octobre 2012 http://www.biotechnologies-vegetales.com/node/311

The AFBV has considered the opinions of ANSES and HCB regarding the highly controversial study carried out on NK 603 maize. These two institutions of the French Republic, known for their independence and their ability to address concerns such as those related to NK 603 maize, state that the procedures and results of this study cannot support the conclusion that transgenic maize is dangerous to the health of rats. The AFBV notes that these conclusions are in line with those made by other equivalent institutions in Europe and the world: the Netherlands, Germany, Belgium, Denmark, New Zealand, and Australia.

With the doubts around this study now clear, AFBV believes that the conclusions of this report should allow consumers and policy makers to draw the correct conclusions:

- Consumers urged to be frightened by unprecedented media hype can be assured about the safety of food they eat, even when that food contains this GMO, which have been authorized for import since 2004.

- The Minister of Agriculture has the duty and responsibility to initiate an information campaign to reassure consumers who have been unjustifiably worried by dramatic allegations. Failure to do so will send a signal of defeat of the government in the eyes of the public. On the other hand, the AFBV fears that the proposal by HCB and ANSES to conduct a new long-term study on NK 603 maize undermines their own previous conclusions which have, heretofore, been reassuring to the consumer.

Reviews and Opinions- GM Safety

- Scientific review:
  - Link
- European reviews:
  - Link
  - Link
- American Medical Association (2012):
  - Link
- Argentine Society of Nutrition (2012):
  - "*It is our SAN position that, based on the compiled evidence to date, Foods derived from transgenic crops have showed to be safe to human and animal health*"
  - Link
- Swiss National Science Foundation:
  - Link

Lay/Public Media Responses

- Reuters 1 and 2
- Forbes 1, 2, and 3
- Discovery News
- MIT
- Daily Kos
- Huffington Post
- BBC
- Daily Mail
- The Telegraph
- Discovery Magazine

Prior Publications- 1

- **Seralini and other co-authors of this paper have published previous statistical re-analyses of existing data on GM crops which have been subject to extreme criticism by regulatory agencies and scientific experts.**
- General commentary- Chassy and Miller: The Science of Things That Aren't So: http://www.forbes.com/sites/henrymiller/2012/02/22/the-science-of-things-that-arent-so/

- **EXAMPLE: The FSANZ response to the Spiroux de Vendomois publication (see below) states that:**

  "In their most recent paper, Séralini and colleagues reject the consensus view and instead propose a cause-and-effect link between the findings and the new pesticides (herbicide or insecticide) specific to each GM corn, or associate the results with unintended effects arising from the genetic modification process itself. The authors do not offer any plausible scientific explanations for their hypothesis, nor do they consider the lack of concordance of the statistics with other investigative processes used in the studies such as pathology, histopathology and histochemistry.

  Séralini and colleagues have distorted the toxicological significance of their results by placing undue emphasis on the statistical treatment of data, and failing to take other relevant factors into account. Reliance solely on statistics to determine treatment related effects in such studies is not indicative of a robust toxicological analysis. There is no corroborating evidence that would lead independently to the conclusion that there were effects of toxicological significance. FSANZ remains confident that the changes reported in these studies are neither sex- nor dose-related and are primarily due to chance alone."

Séralini G.E., Cellier E., de Vendomois J.S. (2007). New analysis of a rat feeding study with a genetically modified maize reveals signs of hepatorenal toxicity. Arch. Environ. Contam. Toxicol. http://www.springerlink.com/content/1432-0703

Spiroux de Vendomois, J.S., Roullier, F., Cellier, D. and Seralini, G-EA comparison of the effects of three GM corn varieties on mammalian health. Int. J. Biol. Sci. 5:706-726, December 15, 2009 http://www.biolsci.org/v05p0706.htm

Prior Publications- 2

Critiques of Spiroux de Vendomois research

- Report of an Expert Panel on the reanalysis by Seralini et al. (2007) of a 90-day study conducted by Monsanto in support of the safety of a genetically modified corn variety (MON 863). 2007. J. Doull , D. Gaylor , H.A. Greim1, D.P. Lovell, B. Lynch, I.C. Munro. Food and Chemical Toxicology 45(11):2073–2085 http://www.sciencedirect.com/science/article/pii/S0278691507003249

- European Food Standards Authority. EFSA reaffirms its risk assessment of genetically modified maize MON 863. http://www.efsa.europa.eu/en/press/news/gmo070628.htm

- FSANZ response to de Vendomois et al. (2009), A comparison of the Effects of Three GM Corn Varieties on Mammalian Health, Int. J. Biol. Sci. 5 (7): 706-726. http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets2009/fsanzresponsetoseral4647.cfm

- FSANZ (update). Feeding studies and GM corn MON863 http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets/feedingstudiesandgmc5604.cfm

- FSANZ response to de Vendomois et al. (2009), A comparison of the Effects of Three GM Corn Varieties on Mammalian Health, Int. J. Biol. Sci. 5 (7): 706-726. http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets2009/fsanzresponsetoseral4647.cfm

- EFSA response to de Vendomois et al. (see Annex 1 of the document linked below) http://www.efsa.europa.eu/en/events/event/gmo100127-m.pdf

- French High Council of Biotechnologies response to de Vendomois as translated by UK ACNFP (Advisory Committee on Novel Foods and Processes)

  http://www.food.gov.uk/multimedia/pdfs/acnfp9612a2

Prior Publications- 3

Seralini and colleagues have five prior publications on the results of exposing unprotected cells in culture to glyphosate, AMPA (primary environmental degradate of glyphosate), glyphosate- based formulations or a surfactant used in some formulated products. (Monsanto critiques of these documents available on request)

- Richard, S., Moslemi, S., Sipahutar, H., Benachour, N., and Seralini, G.-E. 2005. Differential effects of glyphosate and Roundup on human placental cells and aromatase. Environ. Health Perspect. 113:716-720. http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info:doi/10.1289/ehp.7728

- Benachour, N., Sipahutar, H., Moslemi, S., Gasnier, C., Travert, C., and Séralini, G. E. 2007. Time- and dose-dependent effects of Roundup on human embryonic and placental cells. Arch. Environ. Contam. Toxicol. 53:126-133. http://www.springerlink.com/content/d13171q7k863l446/

- Benachour, N., and Séralini, G. E. 2009 Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells. Nora Benachour and Gilles-Eric Seralini. Chem. Res. Toxicol., 22, 97–105. http://pubs.acs.org/doi/pdf/10.1021/tx800218n

- Gasnier, C., Dumont, C., Benachour, N., Clair, E., Chagnon, M., Gilles-Eric Seralini (2009). Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. Toxicology; 262(3):184-91 http://www.sciencedirect.com/science/article/pii/S0300483X09003047

- Émilie Claira, Robin Mesnagea, Carine Traverta, Gilles-Éric Séralini (2012). A glyphosate-based herbicide induces necrosis and apoptosis in mature rat testicular cells in vitro, and testosterone decrease at lower levels. Toxicology in Vitro 26(2):269–279. http://www.sciencedirect.com/science/article/pii/S0887233311003341

Prior Publications- 4

- The Seralini group has also published two publications suggesting that homeopathic remedies can protect cells against purported effects of glyphosate.
- Co-authors are associated with the purveyor of these homeopathic products, although they disclose no conflict of interest.

- Gasnier et al. Dig1 protects against cell death provoked by glyphosate-based herbicides in human liver cell lines. Journal of Occupational Medicine and Toxicology 2010, 5:29
  http://www.occup-med.com/content/5/1/29

- Gasnier et al. Defined plant extracts can protect human cells against combined xenobiotic effects. Journal of Occupational Medicine and Toxicology 2011, 6:3
  http://www.occup-med.com/content/6/1/3

Glyphosate and POEA Safety

GLYPHOSATE TOXICOLOGY DATA (GLOBAL*)

> 390 toxicology studies / 40 years of research/ multiple registrants
Variety of laboratories -Europe, North America, South America, Asia, Australia

Study Type	# studies typically required	Actual # studies available
Absorption, Distribution, Metabolism, Excretion (ADME)	2	23
Acute Toxicity	6	191
Repeat Dose (2 weeks – 1 year)	up to 6	48
DNA / genetic damage	3	69
Long term carcinogenicity (cancer)	2	24
Reproduction and development	3	33
Neurotoxicity	3	5

*Reflects cumulative global data from multiple registrants. Individual dossiers will vary by country, timing, data requirements, and number of collaborating registrants)

Glyphosate Reviews Conclude Favorable Toxicity

- 1987 WHO/FAO JMPR (Joint management of pesticide registrations)
- 1992 Canada
- 1993 US EPA
- 1999 Japan

Monsanto Data

- 2002 ANVISA (Brazil)
- 2002 EU Annex I Listing
- 2004 WHO/FAO JMPR
  - WHO package submitted to ANVISA
  - Cheminova, Monsanto and Syngenta data
- 2010/11 Japan FSC re-review
- 2010 US EPA & Canadian PMRA
  - Data Submission by 2012
  - Review completed by 2015
- 2012 EU Annex 1 Renewal

Ongoing

Multiple Data Submitters

ETHOXYLATED TALLOWAMINE
(SURFACTANT ACUTE TOXICOLOGY AND IRRITATION)

- **Oral LD50** **~1200 mg/kg**
- **Dermal LD50** **> 1260 mg/kg**
- **Skin Irritation** **Can be Irritating to Rabbit Skin**
- **Eye Irritation** **Severely Irritating/Corrosive to Rabbit Eye**

  (Spray solution is slightly irritating)

- **Potential to Cause Allergic Skin Reaction at 100%, but not at lower concentrations (e.g.. < 15%)**

ETHOXYLATED ALKYLAMINE GROUP:
DEVELOPMENTAL TOXICITY AND SUB-CHRONIC STUDIES

- **US EPA recently re-assessed all inert ingredients, including surfactants.**
- **Surfactants were clustered together by chemical structure and studied as groups of closely related compounds.**
- **POEA / Ethoxylated Tallowamine are ethoxylated alkylamines:**

  - **DEVELOPMENTAL TOXICITY**
    - **Studies: Rat Developmental**
      - **No birth defects or other effects observed in offspring**
      - **Maternal toxicity observed in high and mid-doses**
  - **DNA DAMAGE / MUTATION** – Negative
  - **SUBCHRONIC TOXICITY**
    - **Studies: 3-Month Rat & 3-Month Dog**
      - **No target organ toxicity**

Glyphosate –Resources

- Mink et al., 2012. Epidemiologic studies of glyphosate and cancer: A review
- Williams et al., 2012. Developmental and Reproductive Outcomes in Humans and Animals After Glyphosate Exposure: A Critical Analysis
- Mink et al., 2011. Epidemiologic studies of glyphosate and non-cancer health outcomes: A review
- European Commission's Health and Consumer Protection Directorate, 2002
- WHO/FAO
- EPA fact sheet and reregistration of glyphosate

Conclusion from Monsanto Company Response

As a result of methodological failures, incomplete data presentation, and lack of proper statistical analysis, we believe that 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.

We would note in closing that, fundamentally, this paper has found nothing more than the expected chronic health findings for this particular strain of rat, which has a high incidence of tumors and a relatively high rate of mortality in two year studies. In short, there is nothing in this study which would bring into question the conclusion of EFSA that: "In cases where molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence between the GM plant and derived food and feed and its comparator, except for the inserted trait(s), and have not indicated unintended effects, the performance of animal feeding trials with rodents or other (target) animal species (e.g. broilers) is of little additional value if any, and is therefore not deemed necessary on a routine basis"(EFSA, 2011)

Overall conclusion

Due to flaws in the study design, data interpretation and data presentation, it is concluded that the current Seralini et al. article does not provide any new information which would alter the conclusion of NK603 safety or the safety of glyphosate-based herbicide products.

Questions and Discussion

RETIRED SLIDES

Further Details- EFSA initial asse

NOTE- See Final Assesment

Conclusion:

"…study … is inadequately reported with many key
conduct, analysis and reporting being omitted. Without such details it is impossible to give weight to the subsequent 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 …

Séralini *et al.* (2012) draw conclusions on the incidence of tumours based on 10 rats per treatment per sex. .. Given the spontaneous occurrence of tumours in Sprague-Dawley rats, the low number of rats reported in the Séralini *et al.* (2012) publication is insufficient 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 has unclear study objectives and given its inadequate design, analysis and reporting, EFSA finds that it is of insufficient scientific quality for safety assessments. 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."

FURTHER DETAILS- EFSA INITIAL ASSESSMENT(2)

NOTE- See Final Assesment

- The study objective are unclear in the Seralini et al (20
- Seralini et al did not follow the internationally accepte
- The strain of rats chosen is known to be prone to devel over their life.
- Study included insufficient control for all test groups
- Study used low number of animals which is not sufficient to differentiate spontaneous occurrence of tumours from treatment induced tumours.
- No detailed information about composition of diets, storage condition of the feeds over the course of two years, and presence of harmful substance in the feeds used in the study
- No information on diet consumption, residual level of herbicide in diets, and presence of other chemicals contaminants (e.g other pesticides applied on maize)
- It is not reported if the statistical analyses were pre-specified in the protocol (i.e. prior to the start of the study) or in a statistical analysis plan prior to any access to the data.
- Summary statistics for all measured parameters y treatment group and sex are not presented.
- Séralini *et al.* (2012) have chosen an unconventional statistical methodology.
- Clinical observations other than tumours are selectively reported.

EFSA- Final report delayed until Mid-November to allow review of other member reports

http://www.efsa.europa.eu/en/pres

Note- Final report issued 11-28-2012

- News Story
  30 October 2012

  EFSA is due to publish in mid-November its second and final assessment of the Séralini *et al*. publication on the potential toxicity of GM maize NK603 and of a herbicide containing glyphosate.
- EFSA has extended the publication date of its second statement from the end of October until mid-November to allow it to fully consider the assessments of the Séralini *et al*. publication already carried out by EU Member States including Belgium, Denmark, France, Germany and The Netherlands.
- Upon publication of its initial statement on 4 October, EFSA also requested additional information from the study's authors related to experimental design, reporting and analysis of findings in order to help inform the Authority's final assessment.